西藥藥品優良製造規範
（第一部、附則）

PIC/S：Guide to Good Manufacturing Practice for Medicinal Products
（Part I、Annexes）

PE009-17 (25 August 2023)

衛生福利部

中華民國 112 年 8 月

第一部（Part I）

目　錄

附 則（Annexes）

目 錄

第一章　製藥品質系統（PHARMACEUTICAL QUALITY SYSTEM）

原則（PRINCIPLE）	
製造許可的持有者製造藥品時，應確保該藥品適合其預定用途，符合上市許可或符合臨床試驗許可（合適時）的要求，且不會由於其安全性、品質或有效性的不足而使病人陷於危險。該品質目標之達成是高層管理者的責任，且需要公司內各部門及所有階層之人員，以及公司之供應商與經銷商的參與和許諾。為可靠達成該品質目標，應有全面設計並正確實施的製藥品質系統。該系統涵蓋優良製造規範及品質風險管理，應充分文件化，並監測其效果。製藥品質系統的所有部門應適當配置能勝任的人員，以及合適且足夠的廠房、設備與設施。製造許可的持有者及被授權人另有其他法律責任。	The holder of a Manufacturing Authorisation must manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of the Marketing Authorisation or Clinical Trial Authorisation, as appropriate, and do not place patients at risk due to inadequate safety, quality or efficacy. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment by staff in many different departments and at all levels within the company, by the company's suppliers and by its distributors. To achieve this quality objective reliably there must be a comprehensively designed and correctly implemented Pharmaceutical Quality System incorporating Good Manufacturing Practice and Quality Risk Management. It should be fully documented and its effectiveness monitored. All parts of the Pharmaceutical Quality System should be adequately resourced with competent personnel, and suitable and sufficient premises, equipment and facilities. There are additional legal responsibilities for the holder of the Manufacturing Authorisation and for the Authorised Person(s).
品質管理、優良製造規範及品質風險管理的基本概念是相互關聯的。在本章中予以描述，以強調其間之關係及其對於藥品生產及管制之基本的重要性。	The basic concepts of Quality Management, Good Manufacturing Practice (GMP) and Quality Risk Management are inter-related. They are described here in order to emphasise their relationships and their fundamental importance to the production and control of medicinal products.

製藥品質系統[1]（PHARMACEUTICAL QUALITY SYSTEM[1]）	
[1]製造廠須建立並執行有效的「製藥品質保證系統」。「製藥品質系統」一詞用於本章係與 ICH Q10 術語一致，為了本章的目的，此等術語可視為可互換的。	[1] National requirements require to establish and implement an effective pharmaceutical quality assurance system. The term Pharmaceutical Quality System is used in this chapter in the interests of consistency with ICH Q10 terminology. For the purposes of this chapter these terms can be considered interchangeable.
1.1 品質管理是一個廣泛的概念。該概念涵蓋單獨或共同影響產品品質的所有事項。品質管理是經組織之安排的總和，以確保藥品具有預定用途所需之品質。因此，將優良製造規範納入品質管理。	1.1 Quality Management is a wide-ranging concept, which covers all matters, which individually or collectively influence the quality of a product. It is the sum total of the organised arrangements made with the objective of ensuring that medicinal products are of the quality required for their intended use. Quality Management therefore incorporates Good Manufacturing Practice.
1.2 GMP 適用於從研究用藥品的製造、技術移轉、商業製造到產品終止的生命週期階段。但是，如同 ICH Q10 所描述，製藥品質系統可以延伸到製藥開發生命週期階段，雖然其為可選擇的項目，但應會促進創新與持續改善，並且強化製劑開發與製造活動之間的持續連結。	1.2 GMP applies to the lifecycle stages from the manufacture of investigational medicinal products, technology transfer, commercial manufacturing through to product discontinuation. However the Pharmaceutical Quality System can extend to the pharmaceutical development lifecycle stage as described in ICH Q10, which while optional, should facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities.

1.3 當開發新的製藥品質系統或修改既有的系統時，應考慮公司的規模與複雜性。系統的設計應納入適當的風險管理原則，包含適當工具的使用在內。雖然系統的某些層面是涵蓋全公司的，而其他層面是製藥場所專一的，但製藥品質系統的有效性通常是在製藥場所層級加以證明之。	1.3 The size and complexity of the company's activities should be taken into consideration when developing a new Pharmaceutical Quality System or modifying an existing one. The design of the system should incorporate appropriate risk management principles including the use of appropriate tools. While some aspects of the system can be company-wide and others site-specific, the effectiveness of the system is normally demonstrated at the site level.
1.4 適合藥品製造的製藥品質系統應確保下列事項：	1.4 A Pharmaceutical Quality System appropriate for the manufacture of medicinal products should ensure that:
(i) 產品實現是經由設計、規劃、執行、維持與持續改進之系統所達成，以允許持續地產出具有適當品質屬性的產品；	(i) Product realisation is achieved by designing, planning, implementing, maintaining and continuously improving a system that allows the consistent delivery of products with appropriate quality attributes;
(ii) 產品與製程知識在生命週期的所有階段皆加以管理；	(ii) Product and process knowledge is managed throughout all lifecycle stages;
(iii) 藥品之設計與開發方式應考慮優良製造規範的要求；	(iii) Medicinal products are designed and developed in a way that takes account of the requirements of Good Manufacturing Practice;
(iv) 生產和管制作業應予清楚界定，並採用優良製造規範；	(iv) Production and control operations are clearly specified and Good Manufacturing Practice adopted;
(v) 管理責任應予清楚界定；	(v) Managerial responsibilities are clearly specified;
(vi) 為正確之原料與包裝材料的製造、供應與使用、供應商的選擇與監督，以及為確認每次交貨都是來自經核准的供應鏈等進行安排；	(vi) Arrangements are made for the manufacture, supply and use of the correct starting and packaging materials, the selection and monitoring of suppliers and for verifying that each delivery is from the approved supply chain;

(vii) 具備程序，以確保委外活動的管理；	(vii) Processes are in place to assure the management of outsourced activities;
(viii) 經由開發及使用有效的監測與管控系統，對製程性能與產品品質建立並維持管制的狀態；	(viii) A state of control is established and maintained by developing and using effective monitoring and control systems for process performance and product quality;
(ix) 在批次放行及在偏差的調查中，應考慮產品與製程監測的結果，並採取預防行動，以避免在未來發生潛在的偏差；	(ix) The results of product and processes monitoring are taken into account in batch release, in the investigation of deviations, and, with a view to taking preventive action to avoid potential deviations occurring in the future;
(x) 半製品/中間產品的所有必要管制，以及任何其他製程中管制與確效均已執行；	(x) All necessary controls on intermediate products, and any other in-process controls and validations are carried out;
(xi) 經由適合現行製程與產品知識水準之品質改善的實施，促進持續改善；	(xi) Continual improvement is facilitated through the implementation of quality improvements appropriate to the current level of process and product knowledge;
(xii) 考慮法規管理的通報與核准（需要時），對於計劃性變更的先期性評估及其實施前的核准，具有適當的安排；	(xii) Arrangements are in place for the prospective evaluation of planned changes and their approval prior to implementation taking into account regulatory notification and approval where required;
(xiii) 在任何變更實施之後進行評估，以確認達成品質目標，並且對產品品質沒有非預期的不良影響；	(xiii) After implementation of any change, an evaluation is undertaken to confirm the quality objectives were achieved and that there was no unintended deleterious impact on product quality;

(xiv) 在偏差、質疑的產品缺陷與其他問題的調查上，應使用適當程度的根本原因分析。	(xiv) An appropriate level of root cause analysis should be applied during the investigation of deviations, suspected product defects and other problems.
這可採品質風險管理原則予以確定之。若問題的真正根本原因不能確定時，則應考慮辨別最可能的根本原因，並解決該等問題。在懷疑或確認人為錯誤為其原因時，應證明其合理性，以確保未曾忽略製程、程序或基於系統的錯誤或問題（若存在時）。應確認並採取適當的矯正行動與預防行動以回應其調查，該行動的有效性應根據品質風險管理原則加以監測與評估；	This can be determined using Quality Risk Management principles. In cases where the true root cause(s) of the issue cannot be determined, consideration should be given to identifying the most likely root cause(s) and to addressing those. Where human error is suspected or identified as the cause, this should be justified having taken care to ensure that process, procedural or system based errors or problems have not been overlooked, if present. Appropriate corrective actions and/or preventive actions (CAPAs) should be identified and taken in response to investigations. The effectiveness of such actions should be monitored and assessed, in line with Quality Risk Management principles;
(xv) 未經被授權人認可每一生產批次皆已依上市許可及任何有關藥品之生產、管制及放行的法規之要求生產與管制前，該藥品不得銷售或供應；	(xv) Medicinal products are not sold or supplied before an Authorised Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products;

(xvi) 藥品之儲存、運銷及後續的處理應有妥善的安排，以確保在架儲期間能維持其品質；	(xvi) Satisfactory arrangements exist to ensure, as far as possible, that the medicinal products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life;
(xvii) 有自我查核及/或品質稽查的程序，以定期評估製藥品質系統之有效性及適用性。	(xvii) There is a process for self-inspection and/or quality audit, which regularly appraises the effectiveness and applicability of the Pharmaceutical Quality System.
1.5 高層管理者對確保具備充分資源配置之有效的製藥品質系統，並在整個組織中界定、溝通與執行角色、職責與權力，具有最終責任。高層管理者的領導與主動參與製藥品質系統是至關重要的，此領導應確保在組織內的所有階層與製藥場所的工作人員對該製藥品質系統的支持與承諾。	1.5 Senior management has the ultimate responsibility to ensure an effective Pharmaceutical Quality System is in place, adequately resourced and that roles, responsibilities, and authorities are defined, communicated and implemented throughout the organisation. Senior management's leadership and active participation in the Pharmaceutical Quality System is essential. This leadership should ensure the support and commitment of staff at all levels and sites within the organisation to the Pharmaceutical Quality System.
1.6 製藥品質系統之運作應有定期管理審查，並有高層管理者參與，以確認對於產品、製程與系統本身的持續改善機會。	1.6 There should be periodic management review, with the involvement of senior management, of the operation of the Pharmaceutical Quality System to identify opportunities for continual improvement of products, processes and the system itself.
1.7 製藥品質系統應加以界定並文件化。應建立品質手冊或其他等同之文件，並且應含有包括管理人員職責在內之品質管理系統的描述。	1.7 The Pharmaceutical Quality System should be defined and documented. A Quality Manual or equivalent documentation should be established and should contain a description of the quality management system including management responsibilities.
藥品優良製造規範（GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS）	

1.8 優良製造規範（GMP）係品質管理的一部分，用以確保藥品一致地生產及管制，以達到適合其預定用途及如同上市許可、臨床試驗許可或產品規格所要求之品質標準。優良製造規範是與生產及品質管制兩者有關，其基本要求為：	1.8 Good Manufacturing Practice is that part of Quality Management which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the Marketing Authorisation, Clinical Trial Authorisation or product specification. Good Manufacturing Practice is concerned with both production and quality control. The basic requirements of GMP are that:
(i) 所有製造過程均已清楚地界定，按照經驗有系統地檢討，顯示其能一致地製造所要求之品質並符合其規格的藥品；	(i) All manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing medicinal products of the required quality and complying with their specifications;
(ii) 製程的關鍵步驟及對製程的重大變更業經確效；	(ii) Critical steps of manufacturing processes and significant changes to the process are validated;
(iii) 提供優良製造規範所需之資源包括：	(iii) All necessary facilities for GMP are provided including:
● 經適當資格檢定與訓練的人員；	● Appropriately qualified and trained personnel;
● 足夠的廠房與作業空間；	● Adequate premises and space;
● 適當的設備及支援服務；	● Suitable equipment and services;
● 正確的原物料、容器及標籤；	● Correct materials, containers and labels;
● 依製藥品質系統所核定之程序及指令；	● Approved procedures and instructions, in accordance with the Pharmaceutical Quality System;
● 適當之儲存及運送。	● Suitable storage and transport.
(iv) 以清楚且不含糊的表達方式，將指令及程序書寫成指導性的型式。這特別適用於提供的資源；	(iv) Instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided;

(v) 程序被正確地執行，其操作者並經訓練；	(v) Procedures are carried out correctly and operators are trained to do so;
(vi) 製造過程中，以手寫及/或記錄儀器所作紀錄，證明界定的程序與指令所要求之所有步驟皆已實際執行，且產品的數量與品質皆如所預期；	(vi) Records are made, manually and/or by recording instruments, during manufacture which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected;
(vii) 任何顯著的偏差均完整地記錄，並以確定根本原因為目標進行調查，並實施適當的矯正與預防行動；	(vii) Any significant deviations are fully recorded, investigated with the objective of determining the root cause and appropriate corrective and preventive action implemented;
(viii) 包含運銷在內之製造紀錄，應以可理解及可取得的形式保存，以利追溯批次之完整歷程；	(viii) Records of manufacture including distribution which enable the complete history of a batch to be traced are retained in a comprehensible and accessible form;
(ix) 產品的運銷應使其對於產品品質的任何風險降到最低，並考慮優良運銷規範；	(ix) The distribution of the products minimises any risk to their quality and takes account of good distribution practice;
(x) 應有一套自銷售或供應點回收任何批次產品之系統；	(x) A system is available to recall any batch of product, from sale or supply;
(xi) 審查關於產品的申訴，調查品質瑕疵的原因，且對於該瑕疵產品採取適當的措施，以防止其再度發生。	(xi) Complaints about products are examined, the causes of quality defects investigated and appropriate measures taken in respect of the defective products and to prevent reoccurrence.
品質管制（QUALITY CONTROL）	

1.9 品質管制是優良製造規範的一部分，涉及抽樣、規格及檢驗，且與組織、文件與放行程序有關，用以確保必要且相關的試驗已確實執行，並確保品質判定合格前，原物料不會放行使用，產品不會放行銷售或供應。品質管制的基本要求是：	1.9 Quality Control is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. The basic requirements of Quality Control are that:
(i) 具有適當的設施、受過訓練的人員及經認可的程序，以供抽樣和檢驗原料、包裝材料、半製品/中間產品、待分/包裝產品及最終產品，並於適當時為優良製造規範之目的監測環境條件；	(i) Adequate facilities, trained personnel and approved procedures are available for sampling and testing starting materials, packaging materials, intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes;
(ii) 原料、包裝材料、半製品/中間產品、待分/包裝產品及最終產品的樣品應經核准的人員及方法抽取之；	(ii) Samples of starting materials, packaging materials, intermediate products, bulk products and finished products are taken by approved personnel and methods;
(iii) 檢驗方法業經確效；	(iii) Test methods are validated;
(iv) 應以手寫及/或記錄儀器製作紀錄，證明所有要求的抽樣、檢查及檢驗程序皆已實際執行。任何偏差均完整記錄並經調查；	(iv) Records are made, manually and/or by recording instruments, which demonstrate that all the required sampling, inspecting and testing procedures were actually carried out. Any deviations are fully recorded and investigated;

(v) 含符合上市許可或臨床試驗許可的定性與定量組成之有效成分的最終產品，應符合所要求之純度，且密封在適當容器內，並正確地標示；	(v) The finished products contain active ingredients complying with the qualitative and quantitative composition of the Marketing Authorisation or Clinical Trial Authorisation, are of the purity required, and are enclosed within their proper containers and correctly labelled;
(vi) 原物料、半製品/中間產品、待分/包裝產品及最終產品的檢查與檢驗結果均應予記錄，並對照其規格正式評估之。產品評價包含相關生產文件的審核與評估，以及與規定程序偏差的評價；	(vi) Records are made of the results of inspection and that testing of materials, intermediate, bulk, and finished products is formally assessed against specification. Product assessment includes a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures;
(vii) 每批產品，非經被授權人認可符合相關許可之要求，不得放行銷售或供應；	(vii) No batch of product is released for sale or supply prior to certification by an Authorised Person that it is in accordance with the requirements of the relevant authorisations;
(viii) 依照附則 19，應保留足夠的原料與產品的對照樣品，以容許未來必要時對該產品的檢查與檢驗，而且該樣品應保留在其最終包裝中。	(viii) Sufficient reference samples of starting materials and products are retained in accordance with Annex 19 to permit future examination of the product if necessary and that the sample is retained in the final pack.
產品品質檢討（PRODUCT QUALITY REVIEW）	

1.10 所有經許可的藥品，含外銷專用產品，其常規定期性或輪動式的品質檢討應以證實既有製程的一致性、現行規格對原料與最終產品的適當性為目標執行之，以凸顯任何趨勢並確認產品與製程之改善事項。前述之檢討通常應每年執行一次並加以文件化，並考量先前之檢討，且至少包含下列項目：	1.10 Regular periodic or rolling quality reviews of all authorised medicinal products, including export only products, should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product, to highlight any trends and to identify product and process improvements. Such reviews should normally be conducted and documented annually, taking into account previous reviews, and should include at least:
(i) 用於產品之原料及包裝材料，特別是那些來自新來源者之檢討，尤其是原料藥供應鏈之可追溯性的檢討；	(i) A review of starting materials including packaging materials used in the product, especially those from new sources and in particular the review of supply chain traceability of active substances;
(ii) 關鍵之製程中管制及最終產品結果的檢討；	(ii) A review of critical in-process controls and finished product results;
(iii) 不符合既定規格的所有批次及其調查之檢討；	(iii) A review of all batches that failed to meet established specification(s) and their investigation;
(iv) 所有顯著的偏差或不符合、其相關的調查及採取的矯正預防措施效果之檢討；	(iv) A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventive actions taken;
(v) 製程或分析方法所有變更之檢討；	(v) A review of all changes carried out to the processes or analytical methods;
(vi) 上市許可變更所提交/核准/否准文件之檢討，包含外銷專用文件在內；	(vi) A review of Marketing Authorisation variations submitted, granted or refused, including those for third country (export only) dossiers;
(vii) 安定性監測計畫的結果及任何不良趨勢之檢討；	(vii) A review of the results of the stability monitoring programme and any adverse trends;

(viii) 所有與品質相關之退回、申訴、回收及當時所執行調查之檢討；	(viii) A review of all quality-related returns, complaints and recalls and the investigations performed at the time;
(ix) 任何其他先前產品製程或設備矯正措施適當性之檢討；	(ix) A review of adequacy of any other previous product process or equipment corrective actions;
(x) 為新上市許可及變更上市許可所做之上市後許諾之檢討；	(x) For new Marketing Authorisations and variations to Marketing Authorisations, a review of post-marketing commitments;
(xi) 相關設備與公用設施，例如，空調系統（HVAC）、水系統、壓縮氣體等的驗證狀態；	(xi) The qualification status of relevant equipment and utilities, e.g. HVAC, water, compressed gases, etc;
(xii) 如同在第七章所界定之任何合約安排的檢討，確保其為最新。	(xii) A review of any contractual arrangements as defined in Chapter 7 to ensure that they are up to date.
1.11 在製藥品質系統下，製造者與上市許可持有者不同時，雙方應評估本檢討的結果，而且應評估是否採取矯正預防措施或任何再確效。對於持續進行之管理及這些行動的檢討應有管理程序，且在自我查核期間應證明這些程序之有效性。當符合科學正當性時，品質檢討得按其產品類型，例如固體劑型、液體劑型、無菌製劑等予以分組。	1.11 The manufacturer and, where different, Marketing Authorisation holder should evaluate the results of the review and an assessment made as to whether corrective and preventive action or any revalidation should be undertaken, under the Pharmaceutical Quality System. There should be management procedures for the ongoing management and review of these actions and the effectiveness of these procedures verified during self-inspection. Quality reviews may be grouped by product type, e.g. solid dosage forms, liquid dosage forms, sterile products, etc. where scientifically justified.

若上市許可持有者不是製造者時，雙方應有一份界定其各自在產品品質檢討上所負職責之技術協議書。負責批次之最終核定的被授權人與上市許可持有者應確保品質檢討係適時執行且為準確的。	Where the Marketing Authorisation holder is not the manufacturer, there should be a technical agreement in place between the various parties that defines their respective responsibilities in producing the product quality review. The Authorised Person responsible for final batch certification together with the Marketing Authorisation holder should ensure that the quality review is performed in a timely manner and is accurate.
品質風險管理（QUALITY RISK MANAGEMENT）	
1.12 品質風險管理是針對藥品品質風險之評價、管制、溝通及檢討的系統過程。可用前瞻性及回溯性的方式來執行。	1.12 Quality Risk Management is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively.
1.13 品質風險管理的原則為：	1.13 The principles of Quality Risk Management are that:
(i) 品質風險的評估是基於科學知識、製程的經驗，最終並連結至病患之保護；	(i) The evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient;
(ii) 品質風險管理過程的努力、正式化及文件化之程度應與風險程度相稱。	(ii) The level of effort, formality and documentation of the Quality Risk Management process is commensurate with the level of risk.
此外，品質風險管理之過程及應用的實例詳見附則 20 或 ICH Q9。	Examples of the processes and applications of Quality Risk Management can be found inter alia in Annex 20 or ICHQ9.

第二章　組織與人事（PERSONNEL）

原則（PRINCIPLE）	
藥品的正確製造仰賴於人。因此，藥廠有責任配置足夠的合格人員。個別工作人員應清楚瞭解其負責之工作並作成紀錄。所有人員均應認知優良製造規範的原則與其息息相關，並接受職前及持續的訓練，包括與工作有關的衛生指導。	The correct manufacture of medicinal products relies upon people. For this reason there must be sufficient qualified personnel to carry out all the tasks which are the responsibility of the manufacturer. Individual responsibilities should be clearly understood by the individuals and recorded. All personnel should be aware of the principles of Good Manufacturing Practice that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs.
一般規定（GENERAL）	
2.1　藥廠應配置足夠人員，且具必要資格及實務經驗。高層管理者應決定並提供充足與適當的資源（人員、財務、物資、設施及設備等）以執行及維持製藥品質系統，且持續地改進其有效性。賦予每一個人的責任不應過廣，以致對於品質呈現任何風險。	2.1　The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. Senior management should determine and provide adequate and appropriate resources (human, financial, materials, facilities and equipment) to implement and maintain the Pharmaceutical Quality System and continually improve its effectiveness. The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.
2.2　藥廠應有組織圖，其中，生產、品管主管與合適時 2.5 條所提及之品質保證或品質單位主管之間的關係，及被授權人的位置，應清楚地顯示於其管理架構中。	2.2　The manufacturer must have an organisation chart in which the relationships between the heads of Production, Quality Control and where applicable Head of Quality Assurance or Quality Unit referred to in point 2.5 and the position of the Authorised Person(s) are clearly shown in the managerial hierarchy.

2.3	各職位的負責人應有書面工作說明記載的特定職責，並經適當授權，以執行其職責。其職責得委由足以勝任的指定代理人行之。適用優良製造規範之有關人員，其職責不應有漏洞或未經說明的重疊。	2.3	People in responsible positions should have specific duties recorded in written job descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of those personnel concerned with the application of Good Manufacturing Practice.
2.4	高層管理者對於確保具備有效的製藥品質系統以達成品質目標，以及人員之角色與權責在整個組織中被界定、傳達與執行，具有最終責任。高層管理者應建立一個品質政策，描述公司與品質相關之整體意圖與方向，並且應透過參與管理審查,確保製藥品質系統與 GMP 循規的持續適用性與有效性。	2.4	Senior management has the ultimate responsibility to ensure an effective Pharmaceutical Quality System is in place to achieve the quality objectives, and, that roles, responsibilities, and authorities are defined, communicated and implemented throughout the organisation. Senior management should establish a quality policy that describes the overall intentions and direction of the company related to quality and should ensure continuing suitability and effectiveness of the Pharmaceutical Quality System and GMP compliance through participation in management review.
關鍵人員（KEY PERSONNEL）			

2.5 高層管理者應任命關鍵管理人員，包括生產主管、品質管制主管，以及如果這兩個人中至少有一位不負責產品之放行時，為放行之目的所指定的被授權人。重要的職位通常應由專職人員擔任。生產和品質管制部門的主管應相互獨立。大藥廠可能有必要委派人員，擔任 2.7、2.8 及 2.9 條中所列之部分職務。另外，根據公司之規模與組織架構，可指派個別的品質保證主管或品質單位主管；若該職務存在時，於 2.7、2.8 與 2.9 條中所描述的職責，有部分是與品質管制主管及生產主管分擔的，因此高層管理者應謹慎界定其角色與權責。	2.5 Senior Management should appoint Key Management Personnel including the head of Production, the head of Quality Control, and if at least one of these persons is not responsible for the release of products the Authorised Person(s) designated for the purpose. Normally, key posts should be occupied by full-time personnel. The heads of Production and Quality Control must be independent from each other. In large organisations, it may be necessary to delegate some of the functions listed in 2.7, 2.8 and 2.9. Additionally, depending on the size and organisational structure of the company, a separate Head of Quality Assurance or Head of the Quality Unit may be appointed. Where such a function exists usually some of the responsibilities described in 2.7, 2.8 and 2.9 are shared with the Head of Quality Control and Head of Production and senior management should therefore take care that roles, responsibilities, and authorities are defined.
2.6 被授權人之職責可歸納如下：	2.6 The duties of the Authorised Person(s) are described in the national requirements and can be summarised as follows:
a) 被授權人必須確保每一批次藥品已遵循國家有效法律及依照上市許可的要求進行製造與檢查；	a) An Authorised Person must ensure that each batch of medicinal products has been manufactured and checked in compliance with the laws in force in that country and in accordance with the requirements of the Marketing Authorisation;

b) 被授權人必須符合法規的資格要求，他們須在製造許可持有者指派下持續地履行其職責；	b) The Authorised Person(s) must meet the qualification requirements laid down in the national legislation, they shall be permanently and continuously at the disposal of the holder of the Manufacturing Authorisation to carry out their responsibilities;
c) 被授權人之職責可以進行委派，但僅限於另一位被授權人。	c) The responsibilities of an Authorised Person may be delegated, but only to other Authorised Person(s).
2.7 生產部門的主管通常有下列職責：	2.7 The head of Production generally has the following responsibilities:
(i) 為獲得要求的品質，應確保該等產品依適當的文件生產與儲存；	(i) To ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality;
(ii) 核准與生產作業有關的指令，並確保其嚴格的實施；	(ii) To approve the instructions relating to production operations and to ensure their strict implementation;
(iii) 確保生產紀錄已由經授權的人員評估與簽章；	(iii) To ensure that the production records are evaluated and signed by an authorised person;
(iv) 確保其部門、廠房設施與設備的驗證及維護保養；	(iv) To ensure the qualification and maintenance of his department, premises and equipment;
(v) 確保已完成適當的確效；	(v) To ensure that the appropriate validations are done;
(vi) 確保其部門的人員已執行所要求的職前與持續訓練，並依需求進行調適。	(vi) To ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.
2.8 品質管制的主管通常有下列職責：	2.8 The head of Quality Control generally has the following responsibilities:
(i) 合適時，核准或拒用原料、包裝材料、半製品/中間產品、待分/包裝產品及最終產品；	(i) To approve or reject, as he/she sees fit, starting materials, packaging materials, intermediate, bulk and finished products;

	(ii) 確保已執行所有必要的試驗，且相關紀錄也已進行評估；		(ii) To ensure that all necessary testing is carried out and the associated records evaluated;
	(iii) 核准規格、抽樣指令、檢驗方法及其他品質管制程序；		(iii) To approve specifications, sampling instructions, test methods and other Quality Control procedures;
	(iv) 受託檢驗者之核准及監督；		(iv) To approve and monitor any contract analysts;
	(v) 確保其部門、廠房設施與設備的驗證及維護保養；		(v) To ensure the qualification and maintenance of his/her department, premises and equipment;
	(vi) 確保已完成適當的確效；		(vi) To ensure that the appropriate validations are done;
	(vii) 確保其部門的人員已執行所要求的職前與持續訓練，並依需求進行調適。		(vii) To ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.
	品質管制部門的其他職責概述於第六章。		Other duties of Quality Control are summarised in Chapter 6.
2.9	生產和品質管制的主管，以及相關時品質保證主管或品質單位主管，通常有一些分擔或共同負擔之關於品質的職責，特別包括製藥品質系統之設計、有效實施、監測與維護。這些職責應受任何國家法規的規範，包括：	2.9	The heads of Production, Quality Control and where relevant, Head of Quality Assurance or Head of Quality Unit, generally have some shared, or jointly exercised, responsibilities relating to quality including in particular the design, effective implementation, monitoring and maintenance of the Pharmaceutical Quality System. These may include, subject to any national regulations:
	(i) 書面的程序和其他文件的認可，包括修訂在內；		(i) The authorisation of written procedures and other documents, including amendments;
	(ii) 製造環境的監測與管制；		(ii) The monitoring and control of the manufacturing environment;
	(iii) 工廠衛生；		(iii) Plant hygiene;
	(iv) 製程確效；		(iv) Process validation;
	(v) 訓練；		(v) Training;
	(vi) 原物料供應商的認可及監督；		(vi) The approval and monitoring of suppliers of materials;

(vii) 受託製造廠以及其他 GMP 相關之委外活動供應者的認可及監督；	(vii) The approval and monitoring of contract manufacturers and providers of other GMP related outsourced activities;
(viii) 原物料及產品之儲存條件的指示與監測；	(viii) The designation and monitoring of storage conditions for materials and products;
(ix) 紀錄的保存；	(ix) The retention of records;
(x) 符合 GMP 要求之監督；	(x) The monitoring of compliance with the requirements of Good Manufacturing Practice;
(xi) 樣品的檢查、調查與抽取，以便監測可能會影響產品品質的因素；	(xi) The inspection, investigation, and taking of samples, in order to monitor factors which may affect product quality;
(xii) 參與製程性能、產品品質與製藥品質系統之管理審查，並倡導其持續的改進；	(xii) Participation in management reviews of process performance, product quality and of the Pharmaceutical Quality System and advocating continual improvement;
(xiii) 確保具備適時且有效的溝通及陳報流程，以將品質議題提升到適當管理階層的層級。	(xiii) Ensuring that a timely and effective communication and escalation process exists to raise quality issues to the appropriate levels of management.
訓練（TRAINING）	
2.10 藥廠對於因其職責會進入生產及儲存區域或管制實驗室的所有人員(包括技術、維修保養及清潔人員)，以及對於其活動可能影響產品品質的其他人員，應提供訓練。	2.10 The manufacturer should provide training for all the personnel whose duties take them into production and storage areas or into control laboratories (including the technical, maintenance and cleaning personnel), and for other personnel whose activities could affect the quality of the product.

2.11	除了有關製藥品質系統與優良製造規範的理論與實務基本訓練之外，新招募的人員應接受適合於其指定職責之適當訓練。同時也應提供持續的訓練，並應對訓練的實際效果定期予以評估。應有視情況經生產部門或品質管制部門的主管核准的訓練計畫。訓練紀錄應予保存。	2.11	Besides the basic training on the theory and practice of the Pharmaceutical Quality System and Good Manufacturing Practice, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness should be periodically assessed. Training programmes should be available, approved by either the head of Production or the head of Quality Control, as appropriate. Training records should be kept.
2.12	對於在一有污染即產生危害之區域，例如在潔淨區域或在處理高活性、毒性、傳染性或致敏性物質之區域中工作的人員，應給予特別的訓練。	2.12	Personnel working in areas where contamination is a hazard, e.g. clean areas or areas where highly active, toxic, infectious or sensitising materials are handled, should be given specific training.
2.13	對於參訪人員及未受過訓練的人員，盡量不要帶入生產區及品質管制區中。無法避免時，應予事先提供資訊並密切監督，特別是關於個人衛生及規定的防護裝。	2.13	Visitors or untrained personnel should, preferably, not be taken into the production and quality control areas. If this is unavoidable, they should be given information in advance, particularly about personal hygiene and the prescribed protective clothing. They should be closely supervised.
2.14	訓練期間，應充分討論製藥品質系統的概念及所有能增進其理解與執行的措施。	2.14	The Pharmaceutical Quality System and all the measures capable of improving its understanding and implementation should be fully discussed during the training sessions.
人員衛生（PERSONNEL HYGIENE）			

2.15	詳細的衛生計畫應予建立，並針對工廠內的不同需求調適。該計畫應包括人員健康、衛生習慣及服裝等相關程序。因其職責而進入生產區及管制區的每個人員，皆應了解這些程序並嚴格遵守。管理階層應推動衛生計畫並在訓練期間予以廣泛討論。	2.15	Detailed hygiene programmes should be established and adapted to the different needs within the factory. They should include procedures relating to the health, hygiene practices and clothing of personnel. These procedures should be understood and followed in a very strict way by every person whose duties take him into the production and control areas. Hygiene programmes should be promoted by management and widely discussed during training sessions.
2.16	所有人員於雇用時皆應接受體檢。藥廠應有職責建立指令，以確保人員與產品品質可能有關之健康狀況會為藥廠所悉。第一次體檢後，視工作與人員健康之需要，應再執行體檢。	2.16	All personnel should receive medical examination upon recruitment. It must be the manufacturer's responsibility that there are instructions ensuring that health conditions that can be of relevance to the quality of products come to the manufacturer's knowledge. After the first medical examination, examinations should be carried out when necessary for the work and personal health.
2.17	應盡可能採取步驟，確保不會有受到傳染性疾病感染的人或在暴露的身體表面上有開放性傷口的人從事於藥品的製造。	2.17	Steps should be taken to ensure as far as is practicable that no person affected by an infectious disease or having open lesions on the exposed surface of the body is engaged in the manufacture of medicinal products.
2.18	進入製造區的每個人員皆應穿戴適合其所要執行操作之防護裝。	2.18	Every person entering the manufacturing areas should wear protective garments appropriate to the operations to be carried out.
2.19	生產區及儲存區應禁止飲食、嚼食或吸煙，或是儲存食物、飲料、菸類或個人的醫療用品。通常在製造區或產品可能會受到不良影響的任何其他區域中，應禁止任何不合衛生的行為。	2.19	Eating, drinking, chewing or smoking, or the storage of food, drink, smoking materials or personal medication in the production and storage areas should be prohibited. In general, any unhygienic practice within the manufacturing areas or in any other area where the product might be adversely affected should be forbidden.

2.20	工作人員應避免雙手直接接觸暴露的產品及與產品接觸之設備的任何部分。	2.20	Direct contact should be avoided between the operator's hands and the exposed product as well as with any part of the equipment that comes into contact with the products.
2.21	應指導工作人員使用洗手設施。	2.21	Personnel should be instructed to use the hand-washing facilities.
2.22	其他任何特定的要求，例如製造無菌製劑等特殊類別的產品，收載於相關附則中。	2.22	Any specific requirements for the manufacture of special groups of products, for example sterile preparations, are covered in the annexes.
顧問（CONSULTANTS）			
2.23	顧問應有足夠的學識、訓練與經驗或其任何組合，以對其所被聘請之主題提供建議。	2.23	Consultants should have adequate education, training, and experience, or any combination thereof, to advise on the subject for which they are retained.
	顧問的姓名、地址、資格及提供之服務類型的紀錄，應加以保存。		Records should be maintained stating the name, address, qualifications, and type of service provided by these consultants.

第三章　廠房設施與設備（PREMISES AND EQUIPMENT）

原則（PRINCIPLE）	
廠房設施及設備的定位、設計、建造、調適及維護皆應適合於其所要執行的作業。其配置與設計應將產生錯誤的風險降到最低並容許有效的清潔及維護保養，以避免交叉污染、聚積粉塵或污垢，總之應以避免對產品品質有任何不利影響為目標。	Premises and equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt and, in general, any adverse effect on the quality of products.
廠房設施（PREMISES）	
一般規定（General）	
3.1 當與保護產品製造的措施一併考量時，廠房設施應坐落於引起原物料或產品之最低污染風險環境中。	3.1 Premises should be situated in an environment which, when considered together with measures to protect the manufacture, presents minimal risk of causing contamination of materials or products.
3.2 廠房設施應謹慎維護，以確保其修理及維護作業不會危害於產品品質。廠房應予清潔，適當時並依詳細的書面程序消毒之。	3.2 Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products. They should be cleaned and, where applicable, disinfected according to detailed written procedures.
3.3 照明、溫度、濕度及通風均應適當，且不會對製造及儲存中的藥品或設備的正確功能有直接或間接之不利影響。	3.3 Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the medicinal products during their manufacture and storage, or the accurate functioning of equipment.
3.4 廠房設施的設計與配置應提供最大的保護，以防止昆蟲或其他動物的入侵。	3.4 Premises should be designed and equipped so as to afford maximum protection against the entry of insects or other animals.

3.5 為防止未被授權的人員進入廠房，應採取步驟。生產區、儲存區及品質管制區應不得作為非該區工作人員的通路。	3.5 Steps should be taken in order to prevent the entry of unauthorised people. Production, storage and quality control areas should not be used as a right of way by personnel who do not work in them.
生產區（Production Areas）	
3.6 所有產品應經由製造設施之適當設計與操作防止交叉污染。防止交叉污染的措施應與風險相稱。品質風險管理原則應使用於評估及管制風險。	3.6 Cross-contamination should be prevented for all products by appropriate design and operation of manufacturing facilities. The measures to prevent cross-contamination should be commensurate with the risks. Quality Risk Management principles should be used to assess and control the risks.
取決於風險等級，可能需要於專用的廠房設施與設備執行製造及/或分/包裝作業，以管制有些藥品所呈現之風險。	Depending of the level of risk, it may be necessary to dedicate premises and equipment for manufacturing and/or packaging operations to control the risk presented by some medicinal products.
當藥品因為下列任一原因呈現風險時，對其製造需要專用設施：	Dedicated facilities are required for manufacturing when a medicinal product presents a risk because:
i 風險不能經由操作及/或技術措施充分管制，	i the risk cannot be adequately controlled by operational and/ or technical measures,
ii 來自毒理學評估的科學數據無法支持可控制的風險（例如來自高致敏物質的過敏潛在性，如β-內醯胺）或	ii scientific data from the toxicological evaluation does not support a controllable risk (e.g. allergenic potential from highly sensitising materials such as beta-lactams) or
iii 衍生自毒理學評估的相關殘留限量，無法由經確效的分析方法滿意測定。	iii relevant residue limits, derived from the toxicological evaluation, cannot be satisfactorily determined by a validated analytical method.
進一步的指引詳見第五章與附則 2、3、4、5 及 6。	Further guidance can be found in Chapter 5 and in Annexes 2, 3, 4, 5 & 6.

3.7 廠房設施應配合作業順序及所要求的潔淨度等級予以配置，以容許在合乎邏輯順序的相連區域中生產。	3.7 Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.
3.8 作業空間與製程中儲存空間的適當性，應允許設備與原物料有條理且合乎邏輯的放置，使不同藥品或其組成物/組件間之混淆風險降到最低、避免交叉污染，並使任何製造或管制步驟的遺漏或是誤用的風險降到最低。	3.8 The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimise the risk of confusion between different medicinal products or their components, to avoid cross-contamination and to minimise the risk of omission or wrong application of any of the manufacturing or control steps.
3.9 原料與直接包裝材料、半製品/中間產品或待分/包裝產品暴露的環境，其內部表面(牆壁、地板及天花板)應平滑、無裂縫及無開口接縫，且不得脫落微粒物質，並應容易且有效地清潔，如有必要，還可消毒。	3.9 Where starting and primary packaging materials, intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) should be smooth, free from cracks and open joints, and should not shed particulate matter and should permit easy and effective cleaning and, if necessary, disinfection.
3.10 管道、照明裝置、通氣口以及其他設施應經設計與定位以避免產生難以清潔的凹處。為維護保養之目的，應盡量從製造區外進行。	3.10 Pipework, light fittings, ventilation points and other services should be designed and sited to avoid the creation of recesses which are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.
3.11 排水孔的大小應合適，並備有隔氣彎管的集水溝。應盡量避免開放式溝渠，必要時，應為淺溝，以利清潔與消毒。	3.11 Drains should be of adequate size, and have trapped gullies. Open channels should be avoided where possible, but if necessary, they should be shallow to facilitate cleaning and disinfection.

3.12 生產區應有效通風，並備有適合於所處理的產品、在該區域內從事的作業及外在環境等之空調設備（包含溫度，必要時包含濕度與過濾）。	3.12 Production areas should be effectively ventilated, with air control facilities (including temperature and, where necessary, humidity and filtration) appropriate both to the products handled, to the operations undertaken within them and to the external environment.
3.13 原料的秤重，通常應在專為該用途所設計之一間隔離的秤量室內為之。	3.13 Weighing of starting materials usually should be carried out in a separate weighing room designed for such use.
3.14 會產生粉塵的情況 (例如：抽樣、秤重、混合、製程操作及乾燥產品的分/包裝等期間中)，應採取特別的措施，以避免交叉污染並利於清潔。	3.14 In cases where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of dry products), specific provisions should be taken to avoid cross-contamination and facilitate cleaning.
3.15 藥品分/包裝的廠房設施，應特別設計與配置，以避免混雜或交叉污染。	3.15 Premises for the packaging of medicinal products should be specifically designed and laid out so as to avoid mix-ups or cross-contamination.
3.16 生產區應有良好的照明，特別是在執行線上目視管制的場所。	3.16 Production areas should be well lit, particularly where visual on-line controls are carried out.
3.17 製程中管制不會對生產帶來任何風險者，可在生產區內執行。	3.17 In-process controls may be carried out within the production area provided they do not carry any risk to production.
儲存區（Storage Areas）	
3.18 儲存區應有足夠的容量，以容許各種類別的原物料及產品有條理的儲存，包括：原料、包裝材料、半製品/中間產品、待分/包裝產品及最終產品、待驗產品、放行產品、拒用產品、退回產品或回收產品等。	3.18 Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and packaging materials, intermediate, bulk and finished products, products in quarantine, released, rejected, returned or recalled.

3.19 儲存區應經設計或調適，以確保良好的儲存條件。特別是儲存區應保持潔淨與乾燥，並維持在可接受的溫度範圍內。有特別儲存條件要求時(例如溫度及濕度)，應提供這些儲存場所，並加以檢查/核對與監測。	3.19 Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, checked and monitored.
3.20 收貨區及出貨區應保護原物料及產品免於受天氣的影響。收貨區應加以設計並配置，以容許必要時能在儲存前清潔進廠原物料之容器。	3.20 Receiving and dispatch bays should protect materials and products from the weather. Reception areas should be designed and equipped to allow containers of incoming materials to be cleaned where necessary before storage.
3.21 藉由儲存於分開的區域來確保隔離/待驗狀態者，該區域應標識清楚，其進入應限於經授權之人員。任何取代該實體隔離的系統，應提供同等的安全性。	3.21 Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorised personnel. Any system replacing the physical quarantine should give equivalent security.
3.22 原料通常應有隔離的抽樣區域。在儲存區內執行抽樣者，應以可防止污染或交叉污染的方式執行之。	3.22 There should normally be a separate sampling area for starting materials. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.
3.23 對於拒用、回收或退回的原物料或產品應提供隔離的儲存區域。	3.23 Segregated areas should be provided for the storage of rejected, recalled or returned materials or products.
3.24 高活性物質或產品應儲存於安全且牢靠的區域中。	3.24 Highly active materials or products should be stored in safe and secure areas.
3.25 印刷的包裝材料對於藥品的符合性是很重要的，應特別注意這些包裝材料之安全及牢靠的儲存。	3.25 Printed packaging materials are considered critical to the conformity of the medicinal product and special attention should be paid to the safe and secure storage of these materials.
品質管制區（Quality Control Areas）	

3.26 通常，品質管制實驗室應與生產區隔離。這對生物學、微生物學及放射性同位素的管制實驗室特別重要。這些實驗室亦應互相隔離。	3.26 Normally, Quality Control laboratories should be separated from production areas. This is particularly important for laboratories for the control of biological, microbiological and radioisotopes, which should also be separated from each other.
3.27 管制實驗室應設計成適合於在這些實驗室內執行的作業，並應給予足夠空間，以防止混雜及交叉污染。對於樣品與紀錄亦應有足夠且適當的儲存空間。	3.27 Control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross contamination. There should be adequate suitable storage space for samples and records.
3.28 為保護靈敏的儀器設備免於受振動、電子干擾及濕氣等之影響，分開的儀器室可能是必需的。	3.28 Separate rooms may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, etc.
3.29 處理特別物質，例如生物樣品或放射性樣品的實驗室，需要有特別的要求。	3.29 Special requirements are needed in laboratories handling particular substances, such as biological or radioactive samples.
附屬區域（Ancillary Areas）	
3.30 休息室與餐廳應與其他區域隔離。	3.30 Rest and refreshment rooms should be separate from other areas.
3.31 以更衣、盥洗及如廁為目的之設施應易於使用並適合使用之人數。廁所與生產區或儲存區不得直接相通。	3.31 Facilities for changing clothes, and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not directly communicate with production or storage areas.
3.32 維修保養之工場應與生產區隔離並盡可能遠離。在生產區儲存零件及工具者，應儲存在其專用室或專用櫃中。	3.32 Maintenance workshops should as far as possible be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.
3.33 動物室應與其他區域妥善隔離，並有分別的入口（動物的出入口）及空調處理設施。	3.33 Animal houses should be well isolated from other areas, with separate entrance (animal access) and air handling facilities.
設備（EQUIPMENT）	

3.34 製造設備應經設計、配置及維修保養，以符合其預定目的。	3.34 Manufacturing equipment should be designed, located and maintained to suit its intended purpose.
3.35 修理及維修保養作業不得對產品的品質呈現任何危害。	3.35 Repair and maintenance operations should not present any hazard to the quality of the products.
3.36 製造設備之設計，應使其能容易且徹底地清洗。該設備應依詳細的書面程序清洗，並僅以潔淨且乾燥的狀態儲存。	3.36 Manufacturing equipment should be designed so that it can be easily and thoroughly cleaned. It should be cleaned according to detailed and written procedures and stored only in a clean and dry condition.
3.37 洗滌及清潔設備應加以選擇與使用，使其不會成為污染的來源。	3.37 Washing and cleaning equipment should be chosen and used in order not to be a source of contamination.
3.38 設備應以適當的方式安裝，以防止任何錯誤或污染的風險。	3.38 Equipment should be installed in such a way as to prevent any risk of error or of contamination.
3.39 生產設備不得呈現對產品有任何危害。生產設備與產品接觸的部分，其反應性、加成性或吸附性不得高到足以影響產品的品質，而呈現任何危害。	3.39 Production equipment should not present any hazard to products. Parts of production equipment that come into contact with the product must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product and thus present any hazard.
3.40 應備有適當測量範圍與精密度的天平與量測設備，以供生產與管制作業使用。	3.40 Balances and measuring equipment of an appropriate range and precision should be available for production and control operations.
3.41 量測、秤重、記錄及管制之設備應在界定的時間間隔內，使用適當的方法校正並核對之。這些檢測的適當紀錄應予保存。	3.41 Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods. Adequate records of such tests should be maintained.
3.42 固定的管線應清楚標示其內容物，可行時，流向亦應標示。	3.42 Fixed pipework should be clearly labelled to indicate the contents and, where applicable, the direction of flow.

3.43 蒸餾水、去離子水及合適時其他用水之配管應依書面程序執行滅菌處理。該文件應詳載微生物污染的行動限量及應採取的措施。	3.43 Distilled, deionised and, where appropriate, other water pipes should be sanitised according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.
3.44 有缺陷的設備，如果可能，應從生產區及品質管制區移出，或至少清楚標示其為有缺陷的設備。	3.44 Defective equipment should, if possible, be removed from production and quality control areas, or at least be clearly labeled as defective.

第四章　文件（DOCUMENTATION）

原則（PRINCIPLE）	
優良文件是構成品質保證系統必要的部分，而且是符合/遵循GMP要求之操作的關鍵。所使用之各種類型的文件與檔案資料，應在製造廠的品質管理系統中充分地界定。文件可能以多種形式存在，包括以紙本的、電子的或照像的資料。文件製作系統的主要目的，必須建立、管制、監控與記錄所有活動，該等活動會直接或間接影響藥物產品品質的所有層面。品質管理系統除提供各種流程以及任何觀察之評估的充分紀錄外，還應包含足夠的指導細節，以利共同理解這些要求，並使這些要求之持續應用得以證明。	Good documentation constitutes an essential part of the quality assurance system and is key to operating in compliance with GMP requirements. The various types of documents and media used should be fully defined in the manufacturer's Quality Management System. Documentation may exist in a variety of forms, including paper-based, electronic or photographic media. The main objective of the system of documentation utilized must be to establish, control, monitor and record all activities which directly or indirectly impact on all aspects of the quality of medicinal products. The Quality Management System should include sufficient instructional detail to facilitate a common understanding of the requirements, in addition to providing for sufficient recording of the various processes and evaluation of any observations, so that ongoing application of the requirements may be demonstrated.
用於管理與記錄GMP符合性之文件有兩種主要類型，包括指令（指導、要求）與紀錄/報告。應依適當的優良文件製作規範製作相關類型的文件。	There are two primary types of documentation used to manage and record GMP compliance: instructions (directions, requirements) and records/reports. Appropriate good documentation practice should be applied with respect to the type of document.
應實施適當的管制，以確保文件的正確性、完整性、可得性與可讀性。指導文件應無錯誤並且可以以書面取得。「書面」意指在檔案資料上所記錄或文件化的數據，藉以成為可讀取的形式。	Suitable controls should be implemented to ensure the accuracy, integrity, availability and legibility of documents. Instruction documents should be free from errors and available in writing. The term ‘written’ means recorded, or documented on media from which data may be rendered in a human readable form.

所需要的 GMP 文件（按類型） 【REQUIRED GMP DOCUMENTATION (BY TYPE)】	
工廠基本資料（Site Master File）：描述製造廠之GMP相關活動的文件。	**Site Master File:** A document describing the GMP related activities of the manufacturer.
指令（指導或要求）類型【Instructions (directions, or requirements) type】：	
規格：詳細描述在製造期間所使用的或所取得的原物料或產品必須符合的要求。規格是作為品質評估的基礎。	**Specifications:** Describe in detail the requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.
製造配方、操作/加工、分/包裝與檢驗的指令： 提供所要使用之所有原料、設備與電腦化系統（如有）的細節，並且規定所有操作/加工、分/包裝、取樣與檢驗的指導。所要使用的製程中管制與製程分析技術，連同允收標準（合適時），應該加以規定。	**Manufacturing Formulae, Processing, Packaging and Testing Instructions:** Provide detail all the starting materials, equipment and computerised systems (if any) to be used and specify all processing, packaging, sampling and testing instructions. In-process controls and process analytical technologies to be employed should be specified where relevant, together with acceptance criteria.
程序：（或稱為標準作業程序，簡稱SOPs），對於執行某些操作/作業給予指導。	**Procedures:** (Otherwise known as Standard Operating Procedures, or SOPs), give directions for performing certain operations.
計畫書：對於執行與記錄某些需謹慎操作/作業給予指令。	**Protocols:** Give instructions for performing and recording certain discreet operations.
技術協議：委託者與受託者之間對於委外活動的協議。	**Technical Agreements:** Are agreed between contract givers and acceptors for outsourced activities.
紀錄/報告類型（Record/Report type）：	

紀錄：提供所採取之各種行動的證據，以證明遵循指令，例如：活動、事件、調查及在製造批次的情況下，每一個產品批次的歷史，包含其運銷在內。紀錄包括使用於產生其他紀錄的原始數據。對於電子紀錄，受管制的使用者應界定哪些數據要當作原始數據使用。至少，應將所有據以決定品質的數據，界定為原始數據。	**Records:** Provide evidence of various actions taken to demonstrate compliance with instructions, e.g. activities, events, investigations, and in the case of manufactured batches a history of each batch of product, including its distribution. Records include the raw data which is used to generate other records. For electronic records regulated users should define which data are to be used as raw data. At least, all data on which quality decisions are based should be defined as raw data.
分析證明書：提供關於產品或原物料樣品之檢驗結果的摘要[2]，連同對所陳述之規格符合性的評估。	**Certificates of Analysis:** Provide a summary of testing results on samples of products or materials[2] together with the evaluation for compliance to a stated specification.
[2]或者，本證明書可以全部或部分根據來自依照所核准之上市許可檔案文件的批次相關製程分析技術（PAT）、參數或計量學之即時數據（摘要與異常報告）的評估。	[2] Alternatively the certification may be based, in-whole or in-part, on the assessment of real time data (summaries and exception reports) from batch related process analytical technology (PAT), parameters or metrics as per the approved marketing authorisation dossier.
報告：將特定的運用、計畫或調查的執行/處理，連同結果、結論與建議加以文件化。	**Reports:** Document the conduct of particular exercises, projects or investigations, together with results, conclusions and recommendations.
文件的產生與管制（GENERATION AND CONTROL OF DOCUMENTATION）	

4.1	應界定所有文件的類型並遵守之。此等要求同樣適用於文件檔案資料類型的所有形式。複雜性系統需經理解、完善文件化、確效，並具備適當的管制。許多文件（指令及/或記錄）可能以混合形式存在，亦即，有些要件是以電子化為基礎，其它則以紙本為基礎。對於混合系統與同質系統兩者，其正本、法定副本、數據處理與紀錄之關係與管制措施需加以陳述。對於電子文件，例如樣本、表單與主文件應執行適當管制。應具備適當的管制以確保在整個保存期間該記錄的完整性。	4.1	All types of document should be defined and adhered to. The requirements apply equally to all forms of document media types. Complex systems need to be understood, well documented, validated, and adequate controls should be in place. Many documents (instructions and/or records) may exist in hybrid forms, i.e. some elements as electronic and others as paper based. Relationships and control measures for master documents, official copies, data handling and records need to be stated for both hybrid and homogenous systems. Appropriate controls for electronic documents such as templates, forms, and master documents should be implemented. Appropriate controls should be in place to ensure the integrity of the record throughout the retention period.
4.2	文件應經謹慎設計、製作、審核及分發。合適時，該等文件應符合產品規格檔案、製造與上市許可文件的相關部分。來自正本之工作文件的複製，不得因複製過程導入任何錯誤。	4.2	Documents should be designed, prepared, reviewed, and distributed with care. They should comply with the relevant parts of Product Specification Files, Manufacturing and Marketing Authorisation dossiers, as appropriate. The reproduction of working documents from master documents should not allow any error to be introduced through the reproduction process.
4.3	含指令的文件應由適當且經授權的人員核定、簽章並註明日期。文件應具有明確之內容且應為獨特可確認的。生效日期應加以界定。	4.3	Documents containing instructions should be approved, signed and dated by appropriate and authorised persons. Documents should have unambiguous contents and be uniquely identifiable. The effective date should be defined.
4.4	含指令的文件，應以有條理的方式編排且易於核對。文件之格式與語文應配合其預定的用途。標準作業程序、作業指令與方法皆應以強制性的格式書寫。	4.4	Documents containing instructions should be laid out in an orderly fashion and be easy to check. The style and language of documents should fit with their intended use. Standard Operating Procedures, Work Instructions and Methods should be written in an imperative mandatory style.

4.5	品質管理系統內的文件應定期檢討且應保持其最新版本。當一份文件經修訂後，應有一系統運作，以防止作廢文件被誤用。	4.5	Documents within the Quality Management System should be regularly reviewed and kept up-to-date. When a document has been revised, systems should be operated to prevent inadvertent use of superseded documents.
4.6	文件本身不得用手寫，但需手寫填入數據時，應有足夠的空間供此類數據的填入。	4.6	Documents should not be hand-written; although, where documents require the entry of data, sufficient space should be provided for such entries.
優良文件製作規範（GOOD DOCUMENTATION PRACTICES）			
4.7	手寫填入資料時，應以清晰、可讀且擦不掉的方式為之。	4.7	Handwritten entries should be made in clear, legible, indelible way.
4.8	採取每項行動時，即應記錄。因此，與藥品製造有關的所有重要活動皆可追溯。	4.8	Records should be made or completed at the time each action is taken and in such a way that all significant activities concerning the manufacture of medicinal products are traceable.
4.9	文件上對於填入項目所做的任何更改應予簽章並註明日期；該更改應允許讀取原來的資訊。合適時，更改理由應記錄之。	4.9	Any alteration made to the entry on a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.
文件保存（RETENTION OF DOCUMENTS）			
4.10	應清楚界定與每個製造活動相關的紀錄及其存放處。必須具備安全管制，以確保在整個保存期間紀錄的完整性，且合適時必須進行確效。	4.10	It should be clearly defined which record is related to each manufacturing activity and where this record is located. Secure controls must be in place to ensure the integrity of the record throughout the retention period and validated where appropriate.

4.11 對於批次文件，特定的要求適用於必須保存到該批次之末效日期後一年，或保存到在該批次經由被授權人認定後至少五年，兩者取其較長者。對於研究用藥品，批次文件必須保存到所使用之該批次的最終臨床試驗完成後或試驗正式中止後至少五年。對於文件之保存的其它要求，可能敘述於特定類型產品（例如，新興治療藥品）之相關法規中，並規定某些文件應採用較長的保存期限。	4.11 Specific requirements apply to batch documentation which must be kept for one year after expiry of the batch to which it relates or at least five years after certification of the batch by the Authorised Person, whichever is the longer. For investigational medicinal products, the batch documentation must be kept for at least five years after the completion or formal discontinuation of the last clinical trial in which the batch was used. Other requirements for retention of documentation may be described in legislation in relation to specific types of product (e.g. Advanced Therapy Medicinal Products) and specify that longer retention periods be applied to certain documents.
4.12 對於其他類型的文件，保存期限將依其作業活動而定。上市許可資訊的關鍵文件，包含原始數據（例如：與確效或安定性相關者）在內，應在該上市許可仍然有效的期間加以保存。當數據已由一套完整的新數據取代時，將某些文件（例如，支持確效報告或安定性報告的原始數據）廢除，視為可接受的。對此文件廢除的正當性證明應加以文件化，且應考慮批次文件保存的要求；例如，在製程確效數據的情況中，其所伴隨的原始數據應予保存，其期限應至少與基於該確效作業所支持放行的所有批次紀錄的期間相同。	4.12 For other types of documentation, the retention period will depend on the business activity which the documentation supports. Critical documentation, including raw data (for example relating to validation or stability), which supports information in the Marketing Authorisation should be retained whilst the authorization remains in force. It may be considered acceptable to retire certain documentation (e.g. raw data supporting validation reports or stability reports) where the data has been superseded by a full set of new data. Justification for this should be documented and should take into account the requirements for retention of batch documentation; for example, in the case of process validation data, the accompanying raw data should be retained for a period at least as long as the records for all batches whose release has been supported on the basis of that validation exercise.

下節提供所需文件的一些實例。為確保產品品質與病患安全，品質管理系統應敘明所需要的所有文件。	The following section gives some examples of required documents. The quality management system should describe all documents required to ensure product quality and patient safety.
規格（SPECIFICATIONS）	
4.13 原料、包裝材料及最終產品，應有適當經核准且註明日期的規格。	4.13 There should be appropriately authorised and dated specifications for starting and packaging materials, and finished products.
原料及包裝材料的規格（Specifications for starting and packaging materials）	
4.14 原料及直接包裝或印刷包裝材料之規格，如果可行，應包括下列項目:	4.14 Specifications for starting and primary or printed packaging materials should include or provide reference to, if applicable:
a) 原物料的描述，包括：	a) A description of the materials, including:
- 指定的名稱及內部的參考代碼；	- The designated name and the internal code reference;
- 藥典個論的參考資料（如有時）；	- The reference, if any, to a pharmacopoeial monograph;
- 認可的供應商，及其原始的生產者（如可能時）；	- The approved suppliers and, if reasonable, the original producer of the material;
- 印刷材料的樣本；	- A specimen of printed materials;
b) 抽樣、檢驗的指示；	b) Directions for sampling and testing;
c) 具有合格標準範圍之定性及定量的要求；	c) Qualitative and quantitative requirements with acceptance limits;
d) 儲存的條件及注意事項；	d) Storage conditions and precautions;
e) 再驗前的最長儲存期間。	e) The maximum period of storage before re-examination.
半製品/中間產品及待分/包裝產品的規格 （Specifications for intermediate and bulk products）	
4.15 對於關鍵步驟的、採購或發送之半製品/中間產品與待分/包裝產品應具有規格。合適時，這些規格應類似於原料或最終產品的規格。	4.15 Specifications for intermediate and bulk products should be available for critical steps or if these are purchased or dispatched. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.
最終產品的規格（Specifications for finished products）	

4.16 最終產品規格應包括或提供下列項目：	4.16 Specifications for finished products should include or provide reference to:
a) 產品之指定名稱及其參考代碼（可行時）；	a) The designated name of the product and the code reference where applicable;
b) 配方	b) The formula;
c) 產品劑型及包裝細節的描述；	c) A description of the pharmaceutical form and package details;
d) 抽樣及檢驗的指示；	d) Directions for sampling and testing;
e) 具有合格標準範圍之定性及定量的要求；	e) The qualitative and quantitative requirements, with the acceptance limits;
f) 儲存條件及任何特別處理的注意事項（可行時）；	f) The storage conditions and any special handling precautions, where applicable;
g) 架儲期。	g) The shelf-life.
製造配方及操作指令（MANUFACTURING FORMULA AND PROCESSING INSTRUCTIONS）	
對於所要製造的每一個產品與批量應有經核准的書面製造配方與操作指令。	Approved, written Manufacturing Formula and Processing Instructions should exist for each product and batch size to be manufactured.
4.17 製造配方應包括下列項目:	4.17 The Manufacturing Formula should include:
a) 產品名稱及其規格有關的產品參考代碼；	a) The name of the product, with a product reference code relating to its specification;
b) 產品劑型、含量及批量的描述；	b) A description of the pharmaceutical form, strength of the product and batch size;
c) 所有使用之原料及其用量的清單，並應敘明在操作過程中可能喪失之任何物質；	c) A list of all starting materials to be used, with the amount of each, described; mention should be made of any substance that may disappear in the course of processing;
d) 說明預期最終產率及其允收範圍，以及相關半製品/中間產品產率（可行時）。	d) A statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable.
4.18 操作指令應包括下列項目：	4.18 The Processing Instructions should include:

a) 作業場所及主要設備的說明；	a) A statement of the processing location and the principal equipment to be used;
b) 準備關鍵設備所要使用的方法（例如清潔、組裝、校正、滅菌）或該等方法的參考資料；	b) The methods, or reference to the methods, to be used for preparing the critical equipment (e.g. cleaning, assembling, calibrating, sterilising);
c) 檢查其設備與工作場所無先前的產品、亦無非本製程所需的文件或原物料，且該設備是潔淨並適合使用；	c) Checks that the equipment and work station are clear of previous products, documents or materials not required for the planned process, and that equipment is clean and suitable for use;
d) 詳細的逐步操作指令【例如，原物料的檢查/核對、前處理、添加原物料的順序、關鍵製程參數（時間、溫度等）】；	d) Detailed stepwise processing instructions [e.g. checks on materials, pre-treatments, sequence for adding materials, critical process parameters (time, temp etc)];
e) 任何製程中管制的指令及其範圍；	e) The instructions for any in-process controls with their limits;
f) 必要時，待分/包裝產品之儲存要求；可行時，包括其容器、標示及特別的儲存條件；	f) Where necessary, the requirements for bulk storage of the products; including the container, labeling and special storage conditions where applicable;
g) 應遵守的任何特別注意事項。	g) Any special precautions to be observed.
分/包裝指令（Packaging Instructions）	
4.19 每項產品的包裝量與形式應有經核准的分/包裝指令。這些指令通常應包括下列項目或其參考資料：	4.19 Approved Packaging Instructions for each product, pack size and type should exist. These should include, or have a reference to, the following:
a) 產品名稱；包括待分/包裝產品與最終產品的批號；	a) Name of the product; including the batch number of bulk and finished product;
b) 劑型，及其含量（可行時）的描述；	b) Description of its pharmaceutical form, and strength where applicable;
c) 包裝量，以產品在最終容器的數量、重量或容量表示；	c) The pack size expressed in terms of the number, weight or volume of the product in the final container;

d) 所需全部包裝材料的清單，包括其數量、尺寸與型式及每種包裝材料之規格有關的代碼或參考號碼；	d) A complete list of all the packaging materials required, including quantities, sizes and types, with the code or reference number relating to the specifications of each packaging material;
e) 合適時，相關已印刷之包裝材料的實例或複製品，以及產品批號及架儲期打印位置之樣本；	e) Where appropriate, an example or reproduction of the relevant printed packaging materials, and specimens indicating where to apply batch number references, and shelf life of the product;
f) 檢查其設備與工作場所站無先前的產品、亦無非本包裝作業所需的文件或原物料（清線），且該設備是潔淨並適合使用；	f) Checks that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations (line clearance), and that equipment is clean and suitable for use;
g) 應遵行的特別注意事項，包括謹慎檢查作業區與設備，以確認作業開始前已完成分/包裝線的清線工作；	g) Special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin;
h) 分/包裝作業之描述，包括任何重要的輔助作業及所需使用的設備；	h) A description of the packaging operation, including any significant subsidiary operations, and equipment to be used;
i) 製程中管制的細節，並有抽樣指令及允收範圍。	i) Details of in-process controls with instructions for sampling and acceptance limits.
批次製造紀錄（Batch Processing Record）	
4.20 每一製造的批次應保存其批次製造紀錄，且依據現行認可的製造配方及操作指令。並且應該包含下列資訊：	4.20 A Batch Processing Record should be kept for each batch processed. It should be based on the relevant parts of the currently approved Manufacturing Formula and Processing Instructions, and should contain the following information:
a) 產品名稱與批號；	a) The name and batch number of the product;

b) 生產之開始、重要中間階段及完成的日期與時間；	b) Dates and times of commencement, of significant intermediate stages and of completion of production;
c) 執行每一重要製程步驟之作業人員的簽名，以及合適時，這些作業應有核對者的簽名；	c) Identification (initials) of the operator(s) who performed each significant step of the process and, where appropriate, the name of any person who checked these operations;
d) 每一原料的批號及/或分析管制的號碼以及實際秤取之重量（包括所添加之任何收回或重處理的半製品之批號及重量）；	d) The batch number and/or analytical control number as well as the quantities of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);
e) 任何相關之操作作業或事件及使用之主要設備；	e) Any relevant processing operation or event and major equipment used;
f) 製程中管制的紀錄、執行該管制人員的簽名及結果；	f) A record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained;
g) 製造的不同階段及相關階段所獲得產品之產率；	g) The product yield obtained at different and pertinent stages of manufacture;
h) 特別問題之備註，包含來自製造配方及操作指令之任何偏差的詳細記錄，並有經簽章認可；	h) Notes on special problems including details, with signed authorisation for any deviation from the Manufacturing Formula and Processing Instructions;
i) 經由該製程操作的負責人員核准。	i) Approval by the person responsible for the processing operations.
註：經確效的製程如為持續監測與管制時，則自動產生的報告可能侷限於符合性摘要與異常/偏離規格（OOS） 數據報告。	**Note:** Where a validated process is continuously monitored and controlled, then automatically generated reports may be limited to compliance summaries and exception/ out-ofspecification (OOS) data reports.
批次分/包裝紀錄（Batch Packaging Record）	

4.21 每一操作批次或部分批次應保存其批次分/包裝紀錄，該記錄應依據分/包裝指令的相關部分。	4.21 A Batch Packaging Record should be kept for each batch or part batch processed. It should be based on the relevant parts of the Packaging Instructions.
批次分/包裝紀錄應包含下列資訊：	The batch packaging record should contain the following information:
a) 產品名稱與批號；	a) The name and batch number of the product;
b) 分/包裝作業的日期及時間；	b) The date(s) and times of the packaging operations;
c) 執行每一重要分/包裝步驟之作業人員的簽名，以及合適時，這些作業應有核對者的簽名；	c) Identification (initials) of the operator(s) who performed each significant step of the process and, where appropriate, the name of any person who checked these operations;
d) 分/包裝指令之識別與符合性的核對紀錄，至少包含製程中管制的結果；	d) Records of checks for identity and conformity with the packaging instructions, including the results of in-process controls;
e) 執行分/包裝作業的細節，包含使用的設備與分/包裝線的參考資料；	e) Details of the packaging operations carried out, including references to equipment and the packaging lines used;
f) 每當可能時，使用之印刷包裝材料的樣品，包括批次代碼、末效日期及任何附加套印的樣本；	f) Whenever possible, samples of printed packaging materials used, including specimens of the batch coding, expiry dating and any additional overprinting;
g) 特別問題或異常事件之備註，包含來自分/包裝指令之任何偏差的詳細記錄，並有經簽章認可；	g) Notes on any special problems or unusual events including details, with signed authorisation for any deviation from the Packaging Instructions;

h) 所有發出、使用、銷毀或退回庫存之印刷的包裝材料與待分/包裝產品的數量、參考號碼或其識別，及所得之產品數量，以提供適當的數量調和。在分/包裝期間備有穩固的電子管制時，不包含這個資訊可能具有其正當性；	h) The quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of obtained product, in order to provide for an adequate reconciliation. Where there are robust electronic controls in place during packaging there may be justification for not including this information;
i) 經由該分/包裝作業的負責人員核准。	i) Approval by the person responsible for the packaging operations.
程序與紀錄（PROCEDURES AND RECORDS）	
接收（Receipt）	
4.22 每一原料（包括待分/包裝產品、半製品/中間產品或最終產品）、直接包裝材料、間接包裝材料及印刷包裝材料於每次交貨時的接收，皆應有書面程序與紀錄。	4.22 There should be written procedures and records for the receipt of each delivery of each starting material, (including bulk, intermediate or finished goods), primary, secondary and printed packaging materials.
4.23 接收紀錄應包括：	4.23 The records of the receipts should include:
a) 送貨單及容器上原物料之名稱；	a) The name of the material on the delivery note and the containers;
b) 原物料之「廠內」的名稱及/或代碼（如異於a時）；	b) The "in-house" name and/or code of material (if different from a);
c) 接收日期；	c) Date of receipt;
d) 供應商的名稱及製造廠的名稱；	d) Supplier’s name and, manufacturer’s name;
e) 製造廠的批號或參考號碼；	e) Manufacturer’s batch or reference number;
f) 接收的總量及容器的數目；	f) Total quantity and number of containers received;
g) 接收後指定的批號；	g) The batch number assigned after receipt;
h) 任何相關的加註。	h) Any relevant comment.
4.24 應有原料、包裝材料及合適時其他材料的廠內標示、隔離/待驗及儲存的書面程序。	4.24 There should be written procedures for the internal labeling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.
抽樣（Sampling）	

4.25 抽樣應有書面程序。該程序應包括所要使用的方法與設備、抽樣量及應遵守的預防措施，以避免原物料的污染或其品質的降低。	4.25 There should be written procedures for sampling, which include the methods and equipment to be used, the amounts to be taken and any precautions to be observed to avoid contamination of the material or any deterioration in its quality.
檢驗（Testing）	
4.26 在不同製造階段檢驗原物料及產品，應有書面的程序。該程序描述使用的方法及設備。執行的檢驗應加以記錄。	4.26 There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be recorded.
其他（Other）	
4.27 原物料及產品之放行與拒用，特別是由指派之被授權人員對最終產品放行供銷售，應有書面程序。所有紀錄應可供被授權人取得。應備有系統，以顯示特別的觀察所見，以及對於關鍵數據之任何變更。	4.27 Written release and rejection procedures should be available for materials and products, and in particular for the certification for sale of the finished product by the Authorised Person(s). All records should be available to the Authorised Person. A system should be in place to indicate special observations and any changes to critical data.
4.28 應保存每一產品之運銷紀錄，以利必要時該批次的回收。	4.28 Records should be maintained for the distribution of each batch of a product in order to facilitate recall of any batch, if necessary.
4.29 對下列事項應有書面的政策、程序、計畫書、報告及所採取行動或已達成結論的相關紀錄，合適時，包含下列實例：	4.29 There should be written policies, procedures, protocols, reports and the associated records of actions taken or conclusions reached, where appropriate, for the following examples:
– 製程、設備與系統的確效與驗證；	– Validation and qualification of processes, equipment and systems;
– 設備之組裝及校正；	– Equipment assembly and calibration;
– 技術移轉；	– Technology transfer;
– 維護保養、清潔與滅菌處理；	– Maintenance, cleaning and sanitation;
– 人事，包含人員簽名清單、在GMP與技術事務、衣著與衛生上的訓練以及確認訓練的有效性；	– Personnel matters including signature lists, training in GMP and technical matters, clothing and hygiene and verification of the effectiveness of training.
– 環境監測；	– Environmental monitoring;

– 防蟲鼠；	– Pest control;
– 申訴；	– Complaints;
– 回收；	– Recalls;
– 退回；	– Returns;
– 變更管制；	– Change control;
– 偏差與不符合的調查；	– Investigations into deviations and non-conformances;
– 內部品質/GMP符合性稽查；	– Internal quality/GMP compliance audits;
– 紀錄的摘要（合適時）（例如，產品品質檢討）；	– Summaries of records where appropriate (e.g. product quality review);
– 供應商稽查。	– Supplier audits.
4.30 主要的製造與檢驗設備應有清楚的操作程序。	4.30 Clear operating procedures should be available for major items of manufacturing and test equipment.
4.31 應保存主要或關鍵的分析檢驗、生產設備及產品生產區域的日誌。合適時，該日誌應依時序記錄任何使用的區域、設備/方法、校正、維護保養及清潔或維修作業，包含執行這些操作的日期與人員的簽名。	4.31 Logbooks should be kept for major or critical analytical testing, production equipment, and areas where product has been processed. They should be used to record in chronological order, as appropriate, any use of the area, equipment/method, calibrations, maintenance, cleaning or repair operations, including the dates and identity of people who carried these operations out.
4.32 品質管理系統內的文件清單應加以維護。	4.32 An inventory of documents within the Quality Management System should be maintained.

第五章　生產（PRODUCTION）

原則（PRINCIPLE）	
生產作業應遵循清楚界定的程序，且符合優良製造規範的原則，以獲得要求之品質的產品，並應符合相關的製造及上市許可。	Production operations must follow clearly defined procedures; they must comply with the principles of Good Manufacturing Practice in order to obtain products of the requisite quality and be in accordance with the relevant manufacturing and marketing authorisations.
一般規定（GENERAL）	
5.1　生產應由能勝任者執行與監督。	5.1　Production should be performed and supervised by competent people.
5.2　原物料與產品的所有處理，例如接收、待驗、抽樣、儲存、標示、調配、製造、分/包裝及運銷，應依書面程序或指令執行，必要時應予記錄。	5.2　All handling of materials and products, such as receipt and quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded.
5.3　所有進廠的原物料應予核對，以確保託運物與訂單相符。必要時，容器應予清潔，並以規定的資訊標示。	5.3　All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labelled with the prescribed information.
5.4　容器之破損及對原物料品質可能產生其不利影響的任何其他問題，應予調查、記錄並提報給品質管制部門。	5.4　Damage to containers and any other problem which might adversely affect the quality of a material should be investigated, recorded and reported to the Quality Control Department.
5.5　進廠原物料及最終產品在接收或加工後，應即為實體或行政管理上的隔離，直到其經放行供使用或運銷為止。	5.5　Incoming materials and finished products should be physically or administratively quarantined immediately after receipt or processing, until they have been released for use or distribution.
5.6　採購的半製品/中間產品或待分/包裝產品，在接收時應視同原料處理。	5.6　Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.

5.7	所有原物料及產品皆應在藥廠建立的適當條件下，並以有條理的方式儲存，以容許批次的區隔及庫存品的輪換。	5.7	All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation.
5.8	視需要,應核對產率及進行重量/數量調和，以確保無超出允收範圍的差異。	5.8	Checks on yields, and reconciliation of quantities, should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.
5.9	不同產品的生產作業，不得在同一作業室內同時或接續地執行，除非無混雜或交叉污染的風險。	5.9	Operations on different products should not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross-contamination.
5.10	製程的每一階段，皆應防止原物料及產品受微生物及其他污染。	5.10	At every stage of processing, materials and products should be protected from microbial and other contamination.
5.11	處理乾燥的原物料及產品時，應採取特別的防範措施，以防止粉塵的產生及散佈。特別適用於高危險性物質的處理，包括高致敏性物質在內。	5.11	When working with dry materials and products, special precautions should be taken to prevent the generation and dissemination of dust. This applies particularly to the handling of highly hazardous, including highly sensitising materials.
5.12	操作全程中，所有原物料、半製品容器、設備的主要項目及合適時使用的操作室皆應標示，否則，應以操作中產品或原物料、其含量（如果可行）及批號等標示予以識別。可行時，該標示亦應提及生產階段。	5.12	At all times during processing, all materials, bulk containers, major items of equipment and where appropriate rooms used should be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and batch number. Where applicable, this indication should also mention the stage of production.

5.13	用於容器、設備或作業場所的標示卡應清楚、明確，且使用公司一致的格式。標籤上除文字外，使用顏色標示其狀態（例如：待驗、合格、拒用、待清潔/已清潔），通常是有幫助的。	5.13	Labels applied to containers, equipment or premises should be clear, unambiguous and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colours to indicate status (for example, quarantined, accepted, rejected, clean).
5.14	為確保用於將原物料及產品從一個區域輸送到另外一個區域的管線及其他設備係以正確的方式連接，應執行檢查。	5.14	Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of materials and products from one area to another are connected in a correct manner.
5.15	應盡可能避免來自指令或作業程序的任何偏差。發生偏差時，應由權責人員以書面認可，適當時需有品質管制部門的參與。	5.15	Any deviation from instructions or procedures should be avoided as far as possible. If a deviation occurs, it should be approved in writing by a competent person, with the involvement of the Quality Control department when appropriate.
5.16	進入生產廠房應限於被授權人員。	5.16	Access to production premises should be restricted to authorised personnel.
生產中交叉污染的防止 （PREVENTION OF CROSS-CONTAMINATION IN PRODUCTION）			
5.17	通常，非藥品之生產應避免在預定生產藥品的區域與設備中為之。但如適用時，可採取下文和第 3 章所述之防止藥品交叉污染的措施。工業毒物，如殺蟲劑（除非用於製造藥品）與除草劑之生產及/或儲存，不得出現於藥品生產及/或儲存之區域。	5.17	Normally, the production of non-medicinal products should be avoided in areas and with equipment destined for the production of medicinal products but, where justified, could be allowed where the measures to prevent cross-contamination with medicinal products described below and in Chapter 3 can be applied. The production and/or storage of technical poisons, such as pesticides (except where these are used for manufacture of medicinal products) and herbicides, should not be allowed in areas used for the manufacture and / or storage of medicinal products.

5.18	應防止原料或產品被另一原物料或產品污染。該意外交叉污染的風險，源於製程中未管制之原料藥、其他原物料（起始或製程中）及產品所產生的粉塵、氣體、蒸氣、氣霧、基因材料或微生物、設備上的殘留物及因作業人員的服裝等，應被評估。該風險的嚴重性隨污染物的性質及被污染的產品而異，交叉污染尤對以注射及長期投用的產品之使用最具風險。但是，根據污染的性質與程度，所有產品的污染都會給患者的安全帶來風險。	5.18	Contamination of a starting material or of a product by another material or product should be prevented. This risk of accidental cross-contamination resulting from the uncontrolled release of dust, gases, vapours, aerosol, genetic materials or organisms from active substances, other materials (starting or in-process) and products in process, from residues on equipment, and from operators' clothing should be assessed. The significance of this risk varies with the nature of the contaminant and that of the product being contaminated. Products in which cross-contamination is likely to be most significant are those administered by injection and those given over a long time. However, contamination of all products poses a risk to patient safety dependent on the nature and extent of contamination.
5.19	交叉污染應依第三章所述，經由注意廠房設施與設備之設計予以防止。應該注意製程設計與任何相關技術或組織之措施的實施，包括有效且可再現的清潔程序，以控制交叉污染的風險。	5.19	Cross-contamination should be prevented by attention to design of the premises and equipment as described in Chapter 3. This should be supported by attention to process design and implementation of any relevant technical or organizational measures, including effective and reproducible cleaning processes to control risk of cross-contamination.

5.20	品質風險管理過程（包括效價及毒理學評估）應加以使用，以評估及管制由所製造之產品呈現的交叉污染風險。包括的因素有設施/設備的設計與使用、人流及物流、微生物學上的管制、原料藥之理化特性、製程特性及清潔程序，以及由產品評估中所建立關於相關限量之分析能力，也應加以考慮。品質風險管理過程的結果應成為確定哪些廠房設施與設備應專用於特定產品或產品家族的必要性及程度之基礎。這可能包括專用特定的產品接觸零件或整個生產設施。證明合理時，在多產品共用設施內，將生產活動限制在隔離的、自足圍堵的生產區域是可以接受的。	5.20	A Quality Risk Management process, which includes a potency and toxicological evaluation, should be used to assess and control the cross-contamination risks presented by the products manufactured. Factors including; facility/equipment design and use, personnel and material flow, microbiological controls, physico-chemical characteristics of the active substance, process characteristics, cleaning processes and analytical capabilities relative to the relevant limits established from the evaluation of the products should also be taken into account. The outcome of the Quality Risk Management process should be the basis for determining the necessity for and extent to which premises and equipment should be dedicated to a particular product or product family. This may include dedicating specific product contact parts or dedication of the entire manufacturing facility. It may be acceptable to confine manufacturing activities to a segregated, self contained production area within a multiproduct facility, where justified.
5.21	品質風險管理過程的結果應作為確定控制交叉污染風險所需之技術及組織措施程度的基礎。這些可能包括但不侷限於以下內容：	5.21	The outcome of the Quality Risk Management process should be the basis for determining the extent of technical and organisational measures required to control risks for cross-contamination. These could include, but are not limited to, the following:
	技術措施		Technical Measures
	i 專用製造設施（廠房設施與設備）；		i Dedicated manufacturing facility (premises and equipment);

ii	自足圍堵的生產區域，具有獨立的製造設備及獨立的空調（HVAC）系統。將某些公用設施與其他區域之公用設施隔離開來也是可取的；	ii	Self-contained production areas having separate processing equipment and separate heating, ventilation and air-conditioning (HVAC) systems. It may also be desirable to isolate certain utilities from those used in other areas;
iii	製程、廠房設施與設備之設計，使製程、維護及清潔作業期間之交叉污染的風險降到最低；	iii	Design of manufacturing process, premises and equipment to minimize risk for cross-contamination during processing, maintenance and cleaning;
iv	使用「密閉系統」操作及設備之間原物料/產品之移轉；	iv	Use of "closed systems" for processing and material/product transfer between equipment;
v	使用實體屏障系統（包括隔離裝置）作為圍堵措施；	v	Use of physical barrier systems, including isolators, as containment measures;
vi	以管制之方式移除接近污染物來源的粉塵，例如透過局部抽除；	vi	Controlled removal of dust close to source of the contaminant e.g. through localised extraction;
vii	專用設備、專用產品接觸零件或專用選定之難以清潔的零件（如過濾器），以及專用維護保養工具；	vii	Dedication of equipment, dedication of product contact parts or dedication of selected parts which are harder to clean (e.g. filters), dedication of maintenance tools;
viii	使用一次性使用之拋棄式技術；	viii	Use of single use disposable technologies;
ix	使用易於清潔的設備；	ix	Use of equipment designed for ease of cleaning;
x	適當使用氣鎖室及壓力梯度，以將潛在空氣污染物侷限在特定區域內；	x	Appropriate use of air-locks and pressure cascade to confine potential airborne contaminant within a specified area;
xi	將由未經處理或處理不足之空氣再循環或重新進入所造成的污染風險降至最低；	xi	Minimising the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;

xii 使用經確效其有效性之自動原位清潔系統；	xii Use of automatic clean in place systems of validated effectiveness;
xiii 對於共同的一般洗滌區域，將設備之洗滌區、乾燥區與儲存區予以分開。	xiii For common general wash areas, separation of equipment washing, drying and storage areas.
組織措施	Organisational Measures
i 在時段切換基礎上（以時間分隔之專用）使整個製造設施或自足圍堵生產區域為專用，接著進行經確效其有效性的清潔過程；	i Dedicating the whole manufacturing facility or a self contained production area on a campaign basis (dedicated by separation in time) followed by a cleaning process of validated effectiveness;
ii 在處理有交叉污染高風險產品時，其特定防護裝應留在該區域內；	ii Keeping specific protective clothing inside areas where products with high risk of cross-contamination are processed;
iii 針對呈現較高風險之產品，每一產品時段切換生產後的清潔確認應被視為一種可檢測性工具，以支持其品質風險管理方法之有效性；	iii Cleaning verification after each product campaign should be considered as a detectability tool to support effectiveness of the Quality Risk Management approach for products deemed to present higher risk;
iv 取決於污染風險，為了證明防止空氣浮游污染或機械轉移污染之管制措施的有效性，確認非產品接觸表面的清潔與監控製造區域及/或鄰接區域的空氣；	iv Depending on the contamination risk, verification of cleaning of non product contact surfaces and monitoring of air within the manufacturing area and/or adjoining areas in order to demonstrate effectiveness of control measures against airborne contamination or contamination by mechanical transfer;
v 廢棄物處理、受污染的沖洗水及髒衣服的特定措施；	v Specific measures for waste handling, contaminated rinsing water and soiled gowning;
vi 記錄溢出、意外事件或偏離程序；	vi Recording of spills, accidental events or deviations from procedures;

	vii	廠房設施與設備之清潔過程的設計，使清潔過程本身不會呈現交叉污染風險；	vii Design of cleaning processes for premises and equipment such that the cleaning processes in themselves do not present a cross-contamination risk;
	viii	設計清潔過程的詳細紀錄，以確保依核准之程序完成清潔，並在設備上及製造區域使用清潔狀態標籤；	viii Design of detailed records for cleaning processes to assure completion of cleaning in accordance with approved procedures and use of cleaning status labels on equipment. and manufacturing areas;
	ix	基於時段切換使用共同的一般洗滌區；	ix Use of common general wash areas on a campaign basis;
	x	工作行為之監督，以確保訓練之有效性及符合相關之程序管制。	x Supervision of working behaviour to ensure training effectiveness and compliance with the relevant procedural controls.
5.22		應依規定程序定期檢討防止交叉污染的措施及其有效性。	5.22 Measures to prevent cross-contamination and their effectiveness should be reviewed periodically according to set procedures.
確效（Validation ）			
5.23		確效研究應強化優良製造規範，並依所界定的程序實施。其結果及結論應予記錄。	5.23 Validation studies should reinforce Good Manufacturing Practice and be conducted in accordance with defined procedures. Results and conclusions should be recorded.
5.24		當採用任何新的製造配方或製備方法時，應採取步驟以證明其對例行操作的適用性。使用規定的原物料及設備時，該界定的製程應表現其能生產出與所要求品質一致之產品。	5.24 When any new manufacturing formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality.

5.25	對製造過程可能會影響產品品質及/或製程之再現性的重大修正，包括設備或原物料的任何變更，應加以確效。	5.25	Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and/or the reproducibility of the process should be validated.
5.26	製程及程序應執行定期關鍵性再確效，以確保其維持達成預定結果的能力。	5.26	Processes and procedures should undergo periodic critical re-validation to ensure that they remain capable of achieving the intended results.
原料（STARTING MATERIALS）			
5.27	原料供應商的選擇、資格認可、核准及維護以及其原料之採購與接受，應作為製藥品質系統文件化的一部分。監督程度應該與由個別原料所呈現之風險成正比，考量它們的來源、製造過程、供應鏈的複雜性以及原料在藥品中的最終用途。應保持每一供應商/原料核准的支持性證據。參與這些活動的工作人員應對供應商、供應鏈及相關風險有最新的了解。可能時，原料應直接從原料製造廠購買。	5.27	The selection, qualification, approval and maintenance of suppliers of starting materials, together with their purchase and acceptance, should be documented as part of the pharmaceutical quality system. The level of supervision should be proportionate to the risks posed by the individual materials, taking account of their source, manufacturing process, supply chain complexity and the final use to which the material is put in the medicinal product. The supporting evidence for each supplier / material approval should be maintained. Staff involved in these activities should have a current knowledge of the suppliers, the supply chain and the associated risks involved. Where possible, starting materials should be purchased directly from the manufacturer of the starting material.

5.28	製造廠為原料制定的品質要求應與供應商討論並達成一致。生產、測試和控制，包括其處理、標示、分/包裝與運銷的要求、申訴、回收與拒用程序，應在正式之品質協議或規格中予以文件化。	5.28	The quality requirements established by the manufacturer for the starting materials should be discussed and agreed with the suppliers. Appropriate aspects of the production, testing and control, including handling, labelling, packaging and distribution requirements, complaints, recalls and rejection procedures should be documented in a formal quality agreement or specification.
5.29	對於原料藥與賦形劑供應商的核准及維持，要求如下：	5.29	For the approval and maintenance of suppliers of active substances and excipients, the following is required:
	原料藥		Active substances
	應建立供應鏈之可追溯性，從原料藥之起始原料至最終產品的相關風險應正式評估並定期確認。應採取適當措施，降低原料藥的品質風險。		Supply chain traceability should be established and the associated risks, from active substance starting materials to the finished medicinal product, should be formally assessed and periodically verified. Appropriate measures should be put in place to reduce risks to the quality of the active substance.
	應可獲得每種原料藥（包括原料藥之起始原料）的供應鏈與可追溯性紀錄，並由藥品製造廠保存。		The supply chain and traceability records for each active substance (including active substance starting materials) should be available and be retained by the manufacturer of the medicinal product.
	應對於原料藥之製造廠及運銷商進行稽核，以確認其符合相關之優良製造規範及優良運銷規範要求。製造許可的持有者應自行或透過代表其履行合約的一方確認此符合性。		Audits should be carried out at the manufacturers and distributors of active substances to confirm that they comply with the relevant good manufacturing practice and good distribution practice requirements. The holder of the manufacturing authorisation shall verify such compliance either by himself/herself or through an entity acting on his/her behalf under a contract. For veterinary medicinal products, audits should be conducted based on risk.

	稽核應具適當之期間及範圍，以確保對GMP 進行全面及明確的評估；應考慮到來自於現場其他原料之潛在交叉污染。報告應充分反映在稽核過程中所執行及所見的情況，並明確指出任何不足之處。任何需要的矯正預防行動應予執行。		Audits should be of an appropriate duration and scope to ensure that a full and clear assessment of GMP is made; consideration should be given to potential cross- contamination from other materials on site. The report should fully reflect what was done and seen on the audit with any deficiencies clearly identified. Any required corrective and preventive actions should be implemented.
	應在品質風險管理過程中所界定的期間，進行後續稽核，以確保標準的維持及持續使用核准的供應鏈。		Further audits should be undertaken at intervals defined by the quality risk management process to ensure the maintenance of standards and continued use of the approved supply chain.
	賦形劑		Excipients
	賦形劑及其供應商應根據PIC/S 指引 PI 045-1「適用於人用藥品賦形劑之適當優良製造規範的正式風險評估準則」，基於正式品質風險評估之結果進行適當管制。		Excipients and excipient suppliers should be controlled appropriately based on the results of a formalised quality risk assessment in accordance with the PIC/S Guideline PI 045-1 ‘Guidelines on the formalised risk assessment for ascertaining the appropriate Good Manufacturing Practice for excipients of medicinal products for human use’.
5.30	原料的每一次交貨，應檢查/核對容器包裝的完整性，包括相關時防竄改易顯封緘、送貨單、採購訂單、供應商標示，以及由藥品製造廠維護之經核准的製造廠與供應商資訊之一致性。每次交貨的接收檢查應文件化。	5.30	For each delivery of starting material the containers should be checked for integrity of package, including tamper evident seal where relevant, and for correspondence between the delivery note, the purchase order, the supplier's labels, and approved manufacturer and supplier information maintained by the medicinal product manufacturer. The receiving checks on each delivery should be documented.
5.31	原物料之一次交貨是由不同批次所組成者，每一批次應各自考慮其抽樣、檢驗與放行。	5.31	If one material delivery is made up of different batches, each batch must be considered as separate for sampling, testing and release.

5.32	儲存區的原料應適當地標示 (請參見第十三條)。標籤上應至少記載下列資料：	5.32	Starting materials in the storage area should be appropriately labelled (see section 13). Labels should bear at least the following information:
	i 產品的指定名稱及其內部參考代碼(可行時)；		i The designated name of the product and the internal code reference where applicable;
	ii 接收時所給予的批號；		ii A batch number given at receipt;
	iii 合適時，內容物的狀態(例如：待驗中、檢驗中、放行、拒用)；		iii Where appropriate, the status of the contents (e.g. in quarantine, on test, released, rejected);
	iv 合適時，末效日期或再檢驗的日期。		iv Where appropriate, an expiry date or a date beyond which retesting is necessary.
	採用完全電腦化之儲存系統者，上述所有資料未必需要以易讀的方式印在標籤上。		When fully computerised storage systems are used, all the above information need not necessarily be in a legible form on the label.
5.33	應有適當的程序或措施來確保每一個原料容器之內容物的同一性。已抽樣之原包裝容器應予識別與標示 (請參見第六章)。	5.33	There should be appropriate procedures or measures to assure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn should be identified (see Chapter 6).
5.34	僅有經品質管制部門放行，且還在再驗日期內的原料始可使用。	5.34	Only starting materials which have been released by the Quality Control department and which are within their retest date should be used.
5.35	最終產品製造廠負責上市許可檔案文件中所描述之原料 [3] 的任何測試。可以採用經核准之原料製造廠的部分或全部測試結果，但必須根據附則 8 至少對每批次進行鑑別試驗 [4]。	5.35	Manufacturers of finished products are responsible for any testing of starting materials[3] as described in the marketing authorisation dossier. They can utilise partial or full test results from the approved starting material manufacturer but must, as a minimum, perform identification testing[4] of each batch according to Annex 8.
	[3] 類似的方法應適用於第 5.45 節所述之包裝材料。		[3] A similar approach should apply to packaging materials as stated in section 5.45.

[4] 原料的鑑別試驗應依相關上市許可檔案文件的方法及規格進行。	[4] Identity testing of starting materials should be performed according to the methods and the specifications of the relevant marketing authorisation dossier.
5.36 該委外測試的理論基礎應證明其合理性及文件化，且應符合以下要求：	5.36 The rationale for the outsourcing of this testing should be justified and documented and the following requirements should be fulfilled:
i 為了保持原料的品質特性，並確保測試結果適用於送交之原料，應特別注意運銷管制（運送，批發，儲存與交貨）	i Special attention should be paid to the distribution controls (transport, wholesaling, storage and delivery) in order to maintain the quality characteristics of the starting materials and to ensure that test results remain applicable to the delivered material;
ii 為了確保符合優良製造規範與上市許可檔案文件中所描述之規格及測試方法，藥品製造廠應基於執行原料測試（包括抽樣）場所之風險，於適當間隔，自行或透過第三方稽核之。	ii The medicinal product manufacturer should perform audits, either itself or via third parties, at appropriate intervals based on risk at the site(s) carrying out the testing (including sampling) of the starting materials in order to assure compliance with Good Manufacturing Practice and with the specifications and testing methods described in the marketing authorisation dossier;
iii 原料製造廠/供應商提供之分析證明書，應由具適當資格及經驗之指定人員簽章。該簽章是確保每一批次皆經過核對符合協議的產品規格，除非另外提供。	iii The certificate of analysis provided by the starting material manufacturer/supplier should be signed by a designated person with appropriate qualifications and experience. The signature assures that each batch has been checked for compliance with the agreed product specification unless this assurance is provided separately;

	iv 藥品製造廠應具備處理原料製造廠的適當經驗（包括透過供應商的經驗），包括評估先前收到之批次及在減少內部測試之前的符合性歷史。應考慮原料製造或測試過程中的任何重要變更；		iv The medicinal product manufacturer should have appropriate experience in dealing with the starting material manufacturer (including experience via a supplier) including assessment of batches previously received and the history of compliance before reducing in-house testing. Any significant change in the manufacturing or testing processes should be considered;
	v 為了檢查原料製造廠或供應商提供之分析證明書的可靠性，藥品製造廠亦應基於風險在適當的間隔進行全項檢驗（或透過另外核准的合約實驗室），並將結果進行比較。如果該測試識別出任何差異，則應進行調查並採取適當措施，完成這些措施前，應停止接受原料製造廠或供應商的分析證明書。		v The medicinal product manufacturer should also perform (or via a separately approved contract laboratory) a full analysis at appropriate intervals based on risk and compare the results with the material manufacturer's or supplier's certificate of analysis in order to check the reliability of the latter. Should this testing identify any discrepancy then an investigation should be performed and appropriate measures taken. The acceptance of certificates of analysis from the material manufacturer or supplier should be discontinued until these measures are completed.
5.37	原料只得由指定的人員依書面程序調配，以確保將正確的原料準確地秤入或量入潔淨且適切標示的容器中。	5.37	Starting materials should only be dispensed by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.
5.38	每一經調配之原料及其重量或容量，皆應個別檢查/核對並予以記錄。	5.38	Each dispensed material and its weight or volume should be independently checked and the check recorded.

5.39 每一批次調配的原料應保存在一起，並明顯地標示。	5.39 Materials dispensed for each batch should be kept together and conspicuously labelled as such.
操作作業：半製品/中間產品及待分/包裝產品（ PROCESSING OPERATIONS: INTERMEDIATE AND BULK PRODUCTS）	
5.40 任何操作作業開始前，應採取步驟，以確保作業區及設備是潔淨且無任何現行作業所不需要的原料、產品、產品殘留物或文件。	5.40 Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues or documents not required for the current operation.
5.41 半製品/中間產品或待分/包裝產品應保存在適當的條件下。	5.41 Intermediate and bulk products should be kept under appropriate conditions.
5.42 關鍵製程應經確效(參見本章之「確效」)。	5.42 Critical processes should be validated (see "Validation" in this Chapter).
5.43 任何必要的製程中管制及環境管制均應執行並予記錄。	5.43 Any necessary in-process controls and environmental controls should be carried out and recorded.
5.44 與預期產率的任何顯著偏差均應予記錄並加以調查。	5.44 Any significant deviation from the expected yield should be recorded and investigated.
包裝材料（PACKAGING MATERIALS）	
5.45 直接包裝材料及經印刷的包裝材料之供應商的選擇、驗證、核准及維護應比照原料給予同等注意。	5.45 The selection, qualification, approval and maintenance of suppliers of primary and printed packaging materials shall be accorded attention similar to that given to starting materials.
5.46 經印刷的包裝材料應予特別注意。該材料應儲存在足夠安全的條件中，使其足以排除未經授權的取用。切式標籤及其他散裝之印好的包裝材料應在分別的密閉容器中儲存與搬運，以免混雜。包裝材料應只得由被授權人員，依認可且文件化的程序發放使用。	5.46 Particular attention should be paid to printed materials. They should be stored in adequately secure conditions such as to exclude unauthorised access. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials should be issued for use only by authorised personnel following an approved and documented procedure.

5.47	每一次交貨或每一批次之經印刷的包裝材料或直接包裝材料，均應給予專有的參考號碼或辨識標記。	5.47	Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.
5.48	過期或作廢的直接包裝材料或經印刷的包裝材料應予銷毀，並將該處置加以記錄。	5.48	Outdated or obsolete primary packaging material or printed packaging material should be destroyed and this disposal recorded.
分/包裝作業（PACKAGING OPERATIONS）			
5.49	建立分/包裝作業計畫時應特別注意，將交叉污染、混雜或替代的風險降到最低。除有實體隔離外，不同的產品不得在緊密相鄰處分/包裝。	5.49	When setting up a programme for the packaging operations, particular attention should be given to minimising the risk of cross-contamination, mix-ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation.
5.50	分/包裝作業開始前應採取步驟，以確保作業區、分/包裝線、印刷機及其他設備是潔淨的，且無現行作業所不要求之先前使用的任何產品、原物料或文件。分/包裝線的清線應依適當的查檢表執行。	5.50	Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents previously used, if these are not required for the current operation. The line-clearance should be performed according to an appropriate check-list.
5.51	作業中的產品名稱及批號，應標明在每一個分/包裝站或線上。	5.51	The name and batch number of the product being handled should be displayed at each packaging station or line.
5.52	所有產品及待用的包裝材料，交給分/包裝部門時皆應與分/包裝指令檢查/核對其數量、同一性及一致性。	5.52	All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the Packaging Instructions.
5.53	充填用的容器在充填前應為潔淨的。應注意避免任何污染物並予以移除，例如玻璃碎片及金屬粒子。	5.53	Containers for filling should be clean before filling. Attention should be given to avoid and remove any contaminants such as glass fragments and metal particles.

5.54 通常，充填與密封後應盡快加以標示。若非如此，則應採取適當的程序，以確保不會發生混雜或貼錯標籤。	5.54 Normally, filling and sealing should be followed as quickly as possible by labelling. If it is not the case, appropriate procedures should be applied to ensure that no mix-ups or mislabelling can occur.
5.55 任何印刷作業（例如代碼、末效日期）的正確性，不管是個別進行或是在分/包裝作業的過程中進行，應予以檢查/核對並加以記錄。手工印刷應予注意，並定時再檢查/核對。	5.55 The correct performance of any printing operation (for example code numbers, expiry dates) to be done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand which should be re-checked at regular intervals.
5.56 當使用切式標籤和執行離線套印時，應予特別注意。在幫助避免混雜方面，捲筒式標籤通常優於切式標籤。	5.56 Special care should be taken when using cut-labels and when over-printing is carried out off-line. Roll-feed labels are normally preferable to cut-labels, in helping to avoid mix-ups.
5.57 為確保電子讀碼機、標籤計數器或其他類似的裝置係正確操作，應執行檢查/核對。	5.57 Checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.
5.58 經印刷或凸印在包裝材料上的資訊，應明顯且能阻抗褪色或擦除。	5.58 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.
5.59 於分/包裝期間，產品的線上管制應進行檢查/核對，至少包括下列項目：	5.59 On-line control of the product during packaging should include at least checking the following:
i 包裝的一般外觀；	i General appearance of the packages;
ii 包裝是否完整；	ii Whether the packages are complete;
iii 是否使用正確的產品與包裝材料;	iii Whether the correct products and packaging materials are used;
iv 任何套印是否正確；	iv Whether any over-printing is correct;
v 分/包裝線上監視器的正確運轉。	v Correct functioning of line monitors.
從分/包裝線上取出的樣品不得置回。	Samples taken away from the packaging line should not be returned.

5.60	已涉及異常事件的產品，須經被授權人員的特別查核、調查及認可後，始得再導入分/包裝過程中。應保存該作業之詳細紀錄。	5.60	Products which have been involved in an unusual event should only be reintroduced into the process after special inspection, investigation and approval by authorised personnel. Detailed record should be kept of this operation.
5.61	在待分/包裝產品與印刷之包裝材料的數量及產出單元數目間的數量調和中，觀察到之任何顯著或異常的差異應於放行前進行調查並予以滿意地說明。	5.61	Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated and satisfactorily accounted for before release.
5.62	分/包裝作業一經完成後，任何未使用而印有批號之印刷包裝材料應予銷毀，並將該銷毀加以記錄。未印批號之印刷包裝材料要退回庫存者，應遵循書面程序。	5.62	Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure should be followed if un-coded printed materials are returned to stock.
最終產品（FINISHED PRODUCTS）			
5.63	最終產品應依藥廠既訂條件下保存於隔離待驗區，直到最終放行為止。	5.63	Finished products should be held in quarantine until their final release under conditions established by the manufacturer.
5.64	產品為供販售放行前，最終產品與文件所需之評估規定於第六章(品質管制)。	5.64	The evaluation of finished products and documentation which is necessary before release of product for sale is described in Chapter 6 (Quality Control).
5.65	放行後，最終產品應依藥廠既訂條件作為可用庫存品儲存。	5.65	After release, finished products should be stored as usable stock under conditions established by the manufacturer.
拒用的、收回的以及退回的原物料（REJECTED, RECOVERED AND RETURNED MATERIALS）			

5.66	拒用的原物料及產品應清楚標示其係拒用物品，並分別儲存於限制區中。該物品應退回供應商，或於合適時，予以重處理或銷毀。不論採取任何行動皆應經被授權人員的認可並予記錄。	5.66	Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed. Whatever action is taken should be approved and recorded by authorised personnel.
5.67	拒用產品的重處理應屬例外。該重處理僅在最終產品的品質不受影響、符合規格，且經評估所涉風險後，依界定且經核准的程序執行時方始允許，且其紀錄應予保存。	5.67	The reprocessing of rejected products should be exceptional. It is only permitted if the quality of the final product is not affected, if the specifications are met and if it is done in accordance with a defined and authorised procedure after evaluation of the risks involved. Record should be kept of the reprocessing.
5.68	符合所需品質之先前批次的全部或一部分，在界定的製造階段，併入相同產品之一個批次的收回，應經事先許可。這種收回應在其所涉風險，包含其對架儲期間之任何可能影響之評估後，依界定的程序執行之。該收回應予記錄。	5.68	The recovery of all or part of earlier batches, which conform to the required quality by incorporation into a batch of the same product at a defined stage of manufacture should be authorised beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf life. The recovery should be recorded.
5.69	經過重處理或併入收回之產品的任何最終產品，應由品質管制部門考慮其追加試驗的必要性。	5.69	The need for additional testing of any finished product which has been reprocessed, or into which a recovered product has been incorporated, should be considered by the Quality Control Department.

5.70 從市場退回及已經離開藥廠之管制的產品，應予銷毀，除非其品質毫無疑問是令人滿意的；只有在其已經為品質管制部門依書面程序嚴格評估後，始得考慮重新銷售、重新標示或是併入下一批收回。這種評估中，產品的性質、所要求的任何特別儲存條件、其狀況及歷史，以及自銷出後已經過的時間等皆應列入考慮。縱使基本的化學重處理能使有效成分收回，只要對此產品的品質產生任何疑問，就不得認為其還適合重新出貨或重新使用。採取的任何行動皆應予適當地記錄。	5.70 Products returned from the market and which have left the control of the manufacturer should be destroyed unless without doubt their quality is satisfactory; they may be considered for re-sale, re-labelling or recovery in a subsequent batch only after they have been critically assessed by the Quality Control Department in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for re-issue or re-use, although basic chemical reprocessing to recover active ingredients may be possible. Any action taken should be appropriately recorded.
因製造限制造成產品短缺 （PRODUCT SHORTAGE DUE TO MANUFACTURING CONSTRAINTS）	
5.71 製造廠應向上市許可持有者報告製造作業中可能導致供應異常限制的任何限制條件。這應適時進行，以便於上市許可持有者根據其法定義務向主管機關報告供應限制。	5.71 The manufacturer should report to the marketing authorisation holder (MAH) any constraints in manufacturing operations which may result in abnormal restriction in the supply. This should be done in a timely manner to facilitate reporting of the restriction in supply by the MAH, to the relevant competent authorities, in accordance with its legal obligations.

第六章 品質管制（QUALITY CONTROL）

原則（PRINCIPLE）	
本章應與 GMP 指引的所有相關部分一起研讀。	This chapter should be read in conjunction with all relevant sections of the GMP guide.
品質管制與抽樣、規格與試驗以及組織、文件與放行程序有關，確保必要與相關的檢驗皆已執行，並確保在品質經判斷滿意前，無原物料會被放行供使用，無產品會被放行供銷售或供應。品質管制不侷限於實驗室的作業，而應涉及可能與該產品品質有關的所有決定。將品質管制部門從生產部門獨立出來被認為是品質管制之滿意運作的基礎。	Quality Control is concerned with sampling, specifications and testing as well as the organisation, documentation and release procedures which ensure that the necessary and relevant tests are carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory. Quality Control is not confined to laboratory operations, but must be involved in all decisions which may concern the quality of the product. The independence of Quality Control from Production is considered fundamental to the satisfactory operation of Quality Control.
一般規定（GENERAL）	
6.1 每一個製造許可的持有者均應有品質管制部門。此部門應從其他部門獨立出來，並由具有適當資格及經驗的人員負責。該人員擁有可由其支配之一個或多個品管實驗室。此部門應有適當的資源，以確保有效且可靠地執行所有品質管制的安排。	6.1 Each holder of a manufacturing authorisation should have a Quality Control Department. This department should be independent from other departments, and under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at his disposal. Adequate resources must be available to ensure that all the Quality Control arrangements are effectively and reliably carried out.

6.2	品質管制主管的主要職責概述於第二章。整體而言，品質管制部門亦有其他的職責，例如：制訂、確效並執行所有品質管制程序，監督原物料與產品之對照及/或留存樣品的管制（當適用時），確保原物料與產品容器的正確標示，確保產品安定性的監測，參與和產品品質有關之申訴的調查等。這些作業皆應依書面程序執行，且在必要時，應予記錄。	6.2	The principal duties of the head of Quality Control are summarised in Chapter 2. The Quality Control Department as a whole will also have other duties, such as to establish, validate and implement all quality control procedures, oversee the control of the reference and/or retention samples of materials and products when applicable, ensure the correct labelling of containers of materials and products, ensure the monitoring of the stability of the products, participate in the investigation of complaints related to the quality of the product, etc. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.
6.3	最終產品的評價應包含所有相關的因素，包括生產條件、製程中檢驗的結果、製造（包括分/包裝）文件的檢討、符合最終產品規格及最終包裝產品的檢查。	6.3	Finished product assessment should embrace all relevant factors, including production conditions, results of in-process testing, a review of manufacturing (including packaging) documentation, compliance with Finished Product Specification and examination of the final finished pack.
6.4	為抽樣與調查，合適時，品質管制人員應進入生產區。	6.4	Quality Control personnel should have access to production areas for sampling and investigation as appropriate.
優良品質管制實驗室規範 （GOOD QUALITY CONTROL LABORATORY PRATCTICE）			
6.5	管制實驗室的廠房及設備應符合第三章所定品質管制區之一般及特別的要求。實驗室設備應不得在高風險區域之間例行地移動，以避免意外的交叉污染。尤其是，微生物學實驗室應適當配置，以使交叉污染的風險減到最低。	6.5	Control laboratory premises and equipment should meet the general and specific requirements for Quality Control areas given in Chapter 3. Laboratory equipment should not be routinely moved between high risk areas to avoid accidental cross-contamination. In particular, the microbiological laboratory should be arranged so as to minimize risk of cross-contamination.

6.6 實驗室中的人員、廠房設施及設備應與該製造作業的性質與規模所須執行的工作相稱。在符合第七章委外活動所詳述的原則下，有特別的理由者，得接受使用外部實驗室。這應在品質管制紀錄中加以陳述。	6.6 The personnel, premises, and equipment in the laboratories should be appropriate to the tasks imposed by the nature and the scale of the manufacturing operations. The use of outside laboratories, in conformity with the principles detailed in Chapter 7, Outsourced Activities, can be accepted for particular reasons, but this should be stated in the Quality Control records.
文件（Documentation）	
6.7 實驗室文件的製作應遵照第四章所定的原則。與品質管制有關的重要文件以及下列細節資料應供品質管制部門易於取用：	6.7 Laboratory documentation should follow the principles given in Chapter 4. An important part of this documentation deals with Quality Control and the following details should be readily available to the Quality Control Department:
(i) 規格；	(i) Specifications;
(ii) 描述抽樣、檢驗、紀錄（包含檢驗工作單及/或實驗室筆記本）、記錄與確認的程序；	(ii) Procedures describing sampling, testing, records (including test worksheets and/or laboratory notebooks), recording and verifying;
(iii) 儀器校正/驗證與設備維護保養的程序及紀錄；	(iii) Procedures for and records of the calibration/qualification of instruments and maintenance of equipment;
(iv) 偏離規格及偏離趨勢結果的調查程序；	(iv) A procedure for the investigation of Out of Specification and Out of Trend results;
(v) 檢驗報告及/或分析證明書；	(v) Testing reports and/or certificates of analysis;
(vi) 環境（空氣、水與其他公用設施）監測數據/資料（要求時）；	(vi) Data from environmental (air, water and other utilities) monitoring, where required;
(vii) 檢驗方法的確效紀錄（可行時）。	(vii) Validation records of test methods, where applicable.
6.8 與批次紀錄有關之任何品質管制文件的保存，應遵循第 4 章關於批次文件製作之原則。	6.8 Any Quality Control documentation relating to a batch record should be retained following the principles given in Chapter 4 on retention of batch documentation.

6.9 某些類型的數據（如：檢驗結果、產率、環境的管制）應以允許趨勢評估的方式記錄。任何偏離趨勢或偏離規格數據應提出並進行調查。	6.9 Some kinds of data (e.g. tests results, yields, environmental controls) should be recorded in a manner permitting trend evaluation. Any Out of Trend or Out of Specification data should be addressed and subject to investigation.
6.10 除列入批次文件之資訊外，其他原始數據，例如實驗室筆記本及/或紀錄，皆應予保存且易於取用。	6.10 In addition to the information which is part of the batch documentation, other raw data such as laboratory notebooks and/or records should be retained and readily available.
抽樣（Sampling）	
6.11 抽樣應依經核准之書面程序執行及記錄。該程序描述下列項目：	6.11 The sample taking should be done and recorded in accordance with approved written procedures that describe:
(i) 抽樣的方法；	(i) The method of sampling;
(ii) 使用的設備；	(ii) The equipment to be used;
(iii) 抽取的樣品量；	(iii) The amount of the sample to be taken;
(iv) 任何要求將樣品再細分的指令；	(iv) Instructions for any required sub-division of the sample;
(v) 使用之樣品容器的類型及條件；	(v) The type and condition of the sample container to be used;
(vi) 經抽取樣品之容器的識別；	(vi) The identification of containers sampled;
(vii) 應遵行的任何特殊注意事項，特別是關於無菌的或有毒物質的抽樣；	(vii) Any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials;
(viii) 儲存條件；	(viii) The storage conditions;
(ix) 抽樣設備之清潔與儲存的指令。	(ix) Instructions for the cleaning and storage of sampling equipment.
6.12 樣品對於其取自之原物料或產品批次應有代表性。用以監測製程之最困難的部分，亦可另取其他樣品（例如：製程的開始或結束）為之。所使用的抽樣計畫應基於風險管理方法，並適當地證明其合理性。	6.12 Samples should be representative of the batch of materials or products from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g. beginning or end of a process). The sampling plan used should be appropriately justified and based on a risk management approach.

6.13 樣品容器的標籤應標示其內容物、批號、抽樣日期及樣品所取自之容器。它們應以使混雜的風險減到最低，並使樣品免於受到不良儲存條件的方式進行管理。	6.13 Sample containers should bear a label indicating the contents, with the batch number, the date of sampling and the containers from which samples have been drawn. They should be managed in a manner to minimize the risk of mix-up and to protect the samples from adverse storage conditions.
6.14 關於對照樣品與留存樣品的進一步指引參照附則 19。	6.14 Further guidance on reference and retention samples is given in Annex 19.
檢驗（Testing）	
6.15 檢驗方法應予確效。非執行原始確效的實驗室，使用該檢驗方法時應確認其合適性。根據上市許可或技術檔案中所描述的所有檢驗作業皆應依經核定的方法執行之。	6.15 Testing methods should be validated. A laboratory that is using a testing method and which did not perform the original validation, should verify the appropriateness of the testing method. All testing operations described in the Marketing Authorisation or technical dossier should be carried out according to the approved methods.
6.16 獲得的結果應予記錄。經確認為關鍵品質屬性之參數的結果應進行趨勢分析及檢查/核對，以確保彼此間是一致的。任何計算均應予嚴格驗算。	6.16 The results obtained should be recorded. Results of parameters identified as critical quality attributes should be trended and checked to make sure that they are consistent with each other. Any calculations should be critically examined.
6.17 執行的試驗應予記錄且至少應包括下列數據/資料：	6.17 The tests performed should be recorded and the records should include at least the following data:
(i) 原物料或產品名稱，及其劑型（可行時）；	(i) Name of the material or product and, where applicable, dosage form;
(ii) 批號，及其製造廠及/或供應商（合適時）；	(ii) Batch number and, where appropriate, the manufacturer and/or supplier;
(iii) 相關規格與檢驗程序的參考資料；	(iii) References to the relevant specifications and testing procedures;
(iv) 檢驗的結果，包括觀察、計算及任何檢驗證明書的參考資料；	(iv) Test results, including observations and calculations, and reference to any certificates of analysis;
(v) 檢驗日期；	(v) Dates of testing;

	(vi) 執行該檢驗之人員的簽名；		(vi) Initials of the persons who performed the testing;
	(vii) 合適時，確認檢驗及計算結果之人員的簽名；		(vii) Initials of the persons who verified the testing and the calculations, where appropriate;
	(viii) 核准或拒用（或其他狀態的決定）之清楚說明及指定之負責人員註明日期的簽章；		(viii) A clear statement of approval or rejection (or other status decision) and the dated signature of the designated responsible person;
	(ix) 引述所使用的設備。		(ix) Reference to the equipment used.
6.18	所有製程中管制，包括由生產人員在生產區中所執行的管制，應依品質管制部門認可的方法執行，並記錄其結果。	6.18	All the in-process controls, including those made in the production area by production personnel, should be performed according to methods approved by Quality Control and the results recorded.
6.19	應特別注意實驗室試劑、溶液、玻璃器皿、對照標準品及培養基等之品質，並應依書面的程序製備與管制。管制的程度應與其使用及既有之安定性資料相稱。	6.19	Special attention should be given to the quality of laboratory reagents, solutions, glassware, reference standards and culture media. They should be prepared and controlled in accordance with written procedures. The level of controls should be commensurate to their use and to the available stability data.
6.20	對照標準品應經確認適合其預定用途，其驗證與認證應明確說明和記錄。當有公認來源的公定標準品存在時，應優先用作一級標準品，但如已有文件化證明二級標準品對一級標準品的可追溯性，則允許使用二級標準品。除主管機關另有授權外，這些公定物質應依適當個論中所描述的目的使用。	6.20	Reference standards should be established as suitable for their intended use. Their qualification and certification, as such, should be clearly stated and documented. Whenever compendial reference standards from an officially recognised source exist, these should preferably be used as primary reference standards unless fully justified (the use of secondary standards is permitted once their traceability to primary standards has been demonstrated and is documented). These compendial materials should be used for the purpose described in the appropriate monograph unless otherwise authorised by the National Competent Authority.

6.21	實驗室試劑、溶液、對照標準品與培養基應標記其配製與開封日期及配製人員的簽章。試劑及培養基的末效日期，應與其特別的儲存條件一同標示在標籤上。此外，對於容量分析溶液，應標示其最近一次標定日期及最近的換算係數。	6.21	Laboratory reagents, solutions, reference standards and culture media should be marked with the preparation and opening date and the signature of the person who prepared them. The expiry date of reagents and culture media should be indicated on the label, together with specific storage conditions. In addition, for volumetric solutions, the last date of standardisation and the last current factor should be indicated.
6.22	必要時，應將用於檢驗作業之任何物質（例如：試劑、溶液及對照標準品）的接收日期標示在容器上。使用及儲存的指令應予遵循。某些情形，於接收時或使用前，可能有必要執行試劑材料的鑑別試驗及/或其他試驗。	6.22	Where necessary, the date of receipt of any substance used for testing operations (e.g. reagents, solutions and reference standards) should be indicated on the container. Instructions for use and storage should be followed. In certain cases it may be necessary to carry out an identification test and/or other testing of reagent materials upon receipt or before use.
6.23	除了科學上證明其合理性者外，培養基應依照培養基製造廠的要求製備。所有培養基的效能應在使用前加以確認。	6.23	Culture media should be prepared in accordance with the media manufacturer's requirements unless scientifically justified. The performance of all culture media should be verified prior to use.
6.24	經使用後的微生物學培養基與菌株應根據標準程序進行去污染與處置，以防止交叉污染與殘留物之留存。配製後之微生物學培養基的架儲期應加以建立並文件化，且證明其科學合理性。	6.24	Used microbiological media and strains should be decontaminated according to a standard procedure and disposed of in a manner to prevent the cross-contamination and retention of residues. The in-use shelf life of microbiological media should be established, documented and scientifically justified.
6.25	用於檢驗組成物、原物料或產品的動物，合適時，使用前應予隔離。它們應以能確保其合於預定用途之適用性的方式飼養及管制，且應予識別與標示，並應保存顯示其使用歷程之適當紀錄。	6.25	Animals used for testing components, materials or products, should, where appropriate, be quarantined before use. They should be maintained and controlled in a manner that assures their suitability for the intended use. They should be identified, and adequate records should be maintained, showing the history of their use.

持續進行之安定性計畫（On-going stability programme）	
6.26 藥品上市後，其安定性應依持續的適當計畫進行監測。該計畫將容許檢出與上市包裝中的配方組成關聯之任何安定性的問題（例如，在雜質含量，或溶離圖像描述的變化）。	6.26 After marketing, the stability of the medicinal product should be monitored according to a continuous appropriate programme that will permit the detection of any stability issue (e.g. changes in levels of impurities or dissolution profile) associated with the formulation in the marketed package.
6.27 持續進行的安定性計畫之目的係在產品架儲期全期中監測該產品，並確定在所標示的儲存條件下，該產品的品質仍可預期保持在其規格內。	6.27 The purpose of the on-going stability programme is to monitor the product over its shelf life and to determine that the product remains, and can be expected to remain, within specifications under the labelled storage conditions.
6.28 這主要應用於包裝藥品之販售，但亦應考慮將待分/包裝產品包括到計畫中。例如，當待分/包裝產品在包裝前及/或從製造場所裝運到包裝場所前，儲存一段長的期間時，其對於包裝產品之安定性的衝擊應加以評估，並在週遭的自然條件下研究之。此外，對於歷經長期間之儲存與使用的中間產品也應給予考慮。臨用調配之產品的安定性之研究已在產品開發期間執行者，不需要在一個持續進行的基礎上監測之。然而，臨用調配之產品的安定性於合適時亦可以加以監測。	6.28 This mainly applies to the medicinal product in the package in which it is sold, but consideration should also be given to the inclusion in the programme of bulk product. For example, when the bulk product is stored for a long period before being packaged and/or shipped from a manufacturing site to a packaging site, the impact on the stability of the packaged product should be evaluated and studied under ambient conditions. In addition, consideration should be given to intermediates that are stored and used over prolonged periods. Stability studies on reconstituted product are performed during product development and need not be monitored on an on-going basis. However, when relevant, the stability of reconstituted product can also be monitored.

6.29 持續進行之安定性計畫，應遵循第四章的一般規則，以書面計畫書描述之，並將其結果正式作成一份報告。使用於持續進行之安定性計畫的設備（尤其是安定性試驗箱/艙室）應依循第三章與附則 15 加以驗證並予維護。	6.29 The ongoing stability programme should be described in a written protocol following the general rules of Chapter 4 and results formalised as a report. The equipment used for the ongoing stability programme (stability chambers among others) should be qualified and maintained following the general rules of Chapter 3 and Annex 15.
6.30 對於持續進行之安定性計畫的計畫書，應涵蓋至架儲期間的終點，且應包括但不限於下列的參數：	6.30 The protocol for an on-going stability programme should extend to the end of the shelf life period and should include, but not be limited to, the following parameters:
(i) 每種含量與不同批量之批次數目（合適時）；	(i) Number of batch(es) per strength and different batch sizes, if applicable;
(ii) 相關的物理、化學、微生物學及生物學的檢驗方法；	(ii) Relevant physical, chemical, microbiological and biological test methods;
(iii) 允收標準；	(iii) Acceptance criteria;
(iv) 檢驗方法的參考資料；	(iv) Reference to test methods;
(v) 容器封蓋系統的描述；	(v) Description of the container closure system(s);
(vi) 測試間隔（時間點）；	(vi) Testing intervals (time points);
(vii) 儲存條件的描述（應使用與產品標示一致之標準化的 ICH 長期試驗條件）；	(vii) Description of the conditions of storage (standardised ICH/VICH conditions for long term testing, consistent with the product labelling, should be used);
(viii) 其他特別適用於該藥品的參數。	(viii) Other applicable parameters specific to the medicinal product.
6.31 若持續安定性計畫之計畫書中已證明其正當性並予以文件化者，得與當初在上市許可檔案中所提交之長期安定性試驗的計畫書不同（例如：測試頻率，或配合 ICH 之建議事項更新時）。	6.31 The protocol for the on-going stability programme can be different from that of the initial long term stability study as submitted in the Marketing Authorisation dossier provided that this is justified and documented in the protocol (for example the frequency of testing, or when updating to ICH/VICH recommendations).

6.32 批次數目與測試頻率應能提供足夠的數據量，以容許趨勢分析。除非另有正當理由，否則，所製造之每一含量及每一直接包裝類型的產品，相關時，每年至少應有一個批次包含在安定性計畫中（除非該年中沒有生產）。產品之持續進行的安定性監測通常需要使用動物來測試而無適當經確效的替代技術時，其測試頻率可以考慮風險效益方法。經在計畫書中科學地證明其正當者，得採用籃狀設計與矩陣設計的原理。	6.32 The number of batches and frequency of testing should provide a sufficient amount of data to allow for trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be included in the stability programme (unless none are produced during that year). For products where on-going stability monitoring would normally require testing using animals and no appropriate alternative, validated techniques are available, the frequency of testing may take account of a risk-benefit approach. The principle of bracketing and matrixing designs may be applied if scientifically justified in the protocol.
6.33 某些情況，應在持續進行的安定性計畫中納入追加的批次。例如，製程或包裝有任何重大變更或重大偏差後，應執行持續進行的安定性研究。任何再加工、重處理或收回作業亦應考慮納入。	6.33 In certain situations, additional batches should be included in the on-going stability programme. For example, an on-going stability study should be conducted after any significant change or significant deviation to the process or package. Any reworking, reprocessing or recovery operation should also be considered for inclusion.
6.34 持續進行之安定性試驗的結果，應使關鍵人員，特別是被授權人能夠取得。持續進行的安定性試驗係在待分/包裝或最終產品的製造場所外之另一個場所執行者，相關各方之間應有書面協議。在製造廠應可取得持續安定性試驗的結果，以備供主管機關檢查。	6.34 Results of on-going stability studies should be made available to key personnel and, in particular, to the Authorised Person(s). Where on-going stability studies are carried out at a site other than the site of manufacture of the bulk or finished product, there should be a written agreement between the parties concerned. Results of on-going stability studies should be available at the site of manufacture for review by the competent authority.

6.35 有偏離規格或有顯著非典型趨勢時，應予調查。有任何經證實之偏離規格的結果或顯著的負面趨勢時，對於已放行至市場之受影響的產品批次，應向主管機關提報，並應依優良製造規範指引第八章及與相關主管機關之研商結果，考慮對於市面上產品之批次可能造成的衝擊。	6.35 Out of specification or significant atypical trends should be investigated. Any confirmed out of specification result, or significant negative trend, affecting product batches released on the market should be reported to the relevant competent authorities. The possible impact on batches on the market should be considered in accordance with Chapter 8 of the GMP Guide and in consultation with the relevant competent authorities.
6.36 產生之所有數據/資料的摘要，包含計畫中之任何暫時的結論在內，均應作成書面並予以保存。該摘要應定期檢討。	6.36 A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained. This summary should be subjected to periodic review.
檢驗方法的技術移轉（Technical transfer of testing methods）	
6.37 在移轉一個檢驗方法之前，移轉場所應確認該檢驗方法遵循上市許可或相關技術檔案中所描述的那些方法。檢驗方法之原始確效應進行再次審核，以確保遵循現行 ICH 要求。應執行並記錄差異分析，以確認在技術移轉過程開始之前應該執行的任何補充確效。	6.37 Prior to transferring a test method, the transferring site should verify that the test method(s) comply with those as described in the Marketing Authorisation or the relevant technical dossier. The original validation of the test method(s) should be reviewed to ensure compliance with current ICH/VICH requirements. A gap analysis should be performed and documented to identify any supplementary validation that should be performed, prior to commencing the technical transfer process.
6.38 檢驗方法從一個實驗室（移出實驗室）到另一個實驗室（接收實驗室）的移轉，應於詳細的計畫書中描述。	6.38 The transfer of testing methods from one laboratory (transferring laboratory) to another laboratory (receiving laboratory) should be described in a detailed protocol.
6.39 移轉計畫書應該包括但非侷限於下列參數：	6.39 The transfer protocol should include, but not be limited to, the following parameters:
(i) 待移轉之檢驗項目及相關檢驗方法之識別；	(i) Identification of the testing to be performed and the relevant test method(s) undergoing transfer;

(ii) 追加訓練要求的識別；	(ii) Identification of the additional training requirements;
(iii) 所要檢驗之標準品與樣品的識別；	(iii) Identification of standards and samples to be tested;
(iv) 檢驗品項之任何特別運送與儲存條件的識別；	(iv) Identification of any special transport and storage conditions of test items;
(v) 應基於方法學之現行確效研究以及關於 ICH 要求的允收標準。	(v) The acceptance criteria which should be based upon the current validation study of the methodology and with respect to ICH/VICH requirements.
6.40 在技術移轉過程結束之前，應進行與計畫書偏差的調查。技術移轉報告應將此比較結果予以文件化，適用時，並應確認檢驗方法需要進一步再確效的部分。	6.40 Deviations from the protocol should be investigated prior to closure of the technical transfer process. The technical transfer report should document the comparative outcome of the process and should identify areas requiring further test method revalidation, if applicable.
6.41 合適時，在其他指引中，對於特定檢驗方法（例如，近紅外線光譜法）之移轉所描述的特定要求，應加以論述。	6.41 Where appropriate, specific requirements described in other guidelines should be addressed for the transfer of particular testing methods (e.g. Near Infrared Spectroscopy).

第七章 委外活動（OUTSOURCED ACTIVITIES）

原則（PRINCIPLE）	
GMP 指引所涵蓋之任何委外活動應經適當界定、協議與管制，以避免因誤解而可能導致不滿意品質的產品或作業。委託者與受託者間必須有清楚訂定雙方角色與職責的書面契約。委託者之製藥品質系統應清楚規定，被授權人認可每批次產品放行之完整職責的行使方式。	Any activity covered by the GMP Guide that is outsourced should be appropriately defined, agreed and controlled in order to avoid misunderstandings which could result in a product or operation of unsatisfactory quality. There must be a written contract between the Contract Giver and the Contract Acceptor which clearly establishes the roles and responsibilities of each party. The Pharmaceutical Quality System of the Contract Giver must clearly state the way that the Authorised Person certifying each batch of product for release exercises his/her full responsibility.
一般規定（GENERAL）	
7.1 應有書面契約涵蓋與相關產品或作業有關之委外活動，及與該契約之任何有關的技術安排。	7.1 There should be a written contract covering the outsourced activities, the products or operations to which they are related, and any technical arrangements made in connection with it.
7.2 適用時，對委外活動之所有安排，包括在技術上或其他安排中所建議之任何變更，皆應符合現行法規及相關產品之上市許可。	7.2 All arrangements for the outsourced activities including any proposed changes in technical or other arrangements should be in accordance with regulations in force, and the Marketing Authorisation for the product concerned, where applicable.
7.3 上市許可之持有者與製造者不相同時，應考慮本章節所述之原則做出適當的安排。	7.3 Where the Marketing Authorisation holder and the manufacturer are not the same, appropriate arrangements should be in place, taking into account the principles described in this chapter.
委託者（THE CONTRACT GIVER）	

7.4 委託者的製藥品質系統應包括任何委外活動的管制與審查。委託者應確認備有程序，以確保對委外活動的管制負最終責任。這些程序應包括品質風險管理原則，並且特別包括：	7.4 The Pharmaceutical Quality System of the Contract Giver should include the control and review of any outsourced activities. The Contract Giver is ultimately responsible to ensure processes are in place to assure the control of outsourced activities. These processes should incorporate quality risk management principles and notably include:
7.4.1 在委外活動進行前，委託者應負責評估受託者成功履行委外活動的合法性、合適性及能力。委託者也負責藉由該契約，確保本指引所闡釋之優良製造規範的原則與指引受到遵循；	7.4.1 Prior to outsourcing activities, the Contract Giver is responsible for assessing the legality, suitability and the competence of the Contract Acceptor to carry out successfully the outsourced activities. The Contract Giver is also responsible for ensuring by means of the contract that the principles and guidelines of GMP as interpreted in this Guide are followed;
7.4.2 委託者應提供受託者所有必需的資訊及知識，以使其依產品相關的現行法規及上市許可，正確地履行約定的作業。委託者應確保受託者完全認知與本產品或工作有關之任何可能會對其廠房設施、設備、人員、其他原物料或其他產品造成危害的問題；	7.4.2 The Contract Giver should provide the Contract Acceptor with all the information and knowledge necessary to carry out the contracted operations correctly in accordance with regulations in force, and the Marketing Authorisation for the product concerned. The Contract Giver should ensure that the Contract Acceptor is fully aware of any problems associated with the product or the work which might pose a hazard to his/her premises, equipment, personnel, other materials or other products;
7.4.3 委託者應監督與檢討受託者的表現，以及識別與實施任何需要的改進。	7.4.3 The Contract Giver should monitor and review the performance of the Contract Acceptor and the identification and implementation of any needed improvement.

7.5	委託者應負責審查及評估與委外活動相關之紀錄與結果。無論是由委託者親自或基於受託者之被授權人的確認，委託者應確保受託者所交付之所有產品及原物料皆依 GMP 及上市許可進行處理。	7.5	The Contract Giver should be responsible for reviewing and assessing the records and the results related to the outsourced activities. He/she should also ensure, either by himself/herself, or based on the confirmation of the Contract Acceptor's Authorised Person, that all products and materials delivered to him/her by the Contract Acceptor have been processed in accordance with GMP and the Marketing Authorisation.
受託者（THE CONTRACT ACCEPTOR）			
7.6	受託者應能令人滿意地執行委託者所託付的工作，例如有適當的廠房設施、設備、知識、經驗及能勝任的人員。	7.6	The Contract Acceptor must be able to carry out satisfactorily the work ordered by the Contract Giver such as having adequate premises, equipment, knowledge, experience, and competent personnel.
7.7	受託者應確認所被交付的所有產品、原物料與知識皆符合其預定之目的。	7.7	The Contract Acceptor should ensure that all products, materials and knowledge delivered to him/her are suitable for their intended purpose.
7.8	受託者未經委託者之事先評估及同意，不得將契約所委託的任何工作轉委託給第三方。受託者與任何第三方間所做的安排，應確保包含來自第三方之合適性評估的資訊及知識，以原委託者與受託者間約定的相同方式提供之。	7.8	The Contract Acceptor should not subcontract to a third party any of the work entrusted to him/her under the contract without the Contract Giver's prior evaluation and approval of the arrangements. Arrangements made between the Contract Acceptor and any third party should ensure that information and knowledge, including those from assessments of the suitability of the third party, are made available in the same way as between the original Contract Giver and Contract Acceptor.
7.9	受託者不應做合約條款以外未經授權之變更，因其可能對委託者之委外活動造成品質不良的影響。	7.9	The Contract Acceptor should not make unauthorised changes, outside the terms of the Contract, which may adversely affect the quality of the outsourced activities for the Contract Giver.

7.10	受託者應瞭解委外活動（包含檢驗等）可能會受到主管機關之檢查。	7.10	The Contract Acceptor should understand that outsourced activities, including contract analysis, may be subject to inspection by the competent authorities.
契約（THE CONTRACT）			
7.11	委託者與受託者間應簽訂契約。該契約明定雙方關於委外活動的個別責任及溝通程序。契約中的技術層面應由具有相關委外活動及優良製造規範之適當知識的勝任人員擬定。委外活動的所有安排均應依產品相關之現行法規及上市許可的規定，並為雙方所同意。	7.11	A contract should be drawn up between the Contract Giver and the Contract Acceptor which specifies their respective responsibilities and communication processes relating to the outsourced activities. Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in related outsourced activities and Good Manufacturing Practice. All arrangements for outsourced activities must be in accordance with regulations in force and the Marketing Authorisation for the product concerned and agreed by both parties.
7.12	契約中應清楚載明執行委外活動之每一步驟何方負有責任，例如，知識管理、技術移轉、供應鏈、轉委託、原物料之品質與採購、原物料之檢驗及放行、從事生產及品質管制（包含製程中管制、抽樣及檢驗）。	7.12	The contract should describe clearly which party to the contract has responsibility for conducting each step of the outsourced activity, e.g. knowledge management, technology transfer, supply chain, subcontracting, quality and purchasing of materials, testing and releasing materials, undertaking production and quality controls (including in-process controls, sampling and analysis).
7.13	所有委外活動之相關紀錄應由委託者保存，或可為委託者取得，例如：製造、檢驗及運銷之紀錄及對照樣品。當有申訴或懷疑有瑕疵或調查涉及偽造產品時，應能取得任何與產品品質評估有關的任何紀錄，並應明定於委託者之相關程序中。	7.13	All records related to the outsourced activities, e.g. manufacturing, analytical and distribution records, and reference samples, should be kept by, or be available to, the Contract Giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect or to investigating in the case of a suspected falsified product must be accessible and specified in the relevant procedures of the Contract Giver.

7.14 契約應明訂容許委託者稽查受託者所執行或雙方同意之轉委託商所執行的委外活動。	7.14 The contract should permit the Contract Giver to audit outsourced activities, performed by the Contract Acceptor or their mutually agreed subcontractors.

第八章 申訴與產品回收（COMPLAINTS AND PRODUCT RECALL）

原則（PRINCIPLE）	
為了保護大眾健康，應具備一個系統及適當程序用以記錄、評估、調查及檢討包括潛在品質缺陷在內的申訴，必要時有效與及時自運銷網回收人用藥品及研究用藥品。品質風險管理原則應運用於品質缺陷的調查與評估，以及與產品回收矯正與預防行動及其他風險減低行動相關的決策過程。與本原則相關之指引提供於第一章。	In order to protect public and animal health, a system and appropriate procedures should be in place to record, assess, investigate and review complaints including potential quality defects, and if necessary, to effectively and promptly recall medicinal products for human or veterinary use and investigational medicinal products from the distribution network. Quality Risk Management principles should be applied to the investigation and assessment of quality defects and to the decision-making process in relation to product recalls corrective and preventative actions and other risk-reducing actions. Guidance in relation to these principles is provided in Chapter 1.
當有品質缺陷（製造瑕疵、產品變質、發現仿冒品、不符合上市許可或產品規格檔案或任何其他嚴重品質問題）的情況下，可能導致藥品或研究用藥品回收或供應方面的異常限制時，應及時通知所有相關之主管機關。在市場上之產品被發現不符合上市許可的情況下，需要通知相關主管機關。請參考相關法規要求。	All concerned Competent Authorities should be informed in a timely manner in case of a confirmed quality defect (faulty manufacture, product deterioration, detection of falsification, non-compliance with the marketing authorisation or product specification file, or any other serious quality problems) with a medicinal or investigational medicinal product which may result in the recall of the product or an abnormal restriction in the supply. In situations where product on the market is found to be non-compliant with the marketing authorisation, there may be a requirement to notify concerned Competent Authorities. Reference should be made to relevant legislative requirements.

若有委外活動，合約應描述製造廠、上市許可持有者及/或委託者以及任何其他相關之第三方，在缺陷產品之評估、決策、傳播資訊與實施風險減低行動方面的角色及責任。有關合約的指引提供於第七章。該等合約亦應敘述如何聯繫品質缺陷管理及回收議題之各方責任者。	In case of outsourced activities, a contract should describe the role and responsibilities of the manufacturer, the marketing authorisation holder and/or sponsor and any other relevant third parties in relation to assessment, decision-making, and dissemination of information and implementation of risk-reducing actions relating to a defective product. Guidance in relation to contracts is provided in Chapter 7. Such contracts should also address how to contact those responsible at each party for the management of quality defect and recall issues.
人事與組織（PERSONNEL AND ORGANISATION）	
8.1 應由經過適當訓練及有經驗之人員，負責管理申訴與品質缺陷之調查，並決定採取之措施以管理由這些問題（包括回收）所帶來的任何潛在風險。除非有其他理由，這些人員應與銷售部門相互獨立。如果這些人員未包括所涉相關批次（一批或多批）放行證明之被授權人，被授權人應及時正式地執行任何調查、任何風險減低行動及任何回收作業。	8.1 Appropriately trained and experienced personnel should be responsible for managing complaint and quality defect investigations and for deciding the measures to be taken to manage any potential risk(s) presented by those issues, including recalls. These persons should be independent of the sales and marketing organisation, unless otherwise justified. If these persons do not include the Authorised Person involved in the certification for release of the concerned batch or batches, the latter should be made formally aware of any investigations, any risk-reducing actions and any recall operations, in a timely manner.
8.2 對於申訴與品質缺陷的處理、評估、調查及檢討，以及實施任何風險減低行動，應有足夠經訓練的人員與資源。對於與主管機關互動之管理，亦應有足夠經訓練的人員與資源。	8.2 Sufficient trained personnel and resources should be made available for the handling, assessment, investigation and review of complaints and quality defects and for implementing any risk-reducing actions. Sufficient trained personnel and resources should also be available for the management of interactions with Competent Authorities.

8.3 應考慮使用跨領域的團隊，包括經適當訓練的品質管理人員在內。	8.3 The use of inter-disciplinary teams should be considered, including appropriately trained Quality Management personnel.
8.4 當申訴與品質缺陷處理在組織內由中央統籌管理的情況下，相關各方的相關角色與職責應加以文件化。但是，中央統籌管理不應導致該問題調查及管理的延誤。	8.4 In situations in which complaint and quality defect handling is managed centrally within an organisation, the relative roles and responsibilities of the concerned parties should be documented. Central management should not, however, result in delays in the investigation and management of the issue.
處理與調查申訴包括可能之品質缺陷在內的程序（PROCEDURES FOR HANDLING AND INVESTIGATING COMPLAINTS INCLUDING POSSIBLE QUALITY DEFECTS）	
8.5 應有書面程序說明接獲申訴時所要採取之行動。所有申訴應加以文件化及評估，以確定是否代表潛在的品質缺陷或其他問題。	8.5 There should be written procedures describing the actions to be taken upon receipt of a complaint. All complaints should be documented and assessed to establish if they represent a potential quality defect or other issue.
8.6 應特別注意確定申訴或疑似品質缺陷是否與偽造有關。	8.6 Special attention should be given to establishing whether a complaint or suspected quality defect relates to falsification.
8.7 由於公司接獲之所有申訴並非均代表實際的品質缺陷，故未指出潛在品質缺陷之申訴應予適當地文件化，並傳達給負責調查與管理這類申訴的相關團隊或人員，例如疑似不良事件。	8.7 As not all complaints received by a company may represent actual quality defects, complaints which do not indicate a potential quality defect should be documented appropriately and communicated to the relevant group or person responsible for the investigation and management of complaints of that nature, such as suspected adverse events.
8.8 為了支持調查所提報的疑似不良事件，應具備程序以利要求調查該批藥品的品質。	8.8 There should be procedures in place to facilitate a request to investigate the quality of a batch of a medicinal product in order to support an investigation into a reported suspected adverse event.
8.9 當啟動品質缺陷調查時，應具備程序以解決至少下列事項：	8.9 When a quality defect investigation is initiated, procedures should be in place to address at least the following:

i	所提報之品質缺陷的描述。	i	The description of the reported quality defect.
ii	品質缺陷程度的判定。對照及/或留存樣品之檢查或檢驗應被視為其中的一部分，在某些情況下，應執行批次製造紀錄、批次認可紀錄及批次運銷紀錄（特別是對溫度敏感的產品）之檢討。	ii	The determination of the extent of the quality defect. The checking or testing of reference and/or retention samples should be considered as part of this, and in certain cases, a review of the batch production record, the batch certification record and the batch distribution records (especially for temperature-sensitive products) should be performed.
iii	需要向申訴人索取有缺陷產品的樣品或者退回品，並且在有提供樣品時，需要進行適當的評估。	iii	The need to request a sample, or the return, of the defective product from the complainant and, where a sample is provided, the need for an appropriate evaluation to be carried out.
iv	基於品質缺陷的嚴重性及程度，評估品質缺陷造成的風險。	iv	The assessment of the risk(s) posed by the quality defect, based on the severity and extent of the quality defect.
v	關於在運銷網中，可能需要採取風險減低行動（如批次或產品回收）或其他行動的決策過程。	v	The decision-making process that is to be used concerning the potential need for risk-reducing actions to be taken in the distribution network, such as batch or product recalls, or other actions.
vi	受回收行動影響之任何市場，對病人藥品可得性衝擊之評估，並應將該衝擊通知相關主管機關。	vi	The assessment of the impact that any recall action may have on the availability of the medicinal product to patients/animals in any affected market, and the need to notify the relevant authorities of such impact.
vii	應就品質缺陷進行內部及外部之溝通與調查。	vii	The internal and external communications that should be made in relation to a quality defect and its investigation.
viii	識別品質缺陷的潛在根本原因。	viii	The identification of the potential root cause(s) of the quality defect.

ix 需要對該問題識別與執行適當矯正與預防行動，並評估該等矯正與預防行動之有效性。	ix The need for appropriate Corrective and Preventive Actions (CAPAs) to be identified and implemented for the issue, and for the assessment of the effectiveness of those CAPAs.
調查與決策（INVESTIGATION AND DECISION-MAKING）	
8.10 所提報與可能之品質缺陷有關的資訊應予記錄，包括所有的原始細節在內。為支持所採取之相關調查及採取行動程度的決定，所有提報之品質缺陷的正確性及範圍應依照品質風險管理原則加以文件化與評估。	8.10 The information reported in relation to possible quality defects should be recorded, including all the original details. The validity and extent of all reported quality defects should be documented and assessed in accordance with Quality Risk Management principles in order to support decisions regarding the degree of investigation and action taken.
8.11 任一批次中如發現或懷疑有品質瑕疵時，應考慮檢查其他批次，或在某些情況下檢查其他產品，以確定其是否也受到影響。特別是可能含有該瑕疵批次之部分或瑕疵組成物的其他批次應加以調查。	8.11 If a quality defect is discovered or suspected in a batch, consideration should be given to checking other batches and in some cases other products, in order to determine whether they are also affected. In particular, other batches which may contain portions of the defective batch or defective components should be investigated.
8.12 品質缺陷調查應包括對過去品質缺陷報告或任何其他相關資訊的檢討，以發現需注意及可能進一步採取法規行動之特定或重發性問題的任何跡象。	8.12 Quality defect investigations should include a review of previous quality defect reports or any other relevant information for any indication of specific or recurring problems requiring attention and possibly further regulatory action.
8.13 在品質缺陷調查過程中及其之後所作出之決定應反映品質缺陷所呈現的風險程度，以及不符合上市許可/產品規格檔案或 GMP 要求的嚴重性。該決定應是及時的並採用與該些問題所呈現之風險程度相稱的方式，以確保病患的安全。	8.13 The decisions that are made during and following quality defect investigations should reflect the level of risk that is presented by the quality defect as well as the seriousness of any non-compliance with respect to the requirements of the marketing authorisation/product specification file or GMP. Such decisions should be timely to ensure that patient and animal safety is maintained, in a way that is commensurate with the level of risk that is presented by those issues.

8.14 由於品質缺陷之性質及程度的全面資訊可能並非總是在調查早期階段可取得，因此在該調查中決策過程仍應確保在適當的時間點採取適當的風險減低行動。所有因品質缺陷而採取之決策與措施皆應加以文件化。	8.14 As comprehensive information on the nature and extent of the quality defect may not always be available at the early stages of an investigation, the decision-making processes should still ensure that appropriate risk-reducing actions are taken at an appropriate time-point during such investigations. All the decisions and measures taken as a result of a quality defect should be documented.
8.15 當品質缺陷可能造成產品回收或產品供應異常限制的情況下，製造廠應及時向上市許可持有者/委託者及所有相關主管機關提報品質缺陷。	8.15 Quality defects should be reported in a timely manner by the manufacturer to the marketing authorisation holder/sponsor and all concerned Competent Authorities in cases where the quality defect may result in the recall of the product or in an abnormal restriction in the supply of the product.
根本原因分析及矯正與預防行動（ROOT CAUSE ANALYSIS AND CORRECTIVE AND PREVENTATIVE ACTIONS）	
8.16 在品質缺陷調查過程中應進行適當程度之根本原因分析工作。若無法確定品質缺陷的根本原因，應考慮識別出最可能的根本原因並解決這些問題。	8.16 An appropriate level of root cause analysis work should be applied during the investigation of quality defects. In cases where the true root cause(s) of the quality defect cannot be determined, consideration should be given to identifying the most likely root cause(s) and to addressing those.
8.17 懷疑或識別人為錯誤為造成品質缺陷的原因時，應正式證明其合理性並小心謹慎，以確保未曾忽略製程、程序或基於系統的錯誤或問題（若存在時）。	8.17 Where human error is suspected or identified as the cause of a quality defect, this should be formally justified and care should be exercised so as to ensure that process, procedural or system-based errors or problems are not overlooked, if present.
8.18 因應品質缺陷應識別並採取合適之矯正與預防行動。應監測並評估該等行動的有效性。	8.18 Appropriate CAPAs should be identified and taken in response to a quality defect. The effectiveness of such actions should be monitored and assessed.
8.19 為需注意特定或重發性問題的任何跡象，應檢討品質缺陷紀錄，且應定期執行趨勢分析。	8.19 Quality defect records should be reviewed and trend analyses should be performed regularly for any indication of specific or recurring problems requiring attention.

產品回收與其他可能之風險減低行動 （PRODUCT RECALLS AND OTHER POTENTIAL RISK-REDUCING ACTIONS）	
8.20 為進行任何回收作業或執行任何其他風險減低行動，應建立書面的程序並定期檢討，且於必要時予以更新。	8.20 There should be established written procedures, regularly reviewed and updated when necessary, in order to undertake any recall activity or implement any other risk-reducing actions.
8.21 產品投放市場後，由於品質缺陷而從運銷網中之任何取回，應視為回收並以回收管理。（此條款不適用於從運銷網中取回（或退回）之產品樣本，以便於調查品質缺陷之問題/提報。）	8.21 After a product has been placed on the market, any retrieval of it from the distribution network as a result of a quality defect should be regarded and managed as a recall. (This provision does not apply to the retrieval (or return) of samples of the product from the distribution network to facilitate an investigation into a quality defect issue/report.)
8.22 回收作業應能快速且在任何時候啟動。在某些情況下可能需要啟動回收作業，以在確定品質缺陷的根本原因和充分程度之前保護民眾健康。	8.22 Recall operations should be capable of being initiated promptly and at any time. In certain cases recall operations may need to be initiated to protect public or animal health prior to establishing the root cause(s) and full extent of the quality defect.
8.23 批次/產品運銷紀錄應易為負責回收的人員取得，且應包含關於批發商與直接供應之客戶的充分資訊（連同地址、上、下班時間的電話/傳真號碼、送交的批次與數量），包含輸出的產品與醫療用樣品在內。	8.23 The batch/product distribution records should be readily available to the persons responsible for recalls, and should contain sufficient information on wholesalers and directly supplied customers (with addresses, phone and/or fax numbers inside and outside working hours, batches and amounts delivered), including those for exported products and medical samples.

8.24 對於研究用藥品，應確認所有試驗場所，並指明目的地國家。對於已獲得上市許可的研究用藥品，其製造廠應與試驗委託者合作，將任何可能與經許可之藥品有關的品質缺陷告知上市許可持有者。試驗委託者應實施盲性產品之快速解盲的程序，這是快速回收的必要條件。試驗委託者應確保該程序僅在必要的範圍披露盲性產品識別性。	8.24 In the case of investigational medicinal products, all trial sites should be identified and the countries of destination should be indicated. In the case of an investigational medicinal product for which a marketing authorisation has been issued, the manufacturer of the investigational medicinal product should, in cooperation with the sponsor, inform the marketing authorisation holder of any quality defect that could be related to the authorised medicinal product. The sponsor should implement a procedure for the rapid unblinding of blinded products, where this is necessary for a prompt recall. The sponsor should ensure that the procedure discloses the identity of the blinded product only in so far as is necessary.
8.25 考慮到民眾健康的潛在風險與建議回收行動可能產生的任何影響，在與相關主管機關研商後，應考慮回收作業須延伸至運銷網之範圍。缺陷之批次由於批次到期（例如具短架儲期的產品）而不提出回收行動的情況下，應通知主管機關。	8.25 Consideration should be given following consultation with the concerned Competent Authorities, as to how far into the distribution network a recall action should extend, taking into account the potential risk to public or animal health and any impact that the proposed recall action may have. The Competent Authorities should also be informed in situations in which no recall action is being proposed for a defective batch because the batch has expired (such as with short shelf-life products.)

8.26 在產品預定回收的情況下，應事先通知所有相關主管機關。對於非常嚴重的問題（即可能嚴重影響病患健康），可能需要在通知主管機關之前採取快速風險減低行動（如產品回收）。可行時，應嘗試於執行前與相關主管機關商定。	8.26 All concerned Competent Authorities should be informed in advance in cases where products are intended to be recalled. For very serious issues (i.e. those with the potential to seriously impact upon patient or animal health), rapid risk-reducing actions (such as a product recall) may have to be taken in advance of notifying the Competent Authorities. Wherever possible, attempts should be made to agree these in advance of their execution with the concerned Competent Authorities.
8.27 應考慮提出之回收作業是否可能以不同的方式影響不同的市場，若在這種情況下，則應制定適當之市場專一性的風險減低行動，並與相關主管機關討論。考慮到其治療用途，在決定風險減低行動（例如回收）之前，應考慮無已許可之替代品的缺藥風險。任何不執行原本所需之風險減低行動的決定都應事先由主管機關同意。	8.27 It should also be considered whether the proposed recall action may affect different markets in different ways, and if this is the case, appropriate market-specific risk-reducing actions should be developed and discussed with the concerned Competent Authorities. Taking account of its therapeutic use the risk of shortage of a medicinal product which has no authorised alternative should be considered before deciding on a risk-reducing action such as a recall. Any decisions not to execute a risk-reducing action which would otherwise be required should be agreed with the Competent Authority in advance.
8.28 回收的產品在等候決定其最終處置方式的期間中，應予識別與標示並隔離儲存於確保安全之區域。所有回收的批次應正式處置，並文件化。將回收產品再加工之任何決定的理論基礎應予文件化並與相關主管機關討論。欲投放市場之任何經再加工批次產品的剩餘架儲期應予考慮。	8.28 Recalled products should be identified and stored separately in a secure area while awaiting a decision on their fate. A formal disposition of all recalled batches should be made and documented. The rationale for any decision to rework recalled products should be documented and discussed with the relevant Competent Authority. The extent of shelf-life remaining for any reworked batches that are being considered for placement onto the market should also be considered.

8.29 回收過程之進度應予記錄直到結束並提出最終報告。該報告應包含送交與收回相關產品/批次的數量調和。	8.29 The progress of the recall process should be recorded until closure and a final report issued, including a reconciliation between the delivered and recovered quantities of the concerned products/batches.
8.30 回收作業之安排的有效性應予定期評估，以確保其穩健並適合使用。該等評估應同時涵蓋上班時段及下班時段，且進行該等評估時，應考慮是否應該執行模擬回收行動。此評估應被文件化並證明其合理性。	8.30 The effectiveness of the arrangements in place for recalls should be periodically evaluated to confirm that they remain robust and fit for use. Such evaluations should extend to both within office-hour situations as well as out-of-office hour situations and, when performing such evaluations, consideration should be given as to whether mock-recall actions should be performed. This evaluation should be documented and justified.
8.31 為了管理品質缺陷所呈現的風險，除回收外，亦可考慮其他可能之風險減低行動。該等行動可能包括向健康照護專業人員發送關於使用可能有缺陷之批次的警示性溝通。這些應由不同個案之基礎加以考慮，並與相關主管機關進行討論。	8.31 In addition to recalls, there are other potential risk-reducing actions that may be considered in order to manage the risks presented by quality defects. Such actions may include the issuance of cautionary communications to healthcare professionals in relation to their use of a batch that is potentially defective. These should be considered on a case-by-case basis and discussed with the concerned Competent Authorities.

第九章 自我查核（SELF INSPECTION）

原則（PRINCIPLE）			
	為監測優良製造規範原則之實施與遵守，應執行自我查核，並就必要的矯正措施提出建議。		Self inspections should be conducted in order to monitor the implementation and compliance wit(with) Good Manufacturing Practice principles and to propose necessary corrective measures.
9.1	人事、廠房、設施、設備、文件、生產、品質管制、藥品的運銷、有關申訴與回收的安排，以及自我查核，皆應依預先安排之計畫的間隔時間進行檢查，以便證實其符合品質保證的原則。	9.1	Personnel matters, premises, equipment, documentation, production, quality control, distribution of the medicinal products, arrangements for dealing with complaints and recalls, and self inspection, should be examined at intervals following a pre-arranged programme in order to verify their conformity with the principles of Quality Assurance.
9.2	自我查核應由公司指定能勝任的人員，以獨立且詳細的方式執行。外部專家的獨立稽核可能也是有用的。	9.2	Self inspections should be conducted in an independent and detailed way by designated competent person(s) from the company. Independent audits by external experts may also be useful.
9.3	所有自我查核應予記錄。報告應包含在檢查期間所執行之所有觀察，合適時，並含矯正措施的建議。後續採取之行動的說明亦應予記錄。	9.3	All self inspections should be recorded. Reports should contain all the observations made during the inspections and, where applicable, proposals for corrective measures. Statements on the actions subsequently taken should also be recorded.

附則 1　無菌藥品的製造（MANUFACTURE OF STERILE MEDICINAL PRODUCTS）

文件結構	
章節	一般概述
1.範圍	本附則之一般原則可以應用到無菌產品外的其他領域。
2.原則	適用於無菌產品製造的一般原則。
3.製藥品質系統	強調 PQS 應用於無菌產品時的具體要求。
4.廠房設施	關於廠房設施設計之特定需求的一般指引，並包括使用屏障技術的廠房設施之驗證指引。
5.設備	設備設計及操作的一般指引。
6.公用設施	關於公用設施（例如水、氣體及真空）的特殊要求的指引。
7.組織與人事	關於特定訓練、知識及技能要求的指引。還給予人員驗證指引。
8.生產及特定技術	關於無菌及最終滅菌過程所採取方法的指引。 關於產品、設備及包裝組件滅菌方法的指引。 還適用於不同技術之特定要求提供指引，例如凍乾技術（lyophilization）及成型-充填-密封技術（ Form-Fill-Seal）。
9.環境與製程監測	本節與第 4 節的指引不同，此處的指引適用於持續例行監測有關的系統設計，設定行動限量與警戒水準以及趨勢數據審查。 本節還提供有關無菌製程模擬（APS） 要求的指引。
10.品質管制	有關無菌產品品質管制的一些特定要求的指引。
11.詞彙	對特定術語的解釋

Document map	
Section Number	General overview
1.Scope	Includes additional areas (other than sterile products) where the general principles of the annex can be applied
2.Principle	General principles as applied to the manufacture of sterile products.
3.Pharmaceutical Quality System (PQS)	Highlights the specific requirements of the PQS when applied to sterile products.
4.Premises	General guidance regarding the specific needs for premises design and also guidance on the qualification of premises including the use of Barrier Technology.
5.Equipment	General guidance on the design and operation of equipment.
6.Utilities	Guidance regarding the special requirements of utilities such as water, gas and vacuum.
7.Personnel	Guidance on the requirements for specific training, knowledge and skills. Also gives guidance regarding the qualification of personnel.
8.Production and specific technologies	Guidance on the approaches to be taken regarding aseptic and terminal sterilization processes. Guidance on the approaches to sterilization of products, equipment and packaging components. Also guidance on different technologies such as lyophilization and Form-Fill-Seal where specific requirements apply.
9.Environmental and process monitoring	This section differs from guidance given in section 4 in that the guidance here applies to ongoing routine monitoring regarding the design of systems and setting of action limits alert levels and reviewing trend data. The section also gives guidance on the requirements of Aseptic Process Simulations (APS).
10.Quality control (QC)	Guidance on some of the specific Quality Control requirements relating to sterile products.
11.Glossary	Explanation of specific terminology.

1.範圍 (Scope)	
無菌產品之製造涵蓋廣泛的無菌產品類型（包括原料藥、賦形劑、直接包裝材料及成品劑型）、包裝規格（由單一到多單元包裝）、製程（從高度自動化系統到手工製程）及技術（例如生物技術、傳統小分子製造系統及密閉系統）。本附則提供的一般指引應被用於設計及控制所有無菌產品製造的廠房設施、設備、系統及程序，並使用品質風險管理（QRM）原則，確保最終產品不受到微生物、微粒及內毒素/熱原的污染。	The manufacture of sterile products covers a wide range of sterile product types (active substance, excipient, primary packaging material and finished dosage form), packed sizes (single unit to multiple units), processes (from highly automated systems to manual processes) and technologies (e.g. biotechnology, classical small molecule manufacturing systems and closed systems). This Annex provides general guidance that should be used in the design and control of facilities, equipment, systems and procedures used for the manufacture of all sterile products applying the principles of Quality Risk Management (QRM), to ensure that microbial, particulate and endotoxin/pyrogen contamination is prevented in the final product.
QRM 完全適用於本文件各章節，通常不會於特定段落中再提及。在指出特定限量、頻率或範圍的地方，這些應被視為最低要求；之所以加以陳述，是基於監管經驗識別出且影響患者安全的歷史事件。	QRM applies to this document in its entirety and will not, normally, be referred to in specific paragraphs. Where specific limits or frequencies or ranges are specified, these should be considered as a minimum requirement. They are stated due to historical regulatory experience of issues that have been identified and have impacted the safety of patients.
本附則的目的是為無菌產品的製造提供指引。然而，一些原則及指引，如污染管制策略、廠房設施設計、潔淨室分級、驗證、確效、監測及人員著衣，可能用於支持其他非無菌產品的製造，例如管制及減少微生物、微粒及內毒素/熱原的污染也被認為重要的某些液劑、乳膏、軟膏及低負荷菌的生物中間產物。如果製造廠選擇將此指引應用於非無菌產品，則製造廠應清楚地記錄已應用哪些原則，並應證明符合這些原則。	The intent of the Annex is to provide guidance for the manufacture of sterile products. However, some of the principles and guidance, such as contamination control strategy, design of premises, cleanroom classification, qualification, validation, monitoring and personnel gowning, may be used to support the manufacture of other products that are not intended to be sterile such as certain liquids, creams, ointments and low bioburden biological intermediates, but where the control and reduction of microbial, particulate and endotoxin/pyrogen contamination is considered important. Where a manufacturer elects to apply guidance herein to non-sterile products, the manufacturer should clearly document which principles have been applied and acknowledge that compliance with those principles should be demonstrated.
2.原則 (Principle)	

2.1 為使微生物、微粒及內毒素/熱原的污染風險降到最低，無菌產品之製造應受制於特別的要求。下述關鍵領域應予以考慮:	2.1 The manufacture of sterile products is subject to special requirements in order to minimize risks of microbial, particulate and endotoxin/pyrogen contamination. The following key areas should be considered:
i. 廠房設施、設備與製程應經過適當設計，驗證及/或確效，並在適用的情況下，根據西藥藥品優良製造規範 （GMP） 的相關章節進行持續確認。應考慮使用適當的技術（例如限制進入屏障系統 (RABS)、隔離裝置、機器人系統、快速/替代方法及連續監測系統）以增加對產品的保護，使其免受來自諸如人員、原物料及周圍環境等潛在之外來內毒素/熱原、微粒及微生物的污染，並協助快速偵測環境及產品中的潛在污染物。	i. Facility, equipment and process should be appropriately designed, qualified and/or validated and where applicable, subjected to ongoing verification according to the relevant sections of the Good Manufacturing Practices (GMP) guide. The use of appropriate technologies (e.g. Restricted Access Barriers Systems (RABS), isolators, robotic systems, rapid/alternative methods and continuous monitoring systems) should be considered to increase the protection of the product from potential extraneous sources of endotoxin/pyrogen, particulate and microbial contamination such as personnel, materials and the surrounding environment, and assist in the rapid detection of potential contaminants in the environment and the product.
ii. 人員應具有充分的資格及經驗、訓練及行為，特別關注在製造、包裝及運銷過程中保護無菌產品所涉及的原則。	ii. Personnel should have adequate qualifications and experience, training and behaviour with a specific focus on the principles involved in the protection of sterile product during the manufacturing, packaging and distribution processes.
iii. 無菌產品製造的過程及監測系統應由具有適當製程、工程及微生物學知識的人員設計、試運轉、驗證、監測及定期審查。	iii. Processes and monitoring systems for sterile product manufacture should be designed, commissioned, qualified, monitored and regularly reviewed by personnel with appropriate process, engineering and microbiological knowledge.
iv. 原料及包裝材料應得到充分管制及測試，以確保其負荷菌及內毒素/熱原水準適合使用。	iv. Raw materials and packaging materials should be adequately controlled and tested to ensure that level of bioburden and endotoxin/pyrogen are suitable for use.

2.2 製程、設備、設施及製造活動應按照 QRM 原則進行管理，以提供主動識別、科學評估及管制潛在品質風險的方法。在使用替代方法的情況下，這些方法應有適當合理證明、風險評估及風險減輕的支持，並應符合本附則的旨意。首先，QRM 應運用於包括廠房設施、設備及流程的適當設計，然後是導入經過良好設計的程序，最後是監測系統的應用，以此作為證明設計及程序已正確實施並且繼續地表現符合預期。僅依靠監測或測試並不能保證無菌。	2.2 Processes, equipment, facilities and manufacturing activities should be managed in accordance with QRM principles to provide a proactive means of identifying, scientifically evaluating and controlling potential risks to quality. Where alternative approaches are used, these should be supported by appropriate rationale, risk assessment and mitigation, and should meet the intent of this Annex.In the first instance, QRM priorities should include appropriate design of the facility, equipment and processes, followed by the implementation of well-designed procedures, and finally application of monitoring systems as the element that demonstrates that the design and procedures have been correctly implemented and continue to perform in line with expectations. Monitoring or testing alone does not give assurance of sterility.
2.3 污染管制策略 (CCS) 應於全廠實施，以規範所有關鍵管制點並評估所有控制（設計、程序、技術及組織(程序 ICH Q7)上的）及監測措施的有效性，以管理藥品品質及安全的風險。CCS 的整合策略應建立穩健的預防污染保證。CCS 應予積極審查，在適當的情況下進行更新，並應推動製造及管制方法的持續改善。其有效性應成為定期管理審查的一部分。如果現有的管制系統已經到位並得到適當的管理，這些系統可能不需要被取代，但應在 CCS 中引述，並且應了解相關聯系統之間的相互作用。	2.3 A Contamination Control Strategy (CCS) should be implemented across the facility in order to define all critical control points and assess the effectiveness of all the controls (design, procedural, technical and organisational) and monitoring measures employed to manage risks to medicinal product quality and safety. The combined strategy of the CCS should establish robust assurance of contamination prevention. The CCS should be actively reviewed and, where appropriate, updated and should drive continual improvement of the manufacturing and control methods. Its effectiveness should form part of the periodic management review. Where existing control systems are in place and are appropriately managed, these may not require replacement but should be referenced in the CCS and the associated interactions between systems should be understood.
2.4 污染控制以及為最大限度降低源自微生物、內毒素/熱原及微粒之污染風險而採取的步驟，它包括一系列相互關聯的事件及措施。這些通常是個別評估、管制及監測的，但它們的總體有效性應一併考慮。	2.4 Contamination control and steps taken to minimize the risk of contamination from microbial, endotoxin/pyrogen and particle sources includes a series of interrelated events and measures. These are typically assessed, controlled and monitored individually but their collective effectiveness should be

	considered together.
2.5 CCS 的建立需要詳細的技術及製程知識。潛在的污染源可歸因於微生物及細胞碎片（例如熱原、內毒素）以及微粒（例如玻璃及其他可目視及不可目視微粒）。 CCS 中要考慮的要素應包括（但不限於）：	2.5 The development of the CCS requires detailed technical and process knowledge. Potential sources of contamination are attributable to microbial and cellular debris (e.g. pyrogen, endotoxin) as well as particulate (e.g. glass and other visible and sub-visible particles). Elements to be considered within a CCS should include (but are not limited to):
i. 工廠及流程的設計，包括相關文件；	i. design of both the plant and processes including the associated documentation;
ii. 廠房設施及設備；	ii. premises and equipment;
iii. 組織與人事；	iii. personnel;
iv. 公用設施；	iv. utilities;
v. 原料管制—包括製程中管制；	v. raw material controls – including in-process controls;
vi. 產品容器及封蓋；	vi. product containers and closures;
vii. 供應商核准—諸如關鍵組件供應商、組件滅菌及一次性使用系統 (SUS) 以及關鍵服務提供商；	vii. vendor approval – such as key component suppliers, sterilisation of components and single use systems (SUS), and critical service providers;
viii. 委外活動及雙方之間關鍵資訊之取得/移轉的管理，例如委託滅菌服務；	viii. management of outsourced activities and availability/transfer of critical information between parties, e.g. contract sterilisation services;
ix. 製程風險管理；	ix. process risk management;
x. 製程確效；	x. process validation;
xi. 滅菌製程的確效；	xi. validation of sterilisation processes;
xii. 預防性維護保養—將設備、公用設施及廠房設施（計畫內及計畫外的維護保養）保養到確保沒有額外污染風險的標準；	xii. preventative maintenance – maintaining equipment, utilities and premises (planned and unplanned maintenance) to a standard that will ensure there is no additional risk of contamination;
xiii. 清潔及消毒；	xiii. cleaning and disinfection;
xiv. 監測系統—包括評估導入科學合理的替代方法以優化環境污染偵測的可行性；	xiv. monitoring systems - including an assessment of the feasibility of the introduction of scientifically sound, alternative methods that optimize the detection of environmental contamination;
xv. 預防機制—趨勢分析、詳細調查、根本原因確定、矯正及預防措施 (CAPA) 以及對綜合調查工具的需求；	xv. prevention mechanisms – trend analysis, detailed investigation, root cause determination, corrective and preventive actions (CAPA) and the need for comprehensive investigational tools;
xvi. 基於上述資訊的持續改進。	xvi. continuous improvement based on

	information derived from the above.
2.6 CCS 應考慮污染管制的所有面向，並進行持續及定期審查，從而在適當時更新製藥品質系統。對現有系統的變更應在實施前後評估對 CCS 的任何影響。	2.6 The CCS should consider all aspects of contamination control with ongoing and periodic review resulting in updates within the pharmaceutical quality system as appropriate. Changes to the systems in place should be assessed for any impact on the CCS before and after implementation.
2.7 製造廠應採取所有必要的步驟及預防措施，以確保在其設施內生產之產品的無菌性。無菌性或其他品質層面不得僅仰賴於最終製程或最終產品的檢驗。	2.7 The manufacturer should take all steps and precautions necessary to assure the sterility of the products manufactured within its facilities. Sole reliance for sterility or other quality aspects should not be placed on any terminal process or finished product test.
3.製藥品質系統 (Pharmaceutical Quality System, PQS)	
3.1 無菌產品的製造是一項複雜的活動，需要特定的管制及措施來確保所生產產品的品質。因此，製造廠的 PQS 應涵蓋並解決無菌產品製造的具體要求，並確保所有活動都得到有效管制，從而將無菌產品中微生物、微粒及內毒素/熱原污染的風險降至最低。除了 GMP 指引(第一部分-藥品基本要求) 第 1 章詳述的 PQS 要求外，無菌產品製造的 PQS 還應確保：	3.1 The manufacture of sterile products is a complex activity that requires specific controls and measures to ensure the quality of products manufactured. Accordingly, the manufacturer's PQS should encompass and address the specific requirements of sterile product manufacture and ensure that all activities are effectively controlled so that the risk of microbial, particulate and endotoxin/pyrogen contamination is minimized in sterile products. In addition to the PQS requirements detailed in Chapter 1 of the GMP Guide (Part I – Basic Requirements for Medicinal Products), the PQS for sterile product manufacture should also ensure that:
i. 一個整合到產品全生命週期的有效風險管理系統，旨在減少微生物污染並確保製造之無菌產品的品質。	i. An effective risk management system is integrated into all areas of the product life cycle with the aim to minimize microbial contamination and to ensure the quality of sterile products manufactured.
ii. 製造廠對所製造之產品以及所採用的對產品品質有影響的設備、工程及製造方法具有足夠的知識及專長。	ii. The manufacturer has sufficient knowledge and expertise in relation to the products manufactured and the equipment, engineering and manufacturing methods employed that have an impact on product quality.
iii. 以正確識別及理解產品風險的方式進行程序、製程或設備失效的根本原因分析，從而實施適當的矯正及預防措施 (CAPA)。	iii. Root cause analysis of procedural, process or equipment failure is performed in such a way that the risk to product is correctly identified and understood so that suitable corrective and preventive actions (CAPA) are implemented.

iv. 風險管理應用於 CCS 的建立及維護，以識別、評估、減少/消除（如適用）及管制污染風險。風險管理應予文件化，並包括有關降低風險及接受殘留風險的決策理由。	iv. Risk management is applied in the development and maintenance of the CCS, to identify, assess, reduce/eliminate (where applicable) and control contamination risks. Risk management should be documented and should include the rationale for decisions taken in relation to risk reduction and acceptance of residual risk.
v. 高階管理層應有效監督整廠及產品生命週期的管制狀態。風險管理結果應定期審查，並在變更期間、在出現重大問題時以及在定期產品品質檢討時，將其結果作為持續品質管理的一部分。	v. Senior management should effectively oversee the state of control throughout the facility and product lifecycle. Risk management outcome should be reviewed regularly as part of the on-going quality management, during change, in the event of a significant emerging problem, and during the periodic product quality review.
vi. 與無菌產品的完成、儲存及運輸相關的過程不應損害無菌產品。應考慮的方面包括：容器完整性、污染及通過確保產品按照查驗登記的儲存條件進行儲存及維護來避免降解的風險。	vi. iProcesses associated with the finishing, storage and transport of sterile products should not compromise the sterile product. Aspects that should be considered include: container integrity, risks of contamination and avoidance of degradation by ensuring that products are stored and maintained in accordance with the registered storage conditions.
vii. 負責無菌產品認可/放行的人員可以適當地使用製造及品質資訊，並在無菌產品的製造及相關的關鍵品質屬性方面擁有足夠的知識及經驗。這是為了讓該等人員確定無菌產品是否按照查驗登記之規格及核准的製程製造及符合所要求的品質。	vii. Persons responsible for the certification/release of sterile products have appropriate access to manufacturing and quality information and possess adequate knowledge and experience in the manufacture of sterile products and the associated critical quality attributes. This is in order to allow such persons to determine if the sterile products have been manufactured in accordance with the registered specifications and approved process and are of the required quality.
3.2 所有不符合項目，例如無菌試驗失敗、環境監測偏差或偏離既定程序，都應在該批的認可/放行之前進行充分調查。調查應確定對製程及產品品質的潛在影響以及是否有任何其他製程或批次受到潛在影響。將某一產品或批次納入或排除在調查範圍內的原因應有明確的理由並記錄。	3.2 All non-conformities, such as sterility test failures, environmental monitoring excursions or deviations from established procedures should be adequately investigated before certification/release of the batch. The investigation should determine the potential impact upon process and product quality and whether any other processes or batches are potentially impacted. The reason for including or excluding a product or batch from the

	scope of the investigation should be clearly justified and recorded.
4.廠房設施 (Premises)	
4.1 無菌產品的製造應在適當的潔淨室中進行，人員進入潔淨室應通過更衣室，更衣室作為人員進入之氣鎖室，如同設備及原物料應經由的氣鎖室。潔淨室及更衣室應維持在適當的潔淨度標準，並提供已通過具適當效率之濾器的空氣。管制及監測應有科學合理證明，及應能有效評估潔淨室、氣鎖室及傳遞箱的環境狀態。	4.1 The manufacture of sterile products should be carried out in appropriate cleanrooms, entry to which should be through change rooms that act as airlocks for personnel and airlocks for equipment and materials. Cleanrooms and change rooms should be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency. Controls and monitoring should be scientifically justified and should effectively evaluate the state of environmental conditions of cleanrooms, airlocks and pass-through hatches.
4.2 組件的準備、產品的製備及充填等不同作業應在潔淨室或設施內採用適當技術面及操作面的隔離措施進行，以防止混雜及污染。	4.2 The various operations of component preparation, product preparation and filling should be carried out with appropriate technical and operational separation measures within the cleanroom or facility to prevent mix up and contamination.
4.3 使用限制性進入屏障系統（RABS）或隔離裝置有利於確保所需之環境條件，並將人員直接介入關鍵性區域導致之微生物污染降到最低。應於 CCS 評估採用前述設備。任何替代使用 RABS 或隔離裝置的方法應證明其合理性。	4.3 Restricted Access Barrier Systems (RABS) or isolators are beneficial in assuring required conditions and minimizing microbial contamination associated with direct human interventions in the critical zone. Their use should be considered in the CCS. Any alternative approaches to the use of RABS or isolators should be justified.
4.4 無菌產品的製造，區分成四個等級的潔淨室/區。	4.4 For the manufacture of sterile products there are four grades of cleanroom/zone.
A 級：高風險作業的關鍵區域，(例如，無菌作業線、充填區、膠塞貯盆、開口的直接包材或是執行受到第一手空氣保護的無菌連接等區域)。通常，此種環境由該處的氣流保護，像是在 RABS 或隔離裝置的單向氣流工作站。單向氣流的維持應予以證明並驗證可涵蓋整個 A 級區域。應透過廠房設施、設備、流程及程序設計，減少作業人員直接（例如，不透過屏障及手套孔技術）介入 A 級區域。	Grade A: The critical zone for high-risk operations (e.g. aseptic processing line, filling zone, stopper bowl, open primary packaging or for making aseptic connections under the protection of first air). Normally, such conditions are provided by a localised airflow protection, such as unidirectional airflow workstations within RABS or isolators. The maintenance of unidirectional airflow should be demonstrated and qualified across the whole of the grade A area. Direct intervention (e.g. without the protection of barrier and glove port technology) into the grade A area by operators should be minimized by

	premises, equipment, process and procedural design.
B 級：對於無菌製備及充填，B 級區作為 A 級區的背景環境(當該 A 級區不是隔離裝置時)。應連續監測壓差。在使用隔離裝置技術的情況下，可以考慮使用低於 B 級的潔淨室（參見第 4.20 點）。	Grade B: For aseptic preparation and filling, this is the background cleanroom for grade A (where it is not an isolator). Air pressure differences should be continuously monitored. Cleanrooms of lower grade than grade B can be considered where isolator technology is used (see paragraph 4.20).
C 級與 D 級：C 級與 D 級區的潔淨室係用於進行無菌充填產品製造中非關鍵性階段或作為隔離裝置之背景環境。最終滅菌產品的製備/充填作業亦可於該區域執行。(有關最終滅菌活動的具體細節，請參見第 8 節)。	Grade C and D: These are cleanrooms used for carrying out less critical stages in the manufacture of aseptically filled sterile products or as a background for isolators. They can also be used for the preparation/filling of terminally sterilised products. (See section 8 for the specific details on terminal sterilisation activities).
4.5 在潔淨室及關鍵區域內，所有暴露的表面均應平滑、不滲透且無破裂，使微粒或微生物的釋出或積聚降到最低。	4.5 In cleanrooms and critical zones, all exposed surfaces should be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particles or micro-organisms.
4.6 為減少粉塵的積聚及利於清潔，不應有難以有效清潔的凹處，因此應儘量減少突出的窗台、儲架、櫃子及設備。門的設計應避免無法清潔的凹處。因此，滑動門可能不合適。	4.6 To reduce accumulation of dust and to facilitate cleaning there should be no recesses that are difficult to clean effectively, therefore projecting ledges, shelves, cupboards and equipment should be kept to a minimum. Doors should be designed to avoid recesses that cannot be cleaned. Sliding doors may be undesirable for this reason.
4.7 潔淨室使用之材料，無論是用於房間的結構還是於房間內使用的物品，都應選擇儘量減少微粒的產生，且可容許重覆使用清潔劑、消毒劑及殺孢劑(如有使用時)。	4.7 Materials used in cleanrooms, both in the construction of the room and for items used within the room, should be selected to minimize generation of particles and to permit the repeated application of cleaning, disinfectant and sporicidal agents where used.
4.8 天花板應設計及密封以防止來自其上方空間的污染。	4.8 Ceilings should be designed and sealed to prevent contamination from the space above them.
4.9 在 A 級區及 B 級區應禁止使用水槽及排水設施。在其他潔淨室中，應在機器、水槽與排水設施之間安裝空氣阻斷裝置。較低等級的潔淨室內，其地板的排水設施應裝配捕集器或水封以從設計上防止逆流，並應定期清潔、消毒及維護。	4.9 Sinks and drains should be prohibited in the grade A and grade B areas. In other cleanrooms, air breaks should be fitted between the machine or sink and the drains. Floor drains in lower grade cleanrooms should be fitted with traps or water seals designed to prevent back flow and should be regularly cleaned, disinfected and maintained.
4.10 設備及原物料轉入及轉出潔淨室及關鍵	4.10 The transfer of equipment and materials into

區域是污染的最大潛在來源之一。任何可能損害潔淨室或關鍵區域潔淨度的活動應加以評估，如果無法完全消除，則應實施適當的管制。	and out of the cleanrooms and critical zones is one of the greatest potential sources of contamination. Any activities with the potential to compromise the cleanliness of cleanrooms or the critical zone should be assessed and if they cannot be eliminated, appropriate controls should be implemented.
4.11 原物料、設備及組件進入 A 級或 B 級區域之轉送應透過單向過程進行。可行時，物品應經過滅菌並通過密封於牆壁中的雙門滅菌器（例如通過雙門高壓滅菌器或去熱原烘箱/隧道）進入該區域。如果物品無法在轉移時進行滅菌，則應確效並實施可達到不會導入污染的相同目標之程序（例如，使用有效的轉移消毒過程、隔離裝置之快速轉移系統，或是氣體或液體原料用的細菌滯留過濾器）。自 A 級及 B 級區域移出的物品（例如原物料、廢棄物、環境樣品）應透過與轉入時不同之單向過程進行。如果無法達成，則應考慮基於時段切換的方法依程序進行移動（原物料進/出），並採取管制措施以避免對轉入物品造成潛在污染。	4.11 The transfer of materials, equipment, and components into the grade A or B areas should be carried out via a unidirectional process. Where possible, items should be sterilised and passed into these areas through double-ended sterilisers (e.g. through a double-door autoclave or depyrogenation oven/tunnel) sealed into the wall. Where sterilisation upon transfer of the items is not possible, a procedure which achieves the same objective of not introducing contamination should be validated and implemented, (e.g. using an effective transfer disinfection process, rapid transfer systems for isolators or, for gaseous or liquid materials, a bacteria-retentive filter). The removal of items from the grade A and B areas (e.g. materials, waste, environmental samples) should be carried out via a separate unidirectional process. If this is not possible, time-based separation of movement (incoming/exiting material) by procedure should be considered and controls applied to avoid potential contamination of incoming items.
4.12 氣鎖室應被設計及用於提供實體隔離，以將不同區域的微生物及微粒污染風險降到最低，並配置在不同等級之間供原物料及人員移動。可行時，供人員進出之氣鎖室應與供原物料移轉之氣鎖室分開。當無法做到這一點，則應考慮基於不同時段依程序分別進行人員或原物料的進出。氣鎖室應以過濾的空氣有效地沖洗，以確保能維持潔淨室之潔淨度等級。在靜態時，氣鎖室最後階段之潔淨度應與將進入之潔淨區的潔淨度等級相同（微生物及總微粒數）。進入與離開 B 級潔淨區，使用各自的更衣室是有必要的。當無法達成，則應考慮基於不同時	4.12 Airlocks should be designed and used to provide physical separation and to minimize microbial and particle contamination of the different areas and should be present for material and personnel moving between different grades. Wherever possible, airlocks used for personnel movement should be separated from those used for material movement. Where this is not practical, time-based separation of movement (personnel/material) by procedure should be considered. Airlocks should be flushed effectively with filtered air to ensure that the grade of the cleanroom is maintained. The final stage of the airlock should, in the “at rest” state, be of the same cleanliness grade

段依程序分別進入/離開。當 CCS 指出具高污染風險，進入及離開生產區域應通過不同的更衣室。氣鎖室應設計如下：	(viable and total particle) as the cleanroom into which it leads. The use of separate change rooms for entering and leaving the grade B area is desirable. Where this is not practical, time-based separation of activities (ingress/egress) by procedure should be considered. Where the CCS indicates that the risk of contamination is high, separate change rooms for entering and leaving production areas should be used. Airlocks should be designed as follows:
i. 人員氣鎖室：供人員進入更高潔淨度之區域（例如，從 D 級區到 C 級區再到 B 級區）。通常，洗手設備應只在更衣室的第一個階段提供，而不應設置在直接進入 B 級區的更衣室中。	i. Personnel airlocks: Areas of increasing cleanliness used for entry of personnel (e.g. from the grade D area to the grade C area to the grade B area). In general hand washing facilities should be provided only in the first stage of the changing room and not be present in changing rooms directly accessing the grade B area.
ii. 原物料氣鎖室：用於原物料及設備的轉送。	ii. Material airlocks: used for materials and equipment transfer.
a. 只有在轉送過程確效期間經過評估並已列入核准清單的原物料及設備，才能經氣鎖室或傳遞箱轉送到 A 級或 B 級區。用於 A 級區的設備及原物料在通過 B 級區時，應予以保護。任何需要例外轉送但未經核准的項目都應經預先核准。其核准應根據製造者的 CCS，實施及記錄適當的風險評估及緩解措施，並應包括由品質保證單位核准的特定消毒及監測計畫。	• Only materials and equipment that have been included on an approved list and assessed during validation of the transfer process, should be transferred into the grade A or grade B areas via an airlock or pass-through hatches. Equipment and materials (intended for use in the grade A area) should be protected when transiting through the grade B area. Any unapproved items that require transfer should be pre-approved as an exception. Appropriate risk assessment and mitigation measures should be applied and recorded as per the manufacturer's CCS and should include a specific disinfection and monitoring programme approved by quality assurance.
b. 傳遞箱應設計為用於保護較高等級的環境，例如主動供應經過濾的空氣進行有效沖洗。	• Pass-through hatches should be designed to protect the higher-grade environment, for example by effective flushing with an active filtered air supply.
c. 原物料或設備從較低等級或未分級區域移動到較高等級潔淨區，應進行與風險相稱並符合 CCS 的清潔及消毒。	• The movement of material or equipment from lower grade or unclassified area to higher grade clean areas should be subject to cleaning and disinfection commensurate with the risk and in line with the CCS.

4.13 對於傳遞箱及氣鎖室（用於原物料及人員），進出之門不應同時開啟。對於通往 A 級及 B 級區域的氣鎖室，應使用互鎖系統。對於通向 C 級及 D 級區域的氣鎖室，應至少使用視覺及/或聽覺警報系統。在需要保持區域隔離的情況下，應建立互鎖門關閉及打開之間的延遲時間。	4.13 For pass-through hatches and airlocks (for material and personnel), the entry and exit doors should not be opened simultaneously. For airlocks leading to the grade A and grade B areas, an interlocking system should be used. For airlocks leading to grade C and D areas, a visual and/or audible warning system should be operated as a minimum. Where required to maintain area segregation, a time delay between the closing and opening of interlocked doors should be established.
4.14 在所有操作條件下，潔淨室應供應經過濾的空氣，並對較低等級的背景環境保持正壓及/或空氣的流動，並應有效的沖洗該區域。不同等級的相鄰潔淨室應具有最小 10 pa（指引值）的壓差。關鍵區域的保護措施應予特別注意。當需要圍堵某些物質，例如致病性的、高毒性的或放射性的產品、活的病毒或細菌原料時，則可能需要修改有關空氣供應及壓力的建議。修改可能包括配置正壓或負壓氣鎖室，以防止有害物質污染周圍區域。對於某些作業，設施（例如潔淨室及空調）的去污染及潔淨室排氣之處理可能是必須的。在圍堵時，又需要空氣流入關鍵區域的情況下，空氣來源應來自相同或更高等級的區域。	4.14 Cleanrooms should be supplied with a filtered air supply that maintains a positive pressure and/or an airflow relative to the background environment of a lower grade under all operational conditions and should flush the area effectively. Adjacent rooms of different grades should have an air pressure difference of a minimum of 10 Pascals (guidance value). Particular attention should be paid to the protection of the critical zone. The recommendations regarding air supplies and pressures may need to be modified where it is necessary to contain certain materials (e.g. pathogenic, highly toxic or radioactive products or live viral or bacterial materials). The modification may include positively or negatively pressurized airlocks that prevent the hazardous material from contaminating surrounding areas. Decontamination of facilities (e.g. the cleanrooms and the heating, ventilation, and air conditioning (HVAC) systems) and the treatment of air leaving a clean area, may be necessary for some operations. Where containment requires air to flow into a critical zone, the source of the air should be from an area of the same or higher grade.
4.15 潔淨室及區域內的空氣流動型態應可視化，以證明空氣不會從較低等級區域流到較高等級區域，並且空氣不會從較不潔淨的區域（例如地板）或通過作業人員或設備流向潔淨等級較高的區域，將污染轉移到潔淨等級較高的區域。如果需要使用單向氣流，則應進行可視化研究以確認其符合性（參見第 4.4 及 4.19	4.15 Airflow patterns within cleanrooms and zones should be visualised to demonstrate that there is no ingress from lower grade to higher grade areas and that air does not travel from less clean areas (such as the floor) or over operators or equipment that may transfer contamination to the higher-grade areas. Where unidirectional airflow is required, visualisation studies should be performed to

點)。當充填後，封閉的產品通過一個小出口轉送到相鄰較低等級的潔淨室，氣流可視化研究應證明該空氣不會從較低等級的潔淨室進入 B 級區域。如果空氣流動被證明對清潔區域或關鍵區域有污染風險，則應採取矯正措施，例如改善設計。空氣流動型態研究應於靜態及動態均執行（例如模擬作業人員的介入)。應保留空氣流動型態的錄影紀錄。在建立設施的環境監測計畫時，應文件化及參考空氣可視化研究的結果。	determine compliance, (see paragraphs 4.4 & 4.19). When filled, closed products are transferred to an adjacent cleanroom of a lower grade via a small egress point, airflow visualization studies should demonstrate that air does not ingress from the lower grade cleanrooms to the grade B area. Where air movement is shown to be a contamination risk to the clean area or critical zone, corrective actions, such as design improvement, should be implemented. Airflow pattern studies should be performed both at rest and in operation (e.g. simulating operator interventions). Video recordings of the airflow patterns should be retained. The outcome of the air visualisation studies should be documented and considered when establishing the facility's environmental monitoring programme.
4.16 潔淨室之間及/或隔離裝置與其背景之間應安裝壓差計。在 CCS 中應考慮壓差的設定值及關鍵性。應連續監測及記錄被界定為關鍵處的壓差。應具備警報系統，以立即顯示及警告作業人員任何空氣供應上的失靈或壓差降低（當其低於被界定為關鍵的設定限值時)。警報信號不應在未經評估的情況下被忽略，並且應該有一個程序來說明發出警報信號時要採取的步驟。如果警報設定了延遲通報，則應以 CCS 對其進行評估及合理證明。其他區域的壓差則應定期監測及記錄。	4.16 Indicators of air pressure differences should be fitted between cleanrooms and/or between isolators and their background. Set-points and the criticality of air pressure differences should be considered within the CCS. Air pressure differences identified as critical should be continuously monitored and recorded. A warning system should be in place to instantly indicate and warn operators of any failure in the air supply or reduction of air pressure differences (below set limits for those identified as critical). The warning signal should not be overridden without assessment and a procedure should be available to outline the steps to be taken when a warning signal is given. Where alarm delays are set, these should be assessed and justified within the CCS. Other air pressure differences should be monitored and recorded at regular intervals.
4.17 設施的設計應允許從 A 級及 B 級區域以外的地方觀察生產活動（例如，通過窗戶或遠端攝影機，可以看到該區域及過程的全貌，以允許在不進入的情況下進行觀察及監督)。在設計新設施或整建現有設施時應考慮這一要求。	4.17 Facilities should be designed to permit observation of production activities from outside the grade A and B areas (e.g. through the provision of windows or remote cameras with a full view of the area and processes to allow observation and supervision without entry). This requirement should be considered when designing new facilities or during refurbishment of existing facilities.

屏障技術	Barrier Technologies
4.18 隔離裝置或 RABS 是不同的技術，與其相關聯的製程，應設計為將 A 級環境與周圍房間的環境隔離以提供保護。製程中，物品進入或移出所帶來的危害應降到最低，並由高性能轉送技術或經過確效的系統提供支持，這些系統可牢靠地防止污染並適用於所相應的技術（指隔離裝置或 RABS）。	4.18 Isolators or RABS, which are different technologies, and the associated processes, should be designed to provide protection through separation of the grade A environment from the environment of the surrounding room. The hazards introduced from entry or removal of items during processing should be minimized and supported by high capability transfer technologies or validated systems that robustly prevent contamination and are appropriate for the respective technology.
4.19 所用技術及製程的設計應確保在關鍵區域維持適當的條件，以在操作過程中保護暴露的產品。	4.19 The design of the technology and processes used should ensure appropriate conditions are maintained in the critical zone to protect the exposed product during operations.
i. 隔離裝置：	i. Isolators:
a. 開放式隔離裝置的設計應確保 A 級條件，在關鍵區域受到第一手空氣保護，且在製造過程中以單向氣流掠過暴露的產品才再排離。	a. The design of open isolators should ensure grade A conditions with first air protection in the critical zone and unidirectional airflow that sweeps over and away from exposed products during processing.
b. 密閉式隔離裝置的設計應確保 A 級條件，在製造過程中對暴露的產品提供適當保護。在進行簡單操作的密閉式隔離裝置中，氣流可能不是完全單向的。但是，任何擾流型式的氣流都不應增加暴露產品的污染風險。如果整個生產線都涵蓋在密閉式隔離裝置中，則應確保在 A 級條件下，關鍵區域受到第一手空氣保護，並且在製造過程中以單向氣流掠過暴露產品才再排離。	b. The design of closed isolators should ensure grade A conditions with adequate protection for exposed products during processing. Airflow may not be fully unidirectional in closed isolators where simple operations are conducted. However, any turbulent airflow should not increase risk of contamination of the exposed product. Where processing lines are included in closed isolators, grade A conditions should be ensured with first air protection in the critical zone and unidirectional airflow that sweeps over and away from exposed products during processing.
c. 負壓隔離裝置僅應在認為必須對產品（例如放射性藥品）進行圍堵時使用，並且應採取特定的風險控制措施以確保關鍵區域不受影響。	c. Negative pressure isolators should only be used when containment of the product is considered essential (e.g. radiopharmaceutical products) and specialized risk control measures should be applied to ensure the critical zone is not compromised.

ii. 限制進入屏障系統 (RABS)：	ii. RABS:
RABS 的設計應確保 A 級條件，在關鍵區域具有單向氣流及第一手空氣的保護。應維持從關鍵區域到背景環境的正向氣流。	The design of RABS should ensure grade A conditions with unidirectional airflow and first air protection in the critical zone. A positive airflow from the critical zone to the supporting background environment should be maintained.
4.20 隔離裝置或 RABS 的背景環境應確保將污染轉移的風險降至最低。	4.20 The background environment for isolators or RABS should ensure the risk of transfer of contamination is minimized.
i. 隔離裝置：	i. Isolators:
a. 開放式隔離裝置的背景環境一般應至少為 C 級。密閉式隔離裝置的背景應至少為 D 級。背景分級應基於風險評估決定，並在 CCS 中闡明其合理性。	a. The background environment for open isolators should generally correspond to a minimum of grade C. The background for closed isolators should correspond to a minimum of grade D. The decision on the background classification should be based on risk assessment and justified in the CCS.
b. 在對隔離裝置的 CCS 進行風險評估時的主要考慮因素應包括（但不限於）：生物去污染程序、自動化程度、手套操作可能危及關鍵製程點的“第一手空氣”保護的影響、可能損失屏障裝置/手套完整性的影響、使用的轉送機制及作業(諸如可能需要在對隔離裝置進行最終生物去污染之前打開門的安裝或維護)。當識別出有額外的製程風險時，除非在 CCS 中適當證明合理性，應考慮使用更高等級的背景。	b. Key considerations when performing the risk assessment for the CCS of an isolator should include (but are not limited to); the bio-decontamination programme, the extent of automation, the impact of glove manipulations that may potentially compromise ‘first air’ protection of critical process points, the impact of potential loss of barrier/glove integrity, transfer mechanisms used and activities such as set-up or maintenance that may require the doors to be opened prior to the final bio-decontamination of the isolator. Where additional process risks are identified, a higher grade of background should be considered unless appropriately justified in the CCS.
c. 應進行開放式隔離裝置交界處之空氣流動型態的研究，以證明沒有空氣侵入。	c. Airflow pattern studies should be performed at the interfaces of open isolators to demonstrate the absence of air ingress.
ii. RABS：	ii. RABS:
用於無菌製備的 RABS 的背景環境應至少為B 級，並且應進行空氣流動型態研究以證明介入期間沒有空氣侵入，適用時，應包括門的開口處。	The background environment for RABS used for aseptic processing, should correspond to a minimum of grade B and airflow pattern studies should be

	performed to demonstrate the absence of air ingress during interventions, including door openings if applicable.
4.21 用於手套系統（指隔離裝置及 RABS）的材料，應證明具有適當的機械及化學耐受性。 手套更換頻率應界定在 CCS 中。	4.21 The materials used for glove systems (for both isolators and RABS) should be demonstrated to have appropriate mechanical and chemical resistance. The frequency of glove replacement should be defined within the CCS.
i. 隔離裝置：	i. Isolators:
a. 對於隔離裝置，手套系統的洩漏測試應使用可證明適用於其任務及重要性的方法進行。應按界定的時間間隔進行測試。 一般來說，手套完整性測試頻率應最少在每批次或連續批生產（campaign）的開始及結束時進行。根據經過確效的連續批生產（campaign）時間長度，可能需要額外的手套完整性測試。手套完整性監測應包括與每次使用及在任何可能影響系統完整性的操作後所進行的目視檢查。對於生產單一單元或小批量的人工無菌製備活動，完整性確認的頻率可能基於其他標準，例如在每一個製造時段的開始及結束時。	a. For isolators, leak testing of the glove system should be performed using a methodology demonstrated to be suitable for the task and criticality. The testing should be performed at defined intervals. Generally glove integrity testing should be performed at a minimum frequency of the beginning and end of each batch or campaign. Additional glove integrity testing may be necessary depending on the validated campaign length. Glove integrity monitoring should include a visual inspection associated with each use and following any manipulation that may affect the integrity of the system. For manual aseptic processing activities where single unit or small batch sizes are produced, the frequency of integrity verification may be based on other criteria, such as the beginning and end of each manufacturing session.
b. 隔離裝置系統的完整性/洩漏測試應按界定的時間間隔進行。	b. Integrity / leak testing of isolator systems should be performed at defined intervals.
ii. RABS：	ii. RABS:
對於 RABS，用於 A 級區域的手套應在安裝前進行滅菌，並在每次產品連續批製造前以確效的方法進行滅菌或有效生物去污染。如果在操作期間暴露於背景環境，則應在每次暴露後使用經核准的方法進行消毒。手套應在每次使用時進行目視檢查，並應定期進行完整性測試。	For RABS, gloves used in the grade A area should be sterilised before installation and sterilised or effectively bio-decontaminated by a validated method prior to each manufacturing campaign. If exposed to the background environment during operation, disinfection using an approved methodology following each exposure should be completed. Gloves should be visually examined with each use, and integrity testing should be performed at

	periodic intervals.
4.22 應適當界定及管制去污染方法（清潔及生物去污染，以及適用時生物材料之去活化）。生物去污染步驟之前的清潔過程是必要的；任何殘留物都可能抑制去污染過程的有效性，並應有證據證明使用的清潔劑及生物去污染劑不會對 RABS 或隔離裝置內生產的產品產生不利影響。	4.22 Decontamination methods (cleaning and bio-decontamination, and where applicable inactivation for biological materials) should be appropriately defined and controlled. The cleaning process prior to the bio-decontamination step is essential; any residues that remain may inhibit the effectiveness of the decontamination process. Evidence should also be available to demonstrate that the cleaning and bio-decontamination agents used do not have adverse impact on the product produced within the RABS or isolator.
i. 對於隔離裝置 其內部的生物去污染過程應自動化、確效及管制在界定的行程參數內，並應包括適當形態的殺孢劑（例如氣態或霧化形式）。手套應適當伸展並將手指分開，以確保與藥劑接觸。使用的方法（清潔及殺孢子的生物去污染）應使隔離裝置的內表面及關鍵區域沒有活的微生物。	i. For isolators The bio-decontamination process of the interior should be automated, validated and controlled within defined cycle parameters and should include a sporicidal agent in a suitable form (e.g. gaseous or vaporized form). Gloves should be appropriately extended with fingers separated to ensure contact with the agent. Methods used (cleaning and sporicidal bio-decontamination) should render the interior surfaces and critical zone of the isolator free from viable microorganisms.
ii. 對於 RABS 殺孢子的消毒應包括例行使用殺孢劑，使用的方法已確效且穩健地證明可以涵蓋內表面的所有區域，並確保為無菌製備提供合適的環境。	ii. For RABS The sporicidal disinfection should include the routine application of a sporicidal agent using a method that has been validated and demonstrated to robustly include all areas of the interior surfaces and ensure a suitable environment for aseptic processing.
潔淨室及潔淨空氣設備驗證	**Cleanroom and clean air equipment qualification**
4.23 用於無菌產品製造之潔淨室及潔淨空氣設備，如單向氣流裝置（UDAFs）、RABS 及隔離裝置，應依所需的環境特性進行驗證。每一製造作業在操作狀態中，均須有適當的環境潔淨度等級，以使處理中之產品或原物料的污染風險降到最低。“靜態”及“動態”狀態下應分別保持適當的潔淨度等級。	4.23 Cleanrooms and clean air equipment such as unidirectional airflow units (UDAFs), RABS and isolators, used for the manufacture of sterile products, should be qualified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate environmental cleanliness level in the operational state in order to minimize the risk of contamination of the product or materials being handled. Appropriate cleanliness levels in the “at rest”

	and “operational” states should be maintained.
4.24 潔淨室及潔淨空氣設備應使用符合附則 15 要求的方法進行驗證。潔淨室驗證（包括分級）應與操作過程的環境監測清楚區分。	4.24 Cleanrooms and clean air equipment should be qualified using methodology in accordance with the requirements of Annex 15. Cleanroom qualification (including classification) should be clearly differentiated from operational environmental monitoring.
4.25 潔淨室及潔淨空氣設備驗證是評估潔淨室或潔淨空氣設備符合其界定之等級及預期用途的整體過程。作為附則 15 的驗證要求的一部分，潔淨室及潔淨空氣設備的驗證應包括（如果與裝置的設計/操作相關時）：	4.25 Cleanroom and clean air equipment qualification is the overall process of assessing the level of compliance of a classified cleanroom or clean air equipment with its intended use. As part of the qualification requirements of Annex 15, the qualification of cleanrooms and clean air equipment should include (where relevant to the design/operation of the installation):
i. 安裝之過濾系統的洩漏及完整性測試，	i. installed filter system leakage and integrity testing,
ii. 氣流測試 -風量及風速，	ii. airflow tests - volume and velocity,
iii. 壓差測試，	iii. air pressure difference test,
iv. 氣流方向測試及其可視化，	iv. airflow direction test and visualisation,
v. 浮游微生物及表面污染，	v. microbial airborne and surface contamination,
vi. 溫度量測測試，	vi. temperature measurement test,
vii. 相對濕度測試，	vii. relative humidity test,
viii. 回復性測試，	viii. recovery test,
ix. 圍堵洩漏測試。	ix. containment leak test.
潔淨室及潔淨空氣設備的驗證可參考 ISO 14644 系列標準。	Reference for the qualification of the cleanrooms and clean air equipment can be found in the ISO 14644 series of standards.
4.26 潔淨室分級是潔淨室驗證的一部分，是一種透過測量潔淨室或潔淨空氣設備的總微粒濃度，再針對其規格評估空氣潔淨度等級的方法。分級應排定時間執行，以避免對製程或產品品質產生任何影響。例如，初始分級應在模擬操作期間進行，而再分級則在模擬操作期間或在無菌製程模擬 （APS） 期間進行。	4.26 Cleanroom classification is part of the cleanroom qualification and is a method of assessing the level of air cleanliness against a specification for a cleanroom or clean air equipment by measuring the total particle concentration. Classification activities should be scheduled and performed in order to avoid any impact on process or product quality. For example, initial classification should be performed during simulated operations and reclassification performed during simulated operations or during aseptic process simulation (APS).
4.27 對於潔淨室分級，應測量等於或大於 0.5 及 5 μm 的微粒總數。該測量應根	4.27 For cleanroom classification, the total of particles equal to or greater than 0.5 and 5 μm

據表 1 中規定的限值同時在靜態及在模擬的動態中進行。

should be measured. This measurement should be performed both at rest and in simulated operations in accordance with the limits specified in Table 1.

表 1：用於分級的最大容許總微粒濃度

等級	每立方公尺等於或大於0.5 μm粒徑之總微粒數的最大限值		每立方公尺等於或大於5 μm粒徑之總微粒數的最大限值	
	靜態	動態	靜態	動態
A	3 520	3 520	未界定(a)	未界定(a)
B	3 520	352 000	未界定(a)	2 930
C	352 000	3 520 000	2 930	29 300
D	3 520 000	未預先訂定(b)	29 300	未預先訂定(b)

(a) 依據 CCS 或歷史趨勢，分級時可以考慮包括 5μm 微粒。

(b) 對於 D 級區，未預先訂定其動態的容許限值。製造廠應根據風險評估及日常數據（適用時）建立動態容許限值。

Table 1: Maximum permitted total particle concentration for classification

Grade	Maximum limits for total particle ≥ 0.5 μm/m^3		Maximum limits for total particle ≥ 5 μm/m^3	
	at rest	in operation	at rest	in operation
A	3 520	3 520	Not specified (a)	Not specified (a)
B	3 520	352 000	Not specified (a)	2 930
C	352 000	3 520 000	2 930	29 300
D	3 520 000	Not predetermined (b)	29 300	Not predetermined (b)

(a) Classification including 5μm particles may be considered where indicated by the CCS or historical trends.

(b) For grade D, in operation limits are not predetermined. The manufacturer should establish in operation limits based on a risk assessment and routine data where applicable.

4.28 對於潔淨室的分級，可參考 ISO 14644 第 1 部分之採樣點的最小數量及其位置。對於無菌操作區域及背景環境（分別為 A 級及 B 級區域），應考慮額外的採樣點，並應評估所有關鍵製程區域，例如充填點及容器封蓋的進料貯盆。關鍵製程位置應由文件化的風險評估及對該區域所執行的製程與操作的知識來決定。

4.28 For classification of the cleanroom, the minimum number of sampling locations and their positioning can be found in ISO 14644 Part 1. For the aseptic processing area and the background environment (the grade A and grade B areas, respectively), additional sample locations should be considered and all critical processing areas such as the point of fill and container closure feeder bowls should be evaluated. Critical processing locations should be determined by documented risk assessment and knowledge of the process and operations to be performed in the area.

4.29 潔淨室分級應在“靜態”及“動態”狀態下進行。

4.29 Cleanroom classification should be carried out in the “at rest” and “in operation” states.

i. “靜態”狀態的定義：所有公用設施的安裝已完成，包括任何正常運行的 HVAC，主要製造設備已按規定安裝但未運轉，並且沒有人員在房間內的情況。

i. The definition of “at rest” state is the condition whereby the installation of all the utilities is complete including any functioning HVAC, with the main manufacturing equipment installed as

	specified but not operating and without personnel present in the room.
ii. “動態”狀態的定義：潔淨室的安裝已完成、HVAC 系統全部運行、設備已安裝並在製造廠界定的操作模式下運轉，且有最大人數在場執行或模擬日常操作的情況。	ii. The definition of “in operation” state is the condition where the installation of the cleanroom is complete, the HVAC system fully operational, equipment installed and functioning in the manufacturer’s defined operating mode with the maximum number of personnel present performing or simulating routine operational work.
iii. 應在完成操作及清線/清潔活動後的“清除”期間達到上表 1 中所訂“靜態”總微粒限值。 “清除”期間（指引值為小於 20 分鐘)應在房間驗證期間確定與記錄。作業中斷時，應依程序執行，以重新回復到已驗證的潔淨狀態。	iii. The total particle limits given in Table 1 above for the “at rest” state should be achieved after a “clean up” period on completion of operations and line clearance/cleaning activities. The "clean up" period (guidance value of less than 20 minutes) should be determined during the qualification of the rooms, documented and adhered to in procedures to reinstate a qualified state of cleanliness if disrupted during operation.
4.30 單向氣流系統供應的風速應在驗證計畫書中明確證明，包括風速測量的位置。風速應予設計、測量及保持，以確保在工作位置有適當的單向空氣流動為產品及開放組件提供保護（例如，發生高風險操作處以及產品及/或組件暴露處）。除非 CCS 另有科學證明，單向氣流系統應在工作位置提供 0.36 – 0.54 m/s 範圍（指引值）內的均勻風速。氣流可視化研究應與風速測量相關。	4.30 The speed of air supplied by unidirectional airflow systems should be clearly justified in the qualification protocol including the location for air speed measurement. Air speed should be designed, measured and maintained to ensure that appropriate unidirectional air movement provides protection of the product and open components at the working position (e.g. where high-risk operations occur and where product and/or components are exposed). Unidirectional airflow systems should provide a homogeneous air speed in a range of 0.36 – 0.54 m/s (guidance value) at the working position, unless otherwise scientifically justified in the CCS. Airflow visualization studies should correlate with the air speed measurement.
4.31 潔淨室的微生物污染程度作為潔淨室驗證的一部分。採樣點的數量應基於文件化的風險評估以及從房間分級、氣流可視化研究以及該區域將要執行的製程與操作的知識所獲得的結果而定。每個級區於驗證期間微生物污染的最大限量見表 2。驗證應包括“靜態”及“動態”兩種狀態。	4.31 The microbial contamination level of the cleanrooms should be determined as part of the cleanroom qualification. The number of sampling locations should be based on a documented risk assessment and the results obtained from room classification, air visualization studies and knowledge of the process and operations to be performed in the area. The maximum limits for microbial

	contamination during qualification for each grade are given in Table 2. Qualification should include both “at rest” and “in operation” states.
表 2：驗證期間最大容許微生物污染程度 **級區** / **空氣樣品 CFU/m³** / **落菌培養皿 (直徑 90 mm) CFU/4 小時 (a)** / **接觸培養皿 (直徑 55 mm) CFU/培養皿** A：無生長 B：10 / 5 / 5 C：100 / 50 / 25 D：200 / 100 / 50	Table 2: Maximum permitted microbial contamination level during qualification **Grade** / **Air sample CFU/m³** / **Settle plates (diameter 90 mm) CFU/4 hours (a)** / **Contact plates (diameter 55 mm) CFU/plate** A: No growth B: 10 / 5 / 5 C: 100 / 50 / 25 D: 200 / 100 / 50
(a) 落菌培養皿應在操作期間暴露並在最多 4 小時後依需要更換。暴露時間應基於復甦研究，且不應使所用的培養基脫水。	(a) Settle plates should be exposed for the duration of operations and changed as required after a maximum of 4 hours. Exposure time should be based on recovery studies and should not allow desiccation of the media used.
註 1：表中針對特定級區列出的所有方法都應用於驗證該特定級區的區域。如果未使用列表中的任何一種方法，或使用了替代方法，則應適當證明所採用的方法是合理的。	Note 1: All methods indicated for a specific grade in the table should be used for qualifying the area of that specific grade. If one of the methods tabulated is not used, or alternative methods are used, the approach taken should be appropriately justified.
註 2:在整份文件中使用 CFU 作為限量的單位。如果使用不同的或新的技術以不同於 CFU 的方式呈現結果，則製造廠應科學地證明該限量的合理性，並在可能的情況下將其與 CFU 相關聯。	Note 2: Limits are applied using CFU throughout the document. If different or new technologies are used that present results in a manner different from CFU, the manufacturer should scientifically justify the limits applied and where possible correlate them to CFU.
註 3：對於人員著衣驗證，應採用表 6 中對接觸培養皿及手套指印的限量。	Note 3: For the qualification of personnel gowning, the limits given for contact plates and glove prints in Table 6 should apply.
註 4：取樣方法不應對製造作業造成污染風險。	Note 4: Sampling methods should not pose a risk of contamination to the manufacturing operations.
4.32 潔淨室及潔淨空氣設備的再驗證應按照規定的程序定期進行。再驗證至少應包括以下內容：	4.32 The requalification of cleanrooms and clean air equipment should be carried out periodically following defined procedures. The requalification should include at a minimum the following:
i. 潔淨室分級（總微粒濃度），	i. cleanroom classification (total particle concentration),

ii. 最終過濾器的完整性測試，	ii. integrity test of final filters,
iii. 風量測量，	iii. airflow volume measurement,
iv. 房室間壓差的確認，	iv. verification of air pressure difference between rooms, and
v. 風速測試	v. air velocity test
（註：對於 B、C 及 D 級，風速測試應根據風險評估進行，並文件化為 CCS 的一部分。但是，對於提供單向氣流的充填區（例如，當充填最終滅菌產品時，或為 A 級區及 RABS 的背景時），風速測試是需要的。對於具有非單向氣流的級區，應以回復性測試的測量替代風速測試）。	(Note: For grade B, C and D the air velocity test should be performed according to a risk assessment documented as part of the CCS. However, it is required for filling zones supplied with unidirectional airflow (e.g. when filling terminally sterilised products or background to grade A and RABS). For grades with non-unidirectional airflow, a measurement of recovery testing should replace velocity testing).
A 級區及 B 級區再驗證的最長時間間隔為 6 個月。	The maximum time interval for requalification of grade A & B areas, is 6 months.
C 級區及 D 級區再驗證的最長時間間隔為 12 個月。	The maximum time interval for requalification of grade C & D areas, is 12 months.
在為矯正不符合規定的設備或設施狀況而實施的補救措施完成後，或在變更設備、設施或製程後(當其適用時)，還應進行至少包括上述試驗的適當再驗證。變更的重要性應由變更管理過程來決定。要考慮的變更範例包括但不限於以下內容：	Appropriate requalification consisting of at least the above tests should also be carried out following completion of remedial action implemented to rectify an out of compliance equipment or facility condition or after changes to equipment, facility or processes as appropriate. The significance of a change should be determined through the change management process. Examples of changes to be considered include but are not limited to the following:
i. 氣流的干擾會影響裝置的運轉。	i. interruption of air movement which affects the operation of the installation,
ii. 改變潔淨室的設計或 HVAC 系統的操作設定參數。	ii. ii. change in the design of the cleanroom or of the operational setting parameters of the HVAC system,
iii. 影響裝置運轉的特殊維護（例如更換最終過濾器）。	iii. special maintenance which affects the operation of the installation (e.g. change of final filters).
消毒	**Disinfection**
4.33 潔淨室的消毒特別重要。應按照書面程序對其進行徹底清潔及消毒。為使消毒有效，應事先進行清潔以去除表面污染。清潔程序應有效去除消毒劑的殘留。應使用一種以上的消毒劑，藉由不同作用方式，以確保其組合使用可有效	4.33 The disinfection of cleanrooms is particularly important. They should be cleaned and disinfected thoroughly in accordance with a written programme. For disinfection to be effective, prior cleaning to remove surface contamination should be performed. Cleaning programmes should effectively remove

的對抗細菌及真菌。消毒應包括定期使用殺孢劑。應定期進行監測，以評估消毒程序的有效性並偵測常在菌類型的變化（例如，微生物對目前使用的消毒方案具耐受性）。	disinfectant residues. More than one type of disinfecting agent should be employed to ensure that where they have different modes of action, their combined usage is effective against bacteria and fungi. Disinfection should include the periodic use of a sporicidal agent. Monitoring should be undertaken regularly in order to assess the effectiveness of the disinfection programme and to detect changes in types of microbial flora (e.g. organisms resistant to the disinfection regime currently in use).
4.34 消毒過程應經過確效。確效研究應證明消毒劑以特定使用方式在該表面材料類型上或具有代表性的材料（證明合理的情況下）之適用性及有效性，並應支持所製備溶液開封後使用的有效期限。	4.34 The disinfection process should be validated. Validation studies should demonstrate the suitability and effectiveness of disinfectants in the specific manner in which they are used and on the type of surface material, or representative material if justified, and should support the in-use expiry periods of prepared solutions.
4.35 A 級及 B 級區域使用的消毒劑及清潔劑在使用前應是無菌的。依照 CCS 的決定，C 級及 D 級區域中使用的消毒劑也可能需要是無菌的。如果消毒劑及清潔劑是由無菌產品製造廠稀釋/製備，則應以防止污染的方式進行，並應監測微生物污染。稀釋液應保存在事先清潔過的容器中（並在可行的情況下進行滅菌），並且只能在規定的期限內儲存。如果使用"市售現成"之消毒劑及清潔劑在成功完成適當的供應商驗證後，可以接受分析證明書或符合性證明書的結果。	4.35 Disinfectants and detergents used in grade A and grade B areas should be sterile prior to use. Disinfectants used in grade C and D may also be required to be sterile where determined in the CCS. Where the disinfectants and detergents are diluted / prepared by the sterile product manufacturer, this should be done in a manner to prevent contamination and they should be monitored for microbial contamination. Dilutions should be kept in previously cleaned containers (and sterilized where applicable) and should only be stored for the defined period. If the disinfectants and detergents are supplied "ready-made" then results from certificates of analysis or conformance can be accepted subject to successful completion of the appropriate vendor qualification.
4.36 當對潔淨室及相關表面使用燻蒸或氣相消毒（例如氣相過氧化氫）時，應了解並確效任何燻蒸劑及分散系統的有效性。	4.36 Where fumigation or vapour disinfection (e.g. Vapour-phase Hydrogen Peroxide) of cleanrooms and associated surfaces are used, the effectiveness of any fumigation agent and dispersion system should be understood and validated.
5.設備 (Equipment)	
5.1 應提供設備設計的書面詳細說明（視情	5.1 A written, detailed description of the equipment design should be available

況可包括製程及設備儀表圖示)。這應為初始驗證文件的一部分並須持續更新。	(including process and instrumentation diagrams as appropriate). This should form part of the initial qualification package and be kept up to date.
5.2 設備的監測需求應在開發初期於"使用者需求規格"中明訂,並在驗證時予以確認。應確認製程及設備的警報事件並評估其趨勢,應基於其關鍵程度來決定警報的評估頻率(關鍵警報須立即審查)。	5.2 Equipment monitoring requirements should be defined in "user requirements specifications" during early stages of development, and confirmed during qualification. Process and equipment alarm events should be acknowledged and evaluated for trends. The frequency at which alarms are assessed should be based on their criticality (with critical alarms reviewed immediately).
5.3 設備、配件及支援服務之設計與安裝,應儘可能使其作業、維護保養及修理能在潔淨區外執行。如果維護保養必須在潔淨室內進行,且在該維修工作期間未維持所要求之潔淨度及/或無菌性的標準者,則應考慮採取預防措施,例如只限指定人員進入工作區域、制定明確規範的工作計畫書及維護保養程序等,還應考慮額外的清潔、消毒及環境監測。倘設備需要滅菌者,應儘可能在完成組裝後為之。	5.3 As far as practicable, equipment, fittings and services should be designed and installed so that operations, maintenance, and repairs can be performed outside the cleanroom. If maintenance has to be performed in the cleanroom, and the required standards of cleanliness and/or asepsis cannot be maintained, then precautions such as restricting access to the work area to specified personnel, generation of clearly defined work protocols and maintenance procedures should be considered. Additional cleaning, disinfection and environmental monitoring should also be considered. If sterilisation of equipment is required, it should be carried out, wherever possible, after complete reassembly.
5.4 清潔程序應經確效,使其能夠:	5.4 The cleaning process should be validated to be able to:
i. 清除任何會對所用消毒劑的有效性產生不利影響的殘留物或碎屑。	i. remove any residue or debris that would detrimentally impact the effectiveness of the disinfecting agent used,
ii. 在清潔程序中及消毒前儘量減少產品的化學、微生物及微粒污染。	ii. minimize chemical, microbial and particulate contamination of the product during the process and prior to disinfection.
5.5 對於無菌製程,直接及間接接觸產品的組件都應進行滅菌。直接接觸產品的組件是指有產品通過的組件,例如充填針或泵。間接接觸產品組件是指不與產品接觸但可能與其他已滅菌品表面接觸的設備組件,其無菌性對整體產品的無菌性至關重要(例如,膠塞貯盆與導軌,以及已滅菌組件等已滅菌物品)。	5.5 For aseptic processes, direct and indirect product contact parts should be sterilised. Direct product contact parts are those that the product passes through, such as filling needles or pumps. Indirect product contact parts are equipment parts that do not contact the product, but may come into contact with other sterilised surfaces, the sterility of which is critical to the overall product sterility (e.g.

	sterilised items such as stopper bowls and guides, and sterilised components).
5.6 所有設備，如滅菌器、空氣處理系統（包括空氣過濾）及水系統都應經過驗證、監測及有計劃地維護保養。維護保養完成後，經核可方可恢復使用。	5.6 All equipment such as sterilisers, air handling systems (including air filtration) and water systems should be subject to qualification, monitoring and planned maintenance. Upon completion of maintenance, their return to use should be approved.
5.7 對產品無菌性至關重要的設備進行計劃外維護保養時，其對產品無菌性的潛在影響應進行評估並予以記錄。	5.7 Where unplanned maintenance of equipment critical to the sterility of the product is to be carried out, an assessment of the potential impact to the sterility of the product should be performed and recorded.
5.8 輸送帶不得通過介於 A 級或 B 級區與較低空氣潔淨度之作業區間的隔板/隔牆，除非該輸送帶本身是持續地滅菌的（例如：在滅菌的隧道中）。	5.8 A conveyor belt should not pass through a partition between a grade A or B area and a processing area of lower air cleanliness, unless the belt itself is continually sterilised (e.g. in a sterilising tunnel).
5.9 微粒計數器，包括採樣管，應經過驗證。對於管徑及彎曲半徑，應考慮製造商建議的規格。除非有正當理由，否則其管長通常不應超過 1 公尺，並且應儘量減少彎曲的次數。應使用具短取樣管的手提式微粒計數器進行潔淨度分級。單向氣流系統中，應使用等速採樣頭（isokinetic sample heads）。它們應以適當方向安置並盡可能靠近關鍵位置，以確保樣本具有代表性。	5.9 Particle counters, including sampling tubing, should be qualified. The manufacturer's recommended specifications should be considered for tube diameter and bend radii. Tube length should typically be no longer than 1m unless justified and the number of bends should be minimized. Portable particle counters with a short length of sample tubing should be used for classification purposes. Isokinetic sampling heads should be used in unidirectional airflow systems. They should be oriented appropriately and positioned as close as possible to the critical location to ensure that samples are representative.
6.公用設施 (Utilities)	
6.1 公用設施系統其管制的性質及程度應與該公用設施相關的產品品質風險相稱。其影響應經由風險評估確定，並將其文件化作為 CCS 的一部分。	6.1 The nature and extent of controls applied to utility systems should be commensurate with the risk to product quality associated with the utility. The impact should be determined via a risk assessment and documented as part of the CCS.
6.2 一般來說，有較高風險的公用設施如下：	6.2 In general, higher risk utilities are those that:
i. 直接接觸產品的公用設施，例如用於洗滌及潤洗的水、用於滅菌的氣體及蒸汽，	i. directly contact product e.g. water for washing and rinsing, gases and steam for sterilisation,
ii. 最終將成為產品一部分的接觸物，	ii. contact materials that will ultimately become part of the product,
iii. 其接觸面會與產品接觸者，	iii. contact surfaces that come into contact with

	the product,
iv. 其它直接影響產品者。	iv. otherwise directly impact the product.
6.3 公用設施的設計、安裝、驗證、操作、維護及監測應確保公用設施系統如預期運作。	6.3 Utilities should be designed, installed, qualified, operated, maintained and monitored in a manner to ensure that the utility system functions as expected.
6.4 高風險公用設施的關鍵參數及關鍵品質屬性的結果應定期進行趨勢分析，以確保系統維持適當能力。	6.4 Results for critical parameters and critical quality attributes of high risk utilities should be subject to regular trend analysis to ensure that system capabilities remain appropriate.
6.5 公用設施系統的安裝紀錄應在該系統的整個生命週期內予以保存。此類紀錄應包括現行圖及示意圖、建築材料清單及系統規格。通常，重要資訊包括以下項目：	6.5 Records of utility system installation should be maintained throughout the system's life-cycle. Such records should include current drawings and schematic diagrams, construction material lists and system specifications. Typically, important information includes attributes such as:
i. 管道流向、坡度、直徑及長度，	i. pipeline flow direction, slopes, diameter and length,
ii. 桶槽及容器的詳細資訊，	ii. tank and vessel details,
iii. 閥門、過濾器、排水管、採樣點及使用點，	iii. valves, filters, drains, sampling and user points,
6.6 管線、管道及其他公用設施不應出現在潔淨室中。如果不可避免，則其安裝應使其不產生凹處、未密封的開口及難以清潔的表面。管線的安裝應允許其外表面的清潔及消毒。	6.6 Pipes, ducts and other utilities should not be present in cleanrooms. If unavoidable, then they should be installed so that they do not create recesses, unsealed openings and surfaces which are difficult to clean. Installation should allow cleaning and disinfection of outer surface of the pipes.
水系統	**Water systems**
6.7 水處理設施及輸送系統，應經設計、建造、安裝、試運轉、驗證、監測及維護保養以防止微生物污染並確保具有適當品質的可靠水源。應採取措施將微粒、微生物污染/增殖及內毒素/熱原存在的風險降至最低（例如有斜度的管道以提供完全排水及避免盲管）。如果系統中包含過濾器，則應特別注意對其進行監測及維護保養。所產製的水應符合現行相關藥典的個論。	6.7 Water treatment plant and distribution systems should be designed, constructed, installed, commissioned, qualified, monitored and maintained to prevent microbiological contamination and to ensure a reliable source of water of an appropriate quality. Measures should be taken to minimize the risk of presence of particulates, microbial contamination/proliferation and endotoxin/pyrogen (e.g. sloping of piping to provide complete drainage and the avoidance of dead legs). Where filters are included in the system, special attention should be given to their monitoring and maintenance. Water produced should comply with the current monograph of the relevant Pharmacopeia.

6.8 水系統應經過驗證及確效，以保持適當的物理、化學及微生物管制程度，同時要考慮到季節變化的影響。	6.8 Water systems should be qualified and validated to maintain the appropriate levels of physical, chemical and microbial control, taking the effect of seasonal variation into account.
6.9 在輸水系統管線中水流應保持亂流，以儘量減少微生物粘附及隨後形成生物膜的風險。應在驗證期間確定流速並定期監測。	6.9 Water flow should remain turbulent through the pipes in water distribution systems to minimize the risk of microbial adhesion, and subsequent biofilm formation. The flow rate should be established during qualification and be routinely monitored.
6.10 注射用水 (WFI) 應使用符合驗證過程中規定規格的水生產，並以微生物生長風險最小的方式儲存及輸送（例如在 70 ℃ 以上恆定循環）。WFI 應透過蒸餾或等同於蒸餾的純化製程生產。這可能包括逆滲透搭配其他適當的技術，例如電去離子 (EDI)、超過濾或奈米過濾。	6.10 Water for injections (WFI) should be produced from water meeting specifications that have been defined during the qualification process, stored and distributed in a manner which minimizes the risk of microbial growth (e.g. by constant circulation at a temperature above 70°C). WFI should be produced by distillation or by a purification process that is equivalent to distillation. This may include reverse osmosis coupled with other appropriate techniques such as electrodeionization (EDI), ultrafiltration or nanofiltration.
6.11 WFI 儲桶配備疏水性細菌滯留通氣過濾器時，過濾器不應成為污染源，並且在安裝前及使用後測試過濾器的完整性。應採取管制措施（例如加熱）以防止過濾器上形成冷凝水。	6.11 Where WFI storage tanks are equipped with hydrophobic bacteria retentive vent filters, the filters should not be a source of contamination and the integrity of the filter tested before installation and after use. Controls should be in place to prevent condensation formation on the filter (e.g. by heating).
6.12 為儘量減少生物膜形成的風險，水系統的滅菌、消毒或再生應按照預定的時間表進行，並且作為超出限值或規格後的補救措施。使用化學品對水系統進行消毒後，應執行經過確效的潤洗/沖洗程序，並應在消毒/再生後對水進行測試。在水系統恢復使用之前，其化學試驗結果應獲得核准，且其微生物/內毒素結果應在使用本系統中的水所生產的批次產品被認可/放行前經確認符合規格並獲得核准。	6.12 To minimize the risk of biofilm formation, sterilisation, disinfection or regeneration of water systems should be carried out according to a predetermined schedule and as a remedial action following out-of-limit or specification results. Disinfection of a water system with chemicals should be followed by a validated rinsing/flushing procedure. Water should be tested after disinfection/regeneration. Chemical testing results should be approved before the water system is returned to use and microbiological/endotoxin results verified to be within specification and approved before batches manufactured using water from the system are considered for certification/release.
6.13 應執行定期持續的水系統化學及微生物	6.13 Regular ongoing chemical and microbial

監測，以確保水持續符合藥典規格。警戒值應以初始驗證數據為基礎，然後根據隨後的再驗證、例行監測及調查期間獲得的數據定期重新評估。應對持續監測數據進行審查，以識別出系統在性能上的任何不利趨勢。採樣計畫應反映 CCS 的要求，並應在指定的時間間隔內涵蓋所有出水口及使用點，以確保定期獲取有代表性的水樣進行分析。採樣計畫應基於驗證數據，且應考慮潛在最差狀況的採樣位置，並應確保每天至少包含一個用於製造過程的代表性水樣。	monitoring of water systems should be performed to ensure that the water continues to meet compendial expectations. Alert levels should be based on the initial qualification data and thereafter periodically reassessed on data obtained during subsequent re-qualifications, routine monitoring, and investigations. Review of ongoing monitoring data should be carried out to identify any adverse trend in system performance. Sampling programmes should reflect the requirements of the CCS and should include all outlets and points of use, at a specified interval, to ensure that representative water samples are obtained for analysis on a regular basis. Sample plans should be based on the qualification data, should consider the potential worst case sampling locations and should ensure that at least one representative sample is included every day of the water that is used for manufacturing processes.
6.14 偏離警戒值應予文件化及審查，並調查以確定該偏離是否為單一（獨立的）事件，或者其結果是否顯示存在不良趨勢或系統劣化。每次偏離行動值都應調查，以確定可能的根本原因以及由於使用該水而對產品品質及製造過程的任何潛在影響。	6.14 Alert level excursions should be documented and reviewed, and include an investigation to determine whether the excursion is a single (isolated) event or if results are indicative of an adverse trend or system deterioration. Each action limit excursion should be investigated to determine the probable root causes and any potential impact on the quality of products and manufacturing processes as a result of the use of the water.
6.15 WFI 系統應包括連續監測系統，例如總有機碳 (TOC) 及導電度，因為與非連續採樣相比，這些系統可以更好地指示整體系統性能。傳感器設置的位置應基於風險。	6.15 WFI systems should include continuous monitoring systems such as Total Organic Carbon (TOC) and conductivity, as these may give a better indication of overall system performance than discrete sampling. Sensor locations should be based on risk.
蒸汽作為直接滅菌劑	**Steam used as a direct sterilising agent**
6.16 純蒸汽（清潔蒸汽）產生器的給水應適當純化。純蒸汽產生器的設計、驗證及操作方式應確保產生的蒸汽品質符合界定的化學及內毒素標準。	6.16 Feed water to a pure steam (clean steam) generator should be appropriately purified. Pure steam generators should be designed, qualified and operated in a manner to ensure that the quality of steam produced meets defined chemical and endotoxin levels.
6.17 用於直接滅菌的蒸汽應具有合適的品質，並且不應含有可能導致產品或設備	6.17 Steam used as a direct sterilising agent should be of suitable quality and should not contain additives at a level which could cause

污染的添加物。對於提供純蒸汽直接對材料或產品接觸表面（例如多孔硬質高壓滅菌器裝載）進行滅菌的純蒸汽產生器，其蒸汽冷凝水應符合現行相關藥典 WFI 的個論（蒸汽冷凝水不強制要求微生物測試）。應制定適當的取樣計劃，以確保定期獲得具有代表性的純蒸汽進行分析。用於滅菌的純蒸汽在其他的品質方面則應根據經過確效的參數定期評估。這些參數應包括以下（除非另有合理理由）：不凝氣體、乾燥度及過熱度。	contamination of product or equipment. For a generator supplying pure steam used for the direct sterilisation of materials or product-contact surfaces (e.g. porous / hard-good autoclave loads), steam condensate should meet the current monograph for WFI of the relevant Pharmacopeia (microbial testing is not mandatory for steam condensate). A suitable sampling schedule should be in place to ensure that representative pure steam is obtained for analysis on a regular basis. Other aspects of the quality of pure steam used for sterilisation should be assessed periodically against validated parameters. These parameters should include the following (unless otherwise justified): non-condensable gases, dryness value (dryness fraction) and superheat.
氣體及真空系統	**Gases and vacuum systems**
6.18 與產品/主要容器表面直接接觸的氣體應具有適當的化學、微粒及微生物的品質。包括油及水含量等所有相關參數應予規定，並考慮氣體的用途、類型及氣體產生系統的設計；如另有現行相關藥典的個論或產品品質要求，亦應符合之。	6.18 Gases that come in direct contact with the product/primary container surfaces should be of appropriate chemical, particulate and microbial quality. All relevant parameters, including oil and water content, should be specified, taking into account the use and type of the gas, the design of the gas generation system and, where applicable, comply with the current monograph of the relevant Pharmacopeia or the product quality requirement.
6.19 無菌製程中使用的氣體應在使用點通過滅菌級過濾器（孔徑最大為 0.22 μm）進行過濾。如果過濾器以批次為基礎使用（例如，用於過濾覆蓋無菌充填產品的氣體）或作為產品容器的通氣過濾器，則應對過濾器進行完整性測試，並將結果作為批次認可/放行過程的一部分進行審查。位於最末段的滅菌過濾器之後的任何傳輸管道或管線都應進行滅菌。當氣體用於製程中時，應在使用點定期對氣體進行微生物監測。	6.19 Gases used in aseptic processes should be filtered through a sterilising grade filter (with a nominal pore size of a maximum of 0.22 μm) at the point of use. Where the filter is used on a batch basis (e.g. for filtration of gas used for overlay of aseptically filled products) or as product vessel vent filter, then the filter should be integrity tested and the results reviewed as part of the batch certification/release process. Any transfer pipework or tubing that is located after the final sterilising grade filter should be sterilised. When gases are used in the process, microbial monitoring of the gas should be performed periodically at the point of use.
6.20 當真空或壓力系統的回流對產品構成潛	6.20 Where backflow from vacuum or pressure systems poses a potential risk to the product,

在風險，該系統關閉時應有防止回流的機制。	there should be mechanism(s) to prevent backflow when the vacuum or pressure system is shut off.
加熱、冷卻及液壓系統	**Heating and cooling and hydraulic systems**
6.21 與液壓、加熱及冷卻系統相關的主要設備項目，應盡可能位於充填室外。應有適當的管制措施來圍堵與系統流體相關的任何溢出及/或交叉污染。	6.21 Major items of equipment associated with hydraulic, heating and cooling systems should, where possible, be located outside the filling room. There should be appropriate controls to contain any spillage and/or cross contamination associated with the system fluids.
6.22 這些系統的任何洩漏可能對產品構成風險，都應該是可偵測的（例如洩漏指示系統）。	6.22 Any leaks from these systems that would present a risk to the product should be detectable (e.g. an indication system for leakage).
7 組織與人事 (Personnel)	
7.1 製造廠在無菌產品的製造及檢驗應確保有足夠的適當人員，適當的資格、訓練及經驗，以及在製造作業所使用的任何特定製造技術，以確保符合適用於製造及處理無菌產品的 GMP。	7.1 The manufacturer should ensure that there are sufficient appropriate personnel, suitably qualified, trained and experienced in the manufacture and testing of sterile products, and any of the specific manufacturing technologies used in the site's manufacturing operations, to ensure compliance with GMP applicable to the manufacture and handling of sterile products.
7.2 應僅有所需之最少人員可在潔淨室。應在初始驗證及 APS 等活動中確定、記錄及考慮潔淨室作業人員的最大數量，以免影響無菌保證。	7.2 Only the minimum number of personnel required should be present in cleanrooms. The maximum number of operators in cleanrooms should be determined, documented and considered during activities such as initial qualification and APS, so as not to compromise sterility assurance.
7.3 所有人員，包括從事清潔、維修保養、監測及進入潔淨室的人員，都應接受定期訓練、著衣驗證及與有關正確製造無菌產品之規範的評估。該訓練應包含衛生以及微生物學的基本原理，還應特別關注潔淨室的作業、污染管制、無菌技術及無菌產品的保護(針對進入 B 級潔淨室及/或介入 A 級潔淨區的作業人員）以及如果產品不能達到無菌時，可能對患者造成的潛在安全影響。訓練應基於人員工作的職能及場地的關鍵程度。	7.3 All personnel including those performing cleaning, maintenance, monitoring and those that access cleanrooms should receive regular training, gowning qualification and assessment in disciplines relevant to the correct manufacture of sterile products. This training should include the basic elements of microbiology and hygiene, with a specific focus on cleanroom practices, contamination control, aseptic techniques and the protection of sterile products (for those operators entering the grade B cleanrooms and/or intervening into grade A) and the potential safety implications to the patient if the product

	is not sterile. The level of training should be based on the criticality of the function and area in which the personnel are working.
7.4 進入A級及B級區域的人員應接受無菌更衣及無菌行為的訓練。無菌更衣程序的遵循性應予評估確認，並至少每年定期再評估確認，且應包括目視及微生物評估（採用的監測位置，包括如戴手套的手指、前臂、胸部及頭罩（面罩/前額）等。其預期的限值參見第 9.30 點）。應僅限於已通過更衣評估並參加過成功的 APS 之適當合格人員，可不受監督進入正在或將要進行無菌操作的 A 級及 B 級區域。	7.4 The personnel accessing grade A and B areas should be trained for aseptic gowning and aseptic behaviours. Compliance with aseptic gowning procedures should be confirmed by assessment and periodic reassessment at least annually, and should involve both visual and microbial assessment (using monitoring locations such as gloved fingers, forearms, chest and hood (facemask / forehead). See paragraph 9.30 for the expected limits). The unsupervised access to the grade A and grade B areas where aseptic operations are or will be conducted should be restricted to appropriately qualified personnel, who have passed the gowning assessment and have participated in a successful APS.
7.5 未符合資格認證之人員不得進入作業中的B級潔淨室或A級區。如果在特殊情況下有此需要，製造廠應制定書面程序，概述將未符合資格認證之人員帶入 B 級及 A 級區域的過程。在未符合資格認證人員的活動期間，由製造廠授權的人員應對其進行監督，並應評估這些活動對區域潔淨度的影響。這些人員的進入應根據 PQS 進行評估及記錄。	7.5 Unqualified personnel should not enter grade B cleanrooms or grade A in operation. If needed in exceptional cases, manufacturers should establish written procedures outlining the process by which unqualified personnel are brought into the grade B and A areas. An authorized person from the manufacturer should supervise the unqualified personnel during their activities and should assess the impact of these activities on the cleanliness of the area. Access by these persons should be assessed and recorded in accordance with the PQS.
7.6 應建立取消人員在潔淨室工作資格或取消其不受監督進入潔淨室資格的系統，這是基於多方面的考慮，這包括持續的評估及/或來自人員監測規劃中識別出的不良趨勢及/或涉及 APS 失敗。一旦被取消資格，在允許作業人員進一步參與無菌操作之前，應完成再訓練及資格再認證。對於會進入 B 級潔淨室或對 A 級區進行介入的作業人員，其再認證應考慮包括參與過一次成功的 APS。	7.6 There should be systems in place for the disqualification of personnel from working in or given unsupervised entry into cleanrooms that is based on aspects including ongoing assessment and/or identification of an adverse trend from the personnel monitoring programme and/or after being implicated in a failed APS. Once disqualified, retraining and requalification should be completed before permitting the operator to have any further involvement in aseptic practices. For operators entering grade B cleanrooms or performing intervention into grade A, this requalification should include consideration of participation in a successful APS.

7.7 高標準的個人衛生及清潔對於防止皮屑過度脫落或增加引入微生物污染的風險是必要的。對參與無菌產品製造的人員應指導其提報可能引起異常數目或類型之污染物脫落的任何特定健康狀況或疾病，並因此排除其進入潔淨室。有關可能引起不適當之微生物危險的人員之健康狀況及擬採取的措施應由指派之勝任人員決定，並在程序中敘述。	7.7 High standards of personal hygiene and cleanliness are essential to prevent excessive shedding or increased risk of introduction of microbial contamination. Personnel involved in the manufacture of sterile products should be instructed to report any specific health conditions or ailments which may cause the shedding of abnormal numbers or types of contaminants and therefore preclude cleanroom access. Health conditions and actions to be taken with regard to personnel who could be introducing an undue microbial hazard should be provided by the designated competent person and described in procedures.
7.8 已參與非目前製造過程使用的人類或動物組織材料或微生物培養物或任何可能對品質產生負面影響的作業（例如微生物污染）之人員，不得進入相關潔淨區，除非其已遵守清楚界定及有效的去污染及進入程序並已完成文件。	7.8 Personnel who have been engaged in the processing of human or animal tissue materials or of cultures of micro-organisms, other than those used in the current manufacturing process, or any activities that may have a negative impact to quality (e.g. microbial contamination), should not enter clean areas unless clearly defined and effective decontamination and entry procedures have been followed and documented.
7.9 手錶、化粧品、珠寶、其他個人物品（如手機）及任何其他非必需品不得帶入潔淨區。潔淨室中使用的電子設備，如果經過適當設計，符合與其使用處潔淨級別的清潔及消毒要求，則可以接受，例如由廠內提供的僅用於潔淨室的手機及平板電腦。此類設備的使用及消毒應包括在 CCS 中。	7.9 Wristwatches, make-up, jewellery, other personal items such as mobile phones and any other non-essential items should not be allowed in clean areas. Electronic devices used in cleanrooms, e.g. mobile phones and tablets, that are supplied by the manufacturer solely for use in the cleanrooms, may be acceptable if suitably designed to permit cleaning and disinfection commensurate with the grade in which they are used. The use and disinfection of such equipment should be included in the CCS.
7.10 潔淨室的著衣及洗手應遵循指定之書面程序，以將潔淨室衣著的污染或帶入潔淨區之污染物降至最低。	7.10 Cleanroom gowning and hand washing should follow a written procedure designed to minimize contamination of cleanroom clothing and/or the transfer of contaminants to the clean areas.
7.11 衣著及其品質應適合於製程與作業區的等級。應以保護產品免於受到污染的方式穿戴。當所選的衣著類型是要為作業	7.11 The clothing and its quality should be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from

人員提供不受產品影響的保護時，它也不應損害對於產品受污染的保護。在著衣之前後，應立即對服裝進行目視檢查，以確保其清潔度及完整性。在離去時還應在出口處檢查服裝的完整性。對於已經滅菌的服裝及眼罩，應給予特別注意，以確保它們已經通過滅菌過程，且還在其規定的保持時間內，並且在使用前還要經過目視檢查以確保包裝是完整的。可重複使用的服裝（包括眼罩），如果發現損壞，應予以更換，或以驗證試驗期間所確定的預定頻率予以更換。服裝的驗證應考慮任何必要的服裝測試要求，包括僅通過目視檢查可能無法識別的服裝損壞。	contamination. When the type of clothing chosen needs to provide the operator protection from the product, it should not compromise the protection of the product from contamination. Garments should be visually checked for cleanliness and integrity immediately prior to and after gowning. Gown integrity should also be checked upon exit. For sterilised garments and eye coverings, particular attention should be taken to ensure they have been subject to the sterilisation process, are within their specified hold time and that the packaging is visually inspected to ensure it is integral before use. Reusable garments (including eye coverings) should be replaced if damage is identified, or at a set frequency that is determined during qualification studies. The qualification of garments should consider any necessary garment testing requirements, including damage to garments that may not be identified by visual inspection alone.
7.12 選擇的衣著應能限制由於作業人員的移動而釋出脫落物。	7.12 Clothing should be chosen to limit shedding due to operators' movement.
7.13 每一潔淨等級區所要求之典型衣著，其說明如下：	7.13 A description of typical clothing required for each cleanliness grade is given below:
i. B 級（包括進入/介入 A 級區）：在無菌衣更衣前應穿著專用的適當服裝（參見第 7.14 點）。在穿戴經過滅菌的衣服時，應戴上經適當滅菌的、未沾粉末的橡皮或塑膠手套。無菌頭套應將所有毛髮（包括面部毛髮）包覆起來，如果其與服裝的其餘部分是分開的，則應將其末端塞入無菌服的領子內。應佩戴無菌面罩及無菌眼罩（例如護目鏡）以覆蓋及包覆所有面部皮膚，並防止液滴及微粒脫落。應穿著適當的滅菌鞋類（例如套靴）。褲管底端應塞在鞋內。衣服的袖口應塞進第二雙無菌手套中，該手套應戴在穿無菌衣時戴的那雙手套上。此類防護服應儘量減少纖維或微粒的脫落，並可將由身體脫落的微粒保留在防護服內。服裝的微粒脫落性及微粒	i. Grade B (including access / interventions into grade A): appropriate garments that are dedicated for use under a sterilised suit should be worn before gowning (see paragraph 7.14). Appropriately sterilised, non-powdered, rubber or plastic gloves should be worn while donning the sterilised garments. Sterile headgear should enclose all hair (including facial hair) and where separate from the rest of the gown, it should be tucked into the neck of the sterile suit. A sterile facemask and sterile eye coverings (e.g. goggles) should be worn to cover and enclose all facial skin and prevent the shedding of droplets and particles. Appropriate sterilised footwear (e.g. over-boots) should be worn. Trouser legs should be tucked inside the footwear. Garment sleeves should be tucked into a second pair of sterile gloves worn over the

保留效率應在服裝驗證試驗期間予以評估。服裝的包裝及摺疊方式應允許作業人員在不接觸服裝外表面的情況下穿上，並防止其接觸到地板。	pair worn while donning the gown. The protective clothing should minimize shedding of fibres or particles and retain particles shed by the body. The particle shedding and the particle retention efficiencies of the garments should be assessed during the garment qualification. Garments should be packed and folded in such a way as to allow operators to don the gown without contacting the outer surface of the garment and to prevent the garment from touching the floor.
ii. C 級：頭髮，面部及口部所有蓄留之鬍鬚，應予覆蓋。應穿著在腕部收緊及高領的單件式或兩件式褲套裝，及適當且經過消毒的鞋子或鞋套。衣著應可儘量減少纖維及微粒的脫落。	ii. Grade C: Hair, beards and moustaches should be covered. A single or two-piece trouser suit gathered at the wrists and with high neck and appropriately disinfected shoes or overshoes should be worn. They should minimize the shedding of fibres and particles.
iii. D 級：頭髮，面部及口部所有蓄留之鬍鬚，應予覆蓋。應穿著一般保護套裝及適當消毒的鞋子或鞋套。為避免任何來自潔淨區外的污染物，應採取適當的措施。	iii. Grade D: Hair, beards and moustaches should be covered. A general protective suit and appropriately disinfected shoes or overshoes should be worn. Appropriate measures should be taken to avoid any ingress of contaminants from outside the clean area.
iv. 即使在 C 級及 D 級區，進行由 CCS 所界定的具有污染風險的活動時，可能會需要額外穿戴手套及口罩。	iv. Additional gowning including gloves and facemask may be required in grade C and D areas when performing activities considered to be a contamination risk as defined by the CCS.
7.14 潔淨室著衣應在適當潔淨等級的更衣室內進行，以確保防護服的潔淨度可以被維持。廠外衣著包括襪子在內(個人內衣除外)，不應帶入直接通往 B 級及 C 級區域的更衣室中。在進入 B 級及 C 級更衣室之前，應穿著覆蓋手臂及腿部全長的一件式或兩件式廠服，以及覆蓋足部的廠襪。廠服及廠襪不應對更衣區或製程存在污染風險。	7.14 Cleanroom gowning should be performed in change rooms of an appropriate cleanliness grade to ensure gown cleanliness is maintained. Outdoor clothing including socks (other than personal underwear) should not be brought into changing rooms leading directly to grade B and C areas. Single or two-piece facility trouser suits, covering the full length of the arms and the legs, and facility socks covering the feet, should be worn before entry to change rooms for grades B and C. Facility suits and socks should not present a risk of contamination to the gowning area or processes.
7.15 每個進入 B 級或 A 級區的作業人員在每次進入時，都應穿上適當尺寸的乾淨、	7.15 Every operator entering grade B or A areas should gown into clean, sterilised protective

經滅菌的防護服裝（包括眼罩及口罩）。無菌服在一個輪班期間內，更換之前的最長穿戴時間應作為服裝驗證的一部分予以界定。	garments (including eye coverings and masks) of an appropriate size at each entry. The maximum period for which the sterilised gown may be worn before replacement during a shift should be defined as part of the garment qualification.
7.16 作業期間應定期消毒手套。如果服裝及手套損壞並存在任何污染產品的風險，應立即更換。	7.16 Gloves should be regularly disinfected during operations. Garments and gloves should be changed immediately if they become damaged and present any risk of product contamination.
7.17 可重複使用的潔淨區衣著應在與生產作業充分隔離的洗衣房中清洗，應使用經過驗證的程序，確保衣著在重複的洗衣過程中不會損壞及/或被纖維或微粒污染。所使用的洗衣設施不應引入污染或交叉污染的風險。衣著的不當處理及使用可能會損壞纖維並增加微粒脫落的風險。洗滌後及包裝前，應目視檢查服裝的損壞及其清潔度。服裝管理過程應作為服裝驗證計畫的一部分進行評估及訂定，並應包括洗衣及滅菌的次數上限。	7.17 Reusable clean area clothing should be cleaned in a laundry facility adequately segregated from production operations, using a qualified process ensuring that the clothing is not damaged and/or contaminated by fibres or particles during the repeated laundry process. Laundry facilities used should not introduce risk of contamination or cross-contamination. Inappropriate handling and use of clothing may damage fibres and increase the risk of shedding of particles. After washing and before packing, garments should be visually inspected for damage and visual cleanliness. The garment management processes should be evaluated and determined as part of the garment qualification programme and should include a maximum number of laundry and sterilisation cycles.
7.18 在潔淨區的活動如對生產過程不重要，則應儘量減少，特別是在無菌作業進行時。人員的移動應緩慢、受控且有序的，以避免由於過度劇烈的活動而造成微粒及微生物的過度脫落。執行無菌操作的作業人員應全程遵循無菌操作技術，以防止氣流變化，從而將品質較低的空氣引入關鍵區域。鄰接關鍵區域的移動應予以限制，並應避免單向氣流(第一手空氣)的路徑受阻。對氣流可視化研究的回顧應被視為訓練計畫的一部分。	7.18 Activities in clean areas that are not critical to the production processes should be kept to a minimum, especially when aseptic operations are in progress. Movement of personnel should be slow, controlled and methodical to avoid excessive shedding of particles and organisms due to over-vigorous activity. Operators performing aseptic operations should adhere to aseptic technique at all times to prevent changes in air currents that may introduce air of lower quality into the critical zone. Movement adjacent to the critical zone should be restricted and the obstruction of the path of the unidirectional (first air) airflow should be avoided. A review of airflow visualisation studies should be considered as part of the training programme.
8 生產及特定技術 (Production and Specific Technologies)	
最終滅菌產品	**Terminally sterilised products**

8.1 組件及原物料的製備至少應在 D 級潔淨室中進行，以降低微生物、內毒素/熱原及微粒污染的風險，使產品適合滅菌。當產品處於高風險或異常風險的微生物污染中(例如，產品會促進微生物生長，產品必須在充填前長時間保存，或產品大部分未在密閉容器中加工），則至少應在 C 級環境中製備。軟膏劑、乳膏劑、懸液劑及乳劑的製備在最終滅菌前應至少在 C 級環境中進行。	8.1 Preparation of components and materials should be performed in at least a grade D cleanroom in order to limit the risk of microbial, endotoxin/pyrogen and particle contamination, so that the product is suitable for sterilisation. Where the product is at a high or unusual risk of microbial contamination (e.g. the product actively supports microbial growth, the product must be held for long periods before filling or the product is not processed mostly in closed vessels), then preparation should be carried out in at least a grade C environment. Preparation of ointments, creams, suspensions and emulsions should be carried out in at least a grade C environment before terminal sterilisation. Specific guidance regarding terminally sterilised veterinary medicinal products can be found within Annex 4 of the GMP Guide.
8.2 直接包裝容器及組件應使用經過確效的程序清潔，以確保微粒、內毒素/熱原及負荷菌的污染被適當控制。	8.2 Primary packaging containers and components should be cleaned using validated processes to ensure that particle, endotoxin/pyrogen and bioburden contamination is appropriately controlled.
8.3 最終滅菌產品的充填，應至少在 C 級環境中進行。	8.3 Filling of products for terminal sterilisation should be carried out in at least a grade C environment.
8.4 當經過 CCS 確認產品存在異常的環境污染風險，例如，充填作業緩慢、容器為廣口、或在密封前必須暴露數秒鐘以上之時間，則產品應在 A 級區充填，充填背景至少為 C 級。	8.4 Where the CCS identifies that the product is at an unusual risk of contamination from the environment because, for example, the filling operation is slow, the containers are wide necked or are necessarily exposed for more than a few seconds before closing, then the product should be filled in grade A with at least a grade C background.
8.5 半製品溶液的操作應包括過濾步驟，於可能的情況下，在充填到最終產品的容器之前使用微生物滯留過濾器以減少負荷菌及微粒之含量；並且在製備及充填之間應訂定容許的最長時間。	8.5 Processing of the bulk solution should include a filtration step with a microorganism retaining filter, where possible, to reduce bioburden levels and particles prior to filling into the final product containers and there should be a maximum permissible time between preparation and filling.
8.6 表 3 中提供在不同級區的作業範例。	8.6 Examples of operations to be carried out in the various grades are given in Table 3
表 3：製備及加工最終滅菌之作業及級區範例	Table 3: Examples of operations and grades for terminally sterilised preparation and processing operations

A 級區	- 當產品的充填處於異常風險時。
C 級區	- 當溶液的調製處於異常風險時。 - 產品的充填。
D 級區	- 供後續充填溶液的製備及組件之準備。

Grade A	- Filling of products, when unusually at risk.
Grade C	- Preparation of solutions, when unusually at risk. - Filling of products.
Grade D	- Preparation of solutions and components for subsequent filling.

無菌製備及操作

8.7 應明確界定無菌製程。應識別、評估及適當管制與無菌製程相關的風險以及要求。工廠的 CCS 應明確界定這些管制措施的允收標準、監控要求及其有效性審查。應描述及實施管制這些風險的方法及程序。應正式記錄被接受的殘留風險。

8.8 無菌環境的製備過程中，在所有作業階段（包括半製品在滅菌之前及之後的階段），以及直到產品被密封在最終容器，應根據藥廠的 CCS 採取預防措施，以儘量減少微生物、內毒素/熱原及微粒之污染。潔淨室中應儘量減少容易產生微粒及纖維的材料存在。

8.9 在可能的情況下，應考慮使用 RABS、隔離裝置或其他系統等設備，以減少對 A 級區之關鍵介入的需要，並將污染風險降至最低。也可以考量機器人及製程自動化的技術來消除直接人為的關鍵介入（例如乾熱隧道、凍乾機自動裝載、原位滅菌）。

8.10 表 4 列出在各種級區環境下進行的作業範例。

表 4：在各種不同級區從事無菌製備及加工作業之範例

A 級區	- 充填設備的無菌組裝。

Aseptic preparation and processing

8.7 The aseptic process should be clearly defined. The risks associated with the aseptic process, and any associated requirements, should be identified, assessed and appropriately controlled. The site's CCS should clearly define the acceptance criteria for these controls, requirements for monitoring and the review of their effectiveness. Methods and procedures to control these risks should be described and implemented. Accepted residual risks should be formally documented.

8.8 Precautions to minimize microbial, endotoxin/pyrogenic and particle contamination should be taken, as per the site's CCS, during the preparation of the aseptic environment, during all processing stages (including the stages before and after bulk product sterilisation), and until the product is sealed in its final container. The presence of materials liable to generate particles and fibres should be minimized in cleanrooms.

8.9 Where possible, the use of equipment such as RABS, isolators or other systems, should be considered in order to reduce the need for critical interventions into grade A and to minimize the risk of contamination. Robotics and automation of processes can also be considered to eliminate direct human critical interventions (e.g. dry heat tunnel, automated lyophilizer loading, sterilisation in place).

8.10 Examples of operations to be carried out in the various environmental grades are given in Table 4.

Table 4: Examples of operations and grades for aseptic preparation and processing operations

Grade A	- Aseptic assembly of filling equipment.

	- 在無菌條件下最後一個滅菌級過濾器後的無菌連接（當已滅菌的產品接觸表面在其連接處有暴露表面）。這些連接處應儘可能使用原位蒸汽滅菌。 - 無菌調製及混合。 - 補充無菌半製品、容器及封蓋。 - 從滅菌器中取出及冷卻未受保護(例如無包裝)的物品。 - 無菌充填線中未包裝之無菌直接包裝組件的暫置及輸送。 - 無菌充填、安瓿及小瓶等容器的密封、打開的或部分封塞的小瓶的轉移。 - 凍乾機裝載。
B 級區	- 做為支持 A 級區之背景（當不在隔離裝置中時）。 - 供等待移入 A 級區的設備、組件及輔助物品在不受周遭環境影響的情況下輸送或暫置。
C 級區	- 待過濾溶液之製備，包括其取樣及調配。
D 級區	- 設備之清潔。 - 清潔後的組件、設備及配件之處理。 - 滅菌前，在 HEPA 過濾氣流下組裝已清潔的組件、設備及配件。 - 使用內建的無菌連接裝置，來組裝已密封及無菌的 SUS。

	- Connections made under aseptic conditions (where sterilised product contact surfaces are exposed) that are post the final sterilising grade filter. These connections should be sterilised by steam-in-place whenever possible. - Aseptic compounding and mixing. - Replenishment of sterile bulk product, containers and closures. - Removal and cooling of unprotected (e.g. with no packaging) items from sterilisers. - Staging and conveying of sterile primary packaging components in the aseptic filling line while not wrapped. - Aseptic filling, sealing of containers such as ampoules, vial closure, transfer of open or partially stoppered vials. - Loading of a lyophilizer.
Grade B	- Background support for grade A (when not in an isolator). - Conveying or staging, while protected from the surrounding environment, of equipment, components and ancillary items for introduction into grade A.
Grade C	- Preparation of solutions to be filtered including sampling and dispensing.
Grade D	- Cleaning of equipment. - Handling of components, equipment and accessories after cleaning. - Assembly under HEPA filtered airflow of cleaned components, equipment and accessories prior to sterilisation. - Assembly of closed and sterilised SUS using intrinsic sterile connection devices.

8.11 對於最終配方無法過濾的無菌產品，應考慮以下因素：	8.11 For sterile products where the final formulation cannot be filtered, the following should be considered
i. 所有與產品及組件接觸的設備在使用	all product and component contact equipment should be sterilised prior to use,

前都應進行滅菌。	
ii. 所有原料或半製品均應滅菌並以無菌操作方式添加。	all raw materials or intermediates should be sterilised and aseptically added,
iii. 待分裝之溶液或半製品應滅菌。	bulk solutions or intermediates should be sterilised.
8.12 與產品直接或間接接觸的已滅菌設備、組件及輔助物品之拆封、組裝及準備，應被視為無菌操作，並在具有 B 級背景的 A 級區中進行。無菌產品的充填線組裝及充填應視為無菌操作，並在具有 B 級背景的 A 級區中進行。在使用隔離裝置的情況下，背景應符合第 4.20 點。	8.12 The unwrapping, assembly and preparation of sterilised equipment, components and ancillary items with direct or indirect product contact should be treated as an aseptic process and performed in grade A with a grade B background. The filling line set-up and filling of the sterile product should be treated as an aseptic process and performed in grade A with a grade B background. Where an isolator is used, the background should be in accordance with paragraph 4.20.
8.13 無菌產品如軟膏、乳膏、懸液劑及乳劑等的製備及充填，當產品及成分暴露在環境中且產品不經後續過濾（通過滅菌級過濾器）或最終滅菌時，應在具有 B 級背景的 A 級區中進行。當使用隔離裝置或 RABS 時，背景應符合第 4.20 點。	8.13 Preparation and filling of sterile products such as ointments, creams, suspensions and emulsions should be performed in grade A with a grade B background when the product and components are exposed to the environment and the product is not subsequently filtered (via a sterilising grade filter) or terminally sterilised. Where an isolator or RABS is used, the background should be in accordance with paragraph 4.20.
8.14 無菌連接應在具有 B 級背景的 A 級區中進行，以減少環境的任何潛在污染，除非隨後進行原位滅菌或使用內建無菌的連接裝置進行。內建無菌連接裝置的設計應降低污染風險。	8.14 Aseptic connections should be performed in grade A with a grade B background unless subsequently sterilised in place or conducted with intrinsic sterile connection devices that minimize any potential contamination from the immediate environment. Intrinsic sterile connection devices should be designed to mitigate risk of contamination.
當使用隔離裝置，其背景應符合第 4.20 點。應適當評估無菌連接並確認其有效性。有關內建無菌連接裝置的要求，參見第 8.129 及 8.130 點。	Where an isolator is used, the background should be in accordance with paragraph 4.20. Aseptic connections should be appropriately assessed and their effectiveness verified. For requirements regarding intrinsic sterile connection devices, see paragraphs 8.129 and 8.130.
8.15 應透過工程設計方法儘量減少無菌操作（包括非內建的無菌連接裝置），例如將設備預先組裝並滅菌。當可行時，與產品接觸的管路及設備應預先組裝並原位滅菌。	8.15 Aseptic manipulations (including non-intrinsic sterile connection devices) should be minimized through the use of engineering design solutions such as preassembled and sterilised equipment. Whenever feasible, product contact piping and equipment should

	be pre-assembled, and sterilised in place.
8.16 應有核准清單，列出在生產過程中可能發生且經允許及驗證的介入（包括常規及矯正性之介入）（參見第 9.34 點）。應仔細設計介入，以確保有效降低環境、過程及產品的污染風險。設計介入的過程應包括考慮對氣流、關鍵表面及產品的任何影響。應儘可能使用工程解決方案，以儘量減少作業人員在介入期間的動作。應全程遵守無菌技術，包括適當使用無菌的工具進行操作。應首先通過風險管理及 APS 對列出常規性及矯正性的介入類型以及如何執行它們的程序，進行評估並保持最新。應只有在特殊情況下才可使用未驗證的介入措施，並適當考慮與介入措施相關的風險且獲得品質部門的授權。介入的細節應根據製造廠的 PQS 進行風險評估、記錄及全面調查。任何未驗證的介入措施都應由品質部門進行徹底評估，並納入批次處置之考量。	8.16 There should be an authorized list of allowed and qualified interventions, both inherent and corrective, that may occur during production (see paragraph 9.34). Interventions should be carefully designed to ensure that the risk of contamination of the environment, process and product is effectively minimized. The process of designing interventions should include the consideration of any impact on air-flows and critical surfaces and products. Engineering solutions should be used whenever possible to minimize incursion by operators during the intervention. Aseptic technique should be observed at all times, including the appropriate use of sterile tools for manipulations. The procedures listing the types of inherent and corrective interventions, and how to perform them, should be first evaluated via risk management and APS and be kept up to date. Non-qualified interventions should only be used in exceptional circumstances, with due consideration of the risks associated with the intervention and with the authorisation of the quality unit. The details of the intervention conducted should be subject to risk assessment, recorded and fully investigated under the manufacturer's PQS. Any non-qualified interventions should be thoroughly assessed by the quality department and considered during batch disposition.
8.17 介入及停機應記錄在批次紀錄中。每條生產線停機或介入都應在批次紀錄中充分記錄，包括相關的時間、事件持續時間及參與的作業人員（參見第 9.34 點）。	8.17 Interventions and stoppages should be recorded in the batch record. Each line stoppage or intervention should be sufficiently documented in batch records with the associated time, duration of the event, and operators involved (ref to paragraph 9.34).
8.18 無菌製備及操作的各工程期間應儘量縮短，並限制在經界定及確效的最長時間內，包括：	8.18 The duration of each aspect of aseptic preparation and processing should be minimized and limited to a defined and validated maximum time, including:
i. 設備、組件及容器的清潔、乾燥及滅菌之間的保持時間；	i. the holding time between equipment, component, and container cleaning, drying and sterilisation;
ii. 已滅菌之設備、組件及容器在使用前及充填/組裝期間的保持時間；	ii. the holding time for sterilised equipment, components, and containers before use and

	during filling/assembly;
iii. 已去污染之環境的保持時間(例如在 RABS 或隔離裝置使用前)；	iii. the holding time for a decontaminated environment, such as the RABS or isolator before use;
iv. 從產品製備開始到滅菌或通過微生物滯留濾器過濾(適用時)，再到無菌充填過程結束的時間。考慮到產品成分及規定的儲存方法，每種產品應分別界定最長允許時間；	iv. the time between the start of the preparation of a product and its sterilisation or filtration through a microorganism-retaining filter (if applicable), through to the end of the aseptic filling process There should be a maximum permissible time for each product that takes into account its composition and the prescribed method of storage;
v. 已滅菌產品在充填前的保持時間；	v. the holding time for sterilised product prior to filling;
vi. 無菌操作時間；	vi. the aseptic processing time;
vii. 充填時間。	vii. the filling time.
8.19 應由在無菌操作方面具有特定專業知識的人員定期觀察無菌作業（包括 APS），以確認作業的正確執行，包括作業人員在潔淨室中的行為，並糾正所見之不適當操作。	8.19 Aseptic operations (including APS) should be observed on a regular basis by personnel with specific expertise in aseptic processing to verify the correct performance of operations including operator behaviour in the cleanroom and address inappropriate practices if detected.
無菌產品的完成	**Finishing of sterile products**
8.20 開口的直接容器應保持在具適當背景（如第 4.20 點所述） 的 A 級條件下。對於部分封塞的小瓶或預充填式的注射容器，請參閱第 8.126 點。	8.20 Open primary packaging containers should be maintained under grade A conditions with the appropriate background for the technology as described in paragraph 4.20. For partially stoppered vials or prefilled syringes (see paragraph 8.126).
8.21 最終容器應採用經過適當確效的方法密封。	8.21 Final containers should be closed by appropriately validated methods.
8.22 當最終容器以熔封方式密封時，例如：吹製-充填-密封（BFS）、成型-充填-密封（FFS）、小容量及大容量注射用袋（SVP & LVP）、玻璃或塑膠安瓿，應評估並確定影響密封完整性的各關鍵參數及變數，並在操作過程中有效地控制與監測。玻璃安瓿、BFS 單元及小容量容器（≤100 ml）應使用經確效的方法進行 100% 完整性測試。大容量容器（>100 ml），在符合科學正當性且有數據證明現有製程的一致性及嚴謹的製程控制下，減少取樣可能是可以接受的。應該注意	8.22 Where final containers are closed by fusion, e.g. Blow-Fill-Seal (BFS), Form-Fill-Seal (FFS), Small and Large Volume Parenteral (SVP & LVP) bags, glass or plastic ampoules, the critical parameters and variables that affect seal integrity should be evaluated, determined, effectively controlled and monitored during operations. Glass ampoules, BFS units and small volume containers (≤100 ml) closed by fusion should be subject to 100% integrity testing using validated methods. For large volume containers (>100 ml) closed by fusion, reduced sampling may be acceptable where scientifically justified

的是，目視檢查不被認為是可接受的完整性測試方法。	and based on data demonstrating the consistency of the existing process, and a high level of process control. It should be noted that visual inspection is not considered as an acceptable integrity test method.
8.23 使用熔封以外之方式密封的產品，應取樣並以確效的方法檢查其完整性。測試頻率應基於所使用之容器及密封系統的知識與經驗。應使用符合科學正當性的抽樣計畫。樣品量應基於供應商管理、包裝組件規格及製程知識等資訊。	8.23 Samples of products using systems other than fusion should be taken and checked for integrity using validated methods. The frequency of testing should be based on the knowledge and experience of the container and closure systems being used. A scientifically justified sampling plan should be used. The sample size should be based on information such as supplier management, packaging component specifications and process knowledge.
8.24 真空下密封的容器，應在認可/放行前之一段界定的適當時間後及架儲期間，測試其真空度的維持。	8.24 Containers sealed under vacuum should be tested for maintenance of vacuum after an appropriate pre-determined period prior to certification/release and during shelf life.
8.25 容器密封完整性的確效，應考慮可能對容器完整性產生負面影響的任何運輸或裝運需求（例如，減壓或極端溫度）。	8.25 The container closure integrity validation should take into consideration any transportation or shipping requirements that may negatively impact the integrity of the container (e.g. by decompression or extreme temperatures).
8.26 如果用於小瓶捲縮封蓋的設備會產生大量微粒，則應採取防止微粒污染的措施，例如將設備放置在配備適當抽氣的實體隔離工作站。	8.26 Where the equipment used to crimp vial caps can generate large quantities of non-viable particle, measures to prevent particle contamination such as locating the equipment at a physically separate station equipped with adequate air extraction should be taken.
8.27 無菌充填產品的小瓶封蓋，可使用滅菌瓶蓋進行無菌操作，或在無菌操作區外進行潔淨操作。採用後者時，小瓶離開無菌操作區之前應受到 A 級條件的保護；之後，封塞的小瓶應以 A 級空氣保護，直到完成鋁蓋捲縮為止。供應 A 級空氣的背景環境至少應符合 D 級區要求。當封蓋是人工作業，則應在適當設計的隔離裝置中的 A 級條件下，或在具有 B 級背景的 A 級區進行。	8.27 Vial capping of aseptically filled products can be undertaken as an aseptic process using sterilised caps or as a clean process outside the aseptic processing area. Where the latter approach is adopted, vials should be protected by grade A conditions up to the point of leaving the aseptic processing area, and thereafter stoppered vials should be protected with a grade A air supply until the cap has been crimped. The supporting background environment of grade A air supply should meet at least grade D requirements. Where capping is a manual process, it should be performed under grade A conditions either in an appropriately designed isolator or in grade

	A with a grade B background.
8.28 當無菌充填產品的封蓋是採提供 A 級空氣保護的潔淨操作時，小瓶之膠塞有漏塞或置放離位者，應在封蓋前移除。另，應具備經適當驗證的自動方法檢測膠塞高度。	8.28 Where capping of aseptically filled sterile product is conducted as a clean process with grade A air supply protection, vials with missing or displaced stoppers should be rejected prior to capping. Appropriately qualified, automated methods for stopper height detection should be in place.
8.29 當封蓋作業站需要人員介入時，應採用適當的技術性及（程序 ICH Q7）上的措施防止直接接觸小瓶，使污染降到最低。RABS 及隔離裝置可能有助於確保所需條件。	8.29 Where human intervention is required at the capping station, appropriate technological and organizational measures should be used to prevent direct contact with the vials and to minimize contamination. RABS and isolators may be beneficial in assuring the required conditions.
8.30 所有已充填的注射用產品容器都應個別檢查外來污染或其他缺陷。缺陷分類及嚴重程度應在驗證期間根據風險與歷史知識決定。需要考慮的因素包括但不限於缺陷對患者及給藥途徑的潛在影響。應該對不同的缺陷類型進行分類並分析批次的表現。當批次缺陷數量異於日常生產時（依據例行及趨勢數據），應進行調查。應建立並維護缺陷資料庫（defect library），該資料庫收集所有已知的缺陷分類。缺陷資料庫應使用於生產和品保人員的教育訓練。初始檢查合格的容器於後續抽樣及檢查，不應發現嚴重缺陷。後續發現任何嚴重缺陷都應啟動調查，因其顯示初始檢查過程可能失敗。	8.30 All filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. Defect classification and criticality should be determined during qualification and based on risk and historical knowledge. Factors to consider include, but are not limited to, the potential impact of the defect to the patient and the route of administration. Different defect types should be categorized and batch performance analysed. Batches with unusual levels of defects, when compared with routine defect numbers for the process (based on routine and trend data), should be investigated. A defect library should be generated and maintained which captures all known classes of defects. The defect library should be used for the training of production and quality assurance personnel. Critical defects should not be identified during any subsequent sampling and inspection of acceptable containers. Any critical defect identified subsequently should trigger an investigation as it indicates a possible failure of the original inspection process.
8.31 當以人工進行檢查時，應在適當且經管制的照明與背景條件下進行。檢查速率應適當管制和驗證。執行檢查的作業人員應至少每年接受一次目視檢查驗證（如果平時有戴眼鏡者於驗證時應佩戴矯正鏡片）。驗證作業應使用取自製造廠	8.31 When inspection is performed manually, it should be conducted under suitable and controlled conditions of illumination and background. Inspection rates should be appropriately controlled and qualified. Operators performing the inspection should undergo visual inspection qualification (whilst

缺陷資料庫套組的適當樣品，並考慮最差狀況（例如檢查時間、產品經由輸送帶系統傳送給作業人員的產線速度、容器尺寸或疲勞度），並應考量包括視力檢查。應儘量減少作業人員的分心，並應在檢查時經常進行適當時間的休息。	wearing corrective lenses, if these are normally worn) at least annually. The qualification should be undertaken using appropriate samples from the manufacturer's defect library sets and taking into consideration worst case scenarios (e.g. inspection time, line speed where the product is transferred to the operator by a conveyor system, container size or fatigue) and should include consideration of eyesight checks. Operator distractions should be minimized and frequent breaks, of an appropriate duration, should be taken from inspection.
8.32 當使用自動方法檢查時，其程序應確效，證明可以檢出可能影響產品品質或安全性的已知缺陷，且其檢出能力應等同或優於人工檢查方法。設備的性能應在啟動前和整個批次中定期使用具有代表性的缺陷品進行挑戰。	8.32 Where automated methods of inspection are used, the process should be validated to detect known defects (which may impact product quality or safety) and be equal to, or better than, manual inspection methods. The performance of the equipment should be challenged using representative defects prior to start up and at regular intervals throughout the batch.
8.33 應記錄檢查的結果，並對缺陷類型和數量進行趨勢分析。也應依據統計學原理對各種缺陷類型的不合格比例進行趨勢分析。當觀察到不良趨勢時，應評估對市場產品的影響以作為調查的一部分。	8.33 Results of the inspection should be recorded and defect types and numbers trended. Reject levels for the various defect types should also be trended based on statistical principles. Impact to product on the market should be assessed as part of the investigation when adverse trends are observed.
滅菌	**Sterilisation**
8.34 可行時，最終產品應使用經過確效與管制的滅菌程序進行最終滅菌，因為這比經過確效與管制的無菌過濾製程及/或無菌操作提供了更高的無菌保證程度。當產品不可能進行最終滅菌，則應考慮使用無菌操作後的最終熱處理，並結合無菌操作以提高無菌保證程度。	8.34 Where possible, finished product should be terminally sterilised, using a validated and controlled sterilisation process, as this provides a greater assurance of sterility than a validated and controlled sterile filtration process and/or aseptic processing. Where it is not possible for a product to undergo terminal sterilisation, consideration should be given to using post-aseptic processing terminal heat treatment, combined with aseptic process to give improved sterility assurance.
8.35 滅菌設備與滅菌週期/程式的選擇、設計與位置，應基於科學原則以及證明滅菌過程可再現及可信賴的數據。應界定所有參數，關鍵者應予管控、監測並記錄。	8.35 The selection, design and location of the equipment and cycle/programme used for sterilisation should be based on scientific principles and data which demonstrate repeatability and reliability of the sterilisation process. All parameters should be defined,

	and where critical, these should be controlled, monitored and recorded.
8.36 所有滅菌過程應予確效。確效研究應考慮產品成分、儲存條件，以及從開始準備待滅菌產品或原物料到滅菌之間的最長時間。在採用任何滅菌過程之前，其對產品及設備的適用性，以及每種裝載的全部待滅物品每次都能達到預期滅菌條件的效能，應藉由物理量測及適當時搭配生物指示劑（BI），進行確效。為有效滅菌，產品全部及設備與組件的所有表面均應受到必要的處理，且相關程序應予設計以確保達到此目的。	8.36 All sterilisation processes should be validated. Validation studies should take into account the product composition, storage conditions and maximum time between the start of the preparation of a product or material to be sterilised and its sterilisation. Before any sterilisation process is adopted, its suitability for the product and equipment, and its efficacy in consistently achieving the desired sterilising conditions in all parts of each type of load to be processed should be validated notably by physical measurements and where appropriate by Biological Indicators (BI). For effective sterilisation, the whole of the product, and surfaces of equipment and components should be subject to the required treatment and the process should be designed to ensure that this is achieved.
8.37 當採用的產品滅菌方法未在現行版的藥典中描述，或用於非單純水溶液的產品時，應特別注意。在可能的情況下，加熱滅菌是首選方法。	8.37 Particular attention should be given when the adopted product sterilisation method is not described in the current edition of the Pharmacopoeia, or when it is used for a product which is not a simple aqueous solution. Where possible, heat sterilisation is the method of choice.
8.38 應為所有滅菌製程建立確效的裝載型式，各裝載型式應定期再確效。最大及最小裝載也應被視為整體裝載確效策略的一部分。	8.38 Validated loading patterns should be established for all sterilisation processes and load patterns should be subject to periodic revalidation. Maximum and minimum loads should also be considered as part of the overall load validation strategy.
8.39 應基於風險按預定的時間間隔檢討及確認滅菌過程的有效性。加熱滅菌週期應以被認為是最差狀況的裝載型式，最低再確效頻率至少每年一次。其他裝載型式應依 CCS 中證明合理的頻率進行確效。	8.39 The validity of the sterilizing process should be reviewed and verified at scheduled intervals based on risk. Heat sterilization cycles should be revalidated with a minimum frequency of at least annually for load patterns that are considered worst case. Other load patterns should be validated at a frequency justified in the CCS.
8.40 應建立並遵守所有滅菌過程的例行操作參數，例如：物理參數及裝載型式。	8.40 Routine operating parameters should be established and adhered to for all sterilisation processes, e.g. physical parameters and loading patterns.
8.41 應有適當機制來偵測不符合確效參數的滅菌週期。應調查任何失敗的或偏離確	8.41 There should be mechanisms in place to detect a sterilisation cycle that does not conform to

效程序的滅菌作業（例如：較長或較短的加熱階段）。	the validated parameters. Any failed sterilisation or sterilisation that deviated from the validated process (e.g. have longer or shorter phases such as heating cycles) should be investigated.
8.42 在適當位置放置合適 BI 應被視為支持滅菌過程確效的一種附加方法。 BI 應根據製造商的說明書進行儲存及使用。當 BI 用於支持確效及/或監控滅菌過程（例如環氧乙烷滅菌），對每一個滅菌週期應進行陽性對照測試。如果使用 BI，則應採取嚴格的預防措施以避免將微生物污染轉移到製造或其他測試過程中。不應僅用 BI 結果推翻其他關鍵參數及製程設計要素。	8.42 Suitable BIs placed at appropriate locations should be considered as an additional method to support the validation of the sterilisation process. BIs should be stored and used according to the manufacturer's instructions. Where BIs are used to support validation and/or to monitor a sterilisation process (e.g. with ethylene oxide), positive controls should be tested for each sterilisation cycle. If BIs are used, strict precautions should be taken to avoid transferring microbial contamination to the manufacturing or other testing processes. BI results in isolation should not be used to override other critical parameters and process design elements.
8.43 BI 的可靠性很重要。應驗證 BI 供應商，且應控制其運輸及儲存條件，避免損害 BI 品質。在使用新的 BI 批次之前，應確認該批次之指示微生物的數量、純度及鑑別。對於其他關鍵參數，例如 D 值與 Z 值，通常可以使用合格供應商提供的批次證明書。	8.43 The reliability of BIs is important. Suppliers should be qualified and transportation and storage conditions should be controlled in order that BI quality is not compromised. Prior to use of a new batch/lot of BIs, the population, purity and identity of the indicator organism of the batch/lot should be verified. For other critical parameters, e.g. D-value, Z-value, the batch certificate provided by the qualified supplier can normally be used.
8.44 應有明確的方法區分未滅菌及已滅菌的產品、設備及組件。用於盛裝產品、其他設備及/或組件之籃子或托盤等器具應清楚地標明（或以電子方式追蹤）產品名稱、批號以及是否已滅菌。當合適時，可以使用如高壓滅菌膠帶或輻射指示劑之類的指示劑來標示該批次（或子批次材料、組件、設備）是否已經過滅菌處理。然而，這些指示劑僅顯示已經歷滅菌過程；它們並不表示產品為無菌或達到要求的無菌保證程度。	8.44 There should be a clear means of differentiating products, equipment and components, which have not been subjected to the sterilisation process from those which have. Equipment such as baskets or trays used to carry products, other items of equipment and/or components should be clearly labelled (or electronically tracked) with the product name and batch number and an indication of whether or not it has been sterilised. Indicators such as autoclave tape, or irradiation indicators may be used, where appropriate, to indicate whether or not a batch (or sub-batch material, component, equipment) has passed through a sterilisation process. However, these indicators show only that the sterilisation process has occurred;

	they do not indicate product sterility or achievement of the required sterility assurance level.
8.45 每次滅菌操作都應有滅菌紀錄。每一個週期都應該有唯一的標識碼。應審查及核准滅菌紀錄的符合性，以作為批次認可/放行程序的一部分。	8.45 Sterilisation records should be available for each sterilisation run. Each cycle should have a unique identifier. Their conformity should be reviewed and approved as part of the batch certification/release procedure.
8.46 需要時，原物料、設備及組件應以適用於特定材質之確效方法進行滅菌。滅菌後應提供適當的保護以防止再次污染。如果滅菌物品在滅菌後不立即使用，則應使用適當密封的包裝儲存，並應建立最長保持時間。在證明合理的情況下，多層無菌包裝的組件，如果無菌包裝的完整性及構造可讓作業人員在將物品轉移到 A 級的過程易於消毒（例如，通過使用多層無菌包裝，每次從較低級區轉移到較高級區時可逐層去除），則不須儲存於潔淨室。如果以密封包裝達到保護，則該包裝作業應在滅菌前進行。	8.46 Where required, materials, equipment and components should be sterilised by validated methods appropriate to the specific material. Suitable protection after sterilisation should be provided to prevent recontamination. If sterilised items are not used immediately after sterilisation, these should be stored using appropriately sealed packaging and a maximum hold time should be established. Where justified, components that have been packaged with multiple sterile packaging layers need not be stored in a cleanroom if the integrity and configuration of the sterile pack allows the items to be readily disinfected during transfer by operators into grade A (e.g. by the use of multiple sterile coverings that can be removed at each transfer from lower to higher grade). Where protection is achieved by containment in sealed packaging, this packaging process should be undertaken prior to sterilisation.
8.47 如果原物料、設備、組件和輔助物品在密封包裝中進行滅菌後轉移到 A 級區，則應使用適當確效的方法（例如，氣鎖室或傳遞箱）進行，同時消毒密封包裝的外部表面。還應考慮使用快速傳送對接口技術。應證明這些方法可有效控制 A 級區及 B 級區域的潛在污染風險，同樣，應證明將物品移入 B 級區及 A 級區的消毒程序，可有效地將包裝上的任何污染降至可接受程度。	8.47 Where materials, equipment, components and ancillary items are sterilised in sealed packaging and then transferred into grade A, this should be done using appropriate validated methods (for example, airlocks or pass-through hatches) with accompanying disinfection of the exterior of the sealed packaging. The use of rapid transfer port technology should also be considered. These methods should be demonstrated to effectively control the potential risk of contamination of the grade A and grade B areas and, likewise, the disinfection procedure should be demonstrated to be effective in reducing any contamination on the packaging to acceptable levels for entry of the item into the grade B and grade A areas.
8.48 對密封於包裝或容器中的原物料、設	8.48 Where materials, equipment, components and

備、組件和輔助物品進行滅菌時，應驗證其包裝能將微粒、微生物、內毒素/熱原或化學污染的風險降至最低，且適用於所選的滅菌方法。包裝密封的程序應予確效。確效應考慮無菌保護屏障系統的完整性、滅菌前的最長保持時間及已滅菌物品的最長架儲期。使用前應檢查每件已滅菌物品之無菌保護屏障系統的完整性。	ancillary items are sterilised in sealed packaging or containers, the packaging should be qualified for minimizing the risk of particulate, microbial, endotoxin/pyrogen or chemical contamination, and for compatibility with the selected sterilisation method. The packaging sealing process should be validated. The validation should consider the integrity of the sterile protective barrier system, the maximum hold time before sterilisation and the maximum shelf life assigned to the sterilised items. The integrity of the sterile protective barrier system for each of the sterilised items should be checked prior to use.
8.49 對於非直接或非間接接觸產品，且為無菌操作所必須，但不能滅菌的原物料、設備、組件及輔助物品，應有有效且經確效的消毒及轉送程序。這些物品一經消毒，應加以保護以防止再次污染。這些物品及其他代表潛在污染的途徑，應涵蓋在環境監測計畫中。	8.49 For materials, equipment, components and ancillary items that are not a direct or indirect product contact part and are necessary for aseptic processing but cannot be sterilised, an effective and validated disinfection and transfer process should be in place. These items, once disinfected, should be protected to prevent recontamination. These items, and others representing potential routes of contamination, should be included in the environmental monitoring programme.
加熱滅菌	**Sterilisation by heat**
8.50 應使用具有適當準確度及精確度的設備，以電子或紙本的方式記錄每一個加熱滅菌週期。系統的控制及監測儀器應具有保障措施及/或冗餘配置，以檢測不符合確效參數要求的週期，並中止或判定該週期失敗（例如，使用雙重控制/雙探針連接到獨立的控制及監測系統）。	8.50 Each heat sterilisation cycle should be recorded either electronically or by hardcopy, using equipment with suitable accuracy and precision. The system should have safeguards and/or redundancy in its control and monitoring instrumentation to detect a cycle not conforming to the validated cycle parameter requirements and abort or fail this cycle (e.g. by the use of duplex/double probes connected to independent control and monitoring systems).
8.51 用於控制及/或記錄的溫度探針的位置應在確效期間確定，並根據系統設計進行選擇，以便正確記錄並代表例行滅菌週期條件。應設計確效研究來證明系統控制及記錄的探針位置的合適性，並應包括在確效期間使用位於相同位置的獨立監測探針確認這些探針的功能及位置。	8.51 The position of the temperature probes used for controlling and/or recording should be determined during the validation and selected based on system design and in order to correctly record and represent routine cycle conditions. Validation studies should be designed to demonstrate the suitability of system control and recording probe locations, and should include the verification of the

	function and location of these probes by the use of an independent monitoring probe located at the same position during validation.
8.52 在開始計算滅菌時間之前，整個裝載應達到要求的溫度。在裝載內使用參考探針控制的滅菌週期，應特別考慮，確保裝載探針的溫度在週期開始前，控制在規定的溫度範圍內。	8.52 The whole of the load should reach the required temperature before measurement of the sterilising time-period starts. For sterilisation cycles controlled by using a reference probe within the load, specific consideration should be given to ensuring the load probe temperature is controlled within defined temperature range prior to cycle commencement.
8.53 加熱滅菌週期的高溫階段完成後，應採取預防措施，以防止滅菌裝載物在冷卻過程中被污染。任何與產品或滅菌物料接觸的冷卻液體或氣體都應經過滅菌。	8.53 After completion of the high temperature phase of a heat sterilisation cycle, precautions should be taken against contamination of a sterilised load during cooling. Any cooling liquid or gas that comes into contact with the product or sterilised material should be sterilised.
8.54 在核准以參數放行的情況下，應有穩健的系統運用於產品生命週期內確效及製程例行監控。該系統應予定期審查。附則 17 提供關於參數放行的進一步指導。	8.54 In those cases where parametric release has been authorized, a robust system should be applied to the product lifecycle validation and the routine monitoring of the manufacturing process. This system should be periodically reviewed. Further guidance regarding parametric release is provided in Annex 17.
濕熱滅菌	**Moist heat sterilisation**
8.55 濕熱滅菌可以使用蒸汽（直接或間接接觸）達成，但也包括其他系統，例如超熱水系統（噴淋或浸泡週期），可用於可能被其他滅菌週期設計造成破損的容器（例如吹製-充填-密封的容器、塑膠軟袋）。	8.55 Moist heat sterilisation can be achieved using steam, (direct or indirect contact), but also includes other systems such as superheated water systems (cascade or immersion cycles) that could be used for containers that may be damaged by other cycle designs (e.g. Blow-Fill-Seal containers, plastic bags).
8.56 除密封於容器中的產品外，待滅菌的物品應是乾燥的，並用可允許空氣移除及蒸汽滲透，且防止滅菌後再次污染的保護性屏障系統進行包裝。從滅菌器中取出後，所有裝載的物品都應是乾燥的。應通過目視檢查確認裝載的乾燥度，作為滅菌過程允收標準的一部分。	8.56 The items to be sterilised, other than products in sealed containers, should be dry, packaged in a protective barrier system which allows removal of air and penetration of steam and prevents recontamination after sterilisation. All loaded items should be dry upon removal from the steriliser. Load dryness should be confirmed by visual inspection as a part of the sterilisation process acceptance.
8.57 對於多孔物品滅菌週期（硬質物品），應監控並記錄過程的時間、溫度及壓力。每件滅菌物品從高壓滅菌器中取出時，	8.57 For porous cycles (hard goods), time, temperature and pressure should be used to monitor the process and be recorded. Each sterilised item should be inspected for

應檢查是否有損壞、包裝材料完整性以及濕氣。任何發現不符合預期用途的物品都應移出製造區域並進行調查。	damage, packaging material integrity and moisture on removal from the autoclave. Any item found not to be fit for purpose should be removed from the manufacturing area and an investigation performed.
8.58 能夠進行預真空滅菌週期的高壓滅菌器，應在整個滅菌期間記錄滅菌艙排水口的溫度。適當時也可以使用裝載探針，但控制系統應保持與裝載確效時相關。對於原位蒸汽滅菌系統，在整個滅菌期間應記錄適當之冷凝水排放點的溫度。	8.58 For autoclaves capable of performing prevacuum sterilisation cycles, the temperature should be recorded at the chamber drain throughout the sterilisation period. Load probes may also be used where appropriate but the controlling system should remain related to the load validation. For steam in place systems, the temperature should be recorded at appropriate condensate drain locations throughout the sterilisation period.
8.59 多孔週期的確效應包括計算平衡時間、暴露時間、壓力及溫度的相關性以及滅菌期間的最低/最高溫度範圍。液體週期的確效應包括溫度、時間及/或 F0。關鍵製程參數應符合規定的限值（包括適當的容許偏差），並作為滅菌確效及例行滅菌週期可接受標準的一部分。	8.59 Validation of porous cycles should include a calculation of equilibration time, exposure time, correlation of pressure and temperature and the minimum/maximum temperature range during exposure. Validation of fluid cycles should include temperature, time and/or F0. Critical processing parameters should be subject to defined limits (including appropriate tolerances) and be confirmed as part of the sterilisation validation and routine cycle acceptance criteria.
8.60 當真空階段是週期的一部分或系統在滅菌後恢復到低於滅菌器周圍環境的壓力時，應定期（通常每週）對滅菌器進行洩漏測試。	8.60 Leak tests on the steriliser should be carried out periodically (normally weekly) when a vacuum phase is part of the cycle or the system is returned, post-sterilisation, to a pressure lower than the environment surrounding the steriliser.
8.61 當滅菌過程包括空氣移除時（例如高壓滅菌器中的多孔裝載、凍乾艙），應充分保證在滅菌前及滅菌過程中去除空氣。對於高壓滅菌器，這應該包括空氣移除測試週期（通常每天進行）或使用空氣檢測系統。待滅菌的裝載設計應支持有效的空氣去除，及易於排水以防止冷凝水的積聚。	8.61 There should be adequate assurance of air removal prior to and during sterilisation when the sterilisation process includes air purging (e.g. porous autoclave loads, lyophilizer chambers). For autoclaves, this should include an air removal test cycle (normally performed on a daily basis) or the use of an air detector system. Loads to be sterilised should be designed to support effective air removal and be free draining to prevent the build-up of condensate.
8.62 應通過適當的週期設計及控制，例如設定正確的壓力、加熱與冷卻的速率以及	8.62 Distortion and damage of non-rigid containers that are terminally sterilised, such as containers produced by Blow-Fill-Seal or

裝載型式，以防止最終滅菌的軟質容器的變形及損壞（例如由吹製-充填-密封或成型-充填-密封技術生產的容器）。	Form-Fill-Seal technologies, should be prevented by appropriate cycle design and control (for instance setting correct pressure, heating and cooling rates and loading patterns).
8.63 當原位蒸汽處理系統用於滅菌時（例如用於固定管道、容器及凍乾機艙體），系統應經過適當設計及確效，確保系統的所有部分都經過所需的處理。在例行使用過程中，應在適當位置監測系統的溫度、壓力及時間，以確保所有區域都得到有效且可重複的滅菌。在初始及定期確效期間，這些位置應被證明具代表性，且與升溫最慢的位置相關。經原位蒸汽滅菌的系統，應該保持完整性，並且當操作需要時，在使用前保持正壓，或配備滅菌級空氣過濾器。	8.63 Where steam in place systems are used for sterilisation (e.g. for fixed pipework, vessels and lyophilizer chambers), the system should be appropriately designed and validated to assure all parts of the system are subjected to the required treatment. The system should be monitored for temperature, pressure and time at appropriate locations during routine use to ensure all areas are effectively and reproducibly sterilised. These locations should be demonstrated as being representative of, and correlated with, the slowest to heat locations during initial and routine validation. Once a system has been sterilised by steam in place, it should remain integral and where operations require, maintained under positive pressure or otherwise equipped with a sterilising vent filter prior to use.
8.64 使用超熱水作為傳熱介質的液體裝載週期中，熱水應持續地接觸所有要求的點位。初始驗證研究應包括整個裝載的溫度測繪。應對設備進行例行檢查，以確保噴嘴（入水處）沒有堵塞，且排水管沒有碎屑。	8.64 In fluids load cycles where superheated water is used as the heat transfer medium, the heated water should consistently reach all of the required contact points. Initial qualification studies should include temperature mapping of the entire load. There should be routine checks on the equipment to ensure that nozzles (where the water is introduced) are not blocked and drains remain free from debris.
8.65 超熱水的高壓滅菌器中對液體裝載的滅菌確效應包括整個裝載的溫度測繪與熱滲透以及再現性研究。裝載物的所有部分應均勻加熱，並在規定的時間內達到要求的溫度。例行溫度監測的探針應與驗證過程中確定的最差狀況位置相關聯。	8.65 Validation of the sterilisation of fluids loads in a superheated water autoclave should include temperature mapping of the entire load and heat penetration and reproducibility studies. All parts of the load should heat up uniformly and achieve the desired temperature for the specified time. Routine temperature monitoring probes should be correlated to the worst case positions identified during the qualification process.
乾熱滅菌	**Dry heat sterilisation**
8.66 乾熱滅菌利用高溫空氣或氣體對產品或物品進行滅菌。乾熱滅菌特別適用於以	8.66 Dry heat sterilisation utilizes high temperatures of air or gas to sterilise a product or article. Dry heat sterilisation is of particular

熱去除難消除的耐熱污染物，例如內毒素/熱原，通常用於製備無菌充填的組件。當在既定限度內例行操作時，產品、組件或設備所暴露之時間及溫度的組合應產生合乎需要且可再現的致死率及/或內毒素/熱原的去活化/去除水準。該過程可以在烘箱中或在連續隧道過程中進行，例如用於玻璃容器的滅菌及去熱原。	use in the thermal removal of difficult-to-eliminate thermally robust contaminants such as endotoxin/pyrogen and is often used in the preparation of components for aseptic filling. The combination of time and temperature to which product, components or equipment are exposed should produce an adequate and reproducible level of lethality and/or endotoxin/pyrogen inactivation/removal when operated routinely within the established limits. The process may be operated in an oven or in a continuous tunnel process, e.g. for sterilisation and depyrogenation of glass containers.
8.67 乾熱滅菌/去熱原隧道的配置應維持適當的壓差及氣流，確保氣流保護 A 級滅菌區的完整性及性能。應評估壓差曲線圖。應評估任何氣流變化的影響，以確保維持加熱曲線。供應到隧道的所有空氣都應至少通過 HEPA 過濾器，並且應進行定期測試（至少每半年一次）以證明空氣過濾器的完整性。任何與已滅菌組件接觸的隧道組件都應進行適當的滅菌或消毒。在確效及/或例行處理期間應考慮的關鍵製程參數應包括但不限於：	8.67 Dry heat sterilisation/depyrogenation tunnels should be configured to ensure that airflow protects the integrity and performance of the grade A sterilising zone by maintaining appropriate pressure differentials and airflow through the tunnel. Air pressure difference profiles should be assessed. The impact of any airflow change should be assessed to ensure the heating profile is maintained. All air supplied to the tunnel should pass through at least a HEPA filter and periodic tests (at least biannually) should be performed to demonstrate air filter integrity. Any tunnel parts that come into contact with sterilised components should be appropriately sterilised or disinfected. Critical process parameters that should be considered during validation and/or routine processing should include, but are not limited to:
i. 輸送帶速度或滅菌區內的停留時間，	i. belt speed or dwell time within the sterilising zone,
ii. 溫度 - 最低及最高溫度，	ii. temperature – minimum and maximum temperatures,
iii. 物料/物品的熱滲透，	iii. heat penetration of the material/article,
iv. 熱分佈/均勻性，	iv. heat distribution/uniformity,
v. 由熱分佈及熱滲透研究相關的壓差曲線所確定的氣流。	v. airflows determined by air pressure difference profiles correlated with the heat distribution and penetration studies.
8.68 當使用熱處理作為任何組件或與產品接觸的設備/原物料的去熱原製程的一部分時，應進行確效研究以證明該製程提供了合適的 Fh 值並使內毒素濃度至少降	8.68 When a thermal process is used as part of the depyrogenation process for any component or product contact equipment/material, validation studies should be performed to

低 3 log10。當達到這一標準時，不用額外的要求來證明滅菌效果。	demonstrate that the process provides a suitable Fh value and results in a minimum 3 log10 reduction in endotoxin concentration. When this is attained, there is no additional requirement to demonstrate sterilisation in these cases.
8.69 確效時應使用加入內毒素的容器，並應透過全面核算對該容器進行謹慎管理。容器應代表正常生產所用的材料（涉及包裝材料的組成、孔隙率、尺寸、額定容量）。還應證明內毒素的含量及回收效率。	8.69 Containers spiked with endotoxin should be used during validation and should be carefully managed with a full reconciliation performed. Containers should be representative of the materials normally processed (in respect to composition of the packaging materials, porosity, dimensions, nominal volume). Endotoxin quantification and recovery efficiency should also be demonstrated.
8.70 乾熱烘箱通常用於直接包裝材料、起始原料或原料藥滅菌或去熱原，但也可用於其他製程。除非保持包裝的完整性，否則在整個滅菌及滅菌後的保持過程中，乾熱烘箱對潔淨度等級相對較低的潔淨區應保持正壓。所有進入烘箱的空氣都應通過 HEPA 過濾器。在驗證及/或例行操作中應考慮的關鍵製程參數應包括但不限於：	8.70 Dry heat ovens are typically employed to sterilise or depyrogenate primary packaging components, starting materials or active substances but may be used for other processes. They should be maintained at a positive pressure relative to lower grade clean areas throughout the sterilisation and post sterilisation hold process unless the integrity of the packaging is maintained. All air entering the oven should pass through a HEPA filter. Critical process parameters that should be considered in qualification and/or routine processing should include, but are not limited to:
i. 溫度，	i. temperature,
ii. 暴露期間/時間，	ii. exposure period/time,
iii. 艙室壓力（用於維持相對高壓），	iii. chamber pressure (for maintenance of over pressure),
iv. 風速，	iv. air speed,
v. 烘箱內的空氣品質，	v. air quality within the oven,
vi. 物料/物品的熱滲透（加熱緩慢的各點），	vi. heat penetration of material/article (slow to heat spots),
vii. 熱分佈/均勻性，	vii. heat distribution/uniformity,
viii. 待滅菌/去熱原物品的裝載型式及配置，包括最小及最大裝載量。	viii. load pattern and configuration of articles to be sterilised/depyrogenated including minimum and maximum loads.
輻射滅菌	**Sterilisation by radiation**
8.71 輻射滅菌主要用於對熱敏感的原物料及產品的滅菌。紫外線照射不是可接受的滅菌方法。有關游離輻射滅菌的指引詳	8.71 Sterilisation by radiation is used mainly for the sterilisation of heat sensitive materials and products. Ultraviolet irradiation is not an acceptable method of sterilisation. Guidance

見附則 12。	regarding ionising radiation sterilisation can be found within Annex 12.
8.72 確效過程應確保已考量產品密度及包裝等變數的影響。	8.72 Validation procedures should ensure that the effects of variation in density of the product and packages are considered.
環氧乙烷滅菌	**Sterilisation with ethylene oxide**
8.73 本方法應只用在沒有其他方法可用的情形。在製程確效期間，應證明環氧乙烷(EO)對產品無損害及其除氣所容許的條件與時間，可將任何殘留的環氧乙烷氣體及其反應產物減低至該類產品或原物料所界定之允許限量。	8.73 This method should only be used when no other method is practicable. During process validation, it should be shown that there is no damaging effect on the product and that the conditions and time allowed for degassing result in the reduction of any residual ethylene oxide (EO) gas and reaction products to defined acceptable limits for the given product or material.
8.74 氣體與微生物細胞直接接觸是必要的，應採取預防措施以避免微生物可能被包覆在諸如晶體或乾燥的蛋白質等物質中。包裝材料的性質、孔隙率及數量會顯著影響滅菌過程。	8.74 Direct contact between gas and microbial cells is essential, precautions should be taken to avoid the presence of organisms likely to be enclosed in material such as crystals or dried protein. The nature, porosity and quantity of packaging materials can significantly affect the process.
8.75 暴露於氣體之前，應使原物料與製程所需的濕度及溫度達到平衡。使用蒸汽對裝載物進行滅菌前的溼度調整，蒸汽應具有適當的品質；在滅菌前達到該狀態所需的時間，應依相對需求加以均衡，縮減至最短。	8.75 Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process. Where steam is used to condition the load for sterilisation, it should be of an appropriate quality. The time required for this should be balanced against the opposing need to minimize the time before sterilisation.
8.76 每一個滅菌週期都應使用適當的生物指示劑進行監控，並將適當數量的測試單元分佈在整個裝載中的特定位置，這些位置在確效期間已被證明是最差狀況。	8.76 Each sterilisation cycle should be monitored with suitable BIs, using the appropriate number of test units distributed throughout the load at defined locations that have been shown to be worst case locations during validation.
8.77 滅菌製程確效及日常監控應考慮的關鍵製程參數，包括但不限於：	8.77 Critical process parameters that could be considered as part of the sterilisation process validation and routine monitoring include, but are not limited to:
i. EO 氣體濃度，	i. EO gas concentration,
i. 壓力，	ii. pressure,
ii. 使用的 EO 氣體量，	iii. amount of EO gas used,
iii. 相對濕度，	iv. relative humidity,
iv. 溫度，	v. temperature,
v. 暴露時間。	vi. exposure time.
8.78 滅菌後，裝載物應通氣以使 EO 氣體及	8.78 After sterilisation, the load should be aerated

/或其反應產物從包裝產品中釋出到預定水準。通氣過程可在滅菌器內及/或單獨的通氣艙或通氣室內進行。通氣階段應作為整體 EO 滅菌製程確效的一部分進行確效。	to allow EO gas and/or its reaction products to desorb from the packaged product to predetermined levels. Aeration can occur within a steriliser chamber and/or in a separate aeration chamber or aeration room. The aeration phase should be validated as part of the overall EO sterilisation process validation.
對無法在最終容器中滅菌的產品進行過濾滅菌	**Filter sterilisation of products which cannot be sterilised in their final container**
8.79 如果產品不能在其最終容器中滅菌，溶液或液體應通過無菌之滅菌級過濾器滅菌（過濾器孔徑最大為 0.22 μm，經過適當確效可獲得無菌濾液），並且隨後無菌充填到先前已滅菌的容器中。所用過濾器的選擇應確保其與產品相容並符合上市許可中的說明（參見第 8.135 點）。	8.79 If the product cannot be sterilised in its final container, solutions or liquids should be sterilised by filtration through a sterile sterilising grade filter (with a nominal pore size of a maximum of 0.22 μm that has been appropriately validated to obtain a sterile filtrate) and subsequently aseptically filled into a previously sterilised container. The selection of the filter used should ensure that it is compatible with the product and as described in the marketing authorization (see paragraph 8.135).
8.80 可以在製程中的多個點使用合適之減少負荷菌的預過濾器及/或滅菌級過濾器，以確保在最終滅菌過濾器前之液體的負荷菌低於管制標準。由於無菌過濾製程與其他滅菌製程相比具潛在額外風險，因此，通過儘可能靠近充填點的無菌滅菌級過濾器所進行之額外過濾，應視為整個 CCS 的一部分。	8.80 Suitable bioburden reduction prefilters and/or sterilising grade filters may be used at multiple points during the manufacturing process to ensure a low and controlled bioburden of the liquid prior to the final sterilising filter. Due to the potential additional risks of a sterile filtration process, as compared with other sterilisation processes, an additional filtration through a sterile sterilising grade filter, as close to the point of fill as possible, should be considered as part of an overall CCS.
8.81 過濾系統組件的選擇及其在過濾系統內的相互連接及排列，包括預過濾器，應基於產品的關鍵品質屬性，並經過合理證明與記錄。過濾系統應儘量減少纖維及微粒的產生，不會導致或促成不可接受的雜質/不純物限量，或具有以其他方式改變產品品質及效能的特性。同樣地，過濾器特性應與液體相容，並且不受待過濾產品的不利影響。應評估產品成分的吸附性及過濾器成分被萃出/浸出（參見第 8.135 點）。	8.81 The selection of components for the filtration system and their interconnection and arrangement within the filtration system, including pre-filters, should be based on the critical quality attributes of the product, justified and documented. The filtration system should minimize the generation of fibres and particles, not cause or contribute to unacceptable levels of impurities, or possess characteristics that otherwise alter the quality and efficacy of the product. Similarly, the filter characteristics should be compatible with the fluid and not be adversely affected by the product to be filtered. Adsorption of

	product components and extraction/leaching of filter components should be evaluated (see paragraph 8.135).
8.82 過濾系統的設計應：	8.82 The filtration system should be designed to:
i. 允許在經過確效的製程參數範圍內操作；	i. allow operation within validated process parameters;
ii. 保持濾液的無菌性；	ii. maintain the sterility of the filtrate;
iii. 儘量減少最末端滅菌級過濾器及產品最終充填之間所需的無菌連接數量；	iii. minimize the number of aseptic connections required between the final sterilising grade filter and the final filling of the product;
iv. 需要時，允許執行清潔程序；	iv. allow cleaning procedures to be conducted as necessary;
v. 允許進行必要的滅菌程序，包括原位滅菌。；	v. allow sterilisation procedures, including sterilisation in place, to be conducted as necessary;
vi. 允許在過濾之前及之後對 0.22 μm 最終滅菌級過濾器進行原位完整性測試，最好是一個密閉系統。應選擇原位完整性測試方法，以避免對產品品質產生任何不利影響。	vi. permit in-place integrity testing, of the 0.22 μm final sterilising grade filter, preferably as a closed system, both prior to, and following filtration as necessary. In-place integrity testing methods should be selected to avoid any adverse impact on the quality of the product.
8.83 液體的無菌過濾應根據相關藥典要求進行確效。確效可以按產品的不同含量或差異進行分組，但應針對最差的情況進行。分組的理由應該合理並文件化。	8.83 Sterile filtration of liquids should be validated in accordance with relevant Pharmacopeia requirements. Validation can be grouped by different strengths or variations of a product but should be done under worst case conditions. The rationale for grouping should be justified and documented.
8.84 在過濾器確效期間，應儘可能使用待過濾的產品執行滅菌級過濾器的細菌滯留試驗。如果要過濾的產品不適合用於細菌滯留測試，則應證明適合的替代產品用於該試驗之合理性。細菌滯留試驗中使用的挑戰微生物應有合理證明。	8.84 During filter validation, wherever possible, the product to be filtered should be used for bacterial retention testing of the sterilising grade filter. Where the product to be filtered is not suitable for use in bacterial retention testing, a suitable surrogate product should be justified for use in the test. The challenge organism used in the bacterial retention test should be justified.
8.85 確效時應考慮及建立的過濾參數應包括但不限於：	8.85 Filtration parameters that should be considered and established during validation should include, but are not limited to:
i. 用於過濾器完整性測試的潤濕液：	i. The wetting fluid used for filter integrity testing:
• 應根據過濾器製造商的建議或待過	• It should be based on the filter

濾液體。應建立適當的完整性測試值規格。	manufacturer's recommendation or the fluid to be filtered. The appropriate integrity test value specification should be established.
• 如果此系統用非產品的液體進行沖洗或原位完整性測試，應採取適當措施以避免對產品品質產生任何有害影響。	• If the system is flushed or integrity tested in-situ with a fluid other than the product, appropriate actions are taken to avoid any deleterious effect on product quality.
ii. 過濾製程條件包括：	ii.Filtration process conditions including:
• 液體預過濾後的保持時間及對生物負荷菌的影響，	• fluid pre-filtration holding time and effect on bioburden,
• 過濾器預處理，必要時使用液體，	• filter conditioning, with fluid if necessary,
• 最長的過濾時間/過濾器與液體接觸的總時間，	• maximum filtration time/total time filter is in contact with the fluid,
• 最大操作壓力，	• maximum operating pressure,
• 流速，	• flow rate,
• 最大過濾量，	• maximum filtration volume,
• 溫度，	• temperature,
• 過濾已知體積的半製品溶液所需的時間及過濾器上、下游的壓差。	• the time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter.
8.86 應實施例行製程管制以確保遵守經確效的過濾參數。關鍵製程參數的結果應包含在批次紀錄中，包括但不限於過濾已知體積之半製品溶液所需的最短時間，及過濾器上、下游的壓差。 製造過程中關鍵參數的任何顯著差異應予記錄與調查。	8.86 Routine process controls should be implemented to ensure adherence to validated filtration parameters. Results of critical process parameters should be included in the batch record, including but not limited to the minimum time taken to filter a known volume of bulk solution and pressure difference across the filter. Any significant difference from critical parameters during manufacturing should be documented and investigated.
8.87 滅菌過濾器組裝應在使用前通過完整性測試進行確認（使用前、滅菌後完整性測試或稱 PUPSIT），以檢查使用前過濾器在準備過程所造成的損壞及完整性損失。用於對液體進行滅菌的滅菌級過濾器，應在使用後先進行非破壞性完整性測試，再從其濾殼(housing)中取出過濾器。完整性測試過程應進行確效，測試結果應與確效期間所建立之過濾器的微生物滯留能力相關。使用的測試實例包括起泡點、擴散流、水侵入或持壓測試。	8.87 The integrity of the sterilised filter assembly should be verified by integrity testing before use (pre-use post sterilisation integrity test or PUPSIT), to check for damage and loss of integrity caused by the filter preparation prior to use. A sterilising grade filter that is used to sterilise a fluid should be subject to a non-destructive integrity test post-use prior to removal of the filter from its housing. The integrity test process should be validated and test results should correlate to the microbial retention capability of the filter established

由於製程限制（例如過濾非常少量的溶液），滅菌後 PUPSIT 可能並不總是可行，這是被認可的。在這些情況下，可以採取替代方法，前提是已經進行了徹底的風險評估，並且通過實施適當的控制措施來降低非完整的(non-integral)過濾系統的任何風險，以達到合規性。在此類風險評估中要考慮的要點應包括但不限於：	during validation. Examples of tests that are used include bubble point, diffusive flow, water intrusion or pressure hold test. It is recognized that PUPSIT may not always be possible after sterilisation due to process constraints (e.g. the filtration of very small volumes of solution). In these cases, an alternative approach may be taken providing that a thorough risk assessment has been performed and compliance is achieved by the implementation of appropriate controls to mitigate any risk of a non-integral filtration system. Points to consider in such a risk assessment should include but are not limited to:
i. 深入了解及管制過濾器滅菌製程，以確保將過濾器損壞的可能性降至最低。	i. in depth knowledge and control of the filter sterilisation process to ensure that the potential for damage to the filter is minimized,
ii. 深入了解及管制供應鏈，包括：	ii. in depth knowledge and control of the supply chain to include:
• 受委託的滅菌廠，	• contract sterilisation facilities,
• 明確的運輸機制，	• defined transport mechanisms,
• 已滅菌過濾器的包裝，防止在運輸及儲存過程中損壞過濾器。	• packaging of the sterilised filter, to prevent damage to the filter during transportation and storage.
iii. 深入的製程知識，例如：	iii. in depth process knowledge such as:
• 特定產品類型，包括微粒負荷量以及是否存在影響過濾器完整性數值的風險，例如改變完整性測試值的可能性，從而防止在使用後過濾器完整性測試期間檢測到非完整的過濾器；以及	• the specific product type, including particle burden and whether there exists any risk of impact on filter integrity values, such as the potential to alter integrity-testing values and therefore prevent the detection of a non-integral filter during a post-use filter integrity test; and
• 在最末端滅菌級過濾器之前執行預過濾及製程步驟，即可在滅菌過濾之前去除微粒負荷並使產品澄清。	• pre-filtration and processing steps, prior to the final sterilising grade filter, which would remove particle burden and clarify the product prior to the sterile filtration.
8.88 關鍵無菌氣體及空氣通氣之過濾器（與產品的無菌性直接相關）的完整性應在使用後通過測試確認，且濾芯應保留在過濾器組合或濾殼中。	8.88 The integrity of critical sterile gas and air vent filters (that are directly linked to the sterility of the product) should be verified by testing after use, with the filter remaining in the filter assembly or housing.
8.89 非關鍵空氣或氣體通氣過濾器的完整性	8.89 The integrity of non-critical air or gas vent

應在適當的時間間隔進行確認及記錄。如果氣體過濾器使用時間較長，則應在安裝時及更換前進行完整性測試。應根據風險規定及監控最長使用時間（例如，可行時，考慮最多使用次數及允許的熱處理/滅菌週期次數）。	filters should be confirmed and recorded at appropriate intervals. Where gas filters are in place for extended periods, integrity testing should be carried out at installation and prior to replacement. The maximum duration of use should be specified and monitored based on risk (e.g. considering the maximum number of uses and heat treatment/ sterilisation cycles permitted as applicable).
8.90 對於氣體過濾，應避免濾芯或過濾設備遭受非預期的受潮或潤濕。	8.90 For gas filtration, unintended moistening or wetting of the filter or filter equipment should be avoided.
8.91 如果滅菌過濾製程已被確效為由多個過濾器組成之系統以達到特定液體的無菌性，則此過濾系統被認為是單一的滅菌單元，系統內的所有過濾器在使用後應通過完整性測試。	8.91 If the sterilising filtration process has been validated as a system consisting of multiple filters to achieve the sterility for a given fluid, the filtration system is considered to be a single sterilising unit and all filters within the system should satisfactorily pass integrity testing after use.
8.92 在冗餘過濾系統中（其中第二個冗餘滅菌級過濾器作為支援，但經確效的滅菌製程只需要一個過濾器），應進行主要滅菌級過濾器的使用後完整性測試，如果證明是完整的，則不需要對冗餘（支援）過濾器進行使用後完整性測試。但是，如果第一個過濾器的使用後完整性測試失敗，則應對第二個（冗餘）過濾器進行使用後完整性測試，同時進行調查及風險評估，以確定導致第一個過濾器測試失敗的原因。	8.92 In a redundant filtration system (where a second redundant sterilising grade filter is present as a backup but the sterilising process is validated as only requiring one filter), post-use integrity test of the primary sterilising grade filter should be performed and if demonstrated to be integral, then a post-use integrity test of the redundant (backup) filter is not necessary. However, in the event of a failure of the post-use integrity test on the primary filter, post-use integrity test on the secondary (redundant) filter should be performed, in conjunction with an investigation and risk assessment to determine the reason for the primary filter test failure.
8.93 負荷菌樣品應從半製品中，以及在緊鄰最末端無菌過濾前取出。如果使用了冗餘的過濾裝置，則應在第一個過濾器之前進行。取樣系統的設計應避免引入污染。	8.93 Bioburden samples should be taken from the bulk product and immediately prior to the final sterile filtration. In case where a redundant filtration set-up is used, it should be taken prior to the first filter. Systems for taking samples should be designed so as not to introduce contamination.
8.94 液體滅菌級過濾器應在單一批次製程後丟棄，同一過濾器不應連續使用超過一個工作日，除非這種使用已確效。	8.94 Liquid sterilising grade filters should be discarded after the processing of a single batch and the same filter should not be used continuously for more than one working day unless such use has been validated.
8.95 如果產品的連續製造已在 CCS 中得到適	8.95 Where campaign manufacture of a product

當證明及確效，過濾器使用者應：	has been appropriately justified in the CCS and validated, the filter user should:
i. 評估並記錄特定液體的無菌過濾製程中，過濾器使用時間相關的風險；	i. assess and document the risks associated with the duration of filter use for the sterile filtration process for a given fluid;
ii. 進行並記錄有效的確效及驗證研究，以證明特定無菌過濾製程及特定液體的過濾器使用的持續時間不會影響最末端滅菌級過濾器的性能或濾液品質；	ii. conduct and document effective validation and qualification studies to demonstrate that the duration of filter use for a given sterile filtration process and for a given fluid does not compromise performance of the final sterilising grade filter or filtrate quality;
iii. 記錄過濾器的最長確效使用時間並予以管制，以確保過濾器的使用不超過確效的最長持續時間。應保留這些管制紀錄；	iii. document the maximum validated duration of use for the filter and implement controls to ensure that filters are not used beyond the validated maximum duration. Records of these controls should be maintained;
iv. 實施管制措施以確保被液體或清潔劑殘留物污染、或以任何其他方式被認為有缺陷的過濾器不會被使用。	iv. implement controls to ensure that filters contaminated with fluid or cleaning agent residues, or considered defective in any other way, are removed from use.
成型-充填-密封 (FFS)	**Form-Fill-Seal (FFS)**
8.96 用於最終滅菌產品的 FFS 機器的條件應符合本附則第 8.3 及 8.4 點的環境要求。用於無菌製造的 FFS 機器的條件應符合本附則第 8.10 點的環境要求。	8.96 The conditions for FFS machines used for terminally sterilised products should comply with the environmental requirements of paragraphs 8.3 and 8.4 of this Annex. The conditions for FFS machines used in aseptic manufacture should comply with the environmental requirements of paragraph 8.10 of this Annex.
8.97 組件製造、供應及處理過程中，應透過適當的管制將 FFS 製程中使用之包裝膜的污染降至最低。由於包裝膜的關鍵性，應實施程序以確保所提供的包裝膜符合界定的規格並具有適當的品質，包括材料厚度及強度、微生物及微粒污染的限量、完整性及相關的印刷圖文。 應在 PQS 中定義、管制包裝膜及相關組件的採樣頻率、負荷菌，以及可行時，內毒素/熱原限量，並在 CCS 中加以考慮。	8.97 Contamination of the packaging films used in the FFS process should be minimized by appropriate controls during component fabrication, supply and handling. Due to the criticality of packaging films, procedures should be implemented to ensure that the films supplied meet defined specifications and are of the appropriate quality, including material thickness and strength, microbial and particulate contamination, integrity and artwork, as relevant. The sampling frequency, the bioburden and, where applicable, endotoxin/pyrogen levels of packaging films and associated components should be defined and controlled within the PQS and considered in the CCS.

8.98 應特別注意了解及評估設備的操作，包括組裝、充填、密封及切割等製程，以便對關鍵製程參數能適當的了解、確效、管制及監測。	8.98 Particular attention should be given to understanding and assessing the operation of the equipment, including set-up, filling, sealing and cutting processes, so that critical process parameters are understood, validated, controlled and monitored appropriately.
8.99 任何與產品接觸的氣體，例如：給容器充氣或用於覆蓋產品的氣體應儘可能於靠近使用點處適當的過濾。應根據第 6.18 及 6.19 點定期確認所用氣體的品質及氣體過濾系統的有效性。	8.99 Any product contact gases, e.g. those used to inflate the container or used as a product overlay, should be appropriately filtered, as close to the point of use as possible. The quality of gases used and the effectiveness of gas filtration systems should be verified periodically in accordance with paragraphs 6.18 and 6.19.
8.100 FFS 驗證期間的管制措施應與 CCS 保持一致。需要考慮的面向包括但不限於：	8.100 The controls identified during qualification of FFS should be in alignment with the CCS. Aspects to be considered include but are not limited to:
i. 確定關鍵區域的界線，	i. determination of the boundaries of the critical zone,
ii. 環境管制及監測，包括機器及它所在的背景，	ii. environmental control and monitoring, both of the machine and the background in which it is placed,
iii. 人員著裝要求，	iii. personnel gowning requirements,
iv. 產品充填線及過濾系統的完整性測試（相關時），	iv. integrity testing of the product filling lines and filtration systems (as relevant),
v. 批次或充填活動的持續時間，	v. duration of the batch or filling campaign,
vi. 包裝膜的管制，包括對包裝膜去污染或滅菌的任何要求，	vi. control of packaging films, including any requirements for film decontamination or sterilisation,
vii. 必要時對設備進行原位清潔及原位滅菌，	vii. cleaning-in-place and sterilisation-in-place of equipment as necessary,
viii. 機器操作、設定及警報管理（相關時）。	viii. machine operation, settings and alarm management (as relevant).
8.101 FFS 的關鍵製程參數應在設備驗證期間確定，並應包括但不限於：	8.101 Critical process parameters for FFS should be determined during equipment qualification and should include, but are not limited to:
i. 根據經過確效的參數設定統一的包裝尺寸及切割；	i. settings for uniform package dimensions and cutting in accordance with validated parameters;

ii. 設定、維護及監測經過確效相關的成型溫度（包括預熱及冷卻）、成型時間及壓力；	ii. setting, maintenance and monitoring of validated forming temperatures (including pre-heating and cooling), forming times and pressures as relevant;
iii. 設定、維護及監測已確效相關的密封溫度、整個密封範圍的密封溫度均勻性、密封時間及壓力；	iii. setting, maintenance and monitoring of validated sealing temperatures, sealing temperature uniformity across the seal, sealing times and pressures as relevant;
iv. 環境及產品溫度；	iv. environmental and product temperature;
v. 批次特定之包裝的密封強度及均一性測試；	v. batch-specific testing of package seal strength and uniformity;
vi. 設定以達到正確的充填量、速度及充填均一性；	vi. settings for correct filling volumes, speeds and uniformity;
vii. 任何附加印刷（批次編碼）、凹凸壓花的設定，以確保單元完整性不受影響；	vii. settings for any additional printing (batch coding), embossing or debossing to ensure that unit integrity is not compromised;
viii. 充填容器完整性測試的方法及參數（參見第 8.22 點）。	viii. methods and parameters for integrity testing of filled containers (see paragraph 8.22).
8.102 在生產過程中應採用適當的程序來確認、監測及記錄 FFS 關鍵製程參數及設備操作。	8.102 Appropriate procedures for the verification, monitoring and recording of FFS critical process parameters and equipment operation should be applied during production.
8.103 操作程序應描述如何偵測、矯正成型及密封的問題。被拒用的單元或密封問題應予記錄及調查。	8.103 Operational procedures should describe how forming and sealing issues are detected and rectified. Rejected units or sealing issues should be recorded and investigated.
8.104 應根據風險制定適當的維護程序，包括對每一單元密封有效性之關鍵模具的維護及檢查計劃。任何被識別出有潛在產品品質問題的議題都應予記錄及調查。	8.104 Appropriate maintenance procedures should be established based on risk, and include maintenance and inspection plans for tooling critical to the effectiveness of unit sealing. Any issues identified that indicate a potential product quality concern should be documented and investigated.
吹製-充填-密封(BFS)	**Blow-Fill-Seal**
8.105 用於製造最終滅菌產品的吹製-充填-密封設備應安裝在至少 D 級環境中。充填點的條件應符合第 8.3 及 8.4 點的環境要求。	8.105 Blow-Fill-Seal equipment used for the manufacture of products which are terminally sterilised should be installed in at least a grade D environment. The conditions at the point of fill should comply with the environmental requirements of paragraphs 8.3 and 8.4.
8.106 BFS 用於無菌製程：	8.106 BFS used for aseptic processing:
i. 用於無菌充填的穿梭式設備，型坯對	i. For shuttle type equipment used for

環境是開放的，因此型坯擠出、吹出塑形及密封的關鍵區域應滿足 A 級條件。充填環境的設計及維護應滿足 A 級條件靜、動態之微生物及總微粒的限值。	aseptic filling, the parison is open to the environment and therefore the areas where parison extrusion, blow-moulding and sealing take place should meet grade A conditions at the critical zones. The filling environment should be designed and maintained to meet grade A conditions for viable and total particle limits both at rest and when in operation.
ii. 用於無菌充填的旋轉式設備，型坯通常一旦成型就成為密閉環境，型坯內的充填環境的設計及維護應滿足 A 級條件靜、動態之微生物及總微粒的限值。	ii. For rotary-type equipment used for aseptic filling, the parison is generally closed to the environment once formed, the filling environment within the parison should be designed and maintained to meet grade A conditions for viable and total particle limits both at rest and when in operation.
iii. 設備應至少安裝在 C 級環境中，前提是使用 A/B 級衣著。在 C 級區域對穿著 A/B 級衣著的作業人員進行微生物監測時，應按照風險管理原則進行，並考慮到作業人員所從事活動所適用的限值及監測頻率。	iii. The equipment should be installed in at least a grade C environment, provided that grade A/B clothing is used. The microbiological monitoring of operators wearing grade A/B clothing in a grade C area, should be performed in accordance with risk management principles, and the limits and monitoring frequencies applied with consideration of the activities performed by these operators.
8.107 由於聚合物在操作過程中的擠出及切割會產生微粒，以及 BFS 設備關鍵充填區的尺寸限制，因此不預期對 BFS 設備的總微粒進行動態監測。但是，應提供數據來證明設備的設計可確保充填製程環境的關鍵區域在動態下滿足 A 級條件。	8.107 Due to the generation of particles from polymer extrusion and cutting during operation, and the restrictive size of critical filling zones of BFS equipment, in operation monitoring of total particle for BFS equipment is not expected. However, data should be available to demonstrate that the design of the equipment ensures that critical zones of the filling process environment would meet grade A conditions in operation.
8.108 BFS 製程的微生物環境監測應基於風險，並根據本附則第 9 節進行設計。應在關鍵製程的整個過程中進行動態微生物監測，包括設備組裝。對於旋轉式 BFS 設備，可能無法監控關鍵充填區。	8.108 Viable environmental monitoring of BFS processes should be risk-based, and designed in accordance with section 9 of this Annex. In operation viable monitoring should be undertaken for the full duration of critical processing, including equipment assembly. For rotary-type BFS equipment, it is acknowledged that monitoring of the critical filling zone may not be possible.
8.109 環境管制及監測計畫應考慮 BFS 製程	8.109 The environmental control and monitoring

產生的移動部件與複雜的氣流路徑以及製程中高熱輸出的影響，(例如，通過使用氣流可視化研究及/或其他等效研究)。環境監測計畫還應考慮空氣過濾器配置、空氣過濾器完整性、冷卻系統完整性（參見第 6.21 點）、設備設計及驗證等因素。	programme should take into consideration the moving parts and complex airflow paths generated by the BFS process and the effect of the high heat outputs of the process, (e.g. through the use of airflow visualization studies and/or other equivalent studies). Environmental monitoring programmes should also consider factors such as air-filter configuration, air-filter integrity, cooling systems integrity (see paragraph 6.21), equipment design and qualification.
8.110 模製容器的擠出、成型或密封過程中與容器關鍵表面接觸的空氣或其他氣體應經適當過濾。應根據第 6.18 及 6.19 點定期確認所用氣體的品質及氣體過濾系統的有效性。	8.110 Air or other gases that make contact with critical surfaces of the container during extrusion, formation or sealing of the moulded container should undergo appropriate filtration. The quality of gas used and the effectiveness of gas filtration systems should be verified periodically in accordance with paragraphs 6.18 and 6.19.
8.111 聚合物顆粒的儲存、取樣及輸配系統應通過適當的設計、管制及維護，來防止聚合物顆粒的微粒及微生物污染。	8.111 Particulate and microbial contamination of the polymer granulate should be prevented by appropriate design, control, and maintenance of the polymer granulate storage, sampling and distribution systems.
8.112 應了解擠出系統為模製容器提供適當無菌保證的能力並予確效。原料聚合物的取樣頻率，負荷菌、以及可行時內毒素/熱原的限量應在 PQS 中界定及管制，並在 CCS 中加以考慮。	8.112 The capability of the extrusion system to provide appropriate sterility assurance for the moulded container should be understood and validated. The sampling frequency, the bioburden and, where applicable, endotoxin/pyrogen levels of the raw polymer should be defined and controlled within the PQS and considered in the CCS.
8.113 相關時，應在充填程序中清楚界定及描述要求停止充填及/或擠出、成型與密封，以及在需要時對充填機進行再滅菌的介入措施，並包含在 APS 中（參見第 9.34、9.35 及 9.36 點）。	8.113 Interventions requiring cessation of filling and/or extrusion, moulding and sealing and, where required, re-sterilisation of the filling machine should be clearly defined and described in the filling procedure, and included in the APS as relevant (see paragraphs 9.34, 9.35 and 9.36).
8.114 BFS 驗證期間確定的管制措施應與廠內的 CCS 保持一致。需要考慮的面向包括但不限於：	8.114 The controls identified during qualification of BFS should be in alignment with the site's CCS. Aspects to be considered include but are not limited to:
i. 確定關鍵區域的界線，	i. determination of the boundaries of the critical zone,
ii. 環境管制及監測，包括機器及它所	ii. environmental control and monitoring, both of the machine and the background

在的背景。	in which it is placed,
iii. 人員著裝要求，	iii. personnel gowning requirements,
iv. 產品充填線及過濾系統的完整性測試（相關時），	iv. integrity testing of the product filling lines and filtration systems (as relevant),
v. 批次或連續充填活動的時間，	v. duration of the batch or filling campaign,
vi. 管制聚合物顆粒，包括輸配系統及關鍵擠出溫度，	vi. control of polymer granulate, including distribution systems and critical extrusion temperatures,
vii. 必要時對設備進行原位清潔及原位滅菌，	vii. cleaning-in-place and sterilisation-in-place of equipment as necessary,
viii. 機器操作、設定及警報管理（相關時）。	viii. machine operation, settings and alarm management (as relevant).
8.115 BFS 的關鍵製程參數應在設備驗證期間確定，應包括但不限於：	8.115 Critical process parameters for BFS should be determined during equipment qualification and should include, but are not limited to:
i. 產品管路及充填針（心軸）的原位清潔及原位滅菌；	i. clean-in-place and sterilisation-in-place of product pipelines and filling needles (mandrels);
ii. 擠出參數的設定、維護及監控，包括溫度、速度及擠出喉部型坯厚度的設定；	ii. setting, maintenance and monitoring of extrusion parameters, including temperature, speed and extruder throat settings for parison thickness;
iii. 型坯溫度的設定、維護及監測，包括產品安定性所需的冷卻速率；	iii. setting, maintenance and monitoring of mould temperatures, including rate of cooling where necessary for product stability;
iv. 添加到模製單元之輔助組件的製備及滅菌，例如瓶蓋；	iv. preparation and sterilisation of ancillary components added to the moulded unit, e.g. bottle caps;
v. 相關時，關鍵之擠出、轉移及充填區域的環境管制、清潔、滅菌及監控；	v. environmental control, cleaning, sterilisation and monitoring of the critical extrusion, transfer and filling areas as relevant;
vi. 在容器的關鍵點測試批次特定的包裝壁厚度；	vi. batch-specific testing of package wall-thickness at critical points of the container;
vii. 設定以達到正確的充填量、速度及充填均一性；	vii. settings for correct filling volumes, speeds and uniformity;
viii. 設定任何附加的印刷（批次資訊）、凹版或凸版壓花，以確保包裝單元的完整性及品質不受影響；	viii. settings for any additional printing (batch coding), embossing or debossing to ensure that unit integrity and quality is not compromised;

ix. 所有充填容器經 100%完整性測試的方法及參數（參見第 8.22 點）；	ix. methods and parameters for integrity testing of 100% of all filled containers (see paragraph 8.22);
x. 設定用於去除充填單元周圍之廢塑料(毛邊去除)的切割器或銑模。	x. settings for cutters or punches used to remove waste plastic surrounding filled units (flash removal).
8.116 在生產過程中應採用適當的程序來確認、監測及記錄 BFS 關鍵製程參數與設備操作。	8.116 Appropriate procedures for the verification, monitoring and recording of BFS critical process parameters and equipment operation should be applied during production.
8.117 作業程序應描述如何檢測及矯正吹製、成型與密封問題。應記錄及調查被拒用單元或密封問題。	8.117 Operational procedures should describe how blowing, forming and sealing issues are detected and rectified. Rejected units or sealing issues should be recorded and investigated.
8.118 如果 BFS 製程包括添加組件到模製容器（例如，為 LVP 瓶添加蓋子），這些組件應適當去污染，並使用潔淨的、受管控的流程添加到製程中。	8.118 Where the BFS process includes the addition of components to moulded containers (e.g. addition of caps to LVP bottles), these components should be appropriately decontaminated and added to the process using a clean, controlled process.
i. 對於無菌製程，應在 A 級條件下添加組件，並使用預先滅菌的組件，以確保關鍵表面的無菌性。	i. For aseptic processes, the addition of components should be performed under grade A conditions, to ensure the sterility of critical surfaces, using pre-sterilised components.
ii. 對於最終滅菌的產品，最終滅菌製程確效應確保組件及模製容器之間所有關鍵產品路徑的無菌性，包括滅菌期間未潤濕的區域。	ii. For terminally sterilised products, the validation of terminal sterilisation processes should ensure the sterility of all critical product pathways between the component and moulded container, including areas that are not wetted during sterilisation.
iii. 應建立及確效測試程序，以確保組件及模製容器的有效密封。	iii. Testing procedures should be established and validated to ensure the effective sealing of components and moulded containers.
8.119 應根據風險制定適當的維護程序，包括對單元密封、完整性及無菌性關鍵品項的維護及檢查計畫。	8.119 Appropriate maintenance procedures should be established based on risk, and include maintenance and inspection plans for items critical to unit sealing, integrity and sterility.
8.120 用於形成容器的模具被認為是關鍵設備，對模具的任何變更或修改都應執行成品容器完整性的評估，並且評估的結果應經由確效支持。任何被識別出有潛在影響產品品質的議題，都應記錄並進	8.120 The moulds used to form containers are considered critical equipment and any changes or modification to moulds should result in an assessment of finished product container integrity, and where the assessment indicates, should be supported by

行調查。	validation. Any issues identified that indicate a potential product quality concern should be documented and investigated.
凍乾	**Lyophilization**
8.121 凍乾是一個關鍵的製程步驟，所有可能影響產品或原物料無菌性的活動，都需要被視為滅菌產品無菌製程的延伸。凍乾設備及其製程的設計應確保產品或原物料在凍乾過程中保持無菌性，藉由避免凍乾產品從充填到完成凍乾過程之間的微生物和微粒污染。所有線上的管制措施應由藥廠的 CCS 決定。	8.121 Lyophilization is a critical process step and all activities that can affect the sterility of the product or material need to be regarded as extensions of the aseptic processing of the sterilised product. The lyophilization equipment and its processes should be designed to ensure that product or material sterility is maintained during lyophilization by preventing microbial and particle contamination between the filling of products for lyophilization, and completion of lyophilization process. All control measures in place should be determined by the site's CCS.
8.122 凍乾機及相關設備（例如托盤、小瓶的支撐環）的滅菌應經確效，並在 APS 時對滅菌週期與使用之間的保持時間做適當的挑戰（參見第 9.33 點）。對凍乾機應根據系統設計定期滅菌。應在維護或清潔後進行重新滅菌。應保護已滅菌的凍乾機及相關設備不受污染。	8.122 The sterilisation of the lyophilizer and associated equipment (e.g. trays, vial support rings) should be validated and the holding time between the sterilisation cycle and use appropriately challenged during APS (see paragraph 9.33). The lyophilizer should be sterilised regularly, based on system design. Re-sterilisation should be performed following maintenance or cleaning. Sterilised lyophilizers and associated equipment should be protected from contamination after sterilisation.
8.123 凍乾機與相關的產品轉移，及裝載/卸載區域的設計應儘可能減少作業人員的介入。凍乾機滅菌的頻率應根據設計及使用過程中與系統污染相關的風險來確定。人工裝載或卸載且沒有屏障技術分離的凍乾機應在每次裝載前進行滅菌。對於由自動化系統裝載及卸載或由密閉屏障系統保護的凍乾機，應證明滅菌頻率之合理性，並文件化作為 CCS 的一部分。	8.123 Lyophilizers and associated product transfer and loading/unloading areas should be designed to minimize operator intervention as far as possible. The frequency of lyophilizer sterilisation should be determined based on the design and risks related to system contamination during use. Lyophilizers that are manually loaded or unloaded with no barrier technology separation should be sterilised before each load. For lyophilizers loaded and unloaded by automated systems or protected by closed barrier systems, the frequency of sterilisation should be justified and documented as part of the CCS.
8.124 在滅菌後及凍乾過程中應保持凍乾機	8.124 The integrity of the lyophilizer should be maintained following sterilisation and during

的完整性。用於保持凍乾機完整性的過濾器應在每次使用該系統前進行滅菌，其完整性測試結果應作為批次認可/放行的一部分。艙室的真空/洩漏完整性測試的頻率應予文件化，應規定容許滲入凍乾機的最大空氣量，並在每個凍乾週期開始時檢查。	lyophilization. The filter used to maintain lyophilizer integrity should be sterilised before each use of the system and its integrity testing results should be part of the batch certification/release. The frequency of vacuum/leak integrity testing of the chamber should be documented and the maximum permitted leakage of air into the lyophilizer should be specified and checked at the start of every cycle.
8.125 應定期檢查凍乾托盤確保無變形或損壞。	8.125 Lyophilization trays should be checked regularly to ensure that they are not misshapen or damaged.
8.126 裝載（及卸載，在凍乾物尚未密封且暴露的情況下）設計的考慮要點包括但不限於：	8.126 Points to consider for the design of loading (and unloading, where the lyophilized material is still unsealed and exposed), include but are not limited to:
i. 應規定凍乾機內的裝載型式並予文件化。	i. The loading pattern within the lyophilizer should be specified and documented.
ii. 將部分封閉的容器轉送到凍乾機時，應始終在 A 級條件下進行，並以儘量減少作業人員直接介入的方式進行處理。應使用輸送帶系統或移動式轉送系統（例如潔淨空氣轉運車、移動式單向氣流工作站）等技術，以確保用於部分封閉容器的轉送系統能維持其潔淨度。或者，經確效的情況下，在 A 級區密封且在 B 級區未重新打開的托盤，可用於保護部分封塞的小瓶（例如適當封閉的盒子）。	ii. The transfer of partially closed containers to a lyophilizer should be undertaken under grade A conditions at all times and handled in a manner designed to minimize direct operator intervention. Technologies such as conveyor systems or portable transfer systems (e.g. clean air transfer carts, portable unidirectional airflow workstations) should be used to ensure that the cleanliness of the system used to transfer the partially closed containers is maintained. Alternatively, where supported by validation, trays closed in grade A and not reopened whilst in the grade B area may be used to protect partially stoppered vials (e.g. appropriately closed boxes).
iii. 運輸裝置及裝載區的通風不應對氣流型態產生不利影響。	iii. Airflow patterns should not be adversely affected by transport devices and venting of the loading zone.
iv. 未密封的容器（例如部分封塞的小瓶）應保持在 A 級條件下，通常應通過實體屏障技術或任何其他適當措施與作業人員隔開。	iv. Unsealed containers (such as partially stoppered vials) should be maintained under grade A conditions and should normally be separated from operators by physical barrier technology or any other appropriate measures.
v. 如果在打開凍乾機艙室之前產品屬	v. Where seating of the stoppers is not

於未完成封塞狀態，則從凍乾機中取出的產品在隨後的處理過程中應保持在 A 級條件下。	completed prior to opening the lyophilizer chamber, product removed from the lyophilizer should remain under grade A conditions during subsequent handling.
vi. 裝載及卸載凍乾機時使用的器具（例如托盤、袋子、定位裝置、鑷子）應是無菌的。	vi. Utensils used during loading and unloading of the lyophilizer (e.g. trays, bags, placing devices, tweezers) should be sterile.
密閉系統	**Closed systems**
8.127 使用密閉系統可以降低來自鄰近環境的微生物、微粒及化學污染的風險。密閉系統應始終設計為減少人工操作的需求及相關風險。	8.127 The use of closed systems can reduce the risk of microbial, particle and chemical contamination from the adjacent environment. Closed systems should always be designed to reduce the need for manual manipulations and the associated risks.
8.128 確保用於無菌製程之密閉系統的所有與產品接觸表面的無菌性至關重要。用於無菌製程之任何密閉系統的設計及選擇，應確保能維持無菌狀態。在末端滅菌級過濾器之後，無菌設備（例如管線/管路）與滅菌產品路徑的連接應設計為無菌連接（例如通過內建無菌連接裝置）。	8.128 It is critical to ensure the sterility of all product contact surfaces of closed systems used for aseptic processing. The design and selection of any closed system used for aseptic processing should ensure maintenance of sterility. Connection of sterile equipment (e.g. tubing/pipework) to the sterilised product pathway after the final sterilising grade filter should be designed to be connected aseptically (e.g. by intrinsic sterile connection devices).
8.129 應採取適當措施確保無菌連接中使用組件的完整性。實現這一目標的方法應在 CCS 中確定及記錄。當存在損害產品無菌性風險時，應考慮進行適當的系統完整性測試。供應商評估應包括可能導致系統喪失無菌性之潛在失敗模式相關數據的整理。	8.129 Appropriate measures should be in place to ensure the integrity of components used in aseptic connections. The means by which this is achieved should be determined and captured in the CCS. Appropriate system integrity tests should be considered when there is a risk of compromising product sterility. Supplier assessment should include the collation of data in relation to potential failure modes that may lead to a loss of system sterility.
8.130 密閉系統所處的背景環境應基於其設計及所採取的製程。對於無菌製程且該系統的完整性可能受到損害的任何風險，該系統應位於 A 級區。如果可以證明系統在每次使用時都保持完整（例如通過壓力測試及/或監控），那麼可以使用較低的級區。應徹底評估級區之間的任何轉送（參見第 4.10 點）。若密閉系統有打開需求時（例如，半製品製	8.130 The background environment in which closed systems are located should be based on their design and the processes undertaken. For aseptic processing and where there are any risks that system integrity may be compromised, the system should be located in grade A. If the system can be shown to remain integral at every usage (e.g. via pressure testing and/or monitoring) then a lower classified area may

造線的維護），則應在適合該原物料的級區進行（例如，用於最終滅菌製程的 C 級區，或用於無菌製程的 A 級區）或進一步清潔及消毒（如為無菌製程則應滅菌）。	be used. Any transfer between classified areas should be thoroughly assessed (see paragraph 4.10). If the closed system is opened (e.g. for maintenance of a bulk manufacturing line) then this should be performed in a classified area appropriate to the materials (e.g. grade C for terminal sterilisation processes, or grade A for aseptic processing) or be subject to further cleaning and disinfection (and sterilisation in case of aseptic processes).
一次性使用系統 (SUS)	**Single use systems (SUS)**
8.131 SUS 是用於製造無菌產品的技術，可替代重複使用的設備。SUS 可以是單一組件，也可以由多個組件組成，例如袋子、過濾器、管線、連接器、閥門、儲存瓶及傳感器。一次性使用系統應設計為減少對人為操作的需求及人工介入的複雜性。	8.131 SUS are those technologies used in manufacture of sterile products which are used as an alternative to reusable equipment. SUS can be individual components or made up of multiple components such as bags, filters, tubing, connectors, valves, storage bottles and sensors. Single use systems should be designed to reduce the need for manipulations and complexity of manual interventions.
8.132 有些與 SUS 相關的特定風險，應作為 CCS 的一部分進行評估。這些風險包括但不限於：	8.132 There are some specific risks associated with SUS which should be assessed as part of the CCS. These risks include but are not limited to:
i. 產品與產品接觸表面之間的相互作用（如吸附，或浸出與萃取），	i. the interaction between the product and product contact surface (such as adsorption, or leachables and extractables),
ii. 相較於固定的可重複使用系統之脆弱本質，	ii. the fragile nature of the system compared with fixed reusable systems,
iii. 增加人工操作(包括檢查及系統處理)與連接的數量及複雜性，	iii. the increase in the number and complexity of manual operations (including inspection and handling of the system) and connections made,
iv. 組裝的複雜性，	iv. the complexity of the assembly,
v. 滅菌級過濾器使用前及使用後完整性測試的性能（參見第 8.87 點），	v. the performance of the pre- and post-use integrity testing for sterilising grade filters (see paragraph 8.87),
vi. 存在孔洞及洩漏的風險，	vi. the risk of holes and leakage,
vii. 打開外包裝時可能危及系統，	vii. the potential for compromising the system at the point of opening the outer packaging,
viii. 微粒污染的風險。	viii. the risk of particle contamination.

8.133 SUS 的滅菌製程應經過確效，並證明對系統性能無不利影響。	8.133 Sterilisation processes for SUS should be validated and shown to have no adverse impact on system performance.
8.134 一次性使用系統(包括滅菌)供應商的評估，對於這些系統的選擇及使用至關重要。對於無菌 SUS，無菌保證的確認應為供應商驗證的一部分，並且應在接收時，檢查每一個單元的滅菌證據。	8.134 Assessment of suppliers of disposable systems including sterilisation is critical to the selection and use of these systems. For sterile SUS, verification of sterility assurance should be performed as part of the supplier qualification and evidence of sterilisation of each unit should be checked on receipt.
8.135 產品與產品接觸表面的吸附及反應性應在製程條件下進行評價。	8.135 The adsorption and reactivity of the product with product contact surfaces should be evaluated under process conditions.
8.136 應評價 SUS 的可萃取物及可浸出物的概貌，以及對產品品質的任何影響，特別是由聚合物材料製成的一次性使用系統。應對每一組件進行評估，以評價可萃取物概貌數據的適用性。對於被認為可浸出物有高風險的組件，包括可能吸收製程物質或與其接觸時間較長的組件，應考慮對可浸出物概貌研究的評估，包括安全性問題。如果應用模擬的製程條件，則應準確反映實際製程，並具有科學依據。	8.136 The extractable and leachable profiles of the SUS and any impact on the quality of the product especially where the system is made from polymer-based materials should be evaluated. An assessment should be carried out for each component to evaluate the applicability of the extractable profile data. For components considered to be at high risk from leachables, including those that may absorb processed materials or those with extended material contact times, an assessment of leachable profile studies, including safety concerns, should be taken into consideration. If applying simulated processing conditions, these should accurately reflect the actual processing conditions and be based on a scientific rationale.
8.137 SUS 應設計為在預期作業條件下的整個製程中保持完整性。如果在例行製程或運輸過程中可能會暴露在更極端的條件下(例如冷凍及解凍過程)，則必須注意一次性使用組件的結構完整性。這應包括確認內建的無菌連接裝置（熱封及機械式密封）在這些條件下保持完整。	8.137 SUS should be designed to maintain integrity throughout processing under the intended operational conditions. Attention to the structural integrity of the single use components is necessary where these may be exposed to more extreme conditions (e.g. freezing and thawing processes) either during routine processing or transportation. This should include verification that intrinsic sterile connection devices (both heat sealed and mechanically sealed) remain integral under these conditions.
8.138 應根據產品及其製程的風險或關鍵性，為 SUS 建立及實施允收標準。接	8.138 Acceptance criteria should be established and implemented for SUS corresponding to the risks or criticality of the products and its

收時，應檢查每件 SUS，以確保它們是按照核准的規格製造、供應和運送的。使用前應對外包裝（例如外部紙箱、產品袋的外觀）、標籤打印及附加文件（例如合格證書及滅菌證明）進行目視檢查，並文件化。	processes. On receipt, each piece of SUS should be checked to ensure that they have been manufactured, supplied and delivered in accordance with the approved specification. A visual inspection of the outer packaging (e.g. appearance of exterior carton, product pouches), label printing, and review of attached documents (e.g. certificate of conformance and proof of sterilisation) should be carried out and documented prior to use.
8.139 SUS 的關鍵人工處理作業，例如組裝及連接，應受到適當的管制，並在 APS 期間進行確認。	8.139 Critical manual handling operations of SUS such as assembly and connections should be subject to appropriate controls and verified during APS.
9.環境與製程監測 (Environmental & process monitoring)	
概述	**General**
9.1 藥廠的環境及製程監測計畫是整體 CCS 的一部分，是用於監測將微生物及微粒污染風險降至最低的管制措施。應該注意的是，將監測系統的每個要項（微生物、浮游微粒及 APS）分開之後的個別可靠性是有限的，所以不應被個別地考量為無菌狀態指標。當一起考量時，其結果有助於確認它們所監測之系統的設計、確效及操作的可靠性。	9.1 The site's environmental and process monitoring programme forms part of the overall CCS and is used to monitor the controls designed to minimize the risk of microbial and particle contamination. It should be noted that the reliability of each of the elements of the monitoring system (viable, non-viable and APS) when taken in isolation is limited and should not be considered individually to be an indicator of asepsis. When considered together, the results help confirm the reliability of the design, validation and operation of the system that they are monitoring.
9.2 該計畫通常由以下要項組成：	9.2 This programme is typically comprised of the following elements:
i. 環境監測—總微粒；	i. environmental monitoring – total particle;
ii. 環境及人員監測—微生物；	ii. environmental and personnel monitoring – viable particle;
iii. 溫度、相對濕度及其他特定性質；	iii. temperature, relative humidity and other specific characteristics;
iv. APS（僅限於無菌製造之產品）。	iv. APS (aseptically manufactured product only).
9.3 來自這些系統之資訊應使用於例行批次認可/放行以及製程檢討或調查期間之定期評估。這適用於最終滅菌及無菌製程，但是，其影響的嚴重程度可能因產品及製程類型而異。	9.3 The information from these systems should be used for routine batch certification/release and for periodic assessment during process review or investigation. This applies for both terminal sterilisation and aseptic processes, however, the criticality of the impact may differ

	depending upon the product and process type.
環境與製程監測	**Environmental and process monitoring**
9.4 應建立文件化的環境監測計畫。環境監測計畫的目的是：	9.4 An environmental monitoring programme should be established and documented. The purpose of the environmental monitoring programme, is to:
i. 確保潔淨室及潔淨空氣設備依設計及法規要求，以持續提供適當的空氣潔淨度環境。	i. Provide assurance that cleanrooms and clean air equipment continue to provide an environment of appropriate air cleanliness, in accordance with design and regulatory requirements.
ii. 有效地偵測出對於環境限值的偏離，以啟動對於產品品質風險的調查及評估。	ii. Effectively detect excursions from environmental limits triggering investigation and assessment of risk to product quality.
應執行風險評估以建立全面的環境監測計畫，亦即採樣位置、監測頻率、監測方法以及培養條件（例如：時間、溫度、好氧及/或厭氧條件）。執行這些風險評估應基於以下的詳細知識：投入製程的原物料及最終產品、設施、設備、特定製程及步驟的關鍵性、所涉及之操作、例行監測數據、於驗證期間所獲得之監測數據以及從環境中所分離出來之代表性菌叢的知識。	Risk assessments should be performed in order to establish this comprehensive environmental monitoring programme, i.e. sampling locations, frequency of monitoring, monitoring methods and incubation conditions (e.g. time, temperature(s), aerobic and/or anaerobic conditions). These risk assessments should be conducted based on detailed knowledge of; the process inputs and final product, the facility, equipment, the criticality of specific processes and steps, the operations involved, routine monitoring data, monitoring data obtained during qualification and knowledge of typical microbial flora isolated from the environment.
該風險評估應包含確定關鍵監測位置，亦即在製程中如有微生物存在則可能會對產品品質產生影響的位置（例如：A 級區、無菌作業區以及與 A 級區直接交界的 B 級區）。還應考量納入空氣可視化研究等其他資訊。這些風險評估應予定期審查，以確認藥廠環境監測計畫的有效性。應考量將監測計畫納入藥廠之整體趨勢分析與 CCS 範圍中。	The risk assessment should include the determination of critical monitoring locations, those locations where the presence of microorganisms during processing may have an impact upon product quality, (e.g. grade A, aseptic processing areas and the grade B areas that directly interface with the grade A area). Consideration of other information such as air visualisation studies should also be included. These risk assessments should be reviewed regularly in order to confirm the effectiveness of the site's environmental monitoring programme. The monitoring programme should be considered in the overall context of the trend analysis and the CCS for the site.
9.5 對潔淨室、潔淨空氣設備以及人員之日常監測，應在所有關鍵製程階段的動態中執行，包括設備組裝。	9.5 Routine monitoring of cleanrooms, clean air equipment and personnel should be performed in operation throughout all critical stages of processing, including equipment set-up.

9.6 諸如溫度及相對濕度等其他特性，應控制在符合產品/製程/人員需求的範圍內，並支持所界定之潔淨度標準（例如：A 級區或 B 級區）的維持。	9.6 Other characteristics, such as temperature and relative humidity, should be controlled within ranges that align with product/processing/personnel requirements and support maintenance of defined cleanliness standards (e.g. grade A or B).
9.7 對於 A 級區的監測應能證明關鍵操作過程中無菌製程條件的維持。應在對於無菌的設備表面、容器、封蓋以及產品造成最高污染風險的位置執行監測。為了在關鍵區域獲得可靠數據，監測位置的選擇以及採樣裝置的方向與定位應合理且適當。	9.7 The monitoring of grade A should demonstrate the maintenance of aseptic processing conditions during critical operations. Monitoring should be performed at locations posing the highest risk of contamination to the sterile equipment surfaces, containers, closures and product. The selection of monitoring locations and the orientation and positioning of sampling devices should be justified and appropriate to obtain reliable data from the critical zones.
9.8 採樣方法不應對製造作業造成污染風險。	9.8 Sampling methods should not pose a risk of contamination to the manufacturing operations.
9.9 應對微生物及總微粒監測的結果設定適當的警戒水準及行動限量。最大總微粒行動限量描述於表 5，最大微生物行動限量描述於表 6。但是，可採用基於數據的趨勢、製程本質或於 CCS 決定之更嚴格的行動限量。微生物及總微粒警戒水準的建立均應基於潔淨室驗證的測試結果，並基於持續的趨勢數據予以定期審查。	9.9 Appropriate alert levels and action limits should be set for the results of viable and total particle monitoring. The maximum total particle action limits are described in Table 5 and the maximum viable particle action limits are described in Table 6. However, more stringent action limits may be applied based on data trending, the nature of the process or as determined within the CCS. Both viable and total particle alert levels should be established based on results of cleanroom qualification tests and periodically reviewed based on ongoing trend data.
9.10 A 級區（僅總微粒）、B 級區、C 級區以及 D 級區之警戒水準的設定，應能使不良趨勢（例如：事件的次數或顯示環境管制劣化的個別事件）被偵測出並予解決。	9.10 Alert levels for grade A (total particle only) grade B, grade C and grade D should be set such that adverse trends (e.g. a numbers of events or individual events that indicate a deterioration of environmental control) are detected and addressed.
9.11 監測程序中應明訂趨勢分析方法。趨勢應包含，但不限於：	9.11 Monitoring procedures should define the approach to trending. Trends should include, but are not limited to:
i. 越來越多的偏離行動限量或警戒水準；	i. increasing numbers of excursions from action limits or alert levels;
ii. 連續偏離警戒水準；	ii. consecutive excursions from alert levels;
iii. 規律但獨立的偏離行動限量可能是有共同的原因（例如：總是在計畫性預	iii. regular but isolated excursion from action limits that may have a common cause, (e.g.

防維護之後發生的單次偏離）；	single excursions that always follow planned preventative maintenance);
iv. 微生物菌叢類型與數量及主要特定微生物的改變。特別應注意採集到微生物可能顯示管制失效、潔淨度劣化或難以管制的微生物，諸如會形成孢子的微生物及黴菌等。	iv. changes in microbial flora type and numbers and predominance of specific organisms. Particular attention should be given to organisms recovered that may indicate a loss of control, deterioration in cleanliness or organisms that may be difficult to control such as spore-forming microorganisms and moulds.
9.12 執行 C 級區及 D 級區潔淨室的動態監測，應基於驗證期間所收集之數據及例行數據，以利有效的趨勢分析。警戒水準及行動限量之要求應取決於所執行之作業的性質。行動限量可能比表 5 及表 6 中所列更嚴格。	9.12 The monitoring of grade C and D cleanrooms in operation should be performed based on data collected during qualification and routine data to allow effective trend analysis. The requirements of alert levels and action limits will depend on the nature of the operations carried out. Action limits may be more stringent than those listed in Table 5 and Table 6.
9.13 如果超過行動限量，則應於作業程序中明訂根本原因調查、對產品潛在影響評估（包括在監測與產生報告之間所生產的批次）以及矯正與預防措施的要求。如果超過警戒水準，則應於操作程序中規定評估及追蹤，其中應包含調查及/或矯正措施以避免環境進一步劣化之考量。	9.13 If action limits are exceeded, operating procedures should prescribe a root cause investigation, an assessment of the potential impact to product (including batches produced between the monitoring and reporting) and requirements for corrective and preventive actions. If alert levels are exceeded, operating procedures should prescribe assessment and follow-up, which should include consideration of an investigation and/or corrective actions to avoid any further deterioration of the environment.
環境監測—總微粒	**Environmental monitoring – total particle**
9.14 應建立總微粒監測計畫以獲得評估潛在污染風險的數據，並確保無菌作業環境維持在驗證狀態。	9.14 A total particle monitoring program should be established to obtain data for assessing potential contamination risks and to ensure the maintenance of the environment for sterile operations in a qualified state.
9.15 每一級區環境監測之浮游微粒濃度限量見表 5。	9.15 The limits for environmental monitoring of airborne particle concentration for each graded area are given in Table 5.
表 5：被允許之總微粒監測的最大濃度。 **級區** / **≧0.5μm/m³ 粒子的最大限量** / **≧5 μm/m³ 粒子的最大限量**	Table 5: Maximum permitted total particle concentration for monitoring. **Grade** / **Maximum limits for total particle ≥ 0.5 μm/m³** / **Maximum limits for total particle ≥ 5 μm/m³**

	靜態	動態	靜態	動態
A	3 520	3 520	29	29
B	3 520	352 000	29	2 930
C	352 000	3520 000	2 930	29 300
D	3 520 000	未預先訂定[a]	29 300	未預先訂定[a]

(a) 對於 D 級區，動態的限量沒有預先訂定。適用時，製造廠應依風險評估及例行數據建立動態的行動限量。

	at rest	in operation	at rest	In operation
A	3 520	3 520	29	29
B	3 520	352 000	29	2 930
C	352 000	352 000	2 930	29 300
D	3 520 000	Not predetermined [a]	29 300	Not predetermined [a]

(a) For grade D, in operation limits are not predetermined. The manufacturer should establish in operation limits based on a risk assessment and on routine data, where applicable.

註 1：表中之"靜態"狀態的微粒限量應在完成操作之後的無人狀態下，於驗證期間所界定之短暫的"清除"期間（指引值小於 20 分鐘）後達到（參見第 4.29 點）。

Note 1: The particle limits given in the table for the "at rest" state should be achieved after a short "clean up" period defined during qualification (guidance value of less than 20 minutes) in an unmanned state, after the completion of operations (see paragraph 4.29).

註 2：由於電子雜訊、迷光、偶合漏失等原因，會偶爾顯示出 A 級區內的大顆粒(尤其是≥ 5μm)，這可能被認為是非真實計數。然而，連貫性或規則性的低計數可能是污染事件的指標，應予調查。此類事件可能顯示室內空氣供應過濾系統的早期故障、設備故障，或者，亦可能係在機器安裝及例行操作期間不良操作的徵兆。

Note 2: The occasional indication of macro particle counts, especially ≥ 5 μm, within grade A may be considered to be false counts due to electronic noise, stray light, coincidence loss etc. However, consecutive or regular counting of low levels may be indicative of a possible contamination event and should be investigated. Such events may indicate early failure of the room air supply filtration system, equipment failure, or may also be diagnostic of poor practices during machine set-up and routine operation.

9.16 對於 A 級區，應在關鍵製程(包括設備組裝)的全程中執行微粒監測。

9.16 For grade A, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly.

9.17 A 級區之 ≥0.5 及 ≥5 μm 的微粒應予連續監測，並以合適之採樣流速（至少每分鐘 28 L [1ft3]），以偵測所有介入、短暫突發事件以及任何的系統劣化。系統應經常將每個個別的樣本結果與警戒水準及行動限量相比對，這樣的頻率可以識別出任何潛在的偏差並即時回應。如果超過警戒水準，則應啟動警報。作業程序中應界定警報時所需採取的行動，包括考慮額外的微生物監測。

9.17 The grade A area should be monitored continuously (for particles ≥0.5 and ≥5 μm) and with a suitable sample flow rate (at least 28 litres (1ft3) per minute) so that all interventions, transient events and any system deterioration is captured. The system should frequently correlate each individual sample result with alert levels and action limits at such a frequency that any potential excursion can be identified and responded to in a timely manner. Alarms should be triggered if alert levels are exceeded. Procedures should define

	the actions to be taken in response to alarms including the consideration of additional microbial monitoring.
9.18 雖然在 B 級區的採樣頻率可能可以降低，但仍建議使用類似的系統。B 級區應以適當的取樣量及頻率執行監測，以使監測程序能夠偵測出任何增加的污染及系統劣化程度。如果超過警戒水準，則警報應會被啟動。	9.18 It is recommended that a similar system be used for the grade B area although the sample frequency may be decreased. The grade B area should be monitored at such a frequency and with suitable sample size that the programme captures any increase in levels of contamination and system deterioration. If alert levels are exceeded, alarms should be triggered.
9.19 監測系統的選擇應考量製造作業中所使用之原物料（例如：包含活微生物、粉末狀產品或放射性藥品）所可能增加之生物、化學或輻射危害的任何風險。	9.19 The selection of the monitoring system should take into account any risk presented by the materials used in the manufacturing operation (e.g. those involving live organisms, powdery products or radiopharmaceuticals) that may give rise to biological, chemical or radiation hazards.
9.20 對於製程中出現污染物而且可能損壞微粒計數器或呈現危害（例如：活微生物、粉末狀產品以及輻射危害）的情況，其所採用的頻率及策略應確保在暴露於風險前、後之環境等級。應考量增加微生物監測，以確保製程的全面監測。此外，應於模擬操作期間執行監測。這類操作應以適當的時間間隔執行，並明訂於 CCS 中。	9.20 In the case where contaminants are present due to the processes involved and would potentially damage the particle counter or present a hazard (e.g. live organisms, powdery products and radiation hazards), the frequency and strategy employed should be such as to assure the environmental classification both prior to and post exposure to the risk. An increase in viable particle monitoring should be considered to ensure comprehensive monitoring of the process. Additionally, monitoring should be performed during simulated operations. Such operations should be performed at appropriate intervals. The approach should be defined in the CCS.
9.21 使用自動化系統所採集之監測樣本量，通常依所使用之系統的採樣速率而定。樣本量不需與用於潔淨室及潔淨空氣設備之正式分級的樣本量相同。監測樣本量之合理性應經證明。	9.21 The size of monitoring samples taken using automated systems will usually be a function of the sampling rate of the system used. It is not necessary for the sample volume to be the same as that used for formal classification of cleanrooms and clean air equipment. Monitoring sample volumes should be justified.
環境及人員監測—微生物	**Environmental and personnel monitoring – viable particle**
9.22 應於執行無菌操作的場所頻繁地使用諸如落菌培養皿、定量空氣採樣器、手套、	9.22 Where aseptic operations are performed, microbial monitoring should be frequent using a combination of methods such as settle

工作服以及表面採樣工具（例如：擦拭及接觸培養皿）等的組合方法監測微生物。所使用之採樣方法應於 CCS 中證明其合理性，且應證明不會對 A 級區及 B 級區氣流型態產生不利影響。潔淨室及設備表面應於操作結束時予以監測。	plates, volumetric air sampling, glove, gown and surface sampling (e.g. swabs and contact plates). The method of sampling used should be justified within the CCS and should be demonstrated not to have a detrimental impact on grade A and B airflow patterns. Cleanroom and equipment surfaces should be monitored at the end of an operation.
9.23 在非執行正常製造作業期間（例如：消毒後、開始製造前、批次完成及停工期之後）的潔淨室內，以及未使用之相關房間內，也應執行微生物監測，以偵測可能影響潔淨室內管制的潛在污染事件。在發生意外事件時，可以使用額外的採樣位置來確認矯正措施（例如：清潔及消毒）的有效性。	9.23 Viable particle monitoring should also be performed within the cleanrooms when normal manufacturing operations are not occurring (e.g. post disinfection, prior to start of manufacturing, on completion of the batch and after a shutdown period), and in associated rooms that have not been used, in order to detect potential incidents of contamination which may affect the controls within the cleanrooms. In case of an incident, additional sample locations may be used as a verification of the effectiveness of a corrective action (e.g. cleaning and disinfection).
9.24 A 級區的關鍵製程應全程持續監測微生物（例如：以空氣採樣器或落菌培養皿），包括設備無菌組裝及關鍵製程。應基於影響無菌製程之風險考量，對 B 級區潔淨室採用類似的方法。監測的執行方式應能偵測出所有介入、短暫突發事件以及任何系統劣化，並避免因監測操作的介入而導致任何風險。	9.24 Continuous viable air monitoring in grade A (e.g. air sampling or settle plates) should be undertaken for the full duration of critical processing, including equipment (aseptic set-up) assembly and critical processing. A similar approach should be considered for grade B cleanrooms based on the risk of impact on the aseptic processing. The monitoring should be performed in such a way that all interventions, transient events and any system deterioration would be captured and any risk caused by interventions of the monitoring operations is avoided.
9.25 風險評估應依所執行之作業及與關鍵區的鄰近程度，來評估人員監測的位置、類型及頻率。監測應包含在製程中定期對人員採樣。對人員採樣應以不會危及製程之方式進行。應特別考量在參與關鍵介入之後（可根據介入程度監測工作服相關部位，但至少一定要監測手套）及每次離開 B 級區潔淨室之人員的監測（手套及工作服）。當在關鍵介入之後對手套執行監測時，應在繼續工作之前更換外層手套。當在關鍵介入後需要監	9.25 A risk assessment should evaluate the locations, type and frequency of personnel monitoring based on the activities performed and the proximity to critical zones. Monitoring should include sampling of personnel at periodic intervals during the process. Sampling of personnel should be performed in such a way that it will not compromise the process. Particular consideration should be given to monitoring personnel following involvement in critical interventions (at a minimum gloves, but may require monitoring of areas of gown as

測工作服時，應在潔淨室內進行後續作業前更換工作服。

applicable to the process) and on each exit from the grade B cleanroom (gloves and gown). Where monitoring of gloves is performed after critical interventions, the outer gloves should be replaced prior to continuation of activity. Where monitoring of gowns is required after critical interventions, the gown should be replaced before further activity in the cleanroom.

9.26 應對在 A 級區及 B 級區的人員執行微生物監測。對於本質是人工操作之作業（例如：無菌調配或充填），其所增加的風險應導致加強工作服的微生物監測，並在 CCS 中證明其合理性。

9.26 Microbial monitoring of personnel in the grade A and grade B areas should be performed. Where operations are manual in nature (e.g. aseptic compounding or filling), the increased risk should lead to enhanced emphasis placed on microbial monitoring of gowns and justified within the CCS.

9.27 當由製造人員執行例行性監測時，應接受品質單位的定期監督（亦請參見第 8.19 點）。

9.27 Where monitoring is routinely performed by manufacturing personnel, this should be subject to regular oversight by the quality unit (refer also to paragraph 8.19).

9.28 製造廠應考量採用合適的替代監測系統，例如快速方法，以加快偵測微生物污染問題並降低產品風險。在經確效證明與已建立之方法等同或更佳後，可以採用這些快速且自動化的微生物監測方法。

9.28 The adoption of suitable alternative monitoring systems such as rapid methods should be considered by manufacturers in order to expedite the detection of microbiological contamination issues and to reduce the risk to product. These rapid and automated microbial monitoring methods may be adopted after validation has demonstrated their equivalency or superiority to the established methods.

9.29 應充分了解所使用之採樣方法及設備，且應備有作業程序以供正確操作與解讀所得結果。應可取得對於所選用採樣方法之回收效率的支持性數據。

9.29 Sampling methods and equipment used should be fully understood and procedures should be in place for the correct operation and interpretation of results obtained. Supporting data for the recovery efficiency of the sampling methods chosen should be available.

9.30 微生物污染的行動限量如表 6 所示

9.30 Action limits for viable particle contamination are shown in Table 6

表 6：微生物污染的最大行動限量

等級	空氣樣品 CFU /m^3	落菌培養皿（直徑 90 mm） CFU /4 小時[a]	接觸培養皿 (直徑55 mm), CFU / plate [b]	手套指印，包括雙手 5 指 CFU/手套

Table 6: Maximum action limits for viable particle contamination

Grade	Air sample cfu/m^3	Settle plates (diam. 90 mm) CFU/4 hours [a]	Contact plates (diam. 55mm), CFU/ plate [b]	Glove print, Including 5 fingers on both hands CFU/

A	無生長(c)			
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

				glove
A	No growth(c)			
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

(a) 落菌培養皿應在作業期間（包括設備組裝）暴露於 A 級區及 B 級區，並在最多 4 小時之後依需要進行更換(暴露時間應基於包含回收研究在內的確效,且不應對所使用之培養基的適用性產生任何負面影響)。

- 對於 C 級區及 D 級區，其暴露時間（最多 4 小時）及頻率應基於 QRM。
- 個別落菌培養皿的暴露時間可以少於 4 小時。

(a) - Settle plates should be exposed in grade A and B areas for the duration of operations (including equipment set-up) and changed as required after a maximum of 4 hours (exposure time should be based on validation including recovery studies and it should not have any negative effect on the suitability of the media used).

- For grade C and D areas, exposure time (with a maximum of 4 hours) and frequency should be based on QRM.
- Individual settle plates may be exposed for less than 4 hours.

(b) 接觸培養皿限量適用於 A 級區及 B 級區內的設備、房間及工作服表面。C 級區及 D 級區通常不需要例行的工作服監測，這取決於該區域功能而定。

(b) Contact plate limits apply to equipment, room and gown surfaces within the grade A and grade B areas. Routine gown monitoring is not normally required for grade C and D areas, depending on their function.

(c) 應注意，對於 A 級區內的任何長菌情形都應予調查。

(c) It should be noted that for grade A, any growth should result in an investigation.

註 1：應注意上表所列出的監測方法類型僅是舉例，也可以使用其他方法，其前提是可符合為產品可能被污染之整個關鍵製程提供資訊的目的（例如：無菌生產線組裝、無菌製程、充填及凍乾機裝載）。

Note 1: It should be noted that the types of monitoring methods listed in the table above are examples and other methods can be used provided they meet the intent of providing information across the whole of the critical process where product may be contaminated (e.g. aseptic line set-up, aseptic processing, filling and lyophilizer loading).

註 2：在整份文件中使用 CFU 作為限量的單位。當使用不同的或新的技術以不同於 CFU 的方式呈現結果時，製造廠應科學地證明被應用之限量的合理性，並在可能的情況下將其與 CFU 相關聯。

Note 2: Limits are applied using CFU throughout the document. If different or new technologies are used that present results in a manner different from CFU, the manufacturer should scientifically justify the limits applied and where possible correlate them to CFU.

9.31 在 A 級區及 B 級區被偵測出來的微生物，應鑑別到種，並評估此類微生物對產品品質（對所涉及之每一批次）及整體管制狀態的潛在影響。對於 C 級區及 D 級區，亦應考量對於在超出行動限量或警戒水準等場合所偵測到的、或在微生物分離後所得到的諸如可形成孢子之微生物與黴菌等難予管制之微生物的

9.31 Microorganisms detected in the grade A and grade B areas should be identified to species level and the potential impact of such microorganisms on product quality (for each batch implicated) and overall state of control should be evaluated. Consideration should also be given to the identification of microorganisms detected in grade C and D areas (for example where action limits or alert levels are exceeded) or following the isolation

鑑別；且以足夠的頻率來維持對於這些區域之當前典型菌叢的了解。	of organisms that may indicate a loss of control, deterioration in cleanliness or that may be difficult to control such as spore-forming microorganisms and moulds and at a sufficient frequency to maintain a current understanding of the typical flora of these areas.
無菌製程模擬 (APS)（亦稱為培養基充填）	**Aseptic process simulation (APS) (also known as media fill)**
9.32 對於無菌操作管制之有效性的定期確認應包含 APS(使用無菌營養培養基及/或替代物代替產品)。APS 不應被視為是確效該無菌製程或該無菌製程之各層面的主要方法。無菌製程之有效性應透過製程設計、遵守製藥品質系統與製程管制、教育訓練以及評估監測數據來確認。適當的營養培養基及/或替代物之選擇應基於其模擬產品於製程中具無菌性風險的產品實質特性之評估。對於諸如以無菌生產的半固體、粉末、固形物、微球體、微脂體以及產品被冷卻或被加熱或被凍乾等其他劑型，在製程階段可能有會間接影響任何被引入之污染微生物的生存能力時，應儘可能開發代表該項操作的近似替代程序。在諸如緩衝劑等替代物被使用為 APS 的一部分時，該替代物不應抑制任何潛在污染物的生長。	9.32 Periodic verification of the effectiveness of the controls in place for aseptic processing should include an APS using a sterile nutrient media and/or surrogate in place of the product. The APS should not be considered as the primary means to validate the aseptic process or aspects of the aseptic process. The effectiveness of the aseptic process should be determined through process design, adherence to the pharmaceutical quality system and process controls, training, and evaluation of monitoring data. Selection of an appropriate nutrient media and/or surrogate should be made based on the ability of the media and/or surrogate to imitate physical product characteristics assessed to pose a risk to product sterility during the aseptic process. Where processing stages may indirectly impact the viability of any introduced microbial contamination, (e.g. aseptically produced semi-solids, powders, solid materials, microspheres, liposomes and other formulations where product is cooled or heated or lyophilized), alternative procedures that represent the operations as closely as possible should be developed. Where surrogate materials, such as buffers, are used in parts of the APS, the surrogate material should not inhibit the growth of any potential contamination.
9.33 APS 應儘可能模擬例行無菌製程，且包含所有關鍵性製造步驟，尤其是：	9.33 The APS should imitate as closely as possible the routine aseptic manufacturing process and include all the critical manufacturing steps, specifically:
i. APS 應評估被使用於製程之原物料在滅菌及去污染行程後直到容器被密封之前被執行的所有無菌操作。	i. The APS should assess all aseptic operations performed subsequent to the sterilisation and decontamination cycles of materials utilised in the process to the

	point where the container is sealed.
ii. 對於不可過濾的產品,任何額外的無菌步驟均應經過評估。	ii. For non-filterable formulations, any additional aseptic steps should be assessed.
iii. 當無菌製造是在惰性氣體環境下執行時,除非意圖執行厭氧模擬,否則應於製程模擬時以空氣取代惰性氣體。	iii. Where aseptic manufacturing is performed under an inert atmosphere, the inert gas should be substituted with air in the process simulation unless anaerobic simulation is intended.
iv. 當製程需要添加無菌粉末時,盛裝可被接受之替代物的容器應與被評價之製程所用的容器相同。	iv. Processes requiring the addition of sterile powders should use an acceptable surrogate material in the same containers as those used in the process under evaluation.
v. 應避免分開模擬個別的單元操作(例如:涉及無菌粉末之乾燥、混合、粉碎及細分的製程)。採取任何個別模擬均應文件化佐證其合理性,並確保個別模擬的總和持續全面地涵蓋整個製程。	v. Separate simulations of individual unit operations (e.g. processes involving drying, blending, milling and subdivision of a sterile powder) should be avoided. Any use of individual simulations should be supported by a documented justification and ensure that the sum total of the individual simulations continues to fully cover the whole process.
vi. 凍乾產品的製程模擬程序應代表整個無菌製程鏈,包括充填、運送、裝載、在艙室停留(chamber dwell)的代表性期間、卸載與密封等經合理界定並予文件化的最差狀況操作參數 。	vi. The process simulation procedure for lyophilized products should represent the entire aseptic processing chain including filling, transport, loading, a representative duration of the chamber dwell, unloading and sealing under specified, documented and justified conditions representing worst case operating parameters.
vii. 除了可能影響污染物存活性或復甦外,凍乾製程模擬應模擬製程的所有層面。例如:應避免溶液沸騰或凍結。在確定 APS 設計時,要考量的因素包括(合適時): • 使用空氣替代氮氣或其他製程氣體來破真空, • 重現凍乾機在滅菌與使用之間的最長時間間隔, • 重現過濾與凍乾之間的最長期間,以及 • 最差狀況下的量化,例如:裝載最大數量的托盤、重現艙室(chamber) 開放於環境中的最長	vii. The lyophilization process simulation should mimic all aspects of the process, except those that may affect the viability or recovery of contaminants. For instance, boiling-over or actual freezing of the solution should be avoided. Factors to consider in determining APS design include, where applicable: • the use of air to break vacuum instead of nitrogen or other process gases, • replicating the maximum interval between sterilisation of the lyophilizer and its use, • replicating the maximum period of time between filtration and lyophilization, and

裝載期間。	• quantitative aspects of worst-case situations, e.g. loading the largest number of trays, replicating the longest duration of loading where the chamber is open to the environment.
9.34 APS 應考量在正常生產及最差狀況下已知會發生的各種無菌操作及介入，且考量下列事項：	9.34 The APS should take into account various aseptic manipulations and interventions known to occur during normal production as well as worst-case situations, and take into account the following:
i. 代表該例行製程的常規及矯正性介入，應以與例行無菌製程相似的方式及頻率執行。	i. Inherent and corrective interventions representative of the routine process should be performed in a manner and frequency similar to that during the routine aseptic process.
ii. APS 中之介入的內容及頻率，應基於對產品無菌性造成風險之評估。	ii. The inclusion and frequency of interventions in the APS should be based on assessed risks posed to product sterility.
9.35 APS 不應被用於證明那些造成非必要污染風險之作業的正當性。	9.35 APS should not be used to justify practices that pose unnecessary contamination risks.
9.36 在制定 APS 計畫時，應考量下列事項：	9.36 In developing the APS plan, consideration should be given to the following:
i. 識別涵蓋相關變因之最差狀況的條件，例如：容器尺寸、作業線速度及對製程的影響。評估的結果應能證明所選變因的合理性。	i. Identification of worst case conditions covering the relevant variables, such as container size and line speed, and their impact on the process. The outcome of the assessment should justify the variables selected.
ii. 確定用於確效之容器/封蓋組合的代表性尺寸。當製程相等性經科學證明合理時，可以考量使用涵括法或矩陣法來確效相同容器/封蓋組合的不同產品。	ii. Determining the representative sizes of container/closure combinations to be used for validation. Bracketing or matrix approach may be considered for validation of the same container/closure configuration for different products where process equivalence is scientifically justified.
iii. 無菌產品及設備在無菌製程中暴露的最大允許保持時間。	iii. Maximum permitted holding times for sterile product and equipment exposed during the aseptic process.
iv. 每個容器的充填量應足以確保培養基接觸到所有可能直接污染無菌產品之所有設備及組件的表面，且應提供足夠的頂部空間以支持潛在微生物的生長，並確保在檢查期間可以偵測到混濁度。	iv. The volume filled per container, which should be sufficient to ensure that the media contacts all equipment and component surfaces that may directly contaminate the sterile product. The volume used should provide sufficient headspace to support potential microbial

	growth and ensure that turbidity can be detected during inspection.
v. 除非意圖模擬厭氧，否則須使用空氣替代例行無菌製程中所使用的任何惰性氣體。在這些情況下，應考量將偶爾的厭氧模擬納入整體確效策略的一部分（參見第 9.33 點第 iii 項）。	v. The requirement for substitution of any inert gas used in the routine aseptic manufacturing process by air unless anaerobic simulation is intended. In these situations, inclusion of occasional anaerobic simulations as part of the overall validation strategy should be considered (see paragraph 9.33 point iii).
vi. 所選定的營養培養基應能供相關藥典所描述之指定對照微生物及代表性環境分離菌(representative local isolates)的生長。	vi. The selected nutrient media should be capable of growing a designated group of reference microorganisms as described by the relevant pharmacopeia and suitably representative local isolates.
vii. 偵測微生物污染的方法應科學地證明其合理性，以確保可靠地偵測到污染。	vii. The method of detection of microbial contamination should be scientifically justified to ensure that contamination is reliably detected.
viii. 製程模擬應有足夠的時間，以挑戰製程、執行介入的作業人員、輪班以及為無菌產品製造提供適當條件之製備環境的能力。	viii. The process simulation should be of sufficient duration to challenge the process, the operators that perform interventions, shift changes and the capability of the processing environment to provide appropriate conditions for the manufacture of a sterile product.
ix. 在製造廠執行不同的或延長的班次時，應設計 APS 以獲取與那些班次相關、且經評估會對產品無菌性造成風險的因素，例如作業人員可以出現在潔淨室中的最長時間。	ix. Where the manufacturer operates different or extended shifts, the APS should be designed to capture factors specific to those shifts that are assessed to pose a risk to product sterility, for example the maximum duration for which an operator may be present in the cleanroom.
x. 模擬正常無菌製造中斷之生產怠工情形（例如換班、重新填裝給料容器、導入附加設備）。	x. Simulating normal aseptic manufacturing interruptions where the process is idle (e.g. shift changeovers, recharging dispensing vessels, introduction of additional equipment)
xi. 確保依照例行生產要求執行環境監測，並貫徹於整個製程模擬期間。	xi. Ensuring that environmental monitoring is conducted as required for routine production, and throughout the entire duration of the process simulation.
xii. 在應用連續批次製造時，例如使用屏障技術或製造無菌原料藥，應考量設計及執行製程模擬，以便模擬連續批	xii. Where campaign manufacturing occurs, such as in the use of Barrier Technologies or manufacture of sterile active substances, consideration should be given

次製造之開始與結束的相關風險，並證明該期間不造成任何風險。	to designing and performing the process simulation so that it simulates the risks associated with both the beginning and the end of the campaign and demonstrating that the campaign duration does not pose any risk.
xiii. 執行“生產後或連續的 APS”之結果，可被用作額外的保證或調查目的；然而，它們的使用應在 CCS 中證明其合理性，且不應取代例行的 APS。如果使用，則應證明任何殘留的產品不會對任何潛在微生物污染的回收產生負面影響。	xiii. The performance of "end of production or campaign APS" may be used as additional assurance or investigative purposes; however, their use should be justified in the CCS and should not replace routine APS. If used, it should be demonstrated that any residual product does not negatively impact the recovery of any potential microbial contamination.
9.37 對於無菌原料藥，其批量應大到足以代表例行操作及在最差狀況下的模擬介入操作，並涵蓋所有可能與無菌產品接觸的表面。此外，所有模擬物（替代物或生長培養基）均應評估其微生物。模擬物應足以滿足被模擬製程的評估，且不應影響微生物的回收。	9.37 For sterile active substances, batch size should be large enough to represent routine operation, simulate intervention operation at the worst case, and cover all surfaces that may come into contact with the sterile product. In addition, all the simulated materials (surrogates or growth medium) should be subjected to microbial evaluation. The simulation materials should be sufficient to satisfy the evaluation of the process being simulated and should not compromise the recovery of micro-organisms.
9.38 APS 的執行應作為初始確效的一部分，至少要有 3 次連續成功的模擬試驗，且涵蓋可能會涉及無菌製程的所有工作輪班，以及經評估會對產品無菌保證有影響的操作實務、設施、服務或設備之任何重大修改(例如：HVAC 系統及設備的修改、製程變更、輪班次數及人員數量、主要設施關閉)。通常，每一無菌製程、每一充填線以及每一輪班班次均應每年重複兩次（約每六個月一次）APS（定期再確效）。每位作業人員每年至少應參與一次成功的 APS。應考量在停工之前的最後一批之後、在長時間沒有使用之前、以及在生產線除役或搬遷之前執行 APS。	9.38 APS should be performed as part of the initial validation, with at least three consecutive satisfactory simulation tests that cover all working shifts that the aseptic process may occur in, and after any significant modification to operational practices, facilities, services or equipment which are assessed to have an impact on the sterility assurance of the product (e.g. modification to the HVAC system, equipment, changes to process, number of shifts and numbers of personnel, major facility shut down). Normally, APS (periodic revalidation) should be repeated twice a year (approximately every six months) for each aseptic process, each filling line and each shift. Each operator should participate in at least one successful APS annually. Consideration should be given to performing an APS after the last batch prior to shut down, before long periods of inactivity

	or before decommissioning or relocation of a line.
9.39 在人工操作（例如：無菌調製或充填）的情況下，每一類型容器、容器封蓋及一序列的設備均應予執行初始確效，應在每位作業人員參與下執行連續 3 次成功的 APS，且每位作業人員大約每 6 個月應以一次 APS 再確效。APS 的批量應模擬例行無菌製造作業使用的批量。	9.39 Where manual operation (e.g. aseptic compounding or filling) occurs, each type of container, container closure and equipment train should be initially validated with each operator participating in at least 3 consecutive successful APS and revalidated with one APS approximately every 6 months for each operator. The APS batch size should mimic that used in the routine aseptic manufacturing process.
9.40 APS 操作（充填）的單元數應足以有效地模擬無菌製造作業中具代表性的所有活動。CCS 中應清楚地闡釋充填單元數之合理性。通常，至少要充填 5,000 到 10,000 單元。對於小批量（例如：小於 5,000 單元），其 APS 的容器數應至少等於生產批次的數量。	9.40 The number of units processed (filled) for APS should be sufficient to effectively simulate all activities that are representative of the aseptic manufacturing process. Justification for the number of units to be filled should be clearly captured in the CCS. Typically, a minimum of 5000 to 10000 units are filled. For small batches (e.g. those under 5000 units), the number of containers for APS should at least equal the size of the production batch.
9.41 已充填的 APS 單元應在培養前予以振搖、旋轉或倒置，以確保培養基與容器的所有內表面接觸。來自 APS 的所有容器封蓋完整之單元均應予以培養及評估，包含有外觀缺陷的單元或經過非破壞性製程管制檢查的單元。如果單元在製程模擬期間被丟棄且未培養，則這些單元應與例行充填期間被丟棄的單元相當；並且僅當與生產 SOP 所明確規定必須丟棄之相同情況時（即介入類型、生產線位置、移除特定單元數），才可移除該單元。在任何情況下，於培養基充填介入期間被移除的單元都不應多於生產期間被移除的單元。例如包含在例行生產期間的組裝過程後或在特定類型之介入後必須移除的單元。為了充分了解製程及評估無菌組裝或強制性生產線清理期間的污染風險，這些單元通常會被單獨培養，並可能不包含在 APS 的允收標準中。	9.41 Filled APS units should be agitated, swirled or inverted before incubation to ensure contact of the media with all interior surfaces in the container. All integral units from the APS should be incubated and evaluated, including units with cosmetic defects or those which have gone through non-destructive in-process control checks. If units are discarded during the process simulation and not incubated, these should be comparable with units discarded during a routine fill, and only if production SOPs clearly specify that units must be removed under the same circumstances (i.e. type of intervention; line location; specific number of units removed). In no case should more units be removed during a media fill intervention than would be cleared during a production run. Examples may include those that must be discarded during routine production after the set-up process or following a specific type of intervention. To fully understand the process and assess contamination risks during aseptic setup or mandatory line clearances, these units

	would typically be incubated separately, and would not necessarily be included in the acceptance criteria for the APS.
9.42 如果製程包含與產品接觸表面接觸但隨後即被丟棄的原物料（例如產品沖洗液），則被丟棄的原物料應該用營養培養基模擬且當作 APS 的一部分予以培養，除非可以清楚地證明廢棄過程不會影響產品的無菌性。	9.42 Where processes include materials that contact the product contact surfaces but are then discarded (e.g. product flushes), the discarded material should be simulated with nutrient media and be incubated as part of the APS, unless it can be clearly demonstrated that this waste process would not impact the sterility of the product.
9.43 已充填的 APS 單元應在透明容器中培養，以確保可目視偵測微生物生長。當產品容器不透明（例如：琥珀色玻璃、不透明塑料）時，可以使用相同構造的透明容器替代，以幫助偵測污染。當無法以相同構造之透明容器替代時，則應開發及確效合適的微生物生長偵測方法。可行時，被從受污染單元中所分離出來的微生物應予鑑別到種，以幫助確定可能的污染物來源。	9.43 Filled APS units should be incubated in a clear container to ensure visual detection of microbial growth. Where the product container is not clear (e.g. amber glass, opaque plastic), clear containers of identical configuration may be substituted to aid in the detection of contamination. When a clear container of identical configuration cannot be substituted, a suitable method for the detection of microbial growth should be developed and validated. Microorganisms isolated from contaminated units should be identified to the species level when practical, to assist in the determination of the likely source of the contaminant.
9.44 如無延遲之必要，則已充填的 APS 單元應立即培養，以達到潛在污染的最可能復甦。培養條件及培養時程的選擇應經過科學闡釋及確效，以提供適當程度的微生物污染偵測靈敏度。	9.44 Filled APS units should be incubated without unnecessary delay to achieve the best possible recovery of potential contamination. The selection of the incubation conditions and duration should be scientifically justified and validated to provide an appropriate level of sensitivity of detection of microbial contamination.
9.45 培養完成後：	9.45 On completion of incubation:
i. 已充填的 APS 單元應由受過適當偵測微生物污染之訓練且經資格驗證的人員檢查。檢查應在利於識別任何微生物污染的條件下執行。	i. Filled APS units should be inspected by personnel who have been appropriately trained and qualified for the detection of microbiological contamination. Inspection should be conducted under conditions that facilitate the identification of any microbial contamination.
ii. 已充填單元的樣品應接種適當範圍的對照菌種及具適當代表性的環境分離菌，以執行陽性對照。	ii. Samples of the filled units should undergo positive control by inoculation with a suitable range of reference organisms and suitably representative local isolates.

9.46 目標應該是零生長。任何受到污染的單元應判定 APS 失敗，且應採取下列措施：	9.46 The target should be zero growth. Any contaminated unit should result in a failed APS and the following actions should be taken:
i. 調查並確定最可能的根本原因；	i. an investigation to determine the most probable root cause(s);
ii. 確定及執行適當的矯正措施；	ii. determination and implementation of appropriate corrective measures;
iii. 應執行足夠次數（通常至少 3 次）之成功的、連續重複的 APS，以證明該製程已回復到管制狀態；	iii. a sufficient number of successful, consecutive repeat APS (normally a minimum of 3) should be conducted in order to demonstrate that the process has been returned to a state of control;
iv. 及時審查自前次成功的 APS 以來與無菌生產有關之所有適當紀錄； a) 審查結果應包含對自上次成功的 APS 以來所製造批次中所潛在之無菌偏離的風險評估。 b) 所有未放行到市場的其他批次均應納入調查範圍。任何有關其放行狀態的決定均應考量調查結果。	iv. a prompt review of all appropriate records relating to aseptic production since the last successful APS; a) The outcome of the review should include a risk assessment of potential sterile breaches in batches manufactured since the last successful APS. b) All other batches not released to the market should be included in the scope of the investigation. Any decision regarding their release status should consider the investigation outcome.
v. 製程模擬失敗之後，該生產線所製造之所有產品均應予隔離，直到製程模擬失敗已被成功解決；	v. all products that have been manufactured on a line subsequent to a process simulation failure should be quarantined until a successful resolution of the process simulation failure has occurred;
vi. 如果根本原因調查顯示失敗與作業人員的活動有關，則應採取措施以限制作業人員的活動，直到已重新完成訓練及資格驗證；	vi. where the root cause investigation indicates that the failure was related to operator activity, actions to limit the operator's activities, until retrained and requalified, should be taken;
vii. 只有成功地完成再確效後才可恢復生產。	vii. production should resume only after completion of successful revalidation.
9.47 所有 APS 的運行應予完整文件化且包含已處理單元（例如：已充填的單元數、已培養及未培養的單元數）的數量調和。文件中應包含已充填及未培養單元數量的合理說明。在 APS 過程中執行的所有介入均應予記錄，包括每次介入的開始及結束時間以及所涉及的人員。所	9.47 All APS runs should be fully documented and include a reconciliation of units processed (e.g. units filled, incubated and not incubated). Justification for filled and non-incubated units should be included in the documentation. All interventions performed during the APS should be recorded, including the start and

有微生物監測數據以及其他測試數據均應記錄於 APS 批次紀錄中。	end time of each intervention and the involved person. All microbial monitoring data as well as other testing data should be recorded in the APS batch record.
9.48 應僅在有書面程序要求商業批次同樣處理的情況下，才可中止 APS 的行程。在這種情況下，應有文件化的調查。	9.48 An APS run should be aborted only under circumstances in which written procedures require commercial lots to be equally handled. An investigation should be documented in such cases.
9.49 在下列情況下，無菌製程應重複初始的確效：	9.49 An aseptic process should be subject to a repeat of the initial validation when:
i. 已長時間未操作該特定的無菌製程；或	i. the specific aseptic process has not been in operation for an extended period of time; or
ii. 製程、設備、程序或環境發生的變化可能會影響無菌製程，或增加新的產品容器或容器-封蓋組合。	ii. there is a change to the process, equipment, procedures or environment that has the potential to affect the aseptic process or an addition of new product containers or container-closure combinations.
10.品質管制 (Quality Control ,QC)	
10.1 應有在微生物學、無菌保證及製程知識方面經適當訓練及經驗的人員，以支持製造作業之設計、環境監測管理，及評估微生物相關事件對於無菌產品安全性之影響的任何調查。	10.1 There should be personnel available with appropriate training and experience in microbiology, sterility assurance and knowledge of the processes to support the design of the manufacturing activities, environmental monitoring regime and any investigation assessing the impact of microbiologically linked events to the safety of the sterile product.
10.2 當監測作業及/或 CCS 指出有需要時，原料、組件及產品之規格應包含微生物、微粒及內毒素/熱原限量之要求。	10.2 Specifications for raw materials, components and products should include requirements for microbial, particulate and endotoxin/pyrogen limits when the need for this has been indicated by monitoring and/or by the CCS.
10.3 對於每一批次無菌充填的產品及最終滅菌的產品皆應執行負荷菌分析，並將其結果視為最終批次審查的一部分。緊接末端滅菌級過濾器或最終滅菌製程前之負荷菌應規定其限量，該限量與要採用之滅菌方法的效能有關。所採樣品應代表最差狀況（例如在保持時間之終點）。對於最終滅菌產品其參數設定為過度滅菌者，負荷菌應在適當排定之時間間隔監測。	10.3 The bioburden assay should be performed on each batch for both aseptically filled product and terminally sterilised products and the results considered as part of the final batch review. There should be defined limits for bioburden immediately before the final sterilising grade filter or the terminal sterilisation process, which are related to the efficiency of the method to be used. Samples should be taken to be representative of the worst case scenario (e.g. at the end of hold time). Where overkill sterilisation parameters are set for terminally sterilised products,

	bioburden should be monitored at suitable scheduled intervals.
10.4對於經許可以參數放行之產品，應制定已充填產品於滅菌行程前負荷菌監測之支持性計畫，且應對每一批次執行負荷菌分析。滅菌前充填單元之取樣位置應基於最差狀況並能代表該批。在負荷菌試驗期間所發現之任何微生物均應予鑑別，並確定其對滅菌製程有效性的影響。合適時，應監測內毒素/熱原含量。	10.4 For products authorised for parametric release, a supporting pre-sterilisation bioburden monitoring programme for the filled product prior to initiating the sterilisation cycle should be developed and the bioburden assay should be performed for each batch. The sampling locations of filled units before sterilisation should be based on a worst case scenario and be representative of the batch. Any organisms found during bioburden testing should be identified and their impact on the effectiveness of the sterilising process determined. Where appropriate, the level of endotoxin/pyrogen should be monitored.
10.5最終產品的無菌試驗，應僅被認為是一系列確保無菌性之關鍵控制下的最後措施。它不能用於確保不符合其設計、程序或確效參數之產品的無菌性。該測試應依產品加以確效。	10.5 The sterility test applied to the finished product should only be regarded as the last in a series of critical control measures by which sterility is assured. It cannot be used to assure sterility of a product that does not meet its design, procedural or validation parameters. The test should be validated for the product concerned.
10.6無菌試驗應在無菌條件下執行。無菌試驗所抽取之樣品應代表整個批次，尤其應包含取自該批次中被認為最具污染風險之部分的樣品，例如：	10.6 The sterility test should be performed under aseptic conditions. Samples taken for sterility testing should be representative of the whole of the batch but should in particular include samples taken from parts of the batch considered to be most at risk of contamination, for example:
i. 對於經無菌充填之產品，其樣品應包含在該批次之開始與結束時的產品。另應基於風險進行額外取樣(例如：在重大介入後所充填之產品)。	i. For products which have been filled aseptically, samples should include containers filled at the beginning and end of the batch. Additional samples, e.g. taken after critical interventions should be considered based on risk.
ii. 對於以最終容器形式加熱滅菌之產品，其所取樣品應能代表最差狀況的位置（例如：在每一裝載之潛在的最冷或加熱最慢的部位）。	ii. For products which have been heat sterilised in their final containers, samples taken should be representative of the worst case locations (e.g. the potentially coolest or slowest to heat part of each load).
iii. 對於經凍乾的產品，其樣品應取自不同的凍乾裝載。	iii. For products which have been lyophilized, samples taken from different lyophilization loads.
註：如果在製造過程產生子批次（例如：最終	Note: Where the manufacturing process results in sub-batches (e.g. for terminally sterilised products)

滅菌產品），則應從每個子批次中抽取無菌試驗用樣品，並對每個子批次樣品執行無菌試驗。另應考量對其他最終產品試驗項目分別執行試驗。	then sterility samples from each sub-batch should be taken and a sterility test for each sub-batch performed. Consideration should also be given to performing separate testing for other finished product tests.
10.7 某些產品可能由於架儲期太短，以致無法在放行前完成無菌試驗以獲得無菌試驗結果。在這些情況下，應採用額外的製程設計與額外的監測，及/或替代檢驗方法以降低被識別出來的風險，並對此進行評估與記錄。	10.7 For some products it may not be possible to obtain a sterility test result prior to release because the shelf life of the product is too short to allow completion of a sterility test. In these cases, the additional considerations of design of the process and additional monitoring and/or alternative test methods required to mitigate the identified risks should be assessed and documented.
10.8 用於試驗前對無菌試驗樣品外部表面去污染的任何過程（例如：氣化過氧化氫、紫外線），不應對試驗方法之靈敏度或樣品的可靠性產生負面影響。	10.8 Any process (e.g. Vaporized Hydrogen Peroxide, Ultra Violet) used to decontaminate the external surfaces of sterility samples prior to testing should not negatively impact the sensitivity of the test method or the reliability of the sample.
10.9 用於產品檢驗的培養基在使用前應依相關藥典執行品質管制檢驗。用於環境監測及 APS 的培養基在使用前應使用經過科學證明及指定的對照微生物，並包含具適當代表性的環境分離菌執行生長效能試驗。培養基品質管制檢驗通常應由終端使用者執行。任何依賴委外檢驗或供應商檢驗的培養基都應證明其合理性，並且應徹底考量在這種情況下的運輸及裝運條件。	10.9 Media used for product testing should be quality control tested according to the related Pharmacopeia before use. Media used for environmental monitoring and APS should be tested for growth promotion before use, using a scientifically justified and designated group of reference microorganisms and including suitably representative local isolates. Media quality control testing should normally be performed by the end user. Any reliance on outsourced testing or supplier testing of media should be justified and transportation and shipping conditions should be thoroughly considered in this case.
10.10 級區之環境監測數據與趨勢數據應作為產品批次核定/放行的一部分予以審查。應有書面程序描述當發現環境監測數據超出趨勢或超出既定限值時所應採取的措施。對於短架儲期產品，可能無法取得製造當時的環境數據；在這些情況下，其符合性應包含對最新可用數據的審查。這些產品的製造廠應考量使用快速/替代之方法。	10.10 Environmental monitoring data and trend data generated for classified areas should be reviewed as part of product batch certification/release. A written procedure should be available that describes the actions to be taken when data from environmental monitoring are found out of trend or exceeding the established limits. For products with short shelf life, the environmental data for the time of manufacture may not be available; in these cases, the compliance should include a review of the most recent available data.

	Manufacturers of these products should consider the use of rapid/alternative methods.
10.11 當快速及自動化微生物方法被使用於一般製造目的時，這些方法應針對相關產品或製程執行確效。	10.11 Where rapid and automated microbial methods are used for general manufacturing purposes, these methods should be validated for the product(s) or processes concerned.

詞彙 (Glossary)	
氣鎖室—用於維持相鄰房間（通常具有不同空氣潔淨度標準）之氣壓管制且有互鎖門的封閉空間。氣鎖室之目的是在於防止微粒物質及微生物污染物從管制程度較低的區域進入管制程度較高的區域。	Airlock – An enclosed space with interlocked doors, constructed to maintain air pressure control between adjoining rooms (generally with different air cleanliness standards). The intent of an airlock is to preclude ingress of particle matter and microorganism contamination from a lesser controlled area.
行動限量—對於諸如微生物或浮游微粒限量等的既定相關數值；當超過該限量時，應啟動適當調查，並依調查結果採取矯正措施。	Action limit – An established relevant measure (e.g. microbial, or airborne particle limits) that, when exceeded, should trigger appropriate investigation and corrective action based on the investigation.
警戒水準—對於在正常操作條件及確效狀態下之微生物或浮游微粒濃度等的潛在性漂移，發出早期警告的既定相關數值；它不一定會為矯正措施提供基礎，但會啟動適當的監視及後續行動，以解決潛在的問題。警戒水準是基於例行的及經過驗證的趨勢數據所建立的，並被定期審查。警戒水準可以基於不良趨勢、超出所設定之限值的個別偏離以及重複事件等多個參數予以建立。	Alert level – An established relevant measure (e.g. microbial, or airborne particle levels) giving early warning of potential drift from normal operating conditions and validated state, which does not necessarily give grounds for corrective action but triggers appropriate scrutiny and follow-up to address the potential problem. Alert levels are established based on routine and qualification trend data and are periodically reviewed. The alert level can be based on a number of parameters including adverse trends, individual excursions above a set limit and repeat events.
無菌製備/製程—在受控環境中處理無菌產品、容器及/或設備；在該環境中對空氣供應、原物料以及人員進行管理，以防止微生物、內毒素/熱原以及微粒污染。	Aseptic preparation/processing – The handling of sterile product, containers and/or devices in a controlled environment in which the air supply, materials and personnel are regulated to prevent microbial, endotoxin/pyrogen and particle contamination.
無菌製程模擬(APS)—對整個無菌製程的模擬，以確認該製程確保產品無菌性的能力。包括與例行製造相關的所有無菌操作，例如：必要時的設備組裝、調配、充填、凍乾及密封等製程。	Aseptic Process Simulation (APS) – A simulation of the entire aseptic manufacturing process in order to verify the capability of the process to assure product sterility. Includes all aseptic operations associated with routine manufacturing, e.g. equipment assembly, formulation, filling, lyophilization and sealing

	processes as necessary.
無菌狀態—經由使用無菌工作區，並以防範暴露的無菌產品受到微生物污染的方式執行作業所達到的管制狀態。	Asepsis – A state of control attained by using an aseptic work area and performing activities in a manner that precludes microbial contamination of the exposed sterile product.
細菌滯留試驗—該試驗用於確效過濾器是否可以從氣體或液體中去除細菌。該試驗通常使用標準微生物(例如：最低濃度為 10^7 cfu/cm^2 的 *Brevundimonas diminuta*) 來執行。	Bacterial retention testing – This test is performed to validate that a filter can remove bacteria from a gas or liquid. The test is usually performed using a standard organism, such as Brevundimonas diminuta at a minimum concentration of 10^7 Colony Forming Units/cm^2.
屏障—將無菌操作區（通常為 A 級區）與其背景環境隔離，以提供該區保護的實體隔離物。此類系統之部分或全部經常使用稱為 RABS 或隔離裝置的屏障技術。	Barrier – A physical partition that affords aseptic processing area (usually grade A) protection by separating it from the background environment. Such systems frequently use in part or totally the Barrier Technologies known as RABS or isolators.
負荷菌—與人員、製造環境(空氣及表面)、設備、產品包裝、原料（包括水）、製程中原物料或最終產品等相關之微生物的總數。	Bioburden – The total number of microorganisms associated with a specific item such as personnel, manufacturing environments (air and surfaces), equipment, product packaging, raw materials (including water), in-process materials, or finished products.
生物去污染—以殺孢子化學藥劑去除活性負荷菌的過程。	Bio-decontamination - A process that eliminates viable bioburden via use of sporicidal chemical agents.
生物指示劑 (BI)—被接種到合適之介質（例如：溶液、容器或封蓋）上的定量微生物，並放置在滅菌器內或裝載內或房間內之位置，以確定物理性或化學性滅菌或消毒週期的效率。挑戰微生物的選定是依其對給定製程的抵抗性來選擇及確效的。由進料批次的 D 值、微生物計數及純度來確定 BI 的品質。	Biological Indicators (BI) – A population of microorganisms inoculated onto a suitable medium (e.g. solution, container or closure) and placed within a steriliser or load or room locations to determine the sterilisation or disinfection cycle efficacy of a physical or chemical process. The challenge microorganism is selected and validated based upon its resistance to the given process. Incoming lot D-value, microbiological count and purity define the quality of the BI.
吹製-充填-密封 (BFS)— 一種將可熱塑顆粒成型為容器，充填產品，然後在連續、整合、自動操作中密封的技術。兩種最常見的 BFS 機器類型是穿梭型（型坯切割）及迴轉型(密封型坯)。	Blow-Fill-Seal (BFS) – A technology in which containers are formed from a thermoplastic granulate, filled with product, and then sealed in a continuous, integrated, automatic operation. The two most common types of BFS machines are the Shuttle type (with Parison cut) and the Rotary type (Closed Parison).

時段切換製造—在界定的時段內，嚴格遵守既定且經過確效的管制措施，依序製造一系列批次的相同產品。	Campaign manufacture – A manufacture of a series of batches of the same product in sequence in a given period of time with strict adherence to established and validated control measures.
級區—包含多個潔淨室的區域（參見潔淨室定義）。	Classified area – An area that contains a number of cleanrooms (see cleanroom definition).
清潔—去除污染物(例如：產品殘留物或消毒劑殘留物)的過程。	Cleaning – A process for removing contamination e.g. product residues or disinfectant residues.
潔淨區—具有明確的微粒及微生物潔淨度標準的區域，通常包含多個相連的潔淨室。	Clean area – An area with defined particle and microbiological cleanliness standards usually containing a number of joined cleanrooms.
潔淨室—經設計、維護及管制，以防止藥品受到微粒及微生物污染的作業室。這樣的作業室會被指定且可重複地符合適當的空氣潔淨度。	Cleanroom – A room designed, maintained, and controlled to prevent particle and microbial contamination of drug products. Such a room is assigned and reproducibly meets an appropriate air cleanliness level.
潔淨室分級—一種經由量測總微粒濃度，然後依潔淨室或潔淨空氣設備之規格，來評估其空氣潔淨度的方法。	Cleanroom classification – A method of assessing the level of air cleanliness against a specification for a cleanroom or clean air equipment by measuring the total particle concentration.
潔淨室驗證—一種評估被分級之潔淨室或潔淨空氣設備是否符合其預期用途的方法。	Cleanroom qualification – A method of assessing the level of compliance of a classified cleanroom or clean air equipment with its intended use.
密閉系統—產品不暴露於周圍環境的系統。例如：可經由使用管線或管子相互連接的半製品容器（例如桶或袋）作為一個系統來實現；當用於無菌產品的情況下，整個系統於連接後進行滅菌。例如（但不限於），在原料藥製造中可見的大規模可重複使用的系統，或在生物藥品製造中可見的拋棄式袋子及歧管系統。在操作結束之前，密閉系統不得被打開。在本附則中所使用的術語“密閉系統”並不指 RABS 或隔離裝置等系統。	Closed system – A system in which the product is not exposed to the surrounding environment. For example, this can be achieved by the use of bulk product holders (such as tanks or bags) that are connected to each other by pipes or tubes as a system, and where used for sterile products, the full system is sterilised after the connections are made. Examples of these can be (but are not limited to) large scale reusable systems, such as those seen in active substance manufacturing, or disposable bag and manifold systems, such as those seen in the manufacture of biological products. Closed systems are not opened until the conclusion of an operation. The use of the term “closed systems” in this Annex does not refer to systems such as RABS or isolator systems.
菌落形成單位 (CFU)— 一個微生物學的術	Colony Forming Unit (CFU) – A microbiological term that describes a single

語，描述源自一種或多種微生物之單一可被偵測的菌落。對於液體樣品，菌落形成單位通常以 CFU/ml 表示；對於空氣樣品，則為 CFU/m^3；對於在諸如落菌培養皿或接觸培養皿等固體介質等樣品，則通常以 CFU/樣品表示。	detectable colony that originates from one or more microorganisms. Colony forming units are typically expressed as CFU per ml for liquid samples, CFU per m^3 for air sample and CFU per sample for samples captured on solid medium such as settle or contact plates.
污染—在生產、抽樣、包裝或重新包裝、儲存或運輸過程中，將具微生物性質的雜質/不純物（微生物的數量及類型、熱原）或外來微粒物質被非期望地引入原物料、半製品/中間產品、原料藥或藥品之內或之上，它們可能對產品品質造成不利影響。	Contamination – The undesired introduction of impurities of a microbiological nature (quantity and type of microorganisms, pyrogen), or of foreign particle matter, into or onto a raw material, intermediate, active substance or drug product during production, sampling, packaging or repackaging, storage or transport with the potential to adversely impact product quality.
污染管制策略 (CCS)— 對微生物、內毒素/熱原以及微粒之一套計畫性的管制，源自對於當前產品及製程的瞭解，以確保製程性能及產品品質。其管制可以包含與原料藥、賦形劑與藥品物料及組件、設施及設備操作條件、製程中管制、最終產品規格，以及與監測及管制相關的方法與頻率。	Contamination Control Strategy (CCS) – A planned set of controls for microorganisms, endotoxin/pyrogen and particles, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to active substance, excipient and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.
矯正性介入—在無菌製程中用以矯正或調整的介入。它們在例行的無菌製程中不以設定的頻率發生。其例子包含清除組件堵塞、止漏、調整傳感器以及更換設備組件等。	Corrective intervention – An intervention that is performed to correct or adjust an aseptic process during its execution. These may not occur at a set frequency in the routine aseptic process. Examples include such as clearing component jams, stopping leaks, adjusting sensors, and replacing equipment components.
關鍵表面—可能直接接觸或直接影響無菌產品或其容器或其封蓋的表面。關鍵表面應於製造作業開始前使成為無菌，並於整個製程中保持無菌性。	Critical surfaces – Surfaces that may come directly into contact with, or directly affect, a sterile product or its containers or closures. Critical surfaces are rendered sterile prior to the start of the manufacturing operation, and sterility is maintained throughout processing.
關鍵區—在無菌操作區內，產品與關鍵表面被暴露於環境中的位置。	Critical zone – A location within the aseptic processing area in which product and critical surfaces are exposed to the environment.
關鍵性介入—在關鍵區之矯正性或常規性介入。	Critical intervention – An intervention (corrective or inherent) into the critical zone.

D 值—將有存活力的生物體數量減到原始數量之 10%所需的滅菌參數值(持續期間或吸收劑量)。	D-value – The value of a parameter of sterilisation (duration or absorbed dose) required to reduce the number of viable organisms to 10 per cent of the original number.
盲管—長度大於其管線內徑 3 倍的非循環管線（其內的流體可能保持靜止)。	Dead leg – Length of non-circulating pipe (where fluid may remain static) that is greater than 3 internal pipe diameters.
除役—當製程、設備或潔淨室被停用且不再被使用的狀態。	Decommission – When a process, equipment or cleanroom are closed and they will not be used again.
去污染—從一個區域、標的物或人體去除或減少任何污染物（化學物質、廢棄物、殘留物或微生物）的整個過程。其所使用的去污染方法（例如：清潔、消毒、滅菌）應經選擇及確效，以達到適合該項被去污染標的之預定用途的潔淨度程度。亦請參見生物去污染。	Decontamination – The overall process of removal or reduction of any contaminants (chemical, waste, residue or microorganisms) from an area, object, or person. The method of decontamination used (e.g. cleaning, disinfection, sterilisation) should be chosen and validated to achieve a level of cleanliness appropriate to the intended use of the item decontaminated. See also Bio-decontamination.
去熱原—被設計用以將熱原物質（例如：內毒素）移除或去活化到規定之最小量的程序。	Depyrogenation – A process designed to remove or inactivate pyrogenic material (e.g. endotoxin) to a specified minimum quantity.
消毒—對微生物之結構或代謝功能進行不可逆的處理，以減少菌數達到適合於界定目的之程序。	Disinfection – The process by which the reduction of the number of microorganisms is achieved by the irreversible action of a product on their structure or metabolism, to a level deemed to be appropriate for a defined purpose.
內毒素—存在於革蘭氏陰性菌細胞壁中的熱原性產物（亦即：脂多醣)。內毒素可導致接受注射之患者出現從發燒到死亡的反應。	Endotoxin – A pyrogenic product (i.e. lipopolysaccharide) present in the Gram negative bacterial cell wall. Endotoxin can lead to reactions in patients receiving injections ranging from fever to death.
平衡時間—從對照量測點達滅菌溫度開始，至裝載內所有點位均達到滅菌溫度所經過的時間。	Equilibration time – Period which elapses between the attainment of the sterilisation temperature at the reference measurement point and the attainment of the sterilisation temperature at all points within the load.
可萃取物—在暴露於極端條件之適當溶劑下，從製程設備表面轉移進入被加工之產品或原物料中的化學成分。	Extractables - Chemical entities that migrate from the surface of the process equipment, exposed to an appropriate solvent at extreme conditions, into the product or material being processed.
第一手空氣—在接觸暴露的產品和產品接	First Air – Refers to filtered air that has not

觸表面之前沒有被干擾，因而在到達關鍵區之前不太有受污染可能的過濾空氣。	been interrupted prior to contacting exposed product and product contact surfaces with the potential to add contamination to the air prior to reaching the critical zone.
過濾器完整性測試—確認過濾器（產品、氣體或 HVAC 的過濾器）保持其截留特性，且在其處理、安裝或製程中沒有被損壞的測試。	Filter Integrity test - A test to confirm that a filter (product, gas or HVAC filter) retain their retentive properties and have not been damaged during handling, installation or processing.
成型-充填-密封(FFS) — 一種自動充填製程，通常用於最終滅菌產品。該製程係將包材薄膜經連續式平面滾輪(flat roll)壓出來以成型直接容器，並同時將產品充填入該容器，再將已充填的直接容器密封的連續製程。FFS 製程可以使用單網系統(single web system)（該製程係將單一的薄膜平面滾輪纏繞在自身周圍以形成一個空腔）或雙網系統(dual web system)（該製程係將兩個薄膜平面滾輪放在一起以形成一個空腔），該類製程通常借助於真空模具或加壓氣體。其所形成的空腔被充填、密封並切成段。該薄膜通常由聚合物材料、聚合物塗層或其他合適的材料所組成。	Form-Fill-Seal (FFS) –An automated filling process, typically used for terminally sterilised products, which constructs the primary container out of a continuous flat roll of packaging film while simultaneously filling the formed container with product and sealing the filled containers in a continuous process. FFS processes may utilize a single web system (where a single flat roll of film is wrapped around itself to form a cavity), or a dual web system (where two flat rolls of film are brought together to form a cavity), often with the aid of vacuum moulds or pressurised gases. The formed cavity is filled, sealed and cut into sections. Films typically consist of a polymeric material, polymeric coated foil or other suitable material.
更衣(著衣)驗證— 以初始及定期的計畫，確立個人穿著整套工作服之能力。	Gowning qualification – A programme that establishes, both initially and on a periodic basis, the capability of an individual to don the complete gown.
A 級空氣供應—所供應之過濾空氣經驗證符合 A 級區總微粒品質，但不需要對該空氣執行連續總微粒監測或符合 A 級區微生物監測限量。專用於保護封蓋尚未經捲縮的全塞小瓶。	Grade A air supply – Air which is passed through a filter qualified as capable of producing grade A total particle quality air, but where there is no requirement to perform continuous total particle monitoring or meet grade A viable monitoring limits. Specifically used for the protection of fully stoppered vials where the cap has not yet been crimped.
HEPA 過濾器—依相關國際標準所規定之高效率微粒空氣過濾器。	HEPA filter – High efficiency particulate air filter specified in accordance with a relevant international standard.
常規的介入—無菌製程不可分割的一部分，是組建(set-up)、例行操作及/或監測（例如：無菌組裝、容器補充、環境採樣）所需的介入。常規的介入是執行無菌製程之程序或工作指示要求的所需介入。	Inherent interventions – An intervention that is an integral part of the aseptic process and is required for either set-up, routine operation and/or monitoring (e.g. aseptic assembly, container replenishment, environmental sampling). Inherent interventions are required

	by procedure or work instruction for the execution of the aseptic process.
內建無菌連接裝置—在連接過程中降低污染風險的裝置；它們可以是機械式的或是熔接式的密封方法。	Intrinsic sterile connection device – A device that reduces the risk of contamination during the connection process; these can be mechanical or fusion sealing.
等速採樣頭—一種採樣頭，被設計用於儘可能不會擾動空氣，以使進入噴嘴的微粒與在沒有噴嘴存在時會通過該區域的微粒相同；亦即採樣情況為空氣進入樣品採樣探針入口的平均速度與在該位置的平均氣流速度幾乎相同（±20%）。	Isokinetic sampling head – A sampling head designed to disturb the air as little as possible so that the same particles go into the nozzle as would have passed the area if the nozzle had not been there (i.e. the sampling condition in which the mean velocity of the air entering the sample probe inlet is nearly the same (± 20 percent) as the mean velocity of the airflow at that location).
隔離裝置— 一種能夠被重複地內部生物去污染的"封閉空間(enclosure)"，其內部工作區符合 A 級區條件，它提供將其內部與外部環境（例如：周圍的潔淨室空氣及人員）不妥協(uncompromised)的持續隔離。有兩種主要類型的隔離裝置： i. 密閉式隔離裝置系統：經由與輔助設備的無菌連接以完成原物料轉移，而不是使用通往周圍環境的開口，從而排除了隔離裝置外部對其內部的污染。密閉式系統在整個操作過程中保持密封。 ii. 開放式隔離裝置系統：被設計為允許原物料在操作期間經由一個或多個開口連續或半連續地進入及/或排出。其開口被設計（例如：使用連續超壓）為可阻止外部污染物進入該隔離裝置。	Isolator – An enclosure capable of being subject to reproducible interior bio-decontamination, with an internal work zone meeting grade A conditions that provides uncompromised, continuous isolation of its interior from the external environment (e.g. surrounding cleanroom air and personnel). There are two major types of isolators: i. Closed isolator systems exclude external contamination of the isolator's interior by accomplishing material transfer via aseptic connection to auxiliary equipment, rather than use of openings to the surrounding environment. Closed systems remain sealed throughout operations. ii. Open isolator systems are designed to allow for the continuous or semi-continuous ingress and/or egress of materials during operations through one or more openings. Openings are engineered (e.g. using continuous overpressure) to exclude the entry of external contaminant into the isolator.
可浸出物—在正常使用及/或儲存條件下，從製程設備或容器的產品接觸表面轉移到產品中的化學物。	Leachables – Chemical entities that migrate into products from the product contact surface of the process equipment or containers under normal condition of use and/or storage.
環境菌—在級區/區域內(尤其是 A 級區及 B 級區)的環境監測、人員監測或在陽性的無菌試驗結果，所經常回收到的具有適當代表性的現場微生物。	Local isolates – Suitably representative microorganisms of the site that are frequently recovered through environmental monitoring within the classified zone/areas especially grade A and B areas, personnel monitoring or

	positive sterility test results.
凍乾— 一種物理-化學乾燥製程，被設計為以昇華方式除去水性及非水性系統中的溶劑，其主要目的是為了達到產品或原物料的安定性。凍乾是冷凍乾燥這個術語的同義詞。	Lyophilization – A physical-chemical drying process designed to remove solvents, by way of sublimation, from both aqueous and non-aqueous systems, primarily to achieve product or material stability. Lyophilization is synonymous to the term freeze-drying.
人工無菌操作—由作業人員對於裝有無菌產品之開放式容器，以人工調製、充填、置放及/或密封的無菌製程。	Manual aseptic processing– An aseptic process where the operator manually compounds, fills, places and /or seals an open container with sterile product.
作業人員—參與操作作業的任何個人，包括生產線組建、充填、維護或與製造活動相關的其他人員。	Operator - Any individual participating in the processing operation, including line set-up, filling, maintenance, or other personnel associated with manufacturing activities.
過度滅菌—足以將具最小D值為1分鐘的微生物，至少減少 12 個 **$\log_{10}$** 的過程。	Overkill sterilisation – A process that is sufficient to provide at least a 12 log10 reduction of microorganisms having a minimum D-value of 1 minute.
型坯—將聚合物由 BFS 機器擠出的“管”狀物，再由該“管”狀物形成容器。	Parison – The "tube" of polymer extruded by the BFS machine from which containers are formed.
傳遞艙—與氣鎖室同義（參見氣鎖室定義），但通常尺寸較小。	Pass-through hatch – Synonymous with airlock (see airlock definition) but typically smaller in size.
患者—人類或動物，包括臨床試驗的參與者。	Patient – Human or animal including participants in a clinical trial.
無菌操作後的終端熱處理— 一種在無菌操作後採用的終端濕熱過程，它已被證明可提供≤10^{-6} 的無菌保證程度，但無法滿足蒸汽滅菌的要求（例如：$F_0 \geq 8$ 分鐘）。這也可能有利於對無法經由過濾去除之病毒的破壞。	Post-aseptic processing terminal heat treatment– A terminal moist heat process employed after aseptic processing which has been demonstrated to provide a sterility assurance level (SAL) $\leq 10^{-6}$ but where the requirements of steam sterilisation (for example, F0≥8 min) are not fulfilled. This may also be beneficial in the destruction of viruses that may not be removed through filtration.
熱原—接受注射之患者會引起發熱反應的物質。	Pyrogen – A substance that induces a febrile reaction in patients receiving injections;
快速轉移系統/接頭 (RTP)—用於將物品轉移入 RABS 或隔離裝置內的系統，以將關鍵區域的風險降至最低。一個例子是帶有 alpha/beta 端口的快速轉移容器。	Rapid Transfer System/Port (RTP) – A System used for the transfer of items into RABS or isolators that minimizes the risk to the critical zone. An example would be a rapid transfer container with an alpha/beta port.
原料—用於生產無菌產品的任何成分，包括那些可能不會出現在最終藥品中的成分。	Raw material – Any ingredient intended for use in the manufacture of a sterile product, including those that may not appear in the final

	drug product.
限制進入屏障系統(RABS)—提供封閉的但非完全密封的環境，滿足規定的空氣品質條件（用於 A 級區無菌操作），並使用硬質壁板及經整合的手套將其內部與周圍潔淨室環境隔開之系統。RABS 的內表面使用殺孢劑消毒及去污染。作業人員使用手套、半套裝、RTP 及其他經整合的傳輸端口來執行操作或將原物料傳送到 RABS 內部。依其設計，門很少被打開(只有在嚴格的預定義的條件下)。	Restricted Access Barrier System (RABS) – System that provides an enclosed, but not fully sealed, environment meeting defined air quality conditions (for aseptic processing grade A), and using a rigid-wall enclosure and integrated gloves to separate its interior from the surrounding cleanroom environment. The inner surfaces of the RABS are disinfected and decontaminated with a sporicidal agent. Operators use gloves, half suits, RTPs and other integrated transfer ports to perform manipulations or convey materials to the interior of the RABS. Depending on the design, doors are rarely opened, and only under strictly pre-defined conditions.
一次性使用系統 (SUS)—與產品接觸的組件僅被使用一次的系統，以取代可被重複使用的設備，諸如不銹鋼的傳輸管線或待分/包裝產品容器等。在本文件中，SUS 涵蓋那些使用於無菌產品製造過程，且通常是由諸如袋子、過濾器、管線、連接器、儲存瓶以及傳感器等拋棄式組件所組成。	Single Use Systems (SUS) – Systems in which product contact components are used only once to replace reusable equipment such as stainless steel transfer lines or bulk containers.SUS covered in this document are those that are used in manufacturing processes of sterile products and are typically made up of disposable components such as bags, filters, tubing, connectors, storage bottles and sensors.
殺孢劑—當以足夠的濃度使用時，可以在規定的接觸時間內破壞細菌及真菌孢子的藥劑。它們被預期會殺死所有的營養型微生物。	Sporicidal agent – An agent that destroys bacterial and fungal spores when used in sufficient concentration for specified contact time. It is expected to kill all vegetative microorganisms.
無菌產品—在本指引中，無菌產品係指一種或多種經過滅菌的組成物在無菌條件下，並最終組成之無菌原料藥或無菌產品。這些組成物包含最終藥品的容器、封蓋塞及組件。或經由最終滅菌製程使變成無菌的產品。	Sterile Product – For purpose of this guidance, sterile product refers to one or more of the sterilised elements exposed to aseptic conditions and ultimately making up the sterile active substance or finished sterile product. These elements include the containers, closures, and components of the finished drug product. Or, a product that is rendered sterile by a terminal sterilisation process.
滅菌級過濾器—在經過適當確效後，可以從液體或氣體中去除所規定之挑戰微生物而產出無菌濾出物一種過濾器。此類過濾器的孔徑通常等於或小於 0.22 μm。	Sterilising grade filter – A filter that, when appropriately validated, will remove a defined microbial challenge from a fluid or gas producing a sterile effluent. Usually such filters have a pore size equal or less than 0.22 μm.
最終滅菌—在產品的最終容器中使用致死的滅菌劑或條件，以達到事先訂定的 10^{-6}	Terminal Sterilisation – The application of a lethal sterilising agent or conditions to a

或更佳的無菌保證程度（SAL）（例如：理論上存在單一個有存活力的微生物的機率或在被滅菌總單元中等於或小於 1 x 10^{-6}（百萬分之一）單元。	product in its final container to achieve a predetermined sterility assurance level (SAL) of 10^{-6} or better (e.g. the theoretical probability of there being a single viable microorganism present on or in a sterilised unit is equal to or less than 1 x 10^{-6} (one in a million)).
亂流—空氣不是單向流動的。潔淨室中的亂流空氣應經由氣流混合稀釋以沖洗潔淨室，並確保維持可接受的空氣品質。	Turbulent airflow – Air that is not unidirectional. Turbulent air in cleanrooms should flush the cleanroom via mixed flow dilution and ensure maintenance of acceptable air quality.
單向氣流—以穩定且均勻的方式，並以足夠的速度在單一方向上移動的氣流，可重複地將微粒從關鍵操作區或檢驗區帶走。	Unidirectional airflow – An airflow moving in a single direction, in a robust and uniform manner, and at sufficient speed, to reproducibly sweep particles away from the critical processing or testing area.
單向氣流(UDAF)櫃—提供過濾單向氣流的櫥櫃型機械裝置（以前稱為層流單元或 LAF）。	Unidirectional Airflow (UDAF) unit – A cabinet supplied with filtered unidirectional airflow (previously referred to as a Laminar Airflow Unit or LAF).
最差狀況— 一組包含操作限制量及各種情境、並涵蓋標準作業程序內最有可能導致製程或產品失敗的條件（當與理想條件相較時），這些條件最有可能，但不一定總是導致產品或製程失敗。	Worst case – A set of conditions encompassing processing limits and circumstances, including those within standard operating procedures, that pose the greatest chance of process or product failure (when compared with ideal conditions). Such conditions have the highest potential to, but do not necessarily always result in product or process failure.
水系統—用於生產、儲存及配送水的系統，其水質通常符合特定藥典等級（例如純水及注射用水 (WFI)）。	Water system – A system for producing, storing and distributing water, usually compliant to a specific pharmacopeia grade (e.g. purified water and water for injection (WFI)).
Z 值—導致生物指示劑 D 值發生 10 倍變化的溫差。	Z-value – The temperature difference that leads to a 10-fold change in the D-value of the biological indicators.

附則 2A 人用再生醫療製劑的製造(MANUFACTURE OF ADVANCED THERAPY MEDICINAL PRODUCTS FOR HUMAN USE

範圍（SCOPE）	
製造再生醫療製劑（Advanced Therapy Medicinal Products, ATMPs）所使用之方法，是擬訂適當法規管制上的一個關鍵因素。因此，ATMPs 主要是依其製造方法而界定。例如，對於基因治療 ATMPs，基因修飾可經由各種方法獲得（例如，病毒與非病毒載體、mRNA、活體外與體內基因體編輯工具)。基因修飾細胞可為人類起源（自體或異體）或動物起源（異種細胞），可為初代或已建立之細胞株。在藥品中，基因修飾細胞或基因治療製劑可單獨或與醫療器材組合呈現。	The methods employed in the manufacture of Advanced Therapy Medicinal Products (ATMPs) are a critical factor in shaping the appropriate regulatory control. ATMPs can be defined therefore largely by reference to their method of manufacture. For example, for gene therapy ATMPs, genetic modifications can be obtained through a variety of methods (e.g. viral & non-viral vectors, mRNA, ex vivo and in vivo genome-editing tools). The genetically modified cells can be of human origin (autologous or allogeneic) or of animal origin (xenogeneic cells), either primary or established cell lines. In a medicinal product, the genetically modified cells or gene therapy products can be presented alone or combined with medical devices.
本附則提供關於 ATMPs（定義於術語彙編）與用於其製造之原料藥的全部範圍之附加與特定指引。本附則適用於研究用 ATMPs 與許可上市之 ATMPs 兩者。當經由國家法規許可時，其亦可適用於在醫院設施中製造及恩慈使用計畫之 ATMP。	This annex provides additional and specific guidance on the full range of ATMPs (as defined in the glossary) and the active substances that are used in their manufacture. This annex applies both to investigational ATMPs and market-authorised ATMPs. It can also be applied to ATMP manufacturing in hospital settings and for compassionate use programs, where authorised by national law.
儘管目前期許本附則以可使用數年為制定目標之一，但該領域快速變化中，為了因應技術變遷、澄清不確定性或特定認知重要替代辦法，未來修訂可能是必要的。	Although one of the objectives of this present annex was to prepare a document that would stand for several years, the field is quickly changing. It is recognised that amendments may be necessary to accommodate technological change, to clarify uncertainty or to specifically recognise important alternatives. Comments are therefore invited at any stage of the life of this edition.
本附則主要分成兩部：	This annex is divided into two main parts:

1. **A 部**包含關於 ATMPs 從管制種批與細胞庫到最終作業活動與測試之製造的補充指引與替代規定。	1. Part A contains supplementary guidance and alternative provisions on the manufacture of ATMPs, from control over seed lots and cell banks through to finishing activities and testing.
2. **B 部**包含關於特定類型之 ATMPs 及其原料的進一步指引。	2. Part B contains further guidance on selected types of ATMPs and its substances.
本附則之應用（APPLICATION OF THIS ANNEX）	
本附則連同 GMP 指引之其他附則提供 GMP 第一部：*藥品基本要求*與第二部：*原料藥基本要求*之補充指引。本附則應與 GMP 指引及其附則合併應用。	This annex, along with several other annexes of the Guide to GMP, provides guidance, which supplements that in Part I: *Basic Requirements for Medicinal Products* and in Part II: *Basic Requirements for active pharmaceutical ingredients* of the PIC/S GMP Guide. This annex is not a stand-alone document and should be applied in conjunction with PIC/S GMP guidelines and annexes. It has, however, been written in a manner that it could enable development of a standalone guide if integrated with PIC/S GMP Part I, Part II, and related annexes.
如果由於產品之本質或技術必需時，且本附則提供特定指引，則遵守本附則是被預期的，且優先於 GMP 指引之其他部分，若未能符合前述原則，應有良好理由，並應用 QRM 原則，將科學理論基礎充分文件化。	Where due to the nature of the product or technical necessities, specific guidance is provided in this annex, compliance with this annex is expected and takes precedence over other sections in the PIC/S GMP Guide unless there are good reasons for not doing so with documented sound scientific rationale applied using QRM principles.
在某些情況下，其他國家法規可能適用於 ATMPs 的起始原料。例如：	In certain cases, other national laws may be applicable to the starting materials for ATMPs. For example:
(a) 作為 ATMPs 起始原料之組織與細胞，可能受其他國家法規管制，該法規涵蓋捐贈、採集、測試、處理、保存、儲存與配送。	(a) Tissues and cells used as starting materials of ATMPs may be subject to other national legislation that cover donation, procurement, testing, processing, preservation, storage and distribution.

(b) 對於使用血液或成分血作為 ATMPs 的起始原料，國家法規可能對捐血者之篩選與血液及成分血的收集與測試提供技術要求。	(b) For blood or blood components used as starting materials for ATMPs, national legislation may provide the technical requirements for the selection of donors and the collection and testing of blood and blood components.
ATMPs 之製造過程為產品專一性的，且不同的設計方法是可能的。應於臨床試驗申請（CTA）或上市許可（MA）申請中描述 GMP 的適當應用、證明其合理性，並依照國家法規。對於界定所需要之製造過程步驟，以製造起始原料、ATMP 原料藥或最終 ATMP，可能需要給予考慮。在有些情況中，ATMP 原料藥與最終產品間之製造過程可被界定為連續的。	The manufacturing process for ATMPs is product-specific and different design approaches are possible. The appropriate application of GMP should be described, justified in the Clinical Trial Application (CTA) or Marketing Authorisation (MA), and in accordance with national law. Consideration may be given to defining which manufacturing process steps are required to manufacture starting materials, ATMP active substance, or the finished ATMP. In some cases, the manufacturing process between the ATMP active substance and the final product can be defined as continuous.
經基因修飾之有機體的製造與管制亦需遵從其他當地的、國家的或地區的要求。在處理任何基因修飾之有機體的設施，應建立適當的圍堵並維持之。為了建立並維持適當生物安全等級，應依照國家法規規定。GMP 及該等要求應共同遵守。	The manufacture and control of genetically modified organisms also needs to comply with other local, national or regional requirements. Appropriate containment should be established and maintained in facilities where any genetically modified organism is handled. Advice should be obtained according to national law in order to establish and maintain the appropriate Biological Safety Level. GMP should be adhered alongside these requirements.

表 1 提供本附則適用之實例。應該注意的是，本表僅為說明性，而非為描述精確範圍，且應當瞭解的是，對應表中所示之製造步驟是否遵守 GMP 或 GMP 原則，取決於適用之國家法規。ATMP 原料藥的製造上，其 GMP 要求的水準是從早期到後來步驟越來越增加。一些早期製造步驟納入本附則的範圍內，並非意謂該等步驟將例行地接受主管機關的檢查。對於那些早期階段，GMP 應用之嚴謹度依國家法規而定。	Table 1 gives examples of where this annex applies. It should be noted that this table is illustrative only and is not meant to describe the precise scope. It should also be understood that adherence to the GMP or GMP principles for the manufacturing steps indicated in the corresponding table is dependent on applicable national legislation. The level of GMP requirements increases from early to later steps in the manufacture of ATMP active substances. The inclusion of some early steps of manufacture within the scope of this annex does not imply that those steps will be routinely subject to inspection by the authorities. According to national legislation more or less stringent approaches on the application of GMP on those early stages may apply.
[1] 本附則之應用適用於以深灰色顯示之製造步驟。以淺灰色顯示之步驟適用本附則之原則。	[1] Application of this annex applies to manufacturing steps illustrated in dark grey. Application of this annex or principles of this annex apply to steps illustrated in light grey apply depending on the requirements of national legislation.
[2] 參照第 5.32 條關於細胞庫與細胞種批之建立。	[2] Refer to points 5.32 for establishment of cell banks and seed lots.
[3] 於基因治療之體外基因修飾細胞，除非另經公告僅適用本附則之原則，其載體製造應適用於本指引。	[3] In the case of gene therapy ex-vivo genetically modified cells, this guide applies to vector manufacturing except where otherwise authorised by national law where principles of GMP should apply.

表 1. 對於在附則 2A 範圍內之製造活動的說明性指引

範例產品	本附則之應用（見註 [1]）			
基因治療：mRNA	線性 DNA 模板之製備	體外無細胞轉錄	mRNA 之純化	配方調製、充填
基因治療：體內病毒載體	質體之製造	MCB、WCB[2] 之建立	載體之製造與純化	配方調製、充填
基因治療：體內非病毒載體（裸露 DNA、脂複合體、聚複合體等）	質體之製造	MCB、WCB[2] 之建立	醱酵與純化	配方調製、充填
基因治療：體外基因修飾細胞	起始組織/細胞之捐贈、採集與測試	質體之製造 載體之製造 [3]	活體外細胞之基因修飾	配方調製、充填
體細胞治療	起始組織/細胞之捐贈、採集與測試	MCB、WCB 或初代細胞批或細胞池 [2] 之建立	細胞分離、培養物純化、與非細胞組成物合併	配方調製、合併、充填
組織工程製劑	起始組織/細胞之捐贈、採集與測試	起始處理、分離與純化，建立 MCB、WCB、初代細胞批或細胞池 [2]	細胞分離、培養物純化、與非細胞組成物合併	配方調製、合併、充填

Table 1. Illustrative guide of manufacturing activities within the scope of Annex 2A

Example Products	Application of this Annex (see note[1])			
Gene therapy: mRNA	Linear DNA template preparation	In vitro cell free transcription	mRNA purification	Formulation, filling
Gene therapy: in vivo viral vectors	Plasmid manufacturing	Establishment of MCB, WCB[2]	Vector manufacturing and purification	Formulation, filling
Gene therapy: in vivo non-viral vectors (naked DNA, lipoplexes, polyplexes, etc.)	Plasmid manufacturing	Establishment of bacterial bank[2]	Fermentation and purification	Formulation, filling
Gene therapy: ex-vivo genetically modified cells	Donation, procurement and testing of starting tissue / cell	Plasmid manufacturing Vector manufacturing[3]	Ex-vivo genetic modification of cells	Formulation, filling
Somatic cell therapy	Donation, procurement and testing of starting tissue / cell	Establishment of MCB, WCB or primary cell lot or cell pool[2]	Cell isolation, culture purification, combination with non-cellular components	Formulation, combination, filling
Tissue engineered products	Donation, procurement and testing of starting tissue / cell	Initial processing, isolation and purification, establish MCB, WCB, primary cell lot or cell pool[2]	Cell isolation, culture purification, combination with non-cellular components	Formulation, combination, filling

以下是將 GMP 應用於 ATMP 製造之部分實例。

<table>
<tr><td colspan="2">圖 1：基因治療 mRNA ATMP 製造之範例</td><td colspan="2">圖 2：體內病毒載體基因治療 ATMP 製造之範例</td><td colspan="3">圖 3：自體 CAR-T 治療 ATMP 製造之範例</td></tr>
<tr>
<td>線性 DNA 模板製備
質體 DNA 建構製備
↓
質體移轉至起始菌落
（例如，大腸桿菌）
↓
純化、線性化與精製
↓
線性 DNA 模板之儲存

或

質體 DNA 建構製備
↓
聚合酶連鎖反應
（PCR）
↓
線性 DNA 模板之儲存</td>
<td>ATMP 製造
轉錄
↓
純化
↓
收成
↓
配方調製
↓
充填
↓
儲存
↓
為病人取用之配送</td>
<td>質體製造
質體 DNA 建構製備
↓
質體移轉至起始菌落
（例如，大腸桿菌）
↓
增殖
↓
調配
↓
儲存</td>
<td>ATMP 製造
建立 MCB 或 WCB
↓
解凍
↓
轉染
↓
誘導
↓
收成
↓
純化
↓
配方調製
↓
無菌過濾
↓
充填
↓
儲存
↓
為病人取用之配送</td>
<td>質體製造
質體 DNA 建構製備
↓
質體移轉至起始菌落
（例如，大腸桿菌）
↓
增殖
↓
調配
↓
儲存</td>
<td>病毒載體產品製造
建立 MCB 或 WCB
↓
解凍
↓
轉染
↓
誘導
↓
收成
↓
純化
↓
無菌過濾
↓
調配
↓
儲存</td>
<td>ATMP 製造
病人細胞之捐贈或採集
↓
轉導
↓
增殖
↓
收成
↓
配方調製
↓
充填
↓
儲存
↓
為病人取用之配送</td>
</tr>
<tr>
<td>• GMP 要求從質體 DNA 建構之早期步驟至後期步驟可能各不相同，但適用國家法規時，應與附則 2A 及 GMP 指引第二部或該等要求之原則保持一致。
• 關於確定 GMP 適當應用之附加資訊請參照第 5.23 條。</td>
<td>• 上市許可持有者（MAH）得證明該等步驟為連續製程生產 ATMP 原料藥與其藥品之合理性。
• 合適時，GMP 第一部與第二部連同適用之附則適用於製造步驟。</td>
<td>• GMP 要求從質體 DNA 建構之早期步驟至後期步驟可能各不相同，但適用國家法規時，應與附則 2A 及 GMP 指引第二部或該等要求之原則保持一致。
• 關於確定 GMP 適當應用之附加資訊請參照第 5.23 條。</td>
<td>• 上市許可持有者得證明等步驟為連續製程生產 ATMP 原料藥與其藥品之合理性。
• 合適時，GMP 第一部與第二部連同適用之附則適用於製造步驟。</td>
<td>• GMP 要求從質體 DNA 建構之早期步驟至後期步驟可能各不相同，但適用國家法規時，應與附則 2A 及 GMP 指引第二部之原則或該等要求之原則保持一致。
• 關於確定 GMP 適當應用之附加資訊請參照第 5.23 條。</td>
<td>• 合適時依照國家法規，應用於病毒載體製造之 GMP 要求，應與附則 2A 及 GMP 第二部或該等要求之原則保持一致。
• 關於確定 GMP 適當應用之附加資訊請參照第 5.23 條。</td>
<td>• 本指引之應用不包括病人細胞之捐贈或採集。
• 上市許可持有者得證明等步驟為連續製程生產 ATMP 原料藥與其藥品之合理性。
• 合適時，GMP 第一部與第二部連同適用之附則適用於製造步驟。</td>
</tr>
</table>

The following are some non-exhaustive examples in the application of GMP to the manufacture of ATMP.

Figure 1: Example of gene therapy mRNA ATMP manufacturing		Figure 2: Example of in vivo viral vector gene therapy ATMP manufacturing		Figure 3: Example of autologous CAR-T therapy ATMP manufacturing		
Linear DNA template preparation	**ATMP Manufacturing**	**Plasmid Manufacturing**	**ATMP Manufacturing**	**Plasmid Manufacturing**	**Viral Vector Product Manufacturing**	**ATMP Manufacturing**
Plasmid DNA construct preparation ↓ Transfer of Plasmid DNA to starter colony (e.g. *E. coli*) ↓ Purification, linearization and polishing ↓ Storage of linear DNA template OR Plasmid DNA construct preparation ↓ Polymerase Chain Reaction (PCR) ↓ Storage of linear DNA template	Transcription ↓ Purification ↓ Harvest ↓ Formulation ↓ Filling ↓ Storage ↓ Distribution for patient access	Plasmid DNA construct preparation ↓ Transfer of Plasmid DNA to starter colony (e.g. *E. coli*) ↓ Expansion ↓ Dispensing ↓ Storage	Establishing MCB or WCB ↓ Thawing ↓ Transfection ↓ Induction ↓ Harvest ↓ Purification ↓ Formulation ↓ Sterile Filtration ↓ Filling ↓ Storage ↓ Distribution for patient access	Plasmid DNA construct preparation ↓ Transfer of Plasmid DNA to starter colony (e.g. *E. coli*) ↓ Expansion ↓ Dispensing ↓ Storage	Establishing MCB or WCB ↓ Thawing ↓ Transfection ↓ Induction ↓ Harvest ↓ Purification ↓ Sterile Filtration ↓ Dispensing ↓ Storage	Donation or procurement of patient cells ↓ Transduction ↓ Expansion ↓ Harvest ↓ Formulation ↓ Filling ↓ Storage ↓ Distribution for patient access
• GMP requirements can vary from early steps in making the plasmid DNA construct to later steps but should align with Annex 2A and PIC/S GMP Guide Part II or principles of these requirements as applicable under national legislation. • Refer to Section 5.23 for additional information in determining the appropriate application of GMP.	• A Marketing Authorisation Holder (MAH) may justify these steps to be a continuous process producing both the ATMP active substance and medicinal product. • PIC/S GMP Part I and Part II along with applicable annexes apply as appropriate to the step of manufacture.	• GMP requirements can vary from early steps in making the plasmid DNA construct to later steps but should align with Annex 2A and PIC/S GMP Guide Part II or principles of these requirements as applicable under national legislation. • Refer to Section 5.23 for additional information in determining the appropriate application of GMP.	• A MAH may justify these steps to be a continuous process producing both the ATMP active substance and medicinal product. • PIC/S GMP Part I and Part II along with applicable annexes apply as appropriate to the step of manufacture.	• GMP requirements can vary from early steps in making the plasmid DNA construct to later steps but should align with principles of Annex 2A and PIC/S GMP Guide Part II or principles of these requirements as applicable under national legislation. • Refer to Section 5.23 for additional information in determining the appropriate application of GMP.	• GMP requirements applied to the manufacture of a viral vector should align with Annex 2A and PIC/S GMP Part II or principles of these requirements as applicable under national legislation. • Refer to Section 5.23 for additional information in determining the appropriate application of GMP.	• The application of this guide does not include the donation or procurement of patient cells. • A MAH may justify these steps to be a continuous process producing both the ATMP active substance and medicinal product. • PIC/S GMP Part I and Part II along with applicable annexes apply as appropriate to the step of manufacture.

原則（PRINCIPLE）	
製造 ATMPs 所涉及之某些特定考慮，係源自於其產品與製程之本質。製造、管制與管理生物藥品的方式，使得有些特別的防範措施是必要的。	The manufacture of ATMPs involves certain specific considerations arising from the nature of the products and the processes. The ways in which biological medicinal products are manufactured, controlled and administered make some particular precautions necessary.
由於在製造過程中所使用之原料與製程條件是經設計以提供特定細胞與微生物的生長，所以，這提供外來微生物污染物（例如，細菌、真菌）生長的機會。此外，有些產品在其對於承受純化技術之廣度的能力可能是有限的，特別是那些經設計以去活化或移除外來病毒污染物的產品。製程、設備、設施、公用設施、製備與添加緩衝劑及試劑之條件及抽樣設計與操作者的訓練，皆屬使該等污染事件減到最少的關鍵考量（亦即，工程與技術管制）。此外，製造過程需經完善設計與管制，以使其對產品不會增加進一步之變異性。	Since materials and processing conditions used in manufacturing processes are designed to provide conditions for the growth of specific cells and microorganisms, this provides an opportunity for extraneous microbial contaminants (e.g. bacteria, fungi) to grow. In addition, some products may be limited in their ability to withstand a wide range of purification techniques, particularly those designed to inactivate or remove adventitious viral contaminants. The design of the processes, equipment, facilities, utilities, the conditions of preparation and addition of buffers and reagents, sampling and training of the operators are key considerations to minimise such contamination events (i.e. engineering and technical controls). In addition, manufacturing processes need to be well designed and controlled so as not to add further variability to the product.
產品規格（例如，在藥典個論、臨床試驗許可與上市許可的規格），將主導原料與物料是否與在何製造階段可以具有經界定的負荷菌量或需為無菌。同樣地，製造必須與明訂於臨床試驗許可或上市許可上之其他規格一致【例如，種批或細胞庫之間的世代數目（倍增、繼代數目）】。	Product specifications such as those in pharmacopoeial monographs, CTA, and MA will dictate whether and to what manufacturing stage substances and materials can have a defined level of bioburden or need to be sterile. Similarly, manufacturing must be consistent with other specifications set out in the CTA or MA (e.g. number of generations (doublings, passages) between the seed lot or cell bank).

對於不能滅菌（例如，經由過濾）的生物原料必須執行無菌操作，以使污染物之導入減到最少。如其存在時，關於特定製造方法之確效（例如，病毒移除或去活化）應參考其他指引文件。適當環境管制與監測之應用，當可行時，下列措施可以顯著減少意外污染與交叉污染的風險，例如：使用結合原位清潔及滅菌系統之密閉系統、使用與產品接觸之無菌拋棄式設備。	For biological materials that cannot be sterilized (e.g. by filtration), processing must be conducted aseptically to minimise the introduction of contaminants. Where they exist, other guidance documents should be consulted on the validation of specific manufacturing methods (e.g. virus removal or inactivation). The application of appropriate environmental controls and monitoring and, wherever feasible, in-situ cleaning and sterilisation systems together with the use of closed systems and sterile disposable product-contact equipment can significantly reduce the risk of accidental contamination and cross-contamination.
ATMP 之品質管制（QC）需結合獨特生物學方法與標準物理-化學含量測定。對於許多細胞來源產品，經由起始原料導入之變異性無法經由製造過程或製程中管制（IPCs）予以克服。起始物與原料之適當管制、完善界定 ATMP 原料藥特性與 ATMP 藥品放行測試，是構成品質管制之關鍵部分。管制應將對於 ATMP 製造所需之生物原料的固有變異性納入考慮。因此，在生物原料藥與藥品的製造上，一個穩健的製造過程是至關重要的，而且製程中管制承擔了特別的重要性。	ATMPs require a combination of unique biological methods and standard physico-chemical assays for their Quality Control (QC). For many cell-based products, there is variability introduced through the starting materials that cannot be overcome by the manufacturing process or In-Process Controls (IPCs). Adequate control of the starting and raw materials, well defined characterisation of the ATMP active substance and ATMP drug product release testing form the crucial part of the QC. Controls should take into consideration the intrinsic variability of the biological material needed for ATMP manufacturing. A robust manufacturing process is therefore crucial and in-process controls take on a particular importance in the manufacture of biological active substances and medicinal products.

A 部：一般指引（PART A: GENERAL GUIDANCE）	
必要時，對於 GMP 指引第一、二部與附則中之各篇，A 部提供替代或補充規定。當本附則為 ATMPs 之製造提供特定指引時（包含其他部分之修改、取代或重複在內），這將清楚地指出。對於 ATMPs 缺乏特定指引時，符合 GMP 指引之其他部分是被預期的。	Part A provides alternative or supplementary provisions to respective sections in Part I, II and annexes of the PIC/S GMP Guide, where necessary. Where this annex provides specific guidance for the manufacture of ATMPs (including modification, replacement or redundancy of other sections), this will be clearly indicated. In the absence of specific guidance for ATMPs, compliance with other sections in the PIC/S GMP Guide is expected.
注意：除另有規定，使用「上市許可持有者」（MAH）術語時，係表示依臨床試驗許可或等同文件使用之研究用 ATMP 的「試驗委託者」。	Note: Where the term Marketing Authorisation Holder (MAH) is used, unless otherwise specified, it should be intended to signify the "Sponsor" for investigational ATMP that is used according to a CTA or equivalent.
對於 GMP 指引第一部之補充規定（SUPPLIMENTARY PROVISIONS TO PIC/S GMP GUIDE PART I）	
第一章 製藥品質系統（CHAPTER 1 PHARMACEUTICAL QUALITY SYSTEM）	
製藥品質系統（Pharmaceutical Quality System）	
1.1 適用時，未經被授權人認可每一生產批次皆已依臨床試驗許可、上市許可與任何有關藥品之生產、管制及放行的法規之要求生產及管制前，該 ATMPs 不得銷售或供應。特殊規定適用於具兩階段放行過程（第 6.14 條所述），或不符合放行規格且無替代處理（第 6.11 至 6.13 條所述）之產品供應。（取代 GMP 指引第一部 1.4 條第 xv 項）	1.1 ATMPs are not sold or supplied before an Authorised Person has certified that each production batch has been produced and controlled in accordance with the requirements of the CTA, MA and any other regulations relevant to the production, control and release of medicinal products as applicable. Special provisions apply for the supply of products that have a two-step release process (described in Section 6.14) or such that do not meet release specifications where there is no alternative treatment available (described in Sections 6.11 to 6.13). (Replaces PIC/S GMP Guide Part I Section 1.4, xv)

品質風險管理（Quality Risk Management）	
1.2 GMP 適用於從研究用藥品的製造、技術移轉、商業製造到產品終止的生命週期階段。生物性製程可能表現其固有變異性，因此，副產物的範圍與性質可能是可變的。所以，詳述於附則 20 之品質風險管理（QRM）原則對此類藥品特別重要，而且應當應用於涵蓋所有開發與製造步驟階段之管制策略的開發，以使其變異性減到最少，並且減少對於污染與交叉污染的機會。（取代 GMP 指引第一部 1.2 條）	1.2 GMP applies to the lifecycle stages from the manufacture of investigational ATMP, technology transfer, and commercial manufacturing through to product discontinuation. The biological processes may display inherent variability, so that the range and nature of by-products may be variable. As a result, Quality Risk Management (QRM) principles as detailed in Annex 20 are particularly important for this class of medicinal products and should be used to develop their control strategy across all stages of development and manufacturing steps to minimise variability and to reduce the opportunity for contamination and cross-contamination. (Replaces PIC/S GMP Guide Part I Section 1.2)
第二章 組織與人事（CHAPTER 2 PERSONNEL）	
2.1 為產品的安全性，人員的健康狀況應納入考慮。在 ATMP 原料藥與藥品的製造與測試區域中的工作人員（包含與清潔、維護保養或品質管制有關者），應針對所製造產品及對其所指定的工作（包括對保護產品、人員與環境的任何特定安全性措施在內）接受相關的訓練與定期再訓練。	2.1 The health status of personnel should be taken into consideration for product safety. Personnel (including those concerned with cleaning, maintenance or quality control) employed in areas where ATMP active substances and products are manufactured and tested should receive training, and periodic retraining, specific to the products manufactured and to the duties assigned to them, including any specific safety measures to protect product, personnel and the environment.
2.2 人員之健康狀態發生任何變化可能對產品品質有不良影響時，應避免其在生產區中工作，並且保存適當的紀錄。工作人員健康的監測應與風險相稱，對於涉及危害性有機體的人員應當尋求醫療建議。對涉及危害性物質之人員的職業健康與安全性（OH&S），應經由國家法規要求給予通盤考慮。	2.2 Any changes in the health status of personnel, which could adversely affect the quality of the product, should prevent work in the production area. Health monitoring of staff should be commensurate with the risk; medical advice should be sought for personnel involved with hazardous organisms. General consideration should be given to Occupational Health & Safety (OH&S) for personnel involved with hazardous substances as required by national law.

2.3 進入製造區的每個人員皆應穿戴適合其所要執行操作之潔淨防護裝。	2.3 Every person entering the manufacturing areas should wear clean protective garments appropriate to the operations to be carried out.
當需要使交叉污染的機會減到最小時，對於所有人員（包含品質管制、維護保養與清潔人員在內）移動的限制，應基於 QRM 原則加以管制。	Where required to minimise the opportunity for cross-contamination, restrictions on the movement of all personnel (including QC, maintenance and cleaning personnel) should be controlled based on QRM principles.
通常，人員不得從暴露於活微生物、基因修飾生物、毒素或動物之區域穿越至處理其他產品、去活化產品或不同有機體的區域。如果該穿越路徑無法避免時，則基於 QRM 原則之污染管制策略（CCS）應加以應用（參照第 3.4 條 CCS）。（取代 GMP 指引第一部 2.18 條）	In general, personnel should not pass from areas of exposure to live micro-organisms, genetically modified organisms, toxins or animals to areas where other products, inactivated products or different organisms are handled. If such route is unavoidable, a Contamination Control Strategy (CCS) based on QRM principles should be applied (refer to Section 3.4 CCS). (Replaces PIC/S GMP Guide Part I Section 2.18)
第三章 廠房設施與設備（CHAPTER 3 PREMISES AND EQUIPMENT）	
廠房設施（PREMISES）	
生產區（Production Areas）	
3.1 所有產品應經由製造廠房設施之適當設計與操作以防止交叉污染。防止交叉污染的措施應與產品品質之風險相稱。QRM 原則應使用以評估及管制風險。	3.1 Cross-contamination should be prevented for all products by appropriate design and operation of manufacturing facilities. The measures to prevent cross- contamination should be commensurate with the risks to product quality. QRM principles should be used to assess and control the risks.
視有些 ATMPs 與其生產所涉及之原料（例如，病毒）所呈現的風險等級，對其製造及/或分/包裝作業，可能需要採用專用廠房設施與設備，以管制其風險。對於呈現無法經由操作及/或技術措施充分管制其風險之 ATMPs 的製造，應使用隔離的生產區域。（取代 GMP 指引第一部 3.6 條）	Depending on the level of risk presented by some ATMPs and the materials involved in their production (for example, viruses), it may be necessary to dedicate premises and equipment for manufacturing and/or packaging operations to control the risk. Segregated production areas should be used for the manufacture of ATMPs presenting a risk that cannot be adequately controlled by operational and/or technical measures. (Replaces PIC/S GMP Guide Part I Section 3.6)

3.2 若適當操作及/或技術管制應用於跨越整個製造步驟順序，經 QRM 原則證明其合理時，則兩種或多種不同 ATMPs／批次於相同區域中同時生產可能被允許。例如：	3.2 Concurrent production of two or more different ATMPs/batches in the same area might be permitted due to adequate operational and/or technical control where justified under QRM principles applied across the entire sequence of manufacturing steps. For example:
(a) 假設採取適當之緩解措施以避免交叉污染或材料混雜，則於同一作業室中同時使用一個以上之密閉隔離裝置（或其他密閉系統）是可以被接受的。	(a) The use of more than one closed isolator (or other closed systems) in the same room at the same time is acceptable, provided that appropriate mitigation measures are taken to avoid cross-contamination or mix-ups of materials.
(b) 當於同一作業室中使用一個以上之隔離裝置操作不同病毒載體時，作業室與設施中之空氣應 100%排放（亦即，不再循環使用）。此外，若同時生產病毒載體時，對於提供密閉、分離及單向之廢棄物處理是必要的。	(b) When more than one isolator is used to process different viral vectors within the same room there should be 100% air exhaustion from the room and the facility (i.e. no recirculation). In addition, in case of concurrent production of viral vectors, it is necessary to provide for closed, separate and unidirectional waste handling.
(c) 於同一作業室中使用一個以上之生物安全櫃（BSC）的可行性，僅於實施有效之技術與組織措施使作業得以分隔，方可被接受。同時使用一個以上之生物安全櫃會帶來額外的風險，因此，應證明所實施之措施是有效的，以避免產品品質與任何混雜的風險。理論基礎應基於 QRM 原則證明其合理性。	(c) The possibility of using more than one biosafety cabinet (BSC) in the same room is only acceptable if effective technical and organisational measures are implemented to separate the activities. The simultaneous use of more than one BSC entails additional risks and, therefore, it should be demonstrated that the measures implemented are effective to avoid risks to the quality of the product and any mix-ups. The rationale should be justified based on QRM principles.
(d) 若其密閉狀態可被證明，於同一區域中使用多個密閉系統是被允許的。（參照第 3.13 條。）	(d) The use of multiple closed systems in the same area is permitted, in the case that their close state can be demonstrated. (refer to point 3.13.)
3.3 圍堵所需要的措施與程序（亦即，對環境與操作人員的安全性）應不得與維護產品品質之措施與程序衝突。	3.3 The measures and procedures necessary for containment (i.e. for environment and operator safety) should not conflict with those for product quality.

3.4 涉及應基於文件化之污染管制策略與 QRM 原則予以隔離的感染性病毒載體之製造活動的情況（例如，溶瘤病毒、具複製能力之載體），應採取特別防範措施。基於污染管制策略與 QRM 原則，製造廠應證明所需之隔離程度的合理性。QRM 過程之結果，應確定須專用於特定產品之廠房設施與設備的必要性與程度。依照國家法規，在有些情況下可能需要專用廠房設施、專用區域或專用設備。將具複製能力之載體/產品或受感染之材料/產品與其他材料/產品同時培養及/或儲存是不被接受的。	3.4 Special precautions should be taken in the case of manufacturing activities involving infectious viral vectors (e.g. oncolytic viruses, replication competent vectors) that should be segregated based on a documented CCS and QRM principles. The manufacturer should justify the level of segregation required based on the CCS and through QRM principles. The outcome of the QRM process should determine the necessity for and extent to which the premises and equipment should be dedicated to a particular product. In some cases, dedicated facilities, dedicated areas or dedicated equipment may be required in accordance with the national law. Simultaneous incubation and/or storage of replication competent vectors/products, or infected materials/products, with other materials/products is not acceptable.
3.5 空氣處理單元應經設計、建置與維護保養，以使在不同製造區域間之交叉污染的風險減到最低，而且，對某些區域可能需要專用的空氣處理單元。基於 QRM 原則，應考慮使用單次通過（single pass）的空氣系統。	3.5 Air handling units should be designed, constructed and maintained to minimise the risk of cross-contamination between different manufacturing areas and may need to be specific for an area. Consideration, based on QRM principles, should be given to the use of single pass air systems.
3.6 在生產過程中，若原物料（例如培養基與緩衝液）必須加以量測或秤重時，基於所界定的標準（例如，在該批次的製造或在時段切換製造的期間），少量庫存可在生產區中保存一段特定時間。（取代 GMP 第一部 3.13 條）	3.6 If materials (such as culture media and buffers) have to be measured or weighed during the production process, small stocks may be kept in the production area for a specified duration based on defined criteria (e.g. duration of manufacture of the batch or of the campaign). (Replaces PIC/S GMP Guide Part I Section 3.13)

3.7 對於操作無菌產品，應使用正壓區域，但是，為圍堵的理由，在病原菌暴露點的特定區域，負壓是可接受的。對於具有特定風險（例如，病原菌）之原物料的無菌操作使用負壓區域或生物安全櫃時，該等操作區域應由適當等級的正壓潔淨區域予以包圍。這些壓力梯度應予以清楚地界定，並以附則 1 所界定之適當的警報裝置進行連續監測。該等區域之設計應具備防止原物料釋放進入周圍環境中，且不損及產品之無菌性保證水準（SAL）之措施，反之亦然。	3.7 Positive pressure areas should be used to process sterile products, but negative pressure in specific areas at the point of exposure of pathogens is acceptable for containment reasons. Where negative pressure areas or BSCs are used for aseptic processing of materials with particular risks (e.g. pathogens), they should be surrounded by a positive pressure clean zone of appropriate Grade. These pressure cascades should be clearly defined and continuously monitored with appropriate alarm settings as defined by Annex 1. The design of such areas should be such that measures put in place to prevent release of material into the surrounding environment should not compromise sterility assurance level (SAL) of the product and vice versa.
3.8 直接關連於產品無菌性（例如，用於維持密閉系統完整性）之空氣通氣過濾器應為疏水性，於使用期間監測（例如：合適時，壓差監測），並根據適當的 QRM 原則，於適當的時間間隔進行完整性測試，以驗證其預定的使用。對於過濾系統，若壓力監測或完整性測試技術上不可行時，可考慮供應商提供之資訊以供核准。但是，此必須考慮污染管制策略作為額外風險因素，尤其是短架儲期 ATMPs，在藥品投用前，批次放行無法獲得微生物學上品質測試時。	3.8 Air vent filters that are directly linked to the sterility of the product (e.g. to maintain the integrity of a closed system) should be hydrophobic, monitored during use (e.g. pressure differential monitoring if appropriate) and validated for their scheduled life span with integrity testing at appropriate intervals based on appropriate QRM principles. If pressure monitoring or integrity testing is technically not feasible for the filter system, vendor supplied information may be considered for approval. However, this has to be taken into account in the CCS as an additional risk factor especially for short shelf life ATMPs, where microbiological quality tests are not available at the time of batch release prior to medical product administration.

3.9 排水系統必須加以設計，以便使排放物可被有效地中和或去除污染，以使交叉污染的風險減到最低。該排水系統必須遵從國家法規，依照與廢棄物之生物危害本質相關的風險，使外在環境污染的風險減到最低。（取代 GMP 指引第一部 3.11 條）	3.9 Drainage systems must be designed so that effluents can be effectively neutralised or decontaminated to minimise the risk of cross-contamination. They must comply with national law to minimize the risk of contamination of the external environment according to the risk associated with the biohazardous nature of waste materials. (Replaces PIC/S GMP Guide Part I Section 3.11)
3.10 切記起始原料潛在污染程度及對該產品的風險，應將生產之廠房設施的微粒與微生物污染等環境管制，調整到適合該產品及其生產步驟之程度。微生物環境監測計畫應補充包括檢測 QRM 原則指示的特定微生物（例如宿主生物、酵母菌、黴菌、厭氧菌等）存在的方法。	3.10 The degree of environmental control of particulate and microbial contamination of the production premises should be adapted to the product and the production step, bearing in mind the potential level of contamination of the starting materials and the risks to the product. The microbiological environmental monitoring programme should be supplemented by the inclusion of methods to detect the presence of specific microorganisms (e.g. host organism, yeasts, moulds, anaerobes, etc.) where indicated by the QRM principles.

3.11 當產品之製程不是密閉且於直接作業室環境中暴露，未有後續微生物去活化過程時（例如，在添加補充劑、培養基、緩衝液、氣體等期間，及操作中），應採用適當之環境條件。對於無菌操作參數，應遵從附則 1（亦即，具有 B 級背景之 A 級）。環境監測計畫應包括浮游微粒污染、微生物污染與壓差之測試及監測。監測位置應考量 QRM 原則予以決定。樣品數目、容量與監測頻率、警戒及行動限值應適當考量 QRM 原則。取樣方法應不對製造操作造成污染風險。製程中需要適當管制時，溫度與相對濕度應加以監測。所有環境監測結果應進行趨勢分析。	3.11 Where processes are not closed and there is exposure of the product to the immediate room environment without a subsequent microbial inactivation process, (e.g. during additions of supplements, media, buffers, gasses, manipulations) appropriate environmental conditions should be applied. For aseptic manipulations parameters in line with Annex 1 (i.e. Grade A with Grade B background) should be applied. The environmental monitoring program should include testing and monitoring of non-viable contamination, viable contamination and air pressure differentials. The monitoring locations should be determined having regards to the QRM principles. The number of samples, volume, and frequency of monitoring, alert and action limits should be appropriate taking into account the QRM principles. Sampling methods should not pose a risk of contamination to the manufacturing operations. Where appropriate control is required in the process, temperature and relative humidity should be monitored. All environmental monitoring results should be trended.

3.12 當無適當製造環境時，僅在例外情況下，對於非密閉製程，如經主管機關核准，且依照臨床試驗許可或上市許可或其他的國家要求時，比上述 3.11 條規定較不嚴格之環境可能可被接受。但是，此選項應視為例外情形，且僅當產品旨於預定治療危及生命而無替代治療選項之情況時方可適用。環境必須加以指定並證明其合理性，以使提供病人的益處超過在較不嚴格環境下製造所造成之顯著風險。若主管機關核准後，當出現技術改進時，製造廠必須尋求建立適當環境。	3.12 Only in exceptional circumstances when an appropriate manufacturing environment is not available, a less stringent environment than that specified in Section 3.11 above may be acceptable for processes that are not closed where approved by the Competent Authority and in accordance with CTA or MA or other national requirements. However, this option should be considered exceptional and applicable only if the product is intended to treat a life-threatening condition where no alternative therapeutic options exist. The environment must be specified and justified to provide patient benefit that outweighs the significant risk created by manufacturing under less stringent environments. If the Competent Authority grants an approval, the manufacturer must pursue establishing the appropriate environment as improvements in the technology occur.
3.13 基於 QRM 評估結果，對於密閉系統，比 B 級背景中之 A 級為低的級區可能是可以接受的。考量產品本質、製程與使用之設備，應根據具體風險決定適當之空氣等級與其監測程度。應使用 QRM 決定所用技術是否支持減少監測，尤其是監測作業可能成為污染來源時。此外亦包含：	3.13 For closed systems, a lower classified area than Grade A in background Grade B might be acceptable based on the outcome of a QRM assessment. The appropriate level of air classification and monitoring should be determined having regard to the specific risks, considering the nature of the product, the manufacturing process and the equipment used. QRM should be used to determine whether the technology used supports reduced monitoring, in particular where monitoring can be a source of contamination. This is in addition to:

(a) 若實施適當之管制措施以避免微生物污染及交叉污染風險時（例如，物流、人流與潔淨度之適當管制），使用下列技術可能可被接受，例如：於一次性無菌拋棄式套組內操作、或使用密閉自動化製造平台操作、或於 C 級中之密閉瓶、袋或醱酵槽中培養。若在後來將材料移至更高等級之潔淨區，應予特別注意。	(a) The use of technologies as e.g. processing inside single use sterile disposable kits, or processing using closed, automated manufacturing platform or incubation in closed flasks, bags or fermenters in Grade C may be acceptable if adequate control measures are implemented to avoid the risk of microbial contamination and cross-contamination (e.g. appropriate control of materials, personnel flows and cleanliness). Particular attention should be paid if the materials are subsequently moved to a clean area of higher Grade.
(b) 若可證明密閉系統在整個使用期間中保持完整，D 級背景可能是可以接受的。	(b) If the closed system can be shown to remain integral throughout the entire usage, a background of Grade D might be acceptable.
應考慮附則 1 關於密閉系統規定之要求。	Requirements of Annex 1 regarding the provision of closed system should be considered.
3.14 在例外情況，當經主管機關核准，且依照臨床試驗許可或上市許可或其他的國家要求時，在非由 ATMP 製造廠或上市許可持有者直接管制之作業場所執行製造步驟是可允許的（包含例如將所用設備置於醫院病房或手術室以執行製造步驟在內）。在該等情況下，應證明該過程依照附則 15、附則 20 與本附則中之原則與指引，維持其確效狀態，該等安排應經由主管機關核准。各方責任應在書面技術協議中加以界定。	3.14 In exceptional circumstances, it is permissible to perform a manufacturing step in premises that are not under direct control of the ATMP manufacturer or MAH (including for example placing equipment used to perform manufacturing steps in hospital wards or theatre) where approved by the Competent Authority and in accordance with CTA or MA or other national requirements. In such cases, it should be demonstrated that the process maintains its validated status in accordance to principles and guidelines in Annex 15, Annex 20 and in this annex. These arrangements should be subject to approval by the Competent Authority. The responsibilities of each parties should be defined in written technical agreements.

設備（EQUIPMENT）	
3.15 生產設備不得呈現對產品有任何危害。生產設備與產品接觸的部分，其反應性、加成性或吸附性不得高到足以影響產品的品質，而呈現任何危害。	3.15 Production equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product and thus present any hazard.
此外，若使用一次性使用系統（亦即，拋棄式系統），製造廠應考慮並確認來自從該等系統衍生之可萃取物、可浸出物、不溶性微粒與不溶性物質對產品的衝擊。應考慮附則 1 關於一次性使用系統之規定。（取代 GMP 第一部 3.39 條）	In addition, if single use systems (i.e. disposable systems) are used, the manufacturer should take into account and verify the impact on the product from extractable, leachable, insoluble particulate and insoluble matter derived from such systems. Annex 1 regarding provisions for single use systems should be considered. (Replaces PIC/S GMP Guide Part I Section 3.39)
3.16 當需使交叉污染風險減到最低時，對於設備移動之限制應加以應用。通常，設備應不得從高風險區域移動至其他區域，或在高風險區域之間移動（例如，對於來自受感染之捐贈者細胞的處理或溶瘤病毒之處理所使用的設備）。當工程及/或技術經檢討調整後，而致設備移動位置不可避免時，其風險應依照 QRM 原則進行評估、降低與監測，以確保有效之交叉污染管制策略（參照第 3.4 條污染管制策略）。經移動後之設備的驗證狀態亦應加以考慮。	3.16 Where required to minimise the risk of cross-contamination, restrictions on the movement of equipment should be applied. In general, equipment should not be moved from high-risk areas to other areas, or between high-risk areas (e.g. equipment used for the handling of cells from infected donors or the handling of oncolytic viruses). Where the relocation of equipment is unavoidable, after reviewing engineering and/ or technical modifications, the risk should be assessed in line with QRM principles, mitigated and monitored to ensure an effective cross-contamination control strategy (refer to Section 3.4 CCS). The qualification status of the equipment moved should also be considered.
3.17 在活有機體與細胞之處理期間所用設備之設計，包含用於取樣的設備在內，應加以考慮，以防止在操作期間的任何污染。	3.17 The design of equipment used during handling of live organisms and cells, including those for sampling, should be considered to prevent any contamination during processing.

3.18 一級圍堵[4]應經設計並定期測試，以確保防止生物物質逸入直接工作環境。	3.18 Primary containment[4] should be designed and periodically tested to ensure the prevention of escape of biological agents into the immediate working environment.
[4] 參見 GMP 術語彙編之「圍堵」。	[4] See Main GMP Glossary on 'Containment'.
3.19 用於支持製造之電子系統必須依照附則 11 與 15 進行驗證。對非用於製造但支持提供製程之生物資訊學（例如，病人基因定序）的材料所執行之任何分析測試應加以確效。該等分析設備於使用前經驗證是被預期的。	3.19 Electronic systems used to support manufacturing must be qualified in accordance with Annex 11 and 15. Any analytical testing performed on materials not used in manufacturing but that support bioinformatics informing the manufacturing process (e.g. patient gene sequencing) should be validated. Such analytical equipment is expected to be qualified prior to use.
第四章 文件（CHAPTER 4 DOCUMENTATION）	
規格（Specifications）	
4.1 ATMP 起始物與原料之規格，可能需要其來源、種源、運銷鏈、製造方法與所使用的管制之額外文件，以確保適當的管制與監督水準，包括其微生物學方面的品質。	4.1 Specifications for ATMP starting and raw materials may need additional documentation on the source, origin, distribution chain, method of manufacture, and controls applied, to assure an appropriate level of control and oversight including their microbiological quality.
4.2 有些產品構成一個批次所需的材料，可能需要予以特別界定。對於自體及與捐贈者配對的情況，所製造的產品應視為一個批次。	4.2 Some products may require specific definition of what materials constitute a batch. For autologous and donor-matched situations, the manufactured product should be viewed as a batch.
可追溯性（Traceability）	
4.3 當使用人類細胞或組織時，依照國家法規，在維持個人隱私與健康相關資訊之保密性同時，從起始物與原料之完整可追溯性是必須的，包含與細胞或組織接觸之所有物質到使用端接收該產品的確認在內。	4.3 Where human cells or tissues are used, full traceability is required from starting and raw materials, including all substances coming into contact with the cells or tissues through to confirmation of the receipt of the products at the point of use whilst maintaining the privacy of individuals and confidentiality of health-related information, according to national legislation.

4.4 對於源自人類之起始原料，細胞/組織/病毒起源（或合適時，細胞株、主細胞庫、種批之鑑別），其供應商識別與採集環境亦應描述。	4.4 For starting materials of human origin, the identification of the supplier and the anatomical environment from which the cells/tissues/virus originates (or, as appropriate, the identification of the cell-line, master cell bank, seed lot) should also be described.
4.5 應建立使 ATMPs 中所含細胞/組織，從捐贈、製造至最終產品遞送到接受者，能雙向追蹤的系統。該系統可為手動的或自動的。其應於整個製造生命週期被使用，以包含臨床試驗批次與商業批次。	4.5 A system that enables the bidirectional tracking of cells/tissues contained in ATMPs from the point of donation, through manufacturing, to the delivery of the finished product to the recipient should be created. This system can be manual or automated. It should be used throughout the manufacturing lifecycle to include clinical trial and commercial batches.
4.6 可追溯性紀錄應作為可稽查之文件保存，並與相關批次紀錄明確地連結。如病人發生不良反應時，該儲存系統應確保可追溯性數據能易於取得。	4.6 Traceability records should be kept as an auditable document and unequivocally linked to the relevant batch record. The storage system should ensure that traceability data allow for easy access, in case of an adverse reaction from the patient.
4.7 除非上市許可/臨床試驗許可或國家法規另有規定，否則細胞與組織來源之產品及個人化 ATMP 的可追溯性紀錄必須保存到該產品的末效日期後 30 年。維持產品對於特殊使用案例之可追溯性，例如與捐贈者配對之細胞，應採取特別注意。當血液成分在藥品製造過程作為起始物或原料使用時，適用關於可追溯性要求與嚴重不良反應與事件通報的國家法規。包含造血細胞在內之人體細胞必須遵從國家法規中關於可追溯性所規定的原則。	4.7 Traceability records for cellular and tissue-based products and for any personalized ATMP must be retained 30 years after the expiry date of the product unless otherwise specified in the MA/CTA or national law. Particular care should be taken to maintain the traceability of products for special use cases, such as donor-matched cells. National requirements in regard to traceability requirements and notification of serious adverse reactions and events apply to blood components when they are used as starting or raw materials in the manufacturing process of medicinal products. Human cells including haematopoietic cells must comply with the principles laid down in national law concerning traceability.

4.8 當異種細胞用作 ATMPs 起始原料時，除非於上市許可/臨床試驗許可或國家法規另有規定，否則捐贈動物之識別的許可資訊應保存 30 年。	4.8 When xenogeneic cells are used as starting materials for ATMPs, information permitting the identification of the donor animal should be kept for 30 years unless otherwise specified in the MA/CTA or national legislation.
第五章 生產（CHAPTER 5 PRODUCTION）	
一般規定（General）	
5.1 ATMPs 必須遵從可適用的國家要求，以使經由人用與動物用藥品傳播動物海綿樣腦症病原體的風險減到最低。	5.1 ATMPs must comply with the applicable national requirements on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products.
基因治療 ATMPs 應備有系統以確保其病毒安全性，該系統確保生產過程中起始物（包括細胞庫與病毒種庫之庫存）與原料之品質。	Viral safety for gene therapy ATMPs should be ensured by having systems in place that ensure the quality of starting (including cell banks and viral seed stocks) and raw materials through the production process.
5.2 涉及具複製能力之載體或來自受感染捐贈者之原料的樣品收集、添加與移轉之情況，應防止病毒/受感染物之釋出。	5.2 The conditions for sample collection, additions and transfers involving replication competent vectors or materials from infected donors should prevent the release of viral/infected material.
5.3 在製程的每一階段，皆應防止原物料與產品受微生物及任何其他污染。應實施適當之污染管制與監測策略（參照第 3.4 條污染管制策略）。對於來自不同捐贈者，與適用時，來自具有不同陽性反應血清標記之捐贈者，其細胞製備作業間交叉污染的風險應特別考慮。（取代 GMP 指引第一部 5.10 條）	5.3 At every stage of processing, materials and products should be protected from microbial and any other contamination. Appropriate contamination control and monitoring strategies should be implemented (refer to Section 3.4 CCS). Particular consideration should be given to the risk of cross-contamination between cell preparations from different donors and, where applicable, from donors having different positive serological markers. (Replaces PIC/S GMP Guide Part I Section 5.10)

5.4 使用抗微生物劑可能是必要的，以減少與活組織及細胞之採集相關的負荷菌。但是，抗微生物劑之使用並非取代無菌製造之要求。當使用抗微生物劑時，其使用應加以記錄；應將其儘快去除，除非臨床試驗許可或上市許可載明可存在於最終產品中（例如，抗生素為最終產品基質的一部分）。此外，對於確保抗微生物劑不干擾任何產品微生物污染測試或無菌性測試，且確保其不存在於最終產品中都很重要（除非於臨床試驗許可或上市許可中明確證明其合理性）。	5.4 The use of antimicrobials may be necessary to reduce bioburden associated with the procurement of living tissues and cells. However, the use of antimicrobials does not replace the requirement for aseptic manufacturing. When antimicrobials are used, their use should be recorded; they should be removed as soon as possible, unless the presence thereof in the finished product is specifically foreseen in the CTA or MA (e.g. antibiotics that are part of the matrix of the finished product). Additionally, it is important to ensure that antimicrobials do not interfere with any product microbial contamination testing or sterility testing, and that they are not present in the finished product (unless specifically justified in the CTA or MA).
5.5 用於容器、設備或廠房設施的標示卡應清晰、完善界定，而且使用製造廠一致的格式。	5.5 Labels applied to containers, equipment or premises should be clear, well defined and in the manufacturer's agreed format.
在標籤的製作、印刷、儲存與應用上應加以注意，包含對患者特定產品或自體產品的任何特定文字在內。對於含有從人類細胞或組織衍生之細胞的產品，捐贈者之標籤應含有提供完整可追溯性所需的所有相關資訊。在自體產品的情況，獨特的病人識別碼與「僅供自體使用」的描述，應標示在外包裝上，或當無外包裝時，則標示在直接包裝容器上或按國家法規其他規定。	Care should be taken in the preparation, printing, storage and application of labels, including any specific text for patient-specific or autologous product. For products containing cells derived from human cells or tissue, donor's labels should contain all relevant information that is needed to provide full traceability. In the case of autologous products, the unique patient identifier and the statement "for autologous use only" should be indicated on the outer packaging or, where there is no outer packaging, on the immediate packaging or as otherwise specified in national law.
若產品錯誤投予之風險可被適當地降低，則替代的標示方法/措施是被允許的。對於為盲性研究用之 ATMPs，在維持病人安全性的同時，其標示「自體使用」之要求，可由確保盲性的條碼或同等替代機制所取代。（取代 GMP 指引第一部 5.13 條）	Alternative approaches/measures are permitted as long as the risk of erroneous administration of the product is adequately mitigated. For investigational ATMPs that are blinded, the requirement to state "autologous use" can be substituted by a barcode or an alternative equivalent mechanism that ensures blinding while maintaining patient safety. (Replaces PIC/S GMP Guide Part I Section 5.13)

5.6 建立直接包裝與間接包裝作業計畫時應予以特別注意，以使交叉污染、混雜或調換的風險降到最低。應遵守無菌性及/或低負荷菌要求，並且隔離策略應加以應用。（取代 GMP 指引第一部 5.49 條）	5.6 When setting up a programme for primary and secondary packaging operations, particular attention should be given to minimising the risk of cross-contamination, mix-ups or substitutions. Sterility and/or low bioburden requirements should be adhered to and segregation strategies should be applied. (Replaces PIC/S GMP Guide Part I Section 5.49)
5.7 如果使用密閉系統生產 ATMPs 時，應進行檢查，以確保設備所有配件皆以正確方式連接，以證明密閉狀態。該等測試應用於自動化系統時應予以特別注意。如果可行並基於 QRM 原則，例如考量由供應商執行測試，則一次性使用系統之完整性應於使用前與可能於使用後以適當頻率加以確認（可能是自動地）。可重複使用之設備於清潔與滅菌後，其完整性應於其使用前加以確認。	5.7 If closed systems are used for the production of ATMPs, checks should be carried out to ensure that all pieces of the equipment are connected in a correct manner to assure the closed state. Special attention should be given to apply these tests to automated systems. If feasible and based on QRM principles, for example considering testing carried out by vendors, the integrity of single use systems should be verified at adequate frequency prior to use and potentially post use, possibly automatically. The integrity of reused equipment should be verified before use after cleaning and sterilisation.
5.8 當系統添加或取出原物料未使用無菌技術時（例如，未使用無菌連接器或未以無菌技術連接過濾器），則該系統就不再被認為密閉。	5.8 A system is no longer considered closed when materials are added or withdrawn without aseptic techniques (e.g. without use of sterile connectors or filters aseptically connected).
5.9 若使用層析法設備，用於時段切換製造與多產品環境時，應對基質、殼體與相關設備（依風險調適）實施適當管制策略。由於殘轉污染之風險，避免同一基質於不同操作階段重複使用。任何該等重複使用皆應經由適當確效數據予以支持。層析法管柱之允收標準、操作條件、再生方法、使用期間與滅菌或滅菌方法應予界定。	5.9 Where chromatography equipment is used, a suitable control strategy for matrices, the housings and associated equipment (adapted to the risks) should be implemented when used in campaign manufacture and in multi-product environments. The re-use of the same matrix at different stages of processing is discouraged due to risk of carryover contamination. Any such re-usage should be supported by appropriate validation data. Acceptance criteria, operating conditions, regeneration methods, life span, and sanitization or sterilisation methods of chromatography columns should be defined.

5.10 在任何超低溫冷凍階段之特定要求，例如，在冷凍或解凍期間溫度變化速率，應予謹慎關注。儲存艙的類型、放入與取出過程，應使交叉污染的風險減到最低，並保持產品的品質且便利其準確的取出。具陽性反應血清標記之產品的安全處理與儲存，應具備文件化的程序。	5.10 Careful attention should be paid to specific requirements at any cryopreservation stages, e.g. the rate of temperature change during freezing or thawing. The type of storage chamber, placement and retrieval process should minimise the risk of cross-contamination, maintain the quality of the products and facilitate their accurate retrieval. Documented procedures should be in place for the secure handling and storage of products with positive serological markers.
5.11 所選定之包裝材料的適用性應予考慮。對於儲存在超低溫（- 60°C 或更低）之容器所使用的印字標籤，其黏著性、耐久性及易讀性應予確認。此外，應用整體方法，使儲存在超低溫期間可能發生對容器封蓋完整性之風險減到最低。應產生基於證據之數據，以支持合適之直接包材的選擇與容器封蓋密封過程之驗證。	5.11 The suitability of selected packaging material should be considered. The adhesiveness, durability and legibility of printed text of labels used for containers that are stored at ultra-low temperatures (- 60 °C or lower) should be verified. Additionally, apply a holistic approach to minimize the risk to container closure integrity (CCI) that can occur during storage at ultra-low temperatures. Evidence- based data should be generated to support the selection of the appropriate primary packaging components and qualification of the container/closure sealing process.
生產中交叉污染的防止（Prevention of Cross-contamination in Production）	
5.12 基於證據之 QRM 過程應加以使用，以評估與管制由所製造之產品呈現的交叉污染風險。考慮的因素包括：	5.12 An evidence-based QRM process should be used to assess and control the cross-contamination risks presented by the products manufactured. Factors to take into account include:
(a) 使用的載體與具複製能力病毒發生的風險（包括從使用複製受限、複製缺陷、條件複製及無法複製之載體所衍生的不同程度風險），	(a) vectors used and the risk of occurrence of replication competent virus (including different level of risk derived from the use of replication limited, replication defective, conditional replication and replication incompetent vectors),
(b) 設施/設備的設計與使用，	(b) facility/equipment design and use,
(c) 人流與物流，	(c) personnel and material flow,
(d) 微生物學上與其他外來病原的管制，	(d) microbiological and other adventitious agent controls,

(e) 起始物/原料藥與原物料之特性，	(e) characteristics of the starting materials/active substance and raw materials,
(f) 製程特性，	(f) process characteristics,
(g) 潔淨室條件，	(g) clean room conditions,
(h) 清潔過程，與	(h) cleaning processes, and
(i) 由產品評估中所建立之相對於相關限量的分析能力。	(i) analytical capabilities relative to the relevant limits established from the evaluation of the products.
QRM 過程的結果應成為確定製程流程、確定廠房設施與設備專用於特定產品之必需性及其專用程度、或應使用一次性使用系統於特定產品之基礎。這可能包括專用特定的產品接觸零件或整個生產製造設施之專用。證明合理時，在多產品共用設施內，將製造活動限制在隔離的、自足圍堵的生產區域是可以被接受的。結果應連同污染管制策略進行檢討。	The outcome of the QRM process should be the basis for determining the process workflow and necessity for and extent to which premises and equipment should be dedicated or single use systems should be used for a particular product. This may include dedicating specific product contact parts or dedication of the entire manufacturing facility. It may be acceptable to confine manufacturing activities to a segregated, self-contained production area within a multiproduct facility, where justified. Results should be reviewed jointly with the CCS.
（取代 GMP 指引第一部 5.20 條）	(Replaces PIC/S GMP Guide Part I Section 5.20)
5.13 對於滅菌、消毒、病毒移除或去活化所使用的方法，應經確效。製造期間執行病毒之去活化或移除過程時，應採取措施，以避免再污染的風險。（參照第 5.19(a)）	5.13 The methods used for sterilisation, disinfection, virus removal or inactivation should be validated. In cases where a virus inactivation or removal process is performed during manufacture, measures to avoid the risk of recontamination should be taken. (refer to Section 5.19(a))

5.14 應具備對於處理活有機體之意外釋放的緊急計畫。該計畫應針對圍堵、操作員保護、清潔、去污染與安全恢復使用等提出方法與程序。意外的溢出，特別是活的有機體，必須快速而且安全地處理。對於各有機體或相關有機體群，應有遵照 QRM 過程之去污染措施。去污染措施應就其有效性加以確效。	5.14 An emergency plan for dealing with accidental release of viable organisms should be in place. This should address methods and procedures for containment, protection of operators, cleaning, decontamination and safe return to use. Accidental spillages, especially of live organisms, must be dealt with quickly and safely. Decontamination measures should be available for each organism or groups of related organisms in line with the QRM process. Decontamination measures should be validated for effectiveness.
5.15 如已明顯被污染時，諸如，經由溢出或氣霧，或者，如果涉及潛在有害有機體時，包含文書作業在內之生產與管制用料，必須充分地消毒，或須經由其他方式將該資訊轉出。在受影響之區域中，對於緊鄰產品與任何其他產品之影響，也應加以評估。	5.15 If obviously contaminated, such as by spills or aerosols, or if a potential hazardous organism is involved, production and control materials, including paperwork, must be adequately disinfected, or the information transferred out by other means. An assessment of the impact on the immediate products and any others in the affected area should also be made.
5.16 應評估關於產品特性（例如，起始原料之生物學特性、耐受純化技術之可能性）與製程（例如，提供外來微生物污染物生長機會之製程的使用）之交叉污染風險。對於不能滅菌的 ATMPs，任何開放性製程（例如，充填）必須執行無菌操作，以使污染物之導入減到最少。	5.16 The risks of cross-contamination should be assessed having regard to the characteristics of the product (e.g. biological characteristics of the starting materials, possibility to withstand purification techniques) and manufacturing process (e.g. the use of processes that provide extraneous microbial contaminants the opportunity to grow). For ATMPs that cannot be sterilised, any open processing (e.g. filling) must be conducted aseptically to minimise the introduction of contaminants.
5.17 可能導致非必要之氣霧形成的任何製造步驟（例如，離心、抽真空作業、均質化與超音波處理），應實施適當減少氣霧產生之措施以避免交叉污染。當操作感染性材料時，應採取特別防範措施。	5.17 In all manufacturing steps that may lead to unwanted formation of aerosols (e.g. centrifugation, working under vacuum, homogenisation, and sonication) appropriate mitigation measures should be implemented to avoid cross- contamination. Special precautions should be taken when working with infectious materials.

5.18 應具備對於防止適合於已識別之風險的交叉污染措施。對於防止交叉污染可考慮下列措施，尤其包含：	5.18 Measures to prevent cross-contamination appropriate to the risks identified should be put in place. Measures that can be considered to prevent cross- contamination include, among others:
(a) 隔離的廠房設施，	(a) segregated premises,
(b) 完全專用的製造設施；或基於時段切換(以時間分隔)的自足圍堵生產區域，接著進行已確效其有效性之清潔作業，	(b) dedicating the entire manufacturing facility or a self-contained production area on a campaign basis (separation in time) followed by a cleaning process of validated effectiveness,
(c) 適當的清潔程序：	(c) adequate cleaning procedures:
i. 清潔程序（技術、減菌步驟次數等）應適合產品與製程之特定特徵；	i. the cleaning procedure (technique, number of sanitation steps, etc.) should be adapted to the specific characteristics of the product and of the manufacturing process;
ii. 應使用風險評估，以確定必要之清潔與去污染程序，包含其頻率在內；	ii. a risk-assessment should be used to determine the cleaning and decontamination procedures that are necessary, including the frequency thereof;
iii. 至少於每批次之間應有適當清潔與去污染；以及	iii. as a minimum, there should be appropriate cleaning and decontamination between each batch; and
iv. 所有清潔與去污染程序應經確效。	iv. all cleaning and decontamination procedures should be validated.
(d) 操作及在各操作設備間之原物料或產品的移轉應使用「密閉系統」；	(d) use of “closed systems” for processing and for material or product transfer between individual processing equipment,
(e) 使用氣鎖室及壓力梯度，以將潛在空氣浮游污染物侷限於特定區域內；	(e) use of air locks and pressure cascade to confine potential airborne contaminant within a specified area,
(f) 使用一次性使用系統；	(f) utilisation of single use systems,
(g) 其他適當的組織措施，諸如：	(g) other suitable organisational measures, such as the:
i. 設備某些零配件（例如，過濾器）專用於具有特定風險概貌之產品類別；	i. dedication of certain parts of equipment (e.g. filters) to a given type of product with a specific risk profile;

ii. 在操作具高污染風險之產品時，將特定防護裝留在該區域內；	ii. keeping specific protective clothing inside areas where products with high-risk of contamination are processed;
iii. 實施適當措施以處理廢棄物、受污染的沖洗水與髒污衣物；以及	iii. implementing adequate measures to handling waste, contaminated rinsing water and soiled gowning; and
iv. 人員移動施加限制。	iv. imposing restrictions on the movement of personnel.
（取代 GMP 指引第一部 5.21 條）	(Replaces PIC/S GMP Guide Part I Section 5.21)
確效（Validation）	
5.19 在製程確效期間，應考量組織/細胞可取得數量之潛在限制。必須實施可獲得最大製程知識之策略。	5.19 During process validation potential limited availability of quantities of tissue/cells has to be taken into account. A strategy on gaining maximum process knowledge has to be implemented.
確效研究應依所界定的程序進行。其結果與結論應予記錄，尤其是：	Validation studies should be conducted in accordance with defined procedures. Results and conclusions should be recorded, in particular:
(a) 早期階段臨床試驗（I 期與 I/II 期）為探索所製造之 ATMPs，是被期望隨各試驗期相關之知識與風險程度進行確效。對於研究用 ATMPs 與經許可之 ATMPs，其所有無菌操作過程與滅菌過程以及病毒去活化或移除，是被預期經確效的。消毒方法之有效性應予證明。對於所有試驗期，都應應用如附則 13 中所概述之原則。	(a) ATMPs manufactured for exploratory, early phase clinical trials (phase I and phase I/II), are expected to be validated proportionately with the knowledge and the risk associated with the respective phase. All aseptic and sterilisation processes as well as virus inactivation or removal for investigational and authorised ATMPs are expected to be validated. The effectiveness of disinfection methods should be proven. For all phases, the principles as outlined in Annex 13 should be applied.

(b) 對於所有無菌製程，無菌製程模擬應作為初始確效之一部分予以執行，並在隨後遵照附則 1 於每六個月重複之。在不頻繁生產的情況時（亦即，如兩批次生產間之間隔超過六個月，但短於一年），於下一批次生產前完成製程模擬測試是可被接受的。上述情況的前提為開始生產前可獲得製程模擬試驗之結果。考量產品本質、產品品質與病人安全性之所有層面，與本方法之任何偏差，需經由 QRM 原則徹底證明其合理性。	(b) For all aseptic processes, aseptic process simulations should be performed as part of initial validation and repeated thereafter every six months in line with Annex 1. In the case of infrequent production (i.e. if the interval between the production of two batches is more than six months but less than a year), it is acceptable that the process simulation test is done prior to manufacturing of the next batch. This is provided that, the results of the process simulation test are available prior to the starting of production. Any deviation from this approach needs to be thoroughly justified by QRM principles considering all aspects of product nature, product quality and patient safety.
(c) 若 ATMP 不是例行性生產（亦即超過一年），則涉及相關作業之人員，於生產開始前無菌製程模擬應執行至少三次。應依照附則 1 應用 QRM 原則。考量產品本質、產品品質與病人安全性之所有層面，與本方法之任何偏差，需經由 QRM 原則徹底證明其合理性。	(c) If the ATMP is not produced on a routine basis (i.e. over a year), the aseptic process simulation should be conducted at least in triplicate prior to the start of manufacturing, involving all relevant operators. QRM principles should be applied in accordance with Annex 1. Any deviation from this approach needs to be thoroughly justified by QRM principles considering all aspects of product nature, product quality and patient safety.

(d) 當起始原料（例如，自體 ATMPs、與捐贈者配對情況下之異體、無細胞擴增至主細胞庫之異體）有短缺時，於製程確效期間使用替代材料是可被接受的。起始原料替代材料之代表性應加以評估，包含例如：捐贈者年齡、使用來自健康捐贈者之原料、解剖學上之來源（例如，股骨相對髂嵴），或其他不同特徵（例如，使用具代表性的細胞種類或使用的細胞其繼代數大於產品規格）。	(d) The use of surrogate material during process validation may be acceptable when there is shortage of the starting materials (e.g. autologous ATMPs, allogeneic in a matched-donor scenario, allogeneic where there is no expansion of cells to MCB). The representativeness of surrogate starting material should be evaluated, including – for example – donor age, use of materials from healthy donors, anatomical source (e.g. femur vs. iliac crest) or other different characteristics (e.g. use of representative cell-types or use of cells at a higher passage number than that foreseen in the product specifications).
(e) 可能時，對於製造過程之關鍵層面，以來自實際起始原料的樣品補充替代材料之使用應加以考慮。例如，修飾自體細胞以治療遺傳性疾病的 ATMP，使用自體細胞之製程確效（受條件影響），可能限於聚焦在基因修飾本身之製程的那些部分。其他層面可用具代表性的替代細胞種類進行確效。	(e) Where possible, consideration should be given to complementing the use of surrogate materials with samples from the actual starting materials for key aspects of the manufacturing process. For instance, in the case of an ATMP based on modification of autologous cells to treat a genetic disorder, process validation using the autologous cells (affected by the condition) may be limited to those parts of the process that focus on the genetic modification itself. Other aspects could be validated using a representative surrogate cell type.
（取代 GMP 指引第一部 5.23 條）	(Replaces PIC/S GMP Guide Part I Section 5.23)
不同種類原物料的管制，包含 ATMP 原料藥在內 **（Control of different types of materials including ATMP Active Substances）**	
5.20 對於原物料供應商的核准與維持，要求如下：	5.20 For the approval and maintenance of suppliers of materials, the following is required:
<u>ATMP 原料藥</u>	<u>ATMP Active substances</u>
供應鏈之可追溯性應予建立。從原料藥之起始原料至最終藥品的相關風險應正式地評估並予定期確認。應具備適當措施，以降低對於原料藥品質的風險。	The supply chain traceability should be established. Associated risks, from active substance starting materials to the finished medicinal product, should be formally assessed and periodically verified. Appropriate measures should be put in place to reduce risks to the quality of the active substance.

對於每種原料藥的供應鏈與可追溯性紀錄應可獲得，並由 ATMP 製造廠保存。	The supply chain and traceability records for each active substance should be available and be retained by the manufacturer of the ATMP.
原物料與製程助劑	Raw materials and process aids
建立製程前與變更原物料時，QRM 過程應評估來自相關原物料之污染風險，及其對整個製程與所得產品之影響。應具備適當措施，以降低對原物料的品質風險。	Prior to setting up the manufacturing process and whenever a change of the respective material is implemented, a QRM process should assess the risk of contamination from the relevant materials as well as their influence on the entire manufacturing process and the resulting product. Appropriate measures should be put in place to reduce risks to the quality of the materials.
在製造與儲存時，與 ATMP 直接接觸之材料	Material directly in contact with the ATMP during manufacture and storage
直接接觸 ATMP 之所有材料應具有適當品質。微生物學上污染之風險應經評估，特別是對一次性使用系統。	All materials that come in direct contact with the ATMP should be of appropriate quality. The risk of microbiological contamination should be assessed especially for single use systems.
（取代 GMP 指引第一部 5.29 條）	(Replaces PIC/S GMP Guide Part I Section 5.29)
5.21 僅由品質單位已放行且在其末效日期或再驗日期內的原物料方可使用。當必要之測試結果取得前，處理原物料可能可被允許，使用可能不合格之原物料的風險及其對其他批次之潛在影響，應當清楚地描述，並且在 QRM 的原則下加以評估。在該等情況中，最終產品應依該等測試的滿意結果，予以放行。（取代 GMP 指引第一部 5.34 條）	5.21 Only materials that have been released by the Quality Unit and that are within their expiration or retest date should be used. Where the results of necessary tests are not available, it may be permissible to process materials before the results of the tests are available, the risk of using a potentially failed material and its potential impact on other batches should be clearly described and assessed under the principles of QRM. In such cases, release of a finished product is conditional on satisfactory results of these tests. (Replaces PIC/S GMP Guide Part I Section 5.34)

5.22 應執行所有原物料供應商（例如，製造廠與運銷商）之定期驗證，以確認其符合相關 GMP 要求。是否需要實地稽核製造廠或運銷商之廠房設施，應基於 QRM 原則加以界定。通常，製程根據其產品風險概貌（Product Risk Profile, PRP）界定為關鍵之所有原物料的供應商必需執行稽核。參考詳述於本附則修改之第七章的規定。	5.22 A regular qualification of the vendors (e.g. manufacturers and distributors) of all materials to confirm that they comply with the relevant GMP requirements should be performed. Whether an on-site audit needs to be performed at a manufacturer's or distributor's premises should be defined based on QRM principles. Generally, audits need to be performed at vendors of all materials defined as critical for the manufacturing process according to its product risk profile (PRP). Refer to provisions detailed in Chapter 7 as modified by this annex.
5.23 QRM 原則應用於整個供應鏈，是了解對於原物料品質風險過程之關鍵部分。可應用描述於 ICH Q8 藥物開發指引中品質源於設計(QbD)之原則：	5.23 Application of QRM principles to the total supply chain is a critical part of the process to understand the risks to material quality. The principles of quality by design (QbD) as described in ICH Q8 Guideline on Pharmaceutical Development could be applied:
(a) 上市許可持有者應經由產品風險概貌（PRP）界定構成 ATMP 原料藥、起始原料、原料與例如一次性使用系統之其他物料、直接包材以及生產期間與其直接接觸之其他材料為何。產品風險概貌應用於證明個別原物料適用之管制水準的合理性。	(a) The MAH should define what constitutes ATMP active substances, starting materials, raw materials and other materials such as single use systems, primary packaging materials and any other materials in direct contact with the product during manufacture by means of Product Risk Profiles (PRP). The PRP should be used to justify the levels of control that apply to individual materials.
(b) 建立 ATMP 之目標產品品質概貌（QTPP）並界定關鍵品質屬性（CQA）與關鍵製程參數（CPP），以適當地確立產品風險概貌。	(b) Establish the Quality Target Product Profile (QTPP) and define the Critical Quality Attributes (CQA) and the Critical Process Parameters (CPP) for the ATMP to establish PRP appropriately.
(c) 從來源至併入最終產品劑型所使用之每種原物料，識別其對於品質、安全性與功能所呈現之風險。考慮的領域應包括但非侷限於：	(c) For each material used, identify the risks presented to the quality, safety and function from its source through to its incorporation in the finished product dosage form. Areas for consideration should include, but are not limited to:

i. 傳播性海綿樣腦症；	i. transmissible spongiform encephalopathy;
ii. 潛在病毒污染；	ii. ii. potential for viral contamination;
iii. 潛在微生物學上的污染或內毒素/熱原污染；	iii. iii. potential for microbiological or endotoxin/pyrogen contamination;
iv. 通常，源自原物料的潛在任何雜質，或作為製程之部分所產生的潛在任何雜質與殘轉；	iv. iv. potential, in general, for any impurity originating from the raw materials, or generated as part of the process and carried over;
v. 宣稱無菌之材料的無菌保證；	v. v. sterility assurance for materials claimed to be sterile;
vi. 在缺乏專用設備及/或設施時，自其他製程殘轉之潛在任何雜質；	vi. vi. potential for any impurities carried over from other processes, in absence of dedicated equipment and/or facilities;
vii. 環境管制與儲存/運輸條件，包括冷鏈管理在內，以及合適時	vii. environmental control and storage/transportation conditions including cold chain management; if appropriate and
viii. 安定性。	viii. stability.
(d) 關於每種原物料之用途與功能，考慮下列事項：	(d) With respect to the use and function of each material, consider the following:
i. 含有該原物料之藥品的產品劑型與用途；	i. pharmaceutical form and use of the medicinal product containing the material;
ii. 在配方組成中原物料之功能，及該原物料對於基因治療製劑之基因表現的影響；	ii. function of the material in the formulation, and for gene therapy products the impact on the gene expression of that material;
iii. 最終產品之功能程度是取決於所評估的原物料，與其進一步管制製程之可能程度（亦即，若基因序列錯誤時，如何可易於檢測與改正，或若產品受到污染時，於製程後期被檢測或改正的可能程度）；	iii. degree of which the function of the final product is dependent from the material assessed and how likely it is to be controlled further into the manufacturing process (i.e. if the gene sequence is wrong how easily can this be detected and corrected or if the product is contaminated how likely can this be detected or corrected later in the manufacturing process);
iv. 相對於最終產品投用時間之原物料製備時間；	iv. time of preparation of the material in respect to the time of administration of the final product;

v. 原物料量，特別是有關小批量最終產品（例如 5-50 mg）；	v. quantity of material with particular reference to the implication of small final product batch sizes (e.g. 5-50 mg);
vi. 在全球性與當地公司層級兩者，與該原物料相關之任何已知品質缺陷/不實摻假；	vi. any known quality defects/fraudulent adulterations, both globally and at a local company level related to the material;
vii. 對 ATMP 之關鍵品質屬性與關鍵製程參數的已知或潛在影響；以及	vii. known or potential impact on the CQA and CPP of the ATMP; and
viii. 已識別或已知與確保病人安全相關的其他因素。	viii. other factors as identified or known to be relevant to assuring patient safety.
(e) 基於上述評估將風險概貌文件化為低度、中度或高度風險，並使用此結果確定產品風險概貌（PRP）。在此基礎上，製造許可持有者應建立並文件化需要具備之 GMP 要件，以便管制與維護目標產品品質概貌（QTPP）。	(e) Document the risk profile as low, medium, or high based on the above assessment and use this outcome to determine the PRP. On this basis, the MAH should establish and document the elements of PIC/S GMP that are needed to be in place in order to control and maintain the QTPP.
(f) 一旦已界定產品風險概貌（PRP）與適當 GMP，應經由諸如下列機轉執行持續風險檢討：	(f) Once the PRP and the appropriate GMP have been defined, ongoing risk review should be performed through mechanisms such as:
i. 與所接收之個別原物料批次有關的缺陷數目；	i. number of defects connected to batches of respective material received;
ii. 該等缺陷之類型/嚴重度；	ii. type/severity of such defects;
iii. 原物料品質之監測與趨勢分析；	iii. monitoring and trend analysis of material quality;
iv. 藥品品質屬性上之趨勢觀察，這將取決於原物料之本質與角色；以及	iv. observation of trends in drug product quality attributes; this will depend on the nature and role of material; and
v. 在原物料製造廠所觀察到之組織、程序或技術/製程的變更。	v. observed organisational, procedural or technical/process changes at the material manufacturer.
(g) 合適時，將產品風險概貌（PRP）納入臨床試驗許可或上市許可中。	(g) Incorporate the PRP into the CTA or MA as applicable.

(h) 目標產品品質概貌（QTPP）一旦在生產過程中經由主管機關核准，就應指導製造廠了解哪些管制是重要且被預期的，及哪些可被減免。製造廠應具備已建立之管制策略，該管制策略係證明對於進廠起始原物料所執行之測試程度的合理性。	(h) The QTPP, once approved in the production process by the Competent Authority, should guide the manufacturer through what controls are important and expected and which can be exempted. The manufacturer should have a control strategy established that justifies the level of testing performed for incoming starting materials.
5.24 對於避免原物料污染，並使原物料的變異性減到最低，應予以特別注意。與產品有關的規格（例如，在藥典個論、臨床試驗許可或上市許可的規格），將決定材料與原物料在何階段是否能有經界定的負荷菌量或需為無菌。	5.24 Particular attention should be paid to avoiding contamination and to minimising the variability of the materials. Specifications related to the product (such as those in pharmacopoeial monographs, CTA, or MA), will dictate whether and to what stage substances and materials can have a defined level of bioburden or need to be sterile.
5.25 對於無法執行最終滅菌，且移除微生物副產物之能力有限的產品，原物料品質與無菌製程所需之管制承擔了較大的重要性。當臨床試驗許可或上市許可規定可允許之負荷菌的類型與限量，例如，在 ATMP 原料藥階段時，該管制策略應提出其維持負荷菌在所規定限度內的方法。	5.25 For products where final sterilisation is not possible and the ability to remove microbial by-products is limited, the controls required for the quality of materials and on the aseptic manufacturing process assume greater importance. Where a CTA or MA provides for an allowable type and level of bioburden, for example at the ATMP active substance stage, the control strategy should address the means by which this is maintained within the specified limits.

5.26 起始原料、原料與在製造及儲存期間與產品直接接觸之材料（例如，一次性使用系統），其供應商的選擇、資格認可、核准及維護連同其採購與接受，應予以文件化作為製藥品質系統的一部分。考量其來源、製程、供應鏈的複雜性與原物料在 ATMP 中的最終用途，監督程度應該與由個別原物料所呈現之風險成正比。對於每一供應商/原物料核准的支持性證據應予保存。參與這些活動的人員應具有供應商、供應鏈與所涉及之相關風險的現行知識。可能時，這些原物料應從製造廠或被製造廠核准之供應商直接購買。（取代 GMP 指引第一部 5.27 條）	5.26 The selection, qualification, approval and maintenance of suppliers of starting materials, raw materials and materials that come in direct contact with the products during manufacture and storage (e.g. single use systems) together with their purchase and acceptance should be documented as part of the pharmaceutical quality system. The level of oversight should be proportionate to the risks posed by the individual materials taking account of their source, manufacturing process, supply chain complexity and the final use to which the material is put in the ATMP. The supporting evidence for each supplier / material approval should be maintained. Personnel involved in these activities should have a current knowledge of the suppliers, the supply chain and the associated risks involved. Where possible, these materials should be purchased directly from the manufacturer or a manufacturer approved supplier. (Replaces PIC/S GMP Guide Part I Section 5.27)
5.27 對於源自人類之起始原料，ATMP 製造廠（或合適時，上市許可持有者）與供應商（包含血液與組織機構在內）之間的協議，應包括關於資訊移轉的清楚規定。尤其應包括可能對所製造 ATMPs 品質與安全性具有影響之由供應商執行的測試結果、可追溯性數據與供應後可能獲得之健康捐贈者資訊的傳遞。為製造目的，人類血液與成分血、造血母細胞、人類組織與細胞捐贈與採集應遵守國家法規。（取代 GMP 指引第一部 5.28 條）	5.27 For starting material of human origin, the agreement between the ATMP manufacturer (or, as appropriate, the MAH) and the supplier (including blood and tissue establishments) should contain clear provisions about the transfer of information. In particular, this should include test results performed by the supplier, traceability data, and transmission of health donor information that may become available after the supply that may have an impact on the quality or safety of the ATMPs manufactured. National laws that are required as part of the donation and procurement of human blood and blood components, haematopoietic progenitor cells, human tissues and cells for manufacturing purposes need to be adhered to. (Replaces PIC/S GMP Guide Part I Section 5.28)

5.28 製造廠對於 QRM 過程中（依照產品風險概貌）分類為關鍵之原物料，於上市許可或臨床試驗許可中所建立的品質要求，應在產品生命週期中與供應商進行討論並達成一致。生產、測試與管制之適當層面，包含其處理、標示、分/包裝與運銷要求、申訴、回收與拒用程序在內，應在正式品質協議中予以文件化。（取代 GMP 指引第一部 5.28 條）	5.28 The quality requirements established by the manufacturer in the MA or CTA for materials classified as critical during QRM process (according to PRP profile) should be discussed and agreed with the suppliers during the product life cycle. Appropriate aspects of the production, testing and control, including handling, labelling, packaging and distribution requirements, complaints, recalls and rejection procedures should be documented in a formal quality agreement. (Replaces PIC/S GMP Guide Part I Section 5.28)
使用人類血液、組織與細胞作為起始原料 **（Human Blood, Tissues and Cells Used as Starting Materials）**	
5.29 用作 ATMPs 起始原料之人類血液、組織與細胞的捐贈、採集與測試，應依照可適用之國家法規執行之。	5.29 The donation, procurement and testing of human blood, tissues and cells used as starting materials for ATMPs should be in accordance with the applicable national law.
(a) 血液、細胞與組織之採集、捐贈與測試，在有些國家是進行管制的。這樣的供應場所必須持有來自主管機關的適當核准，其應作為供應商管理的一部分加以確認之。	(a) The procurement, donation and testing of blood, cells and tissues is regulated in some countries. Such supply sites must hold appropriate approvals from the Competent Authority(ies) which should be verified as part of supplier management.
(b) 對於細胞治療，自細胞採集至其製造與投用病人，其無菌操作的維持應予確保。	(b) For cell therapies, the maintenance of the aseptic processing from time of procurement of cells through manufacturing and administration back into the patient should be ensured.
(c) 當該等人體細胞或組織是輸入時，必須符合同等品質與安全性之國家標準。嚴重不良反應與嚴重不良事件及其可追溯性依國家法規通報。	(c) Where such human cells or tissues are imported, they must meet equivalent national standards of quality and safety. The traceability and serious adverse reaction and serious adverse event notification requirements may be set out in national law.

(d) 可能有一些情況，將會在血液或組織機構中進行用作 ATMPs 起始原料之血液、細胞與組織的處理。這僅於國家法規許可時方被允許（例如，原料會受到損害，而且其處理僅涉及最小操作）。	(d) There may be some instances where processing of blood, tissues and cells used as starting materials for ATMPs will be conducted at blood or tissue establishments. This is permissible only if authorised by national law (e.g. the material would be otherwise compromised and processing involves only minimal manipulation).
(e) 血液、組織與細胞經機構中的權責人員（RP）放行後，始得裝運到 ATMP 製造廠。自此以後，適用一般藥品起始原料管制。由組織機構所提供之所有組織/細胞的測試結果，應提供給藥品的製造廠，並須作為原料適當區隔與儲存決定之依據。當必須在收到來自組織機構測試結果之前開始製造，倘若製造廠具備管制措施，以防止與已由組織機構中權責人員放行之組織與細胞的交叉污染，組織與細胞可以裝運到藥品製造廠。	(e) Blood, tissue and cells are released by the Responsible Person (RP) in the blood or tissue establishment before shipment to the ATMP manufacturer. After that, normal medicinal product starting material controls apply. The test results of all tissues / cells supplied by the tissue establishment should be available to the manufacturer of the medicinal product. Such information must be used to make appropriate material segregation and storage decisions. In cases where manufacturing must be initiated prior to receiving test results from the tissue establishment, tissue and cells may be shipped to the medicinal product manufacturer, provided controls are in place to prevent cross-contamination with tissue and cells that have been released by the RP in the tissue establishment.
(f) 所涉及所有各方之間（例如，製造廠、組織機構、試驗委託者、上市許可持有者）應具備明確界定權責之技術協議。	(f) A technical agreement clearly defining the responsibilities should be in place between all involved parties (e.g. manufacturers, tissue establishment, sponsors, MAH).
(g) 血液、組織與細胞運輸到製造場所，必須由負責各方之間的書面協議加以管制。製造場所應有遵守規定之儲存與運輸條件的文件化證據。	(g) The transport of blood, tissues and cells to the manufacturing site must be controlled by a written agreement between the responsible parties. The manufacturing sites should have documentary evidence of adherence to the specified storage and transport conditions.

(h) 應維持自組織機構至接收者之連續可追溯性要求，包括與細胞或組織接觸的材料在內，反之亦然。	(h) Continuation of traceability requirements started at tissue establishments through to the recipient(s), and vice versa, including materials in contact with the cells or tissues should be maintained.
種批與細胞庫系統（Seed Lot and Cell Bank System）	
5.30 如果異體 ATMP 的生產包含細胞培養或在胚胎與動物的繁殖，則建議使用主病毒種批與工作病毒種批及/或主細胞庫與工作細胞庫系統。這可防止可能來自重複的繼代培養或多代培養之非必要的性質漂移。	5.30 A system of master and working virus seed lots and/or cell banks is recommended if the production of allogeneic ATMP involves cell culture or propagation in embryos and animals. This can prevent the unwanted drift of properties, which might ensue from repeated subcultures or multiple generations.
5.31 種批或細胞庫、原料藥與最終產品之間的世代數目（倍增、繼代數目），應與該上市許可或臨床試驗許可中的規格一致。	5.31 The number of generations (doublings, passages) between the seed lot or cell bank, the active substance and finished product should be consistent with specifications in the MA or CTA.
5.32 作為產品生命週期管理的一部分，種批與細胞庫，包括主世代與工作世代的建立、維護與保存在內，應在適當的 GMP 條件下執行。這應包括經適當管制的環境，以保護種批與細胞庫及其處理的人員。在建立種批與細胞庫的期間，不得同時在相同區域或不得由同一組人處理其他活的或傳染性的物質（例如病毒、細胞株或細胞品系）。對於建立主種批或細胞庫產生之前的所有階段，GMP 原則可能可以加以使用。對於主細胞庫之前（pre-master bank）的所有階段，應備有文件以支持可追溯性。在開發期間，所使用之組成物相關的所有問題，自最初來源尋求與基因開發對產品安全性（例如，生物來源的試劑）之潛在影響，應加以文件化。	5.32 As part of product lifecycle management, establishment of seed lots and cell banks, including master and working generations, as well as maintenance and storage, should be performed under appropriate GMP conditions. This should include an appropriately controlled environment to protect the seed lot and the cell bank and the personnel handling it. During the establishment of the seed lot and cell bank, no other living or infectious material (e.g. virus, cell lines or cell strains) should be handled simultaneously in the same area or by the same persons. For all stages prior to the establishment of the master seed or cell bank generation, principles of GMP may be applied. For all pre-master bank stages, documentation should be available to support traceability. All issues related to components used during the development with potential impact on product safety (e.g. reagents of biological origin) from initial sourcing and genetic development should be documented.

5.33 在建立主細胞庫與工作細胞庫及主種批與工作種批之後，應遵循隔離與放行程序。這應該包括對污染物的充分特性描述與測試。其持續適用性應經由產品之後續生產批次的特性與品質之一致性予以進一步證實之。種批與細胞庫之安定性與復原（recovery）的證據應加以文件化，而且應以允許趨勢評估的方式保存紀錄。	5.33 Following the establishment of master and working cell banks and master and working seed lots, quarantine and release procedures should be followed. This should include adequate characterisation and testing for contaminants. Their on-going suitability for use should be further demonstrated by the consistency of the characteristics and quality of the successive batches of product. Evidence of the stability and recovery of the seeds and banks should be documented and records should be kept in a manner permitting trend evaluation.
5.34 種批與細胞庫應以使其污染或改變之風險減到最低的方式，予以儲存與使用（例如，儲存在密封容器中之液態氮氣相中）。對於在相同區域或設備中不同病毒種及/或細胞之儲存，其管制措施應防止混雜，並且應考慮該原料的傳染本質，以防止交叉污染。	5.34 Seed lots and cell banks should be stored and used in such a way as to minimise the risks of contamination (e.g. stored in the vapour phase of liquid nitrogen in sealed containers) or alteration. Control measures for the storage of different seeds and/or cells in the same area or equipment should prevent mix-up and take into account the infectious nature of the materials to prevent cross-contamination.
5.35 細胞來源的 ATMPs 往往是從來自有限繼代數目所得到的細胞庫存所產生。與主細胞庫及工作細胞庫的兩層系統相異，從細胞庫存所生產操作的次數是受到擴增後均等分裝的數目所限制，並且不涵蓋該產品的整個生命週期。細胞庫存的變更應於上市許可/臨床試驗許可中予以提出，因而應經由確效與可比性計畫書所涵蓋，因為捐贈者間的變異性可能改變產品。	5.35 Cell based ATMPs are often generated from a cell stock obtained from limited number of passages. In contrast with the two-tiered system of Master and Working cell banks, the number of production runs from a cell stock is limited by the number of aliquots obtained after expansion and does not cover the entire life cycle of the product. Cell stock changes should be addressed in the MA/CTA and thereby covered by a validation and comparability protocol, as the inter-donor variability may change the product.
5.36 儲存容器應予密封、清楚地標示，並且保持在適當的溫度。應保存庫存品清單。該儲存溫度，且如使用液態氮時的液位，均應連續監測。偏離設定限值與所採取的矯正與預防行動，應加以記錄。	5.36 Storage containers should be sealed, clearly labelled and kept at an appropriate temperature. A stock inventory must be kept. The storage temperature and, where used, the liquid nitrogen levels should be continuously monitored. Deviation from set limits and corrective and preventive action taken should be recorded.

5.37 將庫存分散並將其存放在不同的地點是必要的，以使全部損失的風險減到最低。在該等地點的管制應提供前段所述的保證。	5.37 It is desirable to split stocks and to store the split stocks at different locations to minimise the risks of total loss. The controls at such locations should provide the assurances outlined in the preceding paragraphs.
5.38 對於庫存的儲存與處理條件，應依相同的程序與參數予以管理。一旦容器從其種批/細胞庫管理系統中移出時，則該等容器應不得退回庫存。	5.38 The storage and handling conditions for stocks should be managed according to the same procedures and parameters. Once containers are removed from the seed lot / cell bank management system, the containers should not be returned to stock.
第六章品質管制（CHAPTER 6 QUALITY CONTROL）	
6.1 製程中管制在確保 ATMPs 品質的一致性上，具有比傳統產品更大的重要性。製程中管制測試，應在生產的適當階段執行，以管制對最終產品品質重要的那些條件。	6.1 In-process controls have a greater importance in ensuring the consistency of the quality of ATMPs than for conventional products. In-process control testing should be performed at appropriate stages of production to control those conditions that are important for the quality of the finished product.
一般規定（General）	
6.2 品質管制主管負責 ATMP 原料藥、起始原料、原料與其他例如直接包裝材料之其他材料，及製造期間直接接觸產品之任何其他材料，以及複合 ATMPs 所使用之醫療器材的管制。此外，品質管制主管負責管制 ATMP 整個製造階段之品質。如為自體產品或與捐贈者配對之異體產品，起始原料來源與接受者間之核對應加以確認。	6.2 The head of quality control is responsible for control of ATMP active substances, starting materials, raw materials and other materials such as primary packaging materials and any other material in direct contact with the product during manufacture as well as medical devices that are used in combined ATMPs. Further, the head of quality control is responsible to control the quality of the ATMP throughout all stages of manufacture. In case of autologous products or allogeneic products in a donor-matched scenario, the match between the origin of the starting material and the recipient should be verified.

6.3 樣品應可代表取自之原物料或產品的批次。亦可採取其他樣品，以監測製程之最差狀況的部分（例如：製程的開始或結束）。所使用的抽樣計畫應適當地證明其合理性，並且基於風險管理方法。某些類型的細胞（例如，在 ATMPs 所使用的自體細胞）可能可獲得的數量有限，倘臨床試驗許可或上市許可允許時，可開發經修改的測試與樣品留存策略，並且加以文件化。（取代 GMP 指引第一部 6.12 條）	6.3 Samples should be representative of the batch of materials or products from which they are taken. Other samples may also be taken to monitor the worst-case part of a process (e.g. beginning or end of a process). The sampling plan used should be appropriately justified and based on a risk management approach. Certain types of cells (e.g. autologous cells used in ATMPs) may be available in limited quantities and, where allowed in the CTA or MA, a modified testing and sample retention strategy may be developed and documented. (Replaces PIC/S GMP Guide Part I Section 6.12)
6.4 樣品容器應具有指示其內容物的標籤，該標籤上並有批號、抽樣日期及樣品所取自之容器。該等容器應以使混雜的風險減到最低，並使樣品免於受到不良儲存條件影響的方式進行管理。當容器太小時，應考量使用經驗證合格之條碼，或其他可允許取得此資訊之方法。（取代 GMP 指引第一部 6.13 條）	6.4 Sample containers should bear a label indicating the contents, with the batch number, the date of sampling and the containers from which samples have been drawn. They should be managed in a manner to minimize the risk of mix-up and to protect the samples from adverse storage conditions. When containers are too small, the use of a qualified bar code or other means that permit access to this information should be considered. (Replaces PIC/S GMP Guide Part I Section 6.13)

6.5 依據附則 19 之要求，應抽取一批次之起始原料、原物料、包裝材料及最終產品的對照樣品。原則上，對照樣品應有足夠量，以對於在臨床試驗許可或上市許可中已預見之批次，允許在至少兩個時機執行全項分析管制。如為連續製程時，ATMP 原料藥將直接轉變成 ATMP 藥品，只需抽取一個 ATMP 藥品之對照樣品。但是，一般認知，由於原物料的稀少或有限的批量，這可能並非總是可行（例如：自體產品、在已配對捐贈情況下的異體產品、超罕見疾病產品、以及以非常小規模生產以供用於首次供人類臨床試驗使用之產品）。在此等情況下，替代方法應於相對應的臨床試驗許可/上市許可中證明其合理性並應經許可。	6.5 In line with requirements of Annex 19, a reference sample of a batch of starting material, raw materials, packaging material and finished product should be drawn. As a general principle, a reference sample should be of sufficient size to permit the carrying out on at least two occasions of the full analytical controls on the batch foreseen in the CTA or MA. In case of a continuous process, where the ATMP active substance will immediately be turned into the ATMP drug product, only a reference sample of the ATMP drug product needs to be drawn. However, it is acknowledged that drawing reference samples may not always be feasible due to scarcity of the materials or limited size of the batches (e.g. autologous products, allogeneic products in a matched donor scenario, products for ultra- rare diseases, and products for use in first-in-man clinical trials with a very small-scale production). In these cases, alternative approaches should be justified and authorised in the corresponding CTA/MA.
6.6 起始原料之樣品通常應於批次放行後保存兩年。但是，一般認知，由於原物料稀少，樣品留存可能具有挑戰性。由於這種固有的侷限性，對於用作自體 ATMPs 與某些異體 ATMPs（例如，已配對捐贈者情況）情況的起始原料，不保存細胞/組織的對照樣品是合理的。在其他情況下，原物料之稀少也是一個考量，抽樣策略可根據風險評估與適當實施之緩解措施進行調整。對於起始原料為已建立細胞庫系統的情況，則無需特別為對照樣品目的保存細胞庫小瓶。	6.6 Samples of the starting materials should generally be kept for two years after the batch release. However, it is acknowledged that the retention of samples may be challenging due to scarcity of the materials. Due to this intrinsic limitation, it is justified not to keep reference samples of the cells/tissues used as starting materials in the case of autologous ATMPs and certain allogeneic ATMPs (i.e. matched donor scenario). In other cases, where the scarcity of the materials is also a concern, the sampling strategy may be adapted based on risk assessment and appropriately implemented mitigation measures. For cases where the starting material is an established cell bank system, there is no need to keep cell bank vials specifically for the purpose of reference samples.

6.7 依附則 19 之要求，每批次之完整包裝的單元樣品（留存樣品）應保存至末效期後至少一年（各國要求可能不同）。但是，自體產品或經證明合理（例如，於已配對捐贈者的情況下）之異體產品，其留存樣品是不被預期的，因以病人組織/細胞之產生量是構成應向病人之投用量。當不可能保存留存樣品時，將標籤之照片或影本納入批次紀錄中是可被接受的。	6.7 In line with requirements of Annex 19, a sample of a fully packaged unit (retention sample) should be kept per batch for at least one year after the expiry date (national requirements might differ). A retention sample is, however, not expected in the case of autologous products or allogeneic products, where justified (e.g. in a matched donor scenario), as the unit produced with the patient's tissues/cells constitutes what should be administered to the patient. When it is not possible to keep a retention sample, photographs or copies of the label are acceptable for inclusion in the batch records.
6.8 短於 6.6 與 6.7 條中所提到之留存期間，可能可基於產品的安定性與架儲期證明其合理性。如為較短架儲期時，製造廠應考慮在延長架儲期之條件下（例如，超低溫冷凍）樣品的保持是否代表預期之目的。例如，將新鮮細胞超低溫冷凍可能會使樣品不適用於表現特徵的目的，但該樣品對於無菌性或病毒安全性管制可能是合適的（樣品的容量可依照預定的目的予以縮減）。當樣品冷凍儲存被認為對預期目的不合適時，製造廠應考慮經科學證明合理性之替代方法。	6.8 Shorter retention periods as mentioned in Section 6.6 and 6.7 might be justified based on the stability and shelf life of the product. In cases of short shelf life, the manufacturer should consider if the retention of the sample under conditions that prolong the shelf life (such as cryopreservation) is representative for the intended purpose. For instance, cryopreservation of fresh-cells may render the sample inadequate for characterisation purposes but the sample may be adequate for sterility or viral safety controls (the volume of the samples can be reduced according to the intended purpose). When cryostorage of a sample is considered inadequate for the intended purpose, the manufacturer should consider alternative approaches that are scientifically justified.
持續進行之安定性計畫（On-going stability programme）	

6.9 若持續進行的安定性計畫之計畫書中已證明其合理性並予以文件化者，得與當初在上市許可檔案中所提交之長期安定性試驗的計畫書不同（例如，測試頻率，或配合 ICH 之建議事項更新時）。調配與解凍之產品的安定性研究是在產品開發期間中執行，而且無需在持續基礎上監測。當整個批次需要投用於病人，在自體產品（或已配對捐贈者情況）時，使用替代材料（亦即，從健康自願者衍生之材料）或其他科學上健全的方法是可接受的。（取代 GMP 指引第一部 6.31 條）	6.9 The protocol for the on-going stability programme can be different from that of the initial long term stability study as submitted in the MA dossier provided that this is justified and documented in the protocol (e.g. the frequency of testing, or when updating to ICH/VICH recommendations). Stability studies on the reconstituted and thawed product are performed during product development and need not be monitored on an on-going basis. The use of surrogate materials (i.e. material derived from healthy volunteers) or alternative scientifically sounds approaches are acceptable in case of autologous products (or matched donor scenario) where the entire batch needs to be administered to the patient. (Replaces PIC/S GMP Guide Part I Section 6.31)
放行（Release）	
6.10 通常，ATMPs 批次應僅於被授權人認可後放行銷售或供應市場。批次放行規格非侷限於分析結果（也參考偏離規格（OOS）結果）。依 GMP 指引第一部 1.4 (xv)、2.6 與 6.34 條，被授權人應審查製程紀錄、環境監測結果、製程參數監測、分析結果與來自標準程序及計畫書之所有偏差，評估各批次產品的品質。批次被認可前，應保存於製造場所或應在隔離狀態下運送至另一場所，該場所已由相關主管機關為該目的之核准（適用時），並於製造廠之品質系統內予以適當地管制。通常，除非證明其合理性，否則不符合放行規格之最終產品，不應投用於病人。	6.10 In general, batches of ATMPs should only be released for sale or supply to the market after certification by an Authorised Person. The batch release specifications are not limited to analytical results (also refer to out of specification (OOS) results). In line with PIC/S GMP Guide Part I Sections 1.4 (xv), 2.6. and 6.34 the Authorised Person should assess the quality of each batch considering processing records, results from environmental monitoring, monitoring of process parameters, analytical results and all deviations from standard procedures and protocols. Until a batch is certified, it should remain at the site of manufacture or be shipped under quarantine to another site, which has been approved for that purpose by the relevant Competent Authority (if applicable) and is controlled appropriately within the manufacturer's quality system. Generally, a finished product that does not meet release specifications should not be administered to a patient unless otherwise justified.

6.11 經國家法規許可時，對於不符合放行規格之產品的投用，可能可以在例外情況下被執行（例如，當沒有可提供相同治療結果之治療方法可用，且投用此不符合規格的產品可以挽救生命時）。	6.11 Where authorised by national law, the administration of a product that does not meet the release specification might be performed under exceptional circumstances (such as when there is no alternative treatment available that would provide the same therapeutic outcome and the administration of the failed products could be lifesaving).
6.12 引述於 6.11 條，當產品不符合放行規格的情況，對於病人治療之責任與決定僅在於治療醫師，並且在本附則權責之外。被授權人、上市許可持有者及/或臨床試驗委託者於提供產品時，應考慮下列事項：	6.12 In cases, referred to in point 6.11, where product does not meet release specification, the responsibility and the decision of the patient treatment are solely of the treating physician and are beyond the remit of this PIC/S annex. The Authorised Person, the MAH and/or the Sponsor of the clinical trial should consider the following in making the product available:
治療醫師應向被授權人與上市許可持有者提供書面的理論基礎及/或要求。	The treating physician should provide in writing a rationale and/or request to the Authorised Person and MAH.
(a) 提供給治療醫師之批次製造紀錄與文件應清楚陳述該批次不符合放行規格，並描述未符合之參數。	(a) Batch manufacturing records and documentation provided to the treating physician should clearly state that the batch has failed the release specifications and describe the parameters that have not been met.
(b) 回應治療醫師的要求時，上市許可持有者應提供其產品投用之風險的評估。但是，投用不符合放行規格之最終產品僅在於治療醫師的決定。	(b) When responding to a treating physician’s request, the MAH should provide its evaluation of the risks of product administration. However, it is solely the physician’s decision to administer the finished product that does not meet release specifications.
(c) 被授權人（或代理人）應依其法律義務，代表上市許可持有者向相關主管機關報告產品之供應。	(c) The Authorised Person (or delegate) should report the supply of the product to the relevant Competent Authorities, on behalf of the MAH in accordance with their legal obligations.

6.13 臨床試驗委託者或上市許可持有者應具備程序，該程序係描述若產品不符合放行規格但可能放行允許治療時，所要採取之步驟。在國家法規範圍內，不符合放行規格之個別情況，可能經由基於風險評估之逐批放行計畫與特定逐案予以解決。	6.13 The clinical trial Sponsor or MAH should have procedures in place that describe steps to be taken if product does not meet release specification but may be released to permit treatment. Individual instances that do not meet release specifications may be addressed through lot-by-lot release programmes and specific case-by-case, risk-based assessments, where such programs exist within national law.
6.14 對於短架儲期的 ATMPs，當已建立之分析測試可能不允許產品投用前之批次認可時，應考慮取得等效數據的替代方法（例如，快速微生物學方法）。	6.14 For ATMPs with a short shelf life, where established analytical tests might not permit batch certification prior to product administration, alternative methods of obtaining equivalent data should be considered (e.g. rapid microbiological methods).
當產品測試時程不允許有效運送至病患時，經主管機關核准，則允許在完成所有產品品質管制前，對短架儲期產品進行批次認可。	Subject to approval from the Competent Authority, batch certification of short shelf life products performed prior to completion of all product quality control is permitted when the testing timelines would not allow for effective distribution to a patient.
(a) 建立在產品與製程性能之加強瞭解上，必須具備適當的管制策略。這必須將起始原料、原料與中間產品之管制與屬性納入考慮。	(a) A suitable control strategy must be in place, built on enhanced understanding of the product and process performance. This must take into account the controls and attributes of starting materials, raw materials and intermediates.
(b) 批次認可之程序應提供整個放行程序的正確與詳細之描述，包含涉及生產與分析數據評估的不同人員之職責在內。	(b) The procedure for batch certification should provide an exact and detailed description of the entire release procedure, including responsibilities of the different personnel involved in assessment of production and analytical data.
(c) 對於短架儲期 ATMP 之批次認可與放行的程序，可採兩個或兩個以上階段執行：	(c) The procedure for batch certification and release of short shelf life ATMP may be carried out in two or more stages:

i. 由指定人員評估之批次操作紀錄、應包含生產條件之環境監測結果(可取得時)、自標準程序與計畫書的所有偏差，以及可獲得的分析結果，以供被授權人進行初始認可審查。	i. Assessment by designated person(s) of batch processing records, results from environmental monitoring (where available) which should cover production conditions, all deviations from standard procedures and protocols as well as the available analytical results for review in preparation for the initial certification by the Authorised Person.
ii. 評估最終分析測試與其他可獲得之資訊，以供被授權人進行最終認可。當得到偏離規格測試結果時，應備有程序以描述所要採取的措施(包含與臨床人員的聯繫在內)。該等事件應進行充分調查並且採取相關的矯正與預防行動，以防止再發生。	ii. Assessment of the final analytical tests and other information available for final certification by the Authorised Person. A procedure should be in place to describe the measures to be taken (including liaison with clinical staff) where out of specification test results are obtained. Such events should be fully investigated and the relevant corrective and preventive actions taken to prevent recurrence.
(d) 增加對製程確效之倚賴，應被視為在沒有完整分析結果之情況下批次放行的支持數據，即使是研究用 ATMP 也是如此。	(d) Increased reliance on process validation should be considered as supporting data for batch release in absence of a complete analytical results panel, even in case of investigational ATMP.
(e) 必須具備製藥品質系統有效性的持續評估，包括以允許趨勢評估方式保存的紀錄。	(e) A continuous assessment of the effectiveness of the pharmaceutical quality system must be in place. This includes the records being kept in a manner, which permits trend evaluation.
去中心化/照護端製造之批次放行過程 **（Batch release process in cases of decentralised / point of care manufacturing）**	

6.15 經由主管機關核准且依照臨床試驗許可或上市許可或其他之國家要求的例外情況下，ATMP 之製造可能於緊鄰病人的現場進行（例如，短架儲期之 ATMPs、與使用冷凍起始原料/最終產品相比較具臨床優勢之新鮮細胞、使用自動化設備的優勢等）。這包括部分於核心場所（central site）製造，並於地區場所（local site）完成之製造模式，亦包括未有製造步驟於核心場所，並將原料藥提供給若干地區場所進行完整製造之製造模式。在該等情況，ATMPs 之製造步驟可能於多場所進行，該等場所可能坐落於治療中心（照護端），包含醫院。預定作為 ATMP 製造之核心場所與衛星場所（satellite sites），其 GMP 製造許可及/或血液、細胞與組織採集及/或製造之許可，依國家法規規定。	6.15 In the exceptional circumstances where approved by the Competent Authority and in accordance with CTA or MA or other national requirements, manufacturing of the ATMP may take place in sites close to the patient (e.g. ATMPs with short shelf life, clinical advantage of using fresh cells as opposed to freezing the starting materials/finished product, advantages of using automated equipment, etc.). This includes manufacturing models where partial manufacturing occurs at a central site and finishing occurs at a local site. It also includes manufacturing models where there are no steps occurring at a central site and the active substance is provided to a number of local sites where full manufacture occurs. In such cases, steps in the manufacturing of the ATMPs may occur in multiple sites that may be also located in treatment centres (point of care) including hospitals. National law might require GMP-manufacturing authorisations and/ or authorisations for the procurement and/or manufacture of blood, cells and tissues intended to be used for ATMP manufacturing at the central site and the satellite sites.
6.16 在去中心化系統下製造 ATMPs 的情況，如於多場所製造會增加產品變異性風險，批次認可與放行過程變得特別重要。特別是，透過批次認可與放行過程，必須確保於任何場所被放行之每批次皆已依臨床試驗許可或上市許可的要求，以及包含符合 GMP 在內的其他相關法規要求予以製造及品質管制。批次認可與放行過程的步驟應以標準作業程序（SOP）予以清楚地文件化。需遵循下列條件：	6.16 The batch certification and release process becomes particularly important in the case of ATMPs manufactured under a decentralised system as manufacturing in multiple sites increases the risk of variability for the product. In particular, through the batch certification and release process it must be ensured that each batch released at any of the sites has been manufactured and quality controlled in accordance with the requirements of the CTA or MA and other relevant regulatory requirements including compliance with GMP. The steps of the batch certification and release process should be clearly documented in a standard operating procedure (SOP). The following conditions need to be respected:

(a)「責任場所」應予以定義。該責任場所負責監督各去中心化場所。於產品生命週期期間，該責任場所：	(a) A "responsible site", should be identified. The responsible site is responsible for the oversight of the decentralised sites. During the product life cycle, the responsible site:
i. 必須具有被授權人；	i. must have availability of an Authorised Person;
ii. 必須確保參與批次認可與放行過程之人員對其工作經過充分資格驗證與訓練；	ii. must ensure that those involved in the batch certification and release process are adequately qualified and trained for their tasks;
iii. 應執行稽核以確認符合批次認可與放行過程（按 SOP 中所描述）；	iii. should perform audits to confirm compliance with the batch certification and release process (as descripted in SOP);
iv. 必須確保責任場所與去中心化場所間具有書面契約/技術協議以建立各方職責，及	iv. must ensure that there is a written contract/technical agreement between the responsible site and the decentralised sites establishing the responsibilities of each party, and
v. 必須確保具有書面安排以供：	v. must ensure that there are written arrangements to:
• 及時向核心場所報告品質缺陷、偏差或不符合性；	• timely report quality defects, deviations or non-conformity to the central site;
• 確保偏差業經調查以識別根本原因，並執行適當之矯正預防措施（合適時）；以及	• ensure deviations are investigated to identify root cause(s) and implement corrective and preventive measures as appropriate; and
• 合適時在被授權人的參與下，確保偏差業經委派人核准（於評估對品質、安全性與有效性影響之後）。	• ensure deviations are approved by a delegated person (after having assessed the impact on quality, safety and efficacy), with the involvement of the Authorised Person as appropriate.

(b) 被授權人對批次認可應負最終責任（該責任無法委託）。但是，責任場所之被授權人應能依去中心化場所之業經資格驗證與訓練的人員所傳送給被授權人的數據/資訊據以放行。針對特殊情況（例如，危及生命之情況或下班期間），在被授權人的指示下，可將放行委任給去中心化場所之經資格驗證與訓練的人員執行。下列條件適用之：	(b) The Authorised Person should have ultimate responsibility for the batch certification (responsibility cannot be delegated). However, it should be possible for the Authorised Person of the responsible site to rely on data/information that is transmitted to the Authorised Person by qualified and trained personnel at the decentralised sites. When permitted by national law, the Authorised Person may delegate release to trained and qualified personnel at the decentralised site to act under the direction of the Authorised Person for exceptional situations (e.g. life threatening cases or off-hours). The following conditions apply:
i. 有詳細規則系統，以決定產品可在不須被授權人事先核准而於地區場所放行的情況，包含不須被授權人介入之偏差在內。若技術容許，該步驟可由經確效之電腦化系統執行。	i. There is a detailed algorithm that determines the cases when the product can be released at the local site without the preliminary approval of the Authorised Person, including deviations that do not require the intervention of the Authorised Person. If technology permits this step can be performed by a validated computer system.
ii. 被授權人於適當證明合理性之時間內審查在去中心化場所發生的所有放行，以確認包含下列之放行的適當性：	ii. The Authorised Person reviews all releases that have occurred at a decentralised site within an appropriately justified timeframe to confirm the adequacy of the releases including:
• 確定該等地區場所可繼續放行；	• determining that the local sites can continue release;
• 是否有任何產品需回收或需發出產品警訊(參見第八章回收條項)；	• if any product needs to be recalled or a product alert needs to be issued (see recall section in Chapter 8);
• 是否有放行程序及/或技術協議中之任何規定需修改；以及	• if any provision in the release procedure and /or technical agreement needs modification; and

• 必要時，沒有被授權人許可前產品不會被放行。	• the product has not been released without Authorised Person authorisation when required.
第七章 委外活動（CHAPTER 7 OUTSOURCED ACTIVITIES）	
其他事項（OTHERS）	
7.1 受許可列管範圍內之起始原料的收集與高度專業化測試（例如，染色體核型測試、外顯子定序），在國家法規允許下，若滿足下列情況，得委外給未經 GMP 許可之第三方：	7.1 Collection of starting materials and highly specialised testing in the jurisdictions that are subject to licensing (e.g. karyotype testing, exome sequencing) can be outsourced to non GMP licensed third party, as allowed by national law, provided:
(a) 品質系統中具理論基礎及合理性證明；	(a) there is a rationale and a justification in the quality system;
(b) 委託者負責確保由受託者證明 GMP 適當水準與產品風險相稱，且使用附則 20 之原則執行活動；以及	(b) the contract giver takes responsibility to ensure that the contract acceptor demonstrates an appropriate level of GMP commensurate to the risk to the product and the activities performed using the principles of Annex 20; and
(c) 合適時，進行適當之驗證/確效（參考附則 15 與附則 20）以證明該等活動不會損及所製造之產品的品質。	(c) that proportionate qualifications/validations as appropriate are conducted (with reference to Annex 15 and Annex 20) to demonstrate that the activities are not detrimental to the quality of the product manufactured.
第八章 申訴與產品回收（CHAPTER 8 COMPLAINTS AND PRODUCT RECALL）	
產品回收及其他可能的風險降低行動（PRODUCT RECALLS AND OTHER POTENTIAL RISK-REDUCING ACTIONS）	
8.1 若在採集之後，獲得捐贈者（人類或動物）的額外健康資訊對產品品質有影響時，需啟動「回溯」程序。這包含風險的分析與對矯正或預防措施需求的分析。	8.1 If additional donor (human or animal) health information becomes available after procurement, which affects product quality, a 'look-back' procedure needs to be initiated. This involves an analysis of the risk(s) and of the need for corrective or preventive measures.
8.2 除回收外，可以考慮其他風險降低行動，以管理由品質缺陷所呈現的風險，例如將適當資訊傳達給健康照護專業人員，該資訊對下列情況可能是重要的：	8.2 In addition to recalls, other risk-reducing actions may be considered to manage the risks presented by quality defects, such as the transmission of appropriate information to healthcare professionals which may be important for:

(a) 單一批次產品（例如，其整個批次已投用之自體 ATMP），或	(a) a single batch product (e.g. autologous ATMP where the entire batch has been administered), or
(b) 中斷病人治療比繼續使用回收產品呈現更高風險。	(b) products where patient treatment interruption presents a higher risk than continued use of the recalled product.
在此等情況下，上市許可持有者/製造廠需要將資訊提供給治療醫師與主管機關。品質缺陷通知、藥物警訊與其他通知亦應按國家法規規定發送。	In such cases, the MAH/manufacturer needs to provide information to the treating physician and to the Competent Authority. Quality defect notifications, pharmacovigilance signals and other notifications should also be sent as set in national law.
（取代 GMP 指引第一部 8.31 條）	(Replaces PICS GMP Guide Part I Section 8.31)
8.3 為測試回收程序（或健康照護專業人員通知）之穩健性，對於執行模擬回收，或將適當資訊對健康照護專業人員之模擬傳達，應納入考慮。該等評估應涵蓋上班時段及下班時段兩種情況。	8.3 In order to test the robustness of the recall procedure (or healthcare professional notification) consideration should be given to performing mock recall or mock transmission of appropriate information to healthcare professionals. Such evaluations should extend to both within office-hour situations as well as out-of- office hour situations.
模擬回收（或將適當資訊對健康照護專業人員之模擬傳達）的頻率，應經由製造廠考量諸如產品開發階段與供應複雜性等因素證明其合理性。對於已許可之產品，除非另有合理性證明，否則建議每年一次的頻率。	The frequency of the mock recall (or mock transmission of appropriate information to healthcare professionals) should be justified by the manufacturer considering factors such as the stage of the product development and the complexity of the supply. For authorised products, a yearly frequency is recommended unless otherwise justified.
（取代 GMP 指引第一部 8.30 條）	(Replaces PICS GMP Guide Part I Section 8.30)

B 部：對特定產品類型的專用指引 （PART B: SPECIFIC GUIDANCE ON SELECTED PRODUCT TYPES）	
B1. 動物來源的產品（B1. ANIMAL SOURCED PRODUCTS）	
本指引適用於動物性原料，包括來自諸如屠宰場機構的原料。由於供應鏈可能廣泛且複雜，所以，基於 QRM 原則之管制需要加以應用，也參見適當藥典個論的要求，包括需要在所界定之階段的特定檢驗在內。應具備證明供應鏈可追溯性[5]與參與者在供應鏈中之明確角色的文件，典型上，包括足夠詳盡且最新之流程圖（process map）在內。	This guidance applies to animal materials, which includes materials from establishments such as abattoirs. Since the supply chains can be extensive and complex, controls based on QRM principles need to be applied, see also requirements of appropriate pharmacopoeial monographs, including the need for specific tests at defined stages. Documentation to demonstrate the supply chain traceability[5] and clear roles of participants in the supply chain, typically including a sufficiently detailed and current process map, should be in place.
[5] 參見 GMP 第五章	[5] See PIC/S GMP Chapter 5
B1.1 對於人類健康須關注之動物疾病應具備監測計畫。當包括世界動物衛生組織等組織匯集其風險評估與風險降低因素時應考慮來自關於國家疾病流行值得信賴之來源的報告。這應藉由國家與地方層級關於衛生監測與管制計畫的資訊加以補充，地方層級之資訊要包括選取該等動物的來源處所（例如，養殖場或飼養場）與在運輸到屠宰場期間的管制措施。	B1.1 Monitoring programmes should be in place for animal disease that is of concern to human health. Organisations should take into account reports from trustworthy sources on national disease prevalence when compiling their assessment of risk and mitigation factors. Such organisations include the World Organisation for Animal Health (OIE, Office International des Epizooties). This should be supplemented by information on health monitoring and control programme(s) at national and local levels, the latter to include the sources (e.g. farm or feedlot) from which the animals are drawn and the control measures in place during transport to the abattoirs.

B1.2 在如屠宰場之機構，起始物與原料的管制措施應包括品質管理系統的適當要素，以確保操作人員訓練、原料可追溯性、管制與一致性的滿意水準。這些措施可取自 GMP 以外的來源，但應顯示提供同等的管制水準。異種起始原料應遵循其他的國家法規。	B1.2 Control measures for starting and raw materials at establishments such as abattoirs should include appropriate elements of a Quality Management System to assure a satisfactory level of operator training, materials traceability, control and consistency. These measures may be drawn from sources outside PIC/S GMP but should be shown to provide equivalent levels of control. Xenogeneic starting material should comply with other national laws.
B1.3 在其通過製造與供應鏈的進程中應具備起始物或原料之管制措施，防止可能影響原料品質之因素的介入，或至少提供該等活動的證據。這包括在初始收集、部分純化與最終純化、儲存場所、轉運站、集貨商與仲介商之場所間的原料移動。可追溯性系統與任何違反紀錄、調查及應採取的行動均應記錄該等安排的細節。	B1.3 Control measures for starting or raw materials should be in place, which prevent interventions, which may affect the quality of materials, or which at least provides evidence of such activities, during their progression through the manufacturing and supply chain. This includes the movement of material between sites of initial collection, partial and final purification(s), storage sites, hubs, consolidators and brokers. Details of such arrangements should be recorded within the traceability system and any breaches recorded, investigated and actions taken.
B1.4 應執行起始物或原料供應商的定期稽查，以確認其在不同製造階段遵從原料的管制。依據問題決定調查的程度，並留有完整文件，也應具備確保採取有效之矯正與預防行動的系統。	B1.4 Regular audits of the starting or raw material supplier should be undertaken which verify compliance with controls for materials at the different stages of manufacture. Issues must be investigated to a depth appropriate to their significance, for which full documentation should be available. Systems should also be in place to ensure that effective corrective and preventive actions are taken.

B1.5 預定用於異種細胞來源之藥品的製造，其細胞、組織與器官，應只從專為此目的圈養繁殖（屏障設施）的動物獲得，而且，在任何情況下均不得使用來自野生動物或屠宰場的細胞、組織與器官。同樣地，也不得使用創始動物（又稱基因轉殖動物）的組織。動物的健康狀況應進行監測，並且加以文件化。	B1.5 Cells, tissues and organs intended for the manufacture of xenogeneic cell based medicinal products should be obtained only from animals that have been bred in captivity (barrier facility) specifically for this purpose and under no circumstances should cells, tissues and organs from wild animals or from abattoirs be used. Tissues of founder animals similarly should not be used. The health status of the animals should be monitored and documented.
B2. 基因治療製劑（GENE THERAPY MEDICINAL PRODUCTS (GTMPs)）	
基因治療製劑有多種類型，合成的 GTMPs 是在本條項的指引範圍之內。細胞來源的基因治療製劑，在第 B3 條項中之一些指引層面，亦可適用。	There are several types of gene therapy products. Synthetic GTMPs are within the scope of the guidance in this section. For cell-based gene therapy products, some aspects of the guidance in Section B3 may also be applicable.
B2.1 GTMPs 之製造與測試引起關於最終產品的安全性與品質之特定問題，及對於接收者與工作人員的安全性問題。對於操作者、環境與病人的安全性及基於生物危害分級之管制的執行，應應用基於風險的方法。國家要求與如可適用時，國際安全性措施應加以應用。	B2.1 The manufacture and testing of GTMPs raises specific issues regarding the safety and quality of the final product and safety issues for recipients and staff. A risk based approach for operator, environment and patient safety and the implementation of controls based on the biological hazard class should be applied. National requirements and, if applicable, international safety measures should be applied.
B2.2 病毒與非病毒載體、核酸（例如，質體、線性 DNA、mRNA、siRNA）及基因修飾細胞之生產應以充分的細節加以描述，以確保產品從起始原料（質體、目標基因與調控序列、細胞庫以及病毒或非病毒載體庫存）到最終產品的可追溯性。	B2.2 A description of the production of viral and non-viral vectors, nucleic acids (e.g. plasmids, linear DNA, mRNA, siRNA) and genetically modified cells should be available in sufficient detail to ensure the traceability of the products from the starting material (plasmids, gene of interest and regulatory sequences, cell banks, and viral or non-viral vector stock) to the finished product.
B2.3 下列考量適用於體外基因轉移至受體細胞：	B2.3 The following considerations apply to the ex-vivo gene transfer to recipient cells:
(a) 可追溯性要求必須加以維持。（參照第 4.3 至 4.8 條）	(a) Traceability requirements must be maintained. (refer to Section 4.3 to 4.8)

(b) 應有從細胞來源至最終產品清楚的批次定義。（參照第 4.2 條）	(b) There should be a clear batch definition, from cell source to final product container(s). (refer Section 4.2)
(c) 對於利用非生物學方法傳遞基因之產品，其物理化學性質應予文件化並加以測試。	(c) For products that utilise non-biological means to deliver the gene, their physico-chemical properties should be documented and tested.
(d) 儘管細胞操作所使用之載體不會是最終產品的一部分，但病毒載體之所有早期製程（例如，質體之設計至建構至製造，與細胞庫的建立）皆被視為是關鍵的，且其品質需進行管制。倘國家要求病毒載體不需於完整 GMP 製造之情況下，在其製造上應應用足夠的品質標準（「GMP 原則」）。	(d) Although the vector used for the manipulation of the cell will not be part of the final product, all early processes (e.g. design to construction to manufacturing of the plasmid, as well as establishment of cell banks) in the manufacture of viral vectors are considered critical and their quality needs to be under control. In the case that due to national requirements the manufacture of viral vectors are not required under full GMP sufficient quality standards ("principles of GMP") should be applied in their manufacture.
病毒載體與質體在「GMP 原則」下之製造 **（Manufacture of Viral Vectors and Plasmids under "principles of GMP"）**	
B2.4 對於病毒載體與質體之製造，合適時，附則 2A 與 GMP 指引第二部之要素可加以考慮（參照表一中淺灰色實例）。	B2.4 Annex 2A and elements of Part II of the PIC/S GMP Guide can be considered for the manufacturing of viral vectors and plasmids where appropriate (refer to the examples in light grey in Table 1).
病毒載體與質體之製造廠應備有品質管理系統，允許其應用指引最相關部分，以確保起始原料品質，同時考慮與最終產品之品質、安全性與有效性相關的風險。	Manufacturers of viral vectors and plasmids should have a quality management system in place that allows them to apply sections of the guideline most relevant to ensure the quality of the starting materials having regard to the relevant risks for the quality, safety and efficacy of the finished product.
B2.5 ATMP 製造廠應負責作為起始原料使用之病毒載體與質體的適當品質。應特別注意在本指引第 5.23 至 5.28 條中所描述之要求。	B2.5 The ATMP manufacturer is responsible for appropriate quality of the viral vectors and plasmids used as starting materials. Special attention should be given to requirements described in section 5.23 to 5.28 of this guideline.

(a) 考慮到由載體對 ATMP 安全性與品質所呈現之風險，ATMP 製造廠應遵循國家要求並應用 QRM，以證明附則 2A 與 GMP 指引第二部要素的哪些條項適用於病毒載體與質體的製造及測試。因此，應實施經界定與管制之製程。	(a) The ATMP manufacturer should follow national requirements and apply QRM considering the risk presented by the vector to the safety and quality of the ATMP to justify which sections of Annex 2A and elements of Part II of the PIC/S GMP Guide are applicable for manufacture and testing of viral vectors and plasmids. A defined and controlled manufacturing process should be implemented as a result.
(b) 對於使用於載體建立或 mRNA GTMPs 早期階段的質體之製造，應應用足夠的品質標準（參照表一）。經由分子生物學方法與在電腦模擬方法上，核酸（質體）製備的設計至建構被視為是在研究與開發範圍內，因此不是各別附則之一部分。	(b) Sufficient quality standards should be applied for the manufacture of plasmids used for the establishment of vectors or early stages of mRNA GTMPs (refer to Table 1). The design through to construction of the nucleic acid (plasmid) preparation by molecular biological and in silico methods is considered under the scope of research and development and therefore not part of the respective Annex.
(c) 附則 1 中的相關規定亦可適用。製造廠應使用 QRM 證明可適用性程度之合理性。通常，可無菌過濾之產品應遵循附則 1 相關條項，否則應遵循無菌製備規定。	(c) Relevant provisions in Annex 1 are also applicable. The manufacturer should justify the applicability extent using QRM. In general, products that can be sterile filtered should follow the relevant sections in the Annex 1, otherwise aseptic manufacturing provisions should be followed.
B2.6 若載體為委外製造，則 ATMP 製造廠應評估載體對於 ATMP 之品質與安全性所呈現的風險，因而選擇能符合國家法規要求之 GMP 標準的合適載體供應商。	B2.6 If the manufacturing of the vectors is outsourced, the ATMP manufacturer should assess the risk presented by the vector to the quality and safety of the ATMP and thereby select a suitable vector supplier that is able to comply with the GMP standards required by national legislation.

附則 2A 適當條項與對特定產品相關之 GMP 指引第二部的要素，應於 ATMP 製造廠與載體製造廠間之協議中決定，並涵蓋相關層面（例如，品質管理、文件、原料、細胞庫、生產、測試與管制、儲存及合適時處理與配送之其他層面）。此外，載體製造廠應為 ATMP 製造廠之供應商驗證計畫的一部分。ATMP 製造廠之監督與進一步測試的程度，應與個別材料帶來之風險相稱。	The appropriate sections of Annex 2A and elements of Part II of the PIC/S GMP Guide relevant for the specific product should be determined in the agreement between the ATMP manufacturer and the vector manufacturer and cover relevant aspects (e.g. quality management, documentation, raw materials, cell banks, production, testing and control, storage, and other aspects of handling and distribution, as appropriate). In addition the vector manufacturer should be part of the ATMP manufacturer's vendor qualification programme. The level of supervision and further testing by the ATMP manufacturer should be proportionate to the risks posed by the individual materials.
B3. 人類體細胞與異種細胞治療製劑及組織工程製劑以及複合 ATMPs（SOMATIC HUMAN AND XENOGENEIC CELL THERAPY PRODUCTS AND TISSUE ENGINEERED PRODUCTS AND COMBINED ATMPs）	
對於細胞來源之基因修飾產品，未分類為 GTMPs 者，在 B2 條項中之一些指引層面，可能可以適用。	For genetically modified cell-based products that are not classified as GTMPs, some aspects of guidance in Section B2 may be applicable.
B3.1 在涉及人類或異種細胞之產品的製造上，可追溯性要求（參照第 4.3 至 4.8 條）與一個批次之定義（參照第 4.2 條）應予以特別注意。	B3.1 In the manufacture of such products involving human or xenogeneic cells special attention should be given to traceability requirements (refer to Section 4.3 to 4.8) and definition of a batch (refer to Section 4.2).
B3.2 可行時，應使用來源經許可之細胞產品、生物分子、生物材料、支架材料、基質與取得藥品或醫療器材許可證的其他物質。	B3.2 Authorised sources of cellular products, bio-molecules, bio-materials, scaffolds, matrices, and other substances that are licensed medicinal products or medical devices should be used where available.
B3.3 在產品的生命週期中，當醫療器材，包含客製化的器材在內，納為產品的一部分時，製造廠與設備供應商間應制定適當之品質協議，以確保該器材的一致品質。	B3.3 During the life cycle of the product where devices, including custom-made devices, are incorporated as part of the product, an appropriate Quality Agreement should be made between manufacturer and device suppliers to assure consistent quality of the device.

附則 2A 與 2B 的共通術語彙編 （COMMON GLOSSARY TO ANNEX 2A AND 2B）	
GMP 主指引（第一部與第二部）中之術語彙編亦適用於附則 2A 與 2B。本共通術語彙編條項僅收納於附則 2A 與 2B 中使用，並且需要進一步解釋的術語。已經存在之定義被認為是合適的。	The Glossary in the main GMP Guide applies also to Annex 2A & B. Entries in this common glossary are only included where the terms are used in Annex 2A & B and require further explanation. Definitions, which already exist, have been deemed appropriate.
ATMP原料藥 於相關臨床試驗許可（CTA）或上市許可（MA）之許可檔案文件中所定義的產品原料藥。ATMP 原料藥是被視為等同於原料藥（API）。	**ATMP Active substance** The active substance of a product is defined in the relevant CTA or MA authorisation dossier. The ATMP active substance is regarded equivalent to an API.
佐劑 可增強對抗抗原之免疫反應的一種化學物質或生物物質。	**Adjuvant** A chemical or biological substance that enhances the immune response against an antigen.
再生醫療製劑（ATMP） ATMP 意指任何下列人用藥品：	**Advanced Therapy Medicinal Products (ATMP)** ATMP means any of the following medicinal products for human use:
(a) 基因治療製劑（GTMP）：	(a) Gene therapy medicinal product (GTMP):
「基因治療製劑」意指具有下列特性之生物藥品：	'GTMP' means a biological medicinal product, which has the following characteristics:
i. 包括一種活性物質，該活性物質包含重組核酸或由重組核酸所組成，用於人類或供人類投用，以調節、修復、置換、添加或刪除基因序列；	i. It contains an active substance, which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;
ii. 其治療、預防或診斷效果，與其所含之重組核酸序列或該序列基因表達之產品直接相關。	ii. Its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

通常GTMPs應不包括依照附則2B管理之對抗傳染病的疫苗。但是主管機關可於有益與合適時（例如，使用相同平台製造之mRNA疫苗），做出應符合附則2A之決定。	Normally GTMPs shall not include vaccines against infectious diseases which would be regulated as per Annex 2B. However, the Competent Authority can make a determination that should follow Annex 2A when this is beneficial and appropriate (e.g. mRNA vaccines that are manufactured using the same platform).
(b) 體細胞治療製劑：	(b) Somatic cell therapy medicinal product:
「體細胞治療製劑」意指具有下列特性之生物藥品：	'Somatic cell therapy medicinal product' means a biological medicinal product, which has the following characteristics:
i. 包含細胞或組織，或由細胞或組織所組成，該細胞或組織已經實質操作（substantial manipulation），以致已經改變其預期臨床用途相關之生物學特性、生理功能或結構特性，或該細胞或組織之預定使用並非對於接受者與捐贈者為相同的基本功能；	i. contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor;
ii. 透過其細胞或組織之藥理學、免疫學或代謝作用，以治療、預防或診斷疾病為其呈現之性質，或可用於人類或供人類投用。	ii. is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.
(c) 組織工程製劑：	(c) Tissue engineered product:
「組織工程製劑」意指：	'Tissue engineered product' means a product that:
i. 包含經工程化之細胞或組織，或由經工程化之細胞或組織所組成，而且	i. contains or consists of engineered cells or tissues, and
ii. 有再生、修復或置換人體組織，為其呈現之性質，或可用於人類或供人類投用。	ii. is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue.

組織工程製劑可能含有人類或動物來源之細胞或組織，或兩者皆有。細胞或組織可能為活的或非活的，其亦可能包含附加物質，例如細胞產物、生物分子、生物材料、化學物質、支架或基質。含有非活的人類或動物細胞及/或組織，或僅由非活的人類或動物細胞及/或組織組成的產品，其不包含任何活細胞或組織，且不是主要經由藥理學、免疫學或代謝而作用者，應從此定義中排除。	A tissue-engineered product may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, bio-molecules, biomaterials, chemical substances, scaffolds or matrices. Products containing or consisting exclusively of non-viable human or animal cells and/or tissues, which do not contain any viable cells or tissues and which do not act principally by pharmacological, immunological or metabolic action, shall be excluded from this definition.
細胞或組織若至少符合下列條件之一，則應被視為「經工程化」：	Cells or tissues shall be considered 'engineered' if they fulfil at least one of the following conditions:
i. 細胞或組織經過實質操作，以達與預定之再生、修復或置換相關的生物學特性、生理功能或結構特性；或者	i. the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved; or
ii. 細胞或組織於接受者體內非預定用於與捐贈者體內相同之基本功能或多個功能。	ii. the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.
(d) 複合 ATMPs：	(d) Combined ATMPs:
「複合 ATMPs」意指符合下列條件之 ATMP：	'Combined ATMP' means an advanced therapy medicinal product that fulfils the following conditions:
i. 作為產品的一個組成部分，其必須包含一個或多個醫療器材，或包含一個或多個主動式植入式醫療器材（active implantable medical devices, AIMD），而且	i. it must incorporate, as an integral part of the product, one or more medical devices or one or more active implantable medical devices, and
ii. 其細胞或組織部分必須含有活細胞或組織，或部分含有非活細胞或組織者，必須易於對人體產生作用，其作用可被認為是所指裝置（devices）的主要作用。	ii. its cellular or tissue part must contain viable cells or tissues or its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to.

(e) 依國家法規在其管轄範圍內分類或決定之 ATMP 產品。	(e) A product that is classified or determined to be an ATMP by the PIC/S participating authority in its own jurisdiction according to national law.
類過敏原 經化學修飾以減少 IgE 反應性的過敏原。	**Allergoids** Allergens, which are chemically modified to reduce IgE reactivity.
抗體 經由與特定抗原結合之 B 淋巴細胞所產生的蛋白質。抗體可以基於其製造方法上的關鍵差異區分成 2 個主要類型。	**Antibody** Proteins produced by the B-lymphocytes that bind to specific antigens. Antibodies may be divided into 2 main types based on key differences in their method of manufacture.
單株抗體（MAb） 得自淋巴細胞之單一殖株或經由重組技術的均質抗體群，並且與一個單一抗原決定位結合。	**Monoclonal antibodies (MAb)** Homogenous antibody population obtained from a single clone of lymphocytes or by recombinant technology and which bind to a single epitope.
多株抗體 在人類與動物體內所產生，與大多數「非自身」分子上之抗原決定位反應，衍生自不同類型之淋巴細胞殖株。	**Polyclonal antibodies** Derived from a range of lymphocyte clones, produced in human and animals in response to the epitopes on most 'non-self' molecules
抗原 能誘導特定免疫反應的物質（例如，毒素、外來蛋白、細菌、組織細胞）。	**Antigens** Substances (e.g. toxins, foreign proteins, bacteria, tissue cells) capable of inducing specific immune responses.
區域 在一建築物內，與任何一種產品或多種產品之製造所關聯的特定一組作業室，它具有一個共同的空氣處理單元。	**Area** A specific set of rooms within a building associated with the manufacturing of any one product or multiple products that has a common air-handling unit.
被授權人 經管理者認可具有必需的基礎科學與技術背景以及經驗的人。	**Authorised Person** Person recognised by the authority as having the necessary basic scientific and technical background and experience.

注意：為了增加 GMP 指引中定義之清晰度，被授權人依據上市許可/臨床試驗許可進行批次認可。認可後，該批次藥品可放行銷售或供應市場。被授權人對產品放行負全部責任。	Note: For expanded clarity beyond the definition in the PIC/S GMP Guide, the Authorised Person performs certification of batches in line with MA/CTA. After certification, the batches of medicinal products can be released for sale or supply to the market. The Authorised Person has the overall responsibility for release of the products.
負荷菌 在原物料、培養基、生物物質、中間產品或產品中所存在之微生物的數目與類型。當其超出規格的數目及/或類型時就視為污染。	**Bioburden** The level and type (i.e. objectionable or not) of micro-organism present in raw materials, media, biological substances, intermediates or products. Regarded as contamination when the level and/or type exceed specifications.
生物藥品 生物藥品是以生物物質為其原料藥的產品。生物物質是經由生物來源所生產或萃取的物質，而且對其特性描述以及品質的判定，需要結合物理、化學與生物學之相關測試以及生產過程及其管制。	**Biological medicinal product** A biological medicinal product is a product, of which the active substance is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control.
生物安全性等級（BSL） 對於安全的處理從 BSL1（最低風險，未必導致人類疾病）到 BSL4（最高風險，導致嚴重疾病，很可能傳播而且無有效的預防或治療）之不同危害範圍的有機體所需要之圍堵條件。	**Biosafety level (BSL)** The containment conditions required to safely handle organisms of different hazards ranging from BSL1 (lowest risk, unlikely to cause human disease) to BSL4 (highest risk, cause severe disease, likely to spread and no effective prophylaxis or treatment available).
時段切換製造 相同產品之一系列批次依序在一定期間內製造，而後，在轉換到另一產品之製造前，嚴格遵守已被接受的管制措施。該等產品不是在相同時間內操作，但可能使用相同的設備。	**Campaign manufacture** The manufacture of a series of batches of the same product in sequence in a given period of time followed by strict adherence to accepted control measures before transfer to another product. The products are not run at the same time but may be run on the same equipment.

密閉系統 使原料藥或產品在製造期間不暴露於直接作業室環境之系統。	**Closed system** Where an active substance or product is not exposed to the immediate room environment during manufacture.
圍堵使用 基因修飾有機體的培養、儲存、使用、運送、銷毀或處置操作，並且使用屏障（物理/化學/生物學）限制其與一般大眾及環境接觸。	**Contained use** An operation, in which genetically modified organisms are cultured, stored, used, transported, destroyed or disposed of and for which barriers (physical / chemical / biological) are used to limit their contact with the general population and the environment.
關鍵製程參數（CPP） 為一個製程參數，其變異性對關鍵品質屬性（CQA）具有影響，因此應加以監測或管制，以確保該製程產生所預期的品質。（ICH Q8R2）	**Critical Process Parameter (CPP)** A process parameter whose variability has an impact on a CQA and therefore should be monitored or controlled to ensure the process produces the desired quality. (ICH Q8R2)
關鍵品質屬性（CQA） 為物理、化學、生物或微生物學的固有性或特性，其應在合適的限值、範圍或分佈內，以確保所預期的產品品質。（ICH Q8R2）	**Critical Quality Attribute (CQA)** A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. (ICH Q8R2)
活體外 在活體外組織或細胞上執行，並回到活體的程序。	**Ex-vivo** Where procedures are conducted on tissues or cells outside the living body and returned to the living body.
餵養細胞 使用於共同培養以維持多能幹細胞的細胞。對於人類胚胎幹細胞培養，典型的餵養層包括小鼠胚胎纖維母細胞（mouse embryonic fibroblasts，MEF）或人類胚胎纖維母細胞，該等細胞已經過處理以防止其分裂。	**Feeder cells** Cells used in co-culture to maintain pluripotent stem cells. For human embryonic stem cell culture, typical feeder layers include mouse embryonic fibroblasts (MEFs) or human embryonic fibroblasts that have been treated to prevent them from dividing.
醱酵槽 在使用（哺乳動物）細胞株的情況中，醱酵槽這一術語應理解為生物反應器。	**Fermenter** In case of (mammalian) cell lines, the term fermenter should be understood as bioreactor.
基因 編譯成一種（或多種）蛋白的 DNA 序列。	**Gene** A sequence of DNA that codes for one (or more) protein(s).

基因轉殖 細胞內基因進行轉殖之過程，涉及遞送系統中所含的表現系統，稱為載體，其可以是病毒也可以是非病毒來源。在基因轉殖後，基因修飾細胞也稱為*轉導細胞（transduced cells）*。	**Gene transfer** A process to transfer a gene in cells, involving an expression system contained in a delivery system known as a vector, which can be of viral, as well as non-viral origin. After gene transfer, genetically modified cells are also termed *transduced cells*.
基因修飾有機體（GMO） 人類以外的一種有機體，其中的基因物質經由非自然發生的交配及/或非自然重組方式進行改變。本附則 GMO 旨在涵蓋非因自然事件發生，而是由人為干預產生之突變。	**Genetically modified organism (GMO)** An organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination. For the purpose of this annex, GMO is intended to cover mutations that are not occurring because of a natural event but are generated by human intervention.
半抗原 低分子量的分子，其本身不具抗原性，除非與一個「攜帶體」分子結合。	**Hapten** A low molecular weight molecule that is not in itself antigenic unless conjugated to a ‘carrier’ molecule.
融合瘤 分泌所需要（單株）抗體的不朽細胞株，而且，典型上是由 B 淋巴細胞與腫瘤細胞融合所衍生。	**Hybridoma** An immortalised cell line that secrete desired (monoclonal) antibodies and are typically derived by fusing B-lymphocytes with tumour cells.
體內 在活的生物體內所進行的程序。	**In-vivo** Procedures conducted in living organisms.
回溯 由於動物或人類物質污染源的存在而未能通過放行試驗時，或在來源動物或人類的考量情況變得顯而易見時，為追溯 ATMPs 原料藥或產品因使用或合併該動物或人類物質可能受不良影響之文件化程序。	**Look-back** Documented procedure to trace ATMPs active substances or products, which may be adversely affected by the use or incorporation of animal or human materials either when such materials fail release tests due to the presence of contaminating agent or when conditions of concern become apparent in the source animal or human.
主細胞庫（MCB） 為均等分裝之單一細胞株，通常自選定之細胞殖株在界定條件下進行製備，分裝到多個容器且於界定條件下儲存。所有工作細胞庫來自主細胞庫。	**Master cell bank (MCB)** An aliquot of a single pool of cells, which generally has been prepared from the selected cell clone under defined conditions, dispensed into multiple containers and stored under defined conditions. The MCB is used to derive all working cell banks.

主基因轉殖庫 同上，但用於基因轉殖植物或動物。	**Master transgenic bank** As above but for transgenic plants or animals.
主病毒種庫（MVS） 同上，但與病毒有關。	**Master virus seed (MVS)** As above, but in relation to viruses.
製造與儲存期間與 ATMP 直接接觸之材料 下為舉例清單（非包含全部）：操作容器（例如，醱酵槽、細胞培養瓶與培養皿、血袋系統、用於自動化製造平台之一次性使用設備、用於分離技術之圓珠、層析管柱材料）、用於儲存之冷凍容器及直接包裝材料。	**Material directly in contact with the ATMP during manufacture and storage** Non exhaustive example list: Processing containers (e.g. fermenters, cell culture flasks and plates, blood bag systems, single use equipment used in automated manufacturing platforms, beads for separation techniques, chromatographic column material), cryo-containers for storage and primary packaging material.
單一品種（純培養物） 在培養中的單一有機體，未被任何其他有機體所污染。	**Monosepsis (axenic)** A single organism in culture, which is not contaminated with any other.
多產品設施 同時或以時段切換模式製造一系列不同 ATMPs 原料藥與產品之設施，並且在該設施內，一連串設備可能專用或非專用於特定的原料藥或產品。	**Multi-product facility** A facility that manufactures, concurrently or in campaign mode, a range of different ATMPs active substances and products and within which equipment train either may or may not be dedicated to specific substances or products.
質體 質體是一段 DNA，通常是與染色體分離，以一個環狀存在於細菌中；它可以經由分子生物技術進行修飾、從細菌純化出，並使用於將其 DNA 轉殖到另一個細胞中。	**Plasmid** A plasmid is a piece of DNA usually present in a bacterial cell as a circular entity separated from the cell chromosome; it can be modified by molecular biology techniques, purified out of the bacterial cell and used to transfer its DNA to another cell.
初代細胞批 經最少的增殖至足夠數量的初代細胞，以供有限數量的使用。	**Primary cell lot** A pool of primary cells minimally expanded to attain a sufficient number for a limited number of applications.

GMP 原則： 附則 2A 結合 GMP 指引與附則，描述 ATMP 原料藥及 ATMP 藥品之製造。然而，該等指引之層面亦與 ATMP 製造的早期階段（例如病毒載體、質體的製造）相關，該等階段於國家法規下不需要完整的 GMP。因此，ATMP 製造廠應確保實施該等材料製造之所有相關 GMP 層面，以確保製程管制與一致性、異常調查及變更管制。	**Principles of GMP:** The Annex 2A in conjunction with PIC/S GMP guidelines and annexes describes the manufacture of ATMP active substances and ATMP drug products. However, aspects of these guidelines are also relevant for early stages in the ATMP manufacture (e.g. manufacture of viral vectors, plasmids) where full GMP is not required under national legislation. As a result, the ATMP manufacturer should make sure that all relevant GMP aspects for the manufacturing of those materials are implemented that ensure process control and consistency, investigation of anomalies and control of change.
製程助劑 用於製造原料藥與藥品之物質，可能存在於最終產品中，例如，抗發泡劑、氣體（puffer）與培養基添加劑（鹽類、pH 指示劑）、未視為原料之酵素。	**Processing aids** Substance used in the manufacture of the active substance and medicinal product, which may be present in the finished product e.g. anti-foaming agents, puffer and media additives (salts, pH indicators), enzymes not considered under raw materials
品質目標產品概貌（QTPP） 藥品品質特性之先期性摘要，經考量藥品之安全性及有效性，理想上能確保所需之品質將被達成。（ICHQ8R2）	**Quality Target Product Profile (QTPP)** A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. (ICHQ8R2)
原物料 製造過程中與產品直接接觸但非必要為最終配方一部分之所有原物料（例如，冷凍保護劑、餵養細胞、試劑、培養基、緩衝劑、血清、酵素、細胞激素及生長因子）。	**Raw materials** All materials that come in direct contact with the product during the manufacturing process but are not necessarily part of the final formulation (e.g. cryoprotectants, feeder cells, reagents, culture media, buffers, serum, enzymes, cytokines, and growth factors).

血液或組織機構權責人員 本術語等同於歐盟「權責人員」術語。該權責人員負責放行起始原料至 ATMP 製造廠。**血液或組織機構：**依本附則之目的，本術語等同於歐盟術語，係指根據國家法規被授權執行人類來源之起始原料處理（最小操作）的設施。	**Responsible Person (RP) for blood or tissue establishment** This term is equivalent to the EU term "Responsible Person". The RP is responsible for the release of the starting material to the ATMP manufacturer. **Blood or tissue establishment:** this term is equivalent to the EU term and for the purpose of this annex is the facility that is authorised according to national law to perform processing (minimal manipulation) of the starting material of human origin.
支架 為一支柱物、遞送載具或基質，其可提供結構或促進細胞及/或生物活性分子的遷移、結合或運送。	**Scaffold** A support, delivery vehicle or matrix that may provide structure for or facilitate the migration, binding or transport of cells and/or bioactive molecules.
體細胞 為構成人體或動物體之細胞，但生殖（生殖細胞株）細胞除外。這些細胞可能是自體的（來自患者）、同種異體的（來自另一個人）或異種異體的（來自動物）活的體細胞，已在活體外進行處理或修改，要提供給人類，以獲得治療、診斷或預防效果。	**Somatic cells** Cells, other than reproductive (germ line) cells, which make up the body of a human or animal. These cells may be autologous (from the patient), allogeneic (from another human being) or xenogeneic (from animals) somatic living cells, that have been manipulated or altered ex vivo, to be administered in humans to obtain a therapeutic, diagnostic or preventive effect.
無特定病原體（SPF） 來自無特定病原體（SPF）動物群體（例如，鳥群或獸群）而使用於生物藥品的生產或品質管制之動物性材料（例如，雞、胚胎或細胞培養物）。該等動物群體是被界定為共享一個共同環境的動物，且其照顧者不與非無特定病原體（non-SPF）群體接觸。	**Specified pathogen free (SPF)** Animal materials (e.g. chickens, embryos or cell cultures) used for the production or quality control of biological medicinal products derived from groups (e.g. flocks or herds) of animals free from specified pathogens (SPF). Such flocks or herds are defined as animals sharing a common environment and having their own caretakers who have no contact with non-SPF groups.
基因轉殖 使一有機體之正常基因組成物中含有外來基因，以供生物藥品材料之表現。	**Transgenic** An organism that contains a foreign gene in its normal genetic component for the expression of biological pharmaceutical materials.

載體 將基因資訊從一個細胞或有機體傳送到另一個細胞或有機體的傳輸媒介，例如，質體、微脂體、病毒。	**Vector** An agent of transmission, which transmits genetic information from one cell or organism to another, e.g. plasmids, liposomes, viruses.
病毒載體 以分子生物技術，從一病毒衍生並藉由保留一些而非全部親代病毒基因之方式進行修飾之載體；如果刪除負責病毒複製能力的基因，則使該載體失去複製能力。	**Viral vector** A vector derived from a virus and modified by means of molecular biology techniques in a way as to retain some, but not all, the parental virus genes; if the genes responsible for virus replication capacity are deleted, the vector is made replication-incompetent.
病毒載體失去/缺乏複製能力 載體沒有複製能力。	**Viral Vector replication incompetent / devoid** No ability of the vector to replicate.
病毒載體複製能力受限/缺陷/條件複製 複製能力受限之載體，其目的可能是用於嵌入目標特定組織或目標細胞類型之預定位置，以達基因治療的臨床療效。	**Viral Vector replication limited / defective / conditional replication** A constrained ability to replicate where the intent is for the vector may be to target a particular tissue or target cell type with a planned integration required for clinical efficacy of the gene therapy.
工作細胞庫（WCB） 衍生自主細胞庫之細胞的均質混合物，均勻分裝於若干容器中，並以確保安定性的方式儲存及預定供生產使用。	**Working cell bank (WCB)** A homogeneous pool of cells preferably derived from a MCB, which are distributed uniformly into a number of containers, stored in such a way to ensure stability and intended for use in production.
工作基因轉殖庫（WTB） 同上，但用於基因轉殖植物或動物。	**Working transgenic bank (WTB)** As above but for transgenic plants or animals.
工作病毒種庫（WVS） 同上，但與病毒有關。	**Working virus seed (WVS)** As above but in relation to viruses.
人畜共通傳染病 會傳染給人類的動物疾病。	**Zoonosis (zoonotic)** Animal diseases that can be transmitted to humans.

附則 2B 人用生物原料藥及產品的製造（MANUFACTURE OF BIOLOGICAL MEDICINAL SUBSTANCES AND PRODUCTS FOR HUMAN USE）

範圍（SCOPE）	
製造人用生物原料藥及生物藥品（生物原料藥及藥品）所使用之方法，是在制訂適當法規管制上的一個關鍵因素。因此，生物原料藥及藥品主要是依其製造方法而界定。本附則是提供經界定為生物藥品，但除再生醫療製劑（Advanced Therapy Medicinal Products, ATMPs）外之全部範圍的原料藥及藥品之指引。ATMPs 不包含於本指引內。ATMPs 之製造請參考 GMP 附則 2A 人用再生醫療製劑之製造。	The methods employed in the manufacture of biological active substances and biological medicinal products for human use ('biological active substances and medicinal products') are a critical factor in shaping the appropriate regulatory control. Biological active substances and medicinal products can be defined therefore largely by reference to their method of manufacture. This annex provides guidance on the full range of active substances and medicinal products defined as biological with the exception of Advanced Therapy Medicinal Products ("ATMPs"). The ATMPs are not covered by the present guideline. Manufacturers of ATMPs should refer to PIC/S Annex 2A Manufacture of Advanced Therapy Medicinal Products for Human Use.
本附則主要分成兩部：	This annex is divided into two main parts:
a) A 部包含從管制製造生物原料藥及藥品之種批與細胞庫至最終作業與測試的補充指引。	a) Part A contains supplementary guidance on the manufacture of biological active substances and medicinal products, from control over seed lots and cell banks through to finishing activities and testing.
b) B 部包含特定類別之生物原料藥及藥品的進一步指引。	b) Part B contains further guidance on selected types of biological active substances and medicinal products.
本附則連同 GMP 指引之其他附則，提供 GMP 第一部與第二部之補充指引。本附則的範圍有兩個方面：	This annex, along with several other annexes of the PIC/S Guide to GMP, provides guidance which supplements that in Part I and in Part II of the Guide. There are two aspects to the scope of this annex:
a) 製造階段–對於生物原料藥成為無菌之前的階段，主要指引為 GMP 第二部。對於生物產品之隨後製造步驟的指引則為 GMP 第一部。	a) Stage of manufacture - for biological active substances to the point immediately prior to their being rendered sterile, the primary guidance source is Part II. Guidance for the subsequent manufacturing steps of biological products are covered in Part I.
b) 產品類別–本附則提供經界定為生物藥品，但除 ATMPs 外之全部範圍的原料藥及產品之指引。	b) Type of product - this annex provides guidance on the full range of medicinal products defined as biological with the exception of ATMPs.

上述兩個方面是顯示於表 1 中，應該注意的是，本表僅為說明性，而非為描述精確範圍。且應當瞭解的是，根據 GMP 之第二部的對應表，在生物原料藥從早期到後來之製造步驟，GMP 的程度是越來越詳盡，但應當始終遵循 GMP 原則。有一些早期之製造步驟納入本附則的範圍內，並非意謂該等步驟將例行地接受主管機關的檢查。	These two aspects are shown in Table 1; it should be noted that this table is illustrative only and is not meant to describe the precise scope. It should also be understood that in line with the corresponding table in Part II of the Guide, the level of GMP increases in detail from early to later steps in the manufacture of biological active substances but GMP principles should always be adhered to. The inclusion of some early steps of manufacture within the scope of this Annex does not imply that those steps will be routinely subject to inspection by the authorities.
抗生素並非被界定為生物藥品，惟，在進行生物性的製造階段，可以使用本附則中的指引。	Antibiotics are not defined as biological medicinal products, however where biological stages of manufacture occur, guidance in this Annex may be used.
對於由分離人類血液或血漿衍生之藥品的指引涵蓋於附則 14。非基因轉殖植物產品的指引涵蓋於附則 7。（附則 7 未涵蓋於西藥藥品優良製造規範之範圍）	Guidance for medicinal products derived from fractionated human blood or plasma is covered in Annex 14 and for non-transgenic plant products in Annex 7.
在某些情況下，其他法規可能適用於生物藥品的起始原料。例如，	In certain cases, other legislation may be applicable to the starting materials for biologicals. For example,
(a) 用作藥品之起始原料的組織與細胞，其捐贈、採集、測試、處理、保存、儲存與配送，依國家法規規定。當該等組織與細胞對供應為本附則範圍內一些生物藥品之原料藥時，適用GMP及其他藥品法規要求。	(a) Tissue and cells used as starting materials for medicinal products, donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells of tissue and cells may be covered by national legislation. Such tissues and cells may provide the active substances for some biological medicinal product within the scope of this annex at which point GMP and other medicinal product legislation requirements apply.
(b) 使用血液或成分血作為藥品的起始原料時，國家法規可能對捐血者之篩選與血液及成分血的收集、測試、處理、保存、儲存與配送予以技術要求。	(b) Blood or blood components used as starting materials for medicinal products, national legislation may provide the technical requirements for the selection of donors, collection, testing, processing, storage, and distribution of human blood and blood components[1].

此外，經基因修飾之有機體的製造與管制需要遵從當地與國家的要求。在處理任何基因修飾之微生物的設施，應建立適當的圍堵並維持之。為了建立並維持適當生物安全性等級，應參照國家法規規定且仍應遵守 GMP 要求。	Additionally, the manufacture and control of genetically modified organisms needs to comply with local and national requirements. Appropriate containment should be established and maintained in facilities where any genetically modified micro-organism is handled[2]. Advice should be obtained according to national legislation in order to establish and maintain the appropriate Biological Safety Level. There should be no conflicts with GMP requirements.

表 1. 對於在附則 2B 範圍內之製造活動的說明性指引

材料類型與來源	產品實例	灰色顯示本指引應用之製造步驟			
1. 動物或植物來源：非基因轉殖	肝素、胰島素、酵素、蛋白質、過敏原萃取物，免疫血清	植物、器官、動物性原料或體液的收集 [3]	裁切、混合及/或起始處理	分離與純化	配方調製、充填
2. 病毒或細菌醱酵/細胞培養	病毒或細菌疫苗；酵素、蛋白質	MCB[4]、WCB、MVS、WVS 的建立與維護	細胞培養及/或醱酵	去活化（適用時）、分離與純化	配方調製、充填
3. 生物技術醱酵/細胞培養 [3]	基因重組產品、單株抗體（MAb）、過敏原、疫苗	MCB[4]與 WCB、MSL、WSL 的建立與維護	細胞培養及/或醱酵	分離、純化、修飾	配方調製、充填
4. 動物來源：基因轉殖	基因重組蛋白質	主基因轉殖庫與工作基因轉殖庫	收集、裁切、混合及/或起始處理	分離、純化、修飾	配方調製、充填
5. 植物來源：基因轉殖	基因重組蛋白質、疫苗、過敏原	主基因轉殖庫與工作基因轉殖庫	栽種、收獲 [5]	起始萃取、分離、純化、修飾	配方調製、充填
6. 人類來源	尿衍生酵素、賀爾蒙	液體的收集 [6]	混合及/或起始處理	分離與純化	配方調製、充填
7. 人類來源	未分類為 ATMPs 之來自細胞或組織的產品，	起始組織/細胞的捐贈、採集與測試 [7]	初始操作，分離與純化，建立 MCB、WCB、初始細胞批或細胞庫	細胞分離、培養、純化、與非細胞成分組合	配方調製、組合、充填

縮寫的解釋，參見術語彙編。

註：

[3] 詳 B 部「B1」對 GMP 原則之適用範圍

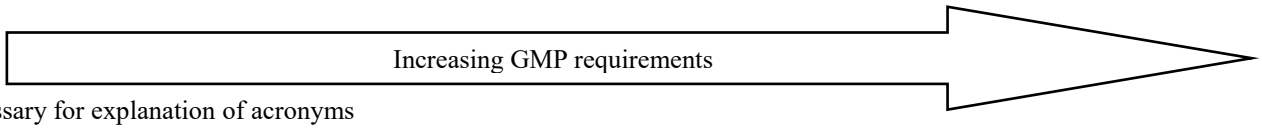
[4] 詳「種批與細胞庫系統」對 GMP 原則之適用範圍

[6] 對 GMP 之原則應用，詳「範圍」之說明

Table 1. Illustrative guide to manufacturing activities within the scope of Annex 2B.

Type and source of material	Example Product	Application of this guide to manufacturing steps shown in grey			
1. Animal or plant sources: non-transgenic	Heparins, insulin, enzymes, proteins, allergen extract, immunosera	Collection of plant, organ, animal material or fluid [3]	Cutting, mixing, and /or initial processing	Isolation and purification	Formulation, Filling
2. Virus or bacteria / fermentation / cell culture	Viral or bacterial vaccines; enzymes, proteins	Establishment & maintenance of MCB[4], WCB, MVS, WVS	Cell culture and/or fermentation	Inactivation when applicable, isolation and purification	Formulation, filling
3. Biotechnology fermentation/ cell culture[3]	Recombinant products, MAb, allergens, vaccines	Establishment & maintenance of MCB[4] and WCB, MSL, WSL	Cell culture and /or fermentation	Isolation, purification, modification	Formulation, filling

4. Animal sources: transgenic	Recombinant proteins	Master and working transgenic bank	Collection, cutting, mixing, and/or initial Processing	Isolation, purification and modification	Formulation, filling
5. Plant sources: Transgenic	Recombinant proteins, vaccines, allergens	Master and working transgenic bank	Growing, harvesting [5]	Initial extraction, isolation, purification, modification	Formulation, filling
6. Human sources	Urine derived enzymes, hormones	Collection of fluid[6]	Mixing, and/or initial processing	Isolation and Purification	Formulation, filling
7. Human sources	Products from cells and tissue, not classified as ATMPs	Donation, procurement and testing of starting tissue/cells[7]	Initial processing, isolation and purification, establish MCB, WCB, primary cell lot or cell pool	Cell isolation, culture, purification, combination with non-cellular components	Formulation, combination, filling



See Glossary for explanation of acronyms

[3] See section B1 for the extent to which GMP principles apply.

[4] See section on 'Seed lot and cell bank system' for the extent to which GMP applies.

[6] For principles of GMP apply, see explanatory text in 'Scope'.

原則（PRINCIPLE）	
製造生物原料藥與藥品所涉及之某些特定考慮，係源自於其產品與製程之本質。製造、管制與管理生物藥品的方式，使得有些特別的防範措施是必要的。	The manufacture of biological active substances and medicinal products involves certain specific considerations arising from the nature of the products and the processes. The ways in which biological medicinal products are manufactured, controlled and administered make some particular precautions necessary.
與採化學與物理技術製造的傳統藥品可具高度一致性不同，生物原料藥及藥品的製造涉及生物性製程與原料，例如，細胞的培養或從活有機體原料的萃取。這些生物性製程可能表現其固有變異性，因此，副產物的範圍與性質可能是可變的。所以，品質風險管理（QRM）原則對此類原料特別重要，而且應當應用於涵蓋所有製造階段之管制策略的開發，以使其變異性減到最少，並且減少其對於污染與交叉污染的機會。	Unlike conventional medicinal products, which are manufactured using chemical and physical techniques capable of a high degree of consistency, the manufacture of biological active substances and medicinal products involves biological processes and materials, such as cultivation of cells or extraction from living organisms. These biological processes may display inherent variability, so that the range and nature of by-products may be variable. As a result, quality risk management (QRM) principles are particularly important for this class of materials and should be used to develop the control strategy across all stages of manufacture so as to minimise variability and to reduce the opportunity for contamination and cross-contamination.

由於在培養過程中所使用之原料與製程條件是設計來提供特定細胞與微生物的生長，所以，這提供了外來微生物污染物增長的機會。此外，某些產品承受寬廣範圍之純化技術的能力可能是有限的，特別是那些經設計以去活化或移除外來病毒污染物的產品。製程、設備、設施、公用設施、製備與添加緩衝劑及試劑之條件及抽樣之設計與操作者的訓練，皆屬使該等污染事件減到最少的關鍵考量。	Since materials and processing conditions used in cultivation processes are designed to provide conditions for the growth of specific cells and microorganisms, this provides extraneous microbial contaminants the opportunity to grow. In addition, some products may be limited in their ability to withstand a wide range of purification techniques particularly those designed to inactivate or remove adventitious viral contaminants. The design of the processes, equipment, facilities, utilities, the conditions of preparation and addition of buffers and reagents, sampling and training of the operators are key considerations to minimise such contamination events.
與產品有關的規格（例如，在藥典個論、臨床試驗許可與上市許可的規格），將決定原料與材料在何階段是否能有一個經界定的負荷菌量或需為無菌。同樣的，製造必須與載於臨床試驗許可或上市許可之規格一致【例如，種批或細胞庫間之世代數目（倍增、繼代數目）】。	Specifications related to products (such as those in Pharmacopoeial monographs, Clinical Trial Authorisation (CTA), and Marketing Authorisation (MA)) will dictate whether and to what stage substances and materials can have a defined level of bioburden or need to be sterile. Similarly, manufacturing must be consistent with other specifications set out in the CTA or MA (e.g. number of generations (doublings, passages) between the seed lot or cell bank).
對於不能滅菌（例如，經由過濾）的生物原料必須執行無菌操作，以使污染物減到最少。當其存在時，應參考其他指引文件確效特定製造方法，例如：病毒移除或去活化。應使用環境管制與監測，以及可行時，使用密閉系統連同原位清潔及原位滅菌系統，可以顯著地減少意外污染與交叉污染的風險。	For biological materials that cannot be sterilized (e.g. by filtration), processing must be conducted aseptically to minimise the introduction of contaminants. Where they exist, other guidance documents should be consulted on the validation of specific manufacturing methods, e.g. virus removal or inactivation. The application of appropriate environmental controls and monitoring and, wherever feasible, in-situ cleaning and sterilisation systems together with the use of closed systems can significantly reduce the risk of accidental contamination and cross-contamination.
管制通常包括生物分析技術，一般而言，該技術比物理-化學測定具有更大的變異性。因此，一個穩健的製造過程是至關重要的，而且製程中管制在生物原料藥及產品的製造上承擔了特別的重要性。	Control usually involves biological analytical techniques, which typically have a greater variability than physico-chemical determinations. A robust manufacturing process is therefore crucial and in-process controls take on a particular importance in the manufacture of biological active substances and medicinal products.

含有人體組織或細胞的生物藥品，必須遵從對人體組織或細胞之編碼、處理、保存、儲存與配送的國家要求。這種原料的採集與測試必須依照適當的品質系統及可適用的國家要求完成之。此外，國家對可追溯性的要求適用於從捐贈者（仍維持捐贈者保密性）至組織機構（庫）可適用的階段，而且，在醫藥法規下再持續延伸至使用該產品的機構。	Biological medicinal products which incorporate human tissues or cells must comply with national requirements for the coding, processing, preservation, storage and distribution of human tissues and cells.[8] Collection and testing of this material must be done in accordance with an appropriate quality system and in accordance with applicable national requirements[9]. Furthermore, national requirements[10] on traceability apply from the donor (while maintaining donor confidentiality) through stages applicable at the Tissue Establishment and then continued under medicines legislation through to the institution where the product is used.
生物原料藥及藥品必須符合可適用的國家指引，以使經由人用與動物用藥品傳遞動物海綿樣腦症病原體的風險降到最低。	Biological active substances and medicinal products must comply with the applicable national guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products.
A 部：一般指引（PART A: GENERAL GUIDANCE）	
人員（PERSONNEL）	
1. 在生物原料藥與藥品的製造與檢驗區域中的工作人員（包含與清潔、維護保養或品質管制有關者）應接受包括保護產品、人員與環境的任何特定安全措施在內之產品製造及其工作相關的訓練與定期再訓練。	1. Personnel (including those concerned with cleaning, maintenance or quality control) employed in areas where biological active substances and products are manufactured and tested should receive training, and periodic retraining, specific to the products manufactured and to their work, including any specific security measures to protect product, personnel and the environment.
2. 為產品的安全性，人員的健康狀況應納入考慮。當需要時，從事生產、維護保養、檢驗與動物照顧（與檢查）之人員應接種適當的特定疫苗，並有定期的健康檢查。	2. The health status of personnel should be taken into consideration for product safety. Where necessary, personnel engaged in production, maintenance, testing and animal care (and inspections) should be vaccinated with appropriate specific vaccines and have regular health checks.
3. 人員之健康狀態發生任何變化可能對產品品質有不良影響時，應排除其在生產區中工作，並且保存適當的紀錄。卡介苗與結核菌素產品的生產，應限由接受免疫狀態或胸部 X 光定期檢查監測的人員執行。工作人員健康的監測程度應與風險對等，對於涉及危害性有機體的人員應當尋求醫療建議。	3. Any changes in the health status of personnel, which could adversely affect the quality of the product, should preclude work in the production area and appropriate records kept. Production of BCG vaccine and tuberculin products should be restricted to staff who are carefully monitored by regular checks of immunological status or chest X-ray. Health monitoring of staff should be commensurate with the risk, medical advice should be sought for personnel involved with hazardous organisms.

4. 當需使交叉污染的機會減到最低，對於所有人員（包含品質管制、維護保養與清潔人員在內）移動的限制，應基於品質風險管理原則加以管制之。通常，人員不得從暴露於活微生物、基因修飾有機體、毒素或動物之區域穿越至處理其他產品、去活化產品或不同有機體的區域。如果該穿越無法避免時，則污染管制措施應基於品質風險管理原則。	4. Where required to minimise the opportunity for cross-contamination, restrictions on the movement of all personnel (including quality control (QC), maintenance and cleaning staff) should be controlled on the basis of QRM principles. In general, personnel should not pass from areas where exposure to live micro-organisms, genetically modified organisms, toxins or animals to areas where other products, inactivated products or different organisms are handled. If such passage is unavoidable, the contamination control measures should be based on QRM principles.
廠房設施與設備（PREMISES AND EQUIPMENT）	
5. 作為管制策略之一部分，切記原料潛在污染程度及對該產品的風險，應將生產之廠房設施的微粒與微生物污染等環境管制，調整到適合該原料藥、中間產品或最終產品及其生產步驟之程度。除在附則 1 之環境監測計畫外，應補充由品質風險管理過程評估所得特定微生物（亦即，宿主有機體、酵母菌、黴菌、厭氧菌等）之存在的檢測方法。	5. As part of the control strategy, the degree of environmental control of particulate and microbial contamination of the production premises should be adapted to the active substance, intermediate or finished product and the production step, bearing in mind the potential level of contamination of the starting materials and the risks to the product. The environmental monitoring programme should be supplemented by the inclusion of methods to detect the presence of specific microorganisms (i.e. host organism, yeasts, moulds, anaerobes, etc) where indicated by the QRM process.
6. 製造與儲存設施、製程與環境分級應經設計，以防止產品受外來污染。儘管在例如醱酵與細胞培養的期間中污染可能變得顯著，但是，防止污染比偵測與移除更適當。當製程不是密閉且產品因而暴露於作業室環境時（例如，在補充劑、培養基、緩衝液、氣體之添加的期間），應已具備相關管制措施，包含基於品質風險管理原則的硬體與環境管制在內。當選擇環境分級梯度與相關的管制時，這些品質風險管理原則應將來自附則 1[11] 之適當部分的原則與指引納入考慮。	6. Manufacturing and storage facilities, processes and environmental classifications should be designed to prevent the extraneous contamination of products. Prevention of contamination is more appropriate than detection and removal, although contamination is likely to become evident during processes such as fermentation and cell culture. Where processes are not closed and there is therefore exposure of the product to the immediate room environment (e.g. during additions of supplements, media, buffers, gasses,) control measures should be put in place, including engineering and environmental controls on the basis of QRM principles. These QRM principles should take into account the principles and guidance from the appropriate sections of Annex 1[11] when selecting environmental classification cascades and associated controls.

[11] 雖附則 1 標題為針對無菌藥品之製造，非強制於無菌產品當其為適當且核准為低負荷菌階段之製程。引用附則 1 係因其為 GMP 指引針對包括 D 級及 C 級區之所有潔淨區域分級的來源。	[11] Although the title of Annex 1 refers to the manufacture of sterile medicinal products it is not the intention to force the manufacture of sterile product at a stage when a low bioburden is appropriate and authorised. Its use is because it is the PIC/S GMP source of guidance on all of the classified manufacturing areas including the lower grades D and C.
7. 處理活細胞應使用專用生產區。製造病原性有機體應使用專用生產區（亦即生物安全性等級 3 或 4）。	7. Dedicated production areas should be used for the handling of live cells. Dedicated production area should be used for the manufacture of pathogenic organisms (i.e. Biosafety level 3 or 4).
8. 當具下列或等同的（當適用於所涉及的產品類別時）考量與措施作為有效防止交叉污染之管制策略的一部分時，則在多產品設施中的製造可能是可以接受的：	8. Manufacture in a multi-product facility may be acceptable where the following, or equivalent (as appropriate to the product types involved) considerations and measures are part of an effective control strategy to prevent cross-contamination:
(a) 具備對設施內之所有細胞、有機體與任何外來病原的關鍵特性之知識（例如，致病性、可檢測性、持久性、對去活化的敏感性）。	(a) Knowledge of key characteristics of all cells, organisms and any adventitious agents (e.g. pathogenicity, detectability, persistence, susceptibility to inactivation) within the same facility.
(b) 當生產的性質來自多個小批次之不同起始原料時，在開發管制策略的期間考慮欲同時作業的可接受性時，應將例如捐贈者的健康狀況與產品之總損失的風險因素列入考慮。	(b) Where production is characterised by multiple small batches from different starting materials, factors such as the health status of donors and the risk of total loss of product should be taken into account when considering the acceptance of concurrent working during development of the control strategy.
(c) 經由處理所有潛在交叉污染途徑並利用一次性組件及例如密閉系統之工程措施防止活有機體與孢子進入非相關的區域或設備。	(c) Live organisms and spores are prevented from entering non-related areas or equipment by addressing all potential routes of cross-contamination and utilizing single use components and engineering measures such as closed systems.
(d) 在後續製造其他產品前，對於移除有機體與孢子的管制措施應將空調系統（HVAC）納入考慮。對於有機體與孢子之移除的清潔與去污染應經確效。	(d) Control measures to remove the organisms and spores before the subsequent manufacture of other products, these control measures should also take the heating, ventilation and air conditioning (HVAC) system into account. Cleaning and decontamination for the organisms and spores should be validated.

(e) 針對所製造之微生物，當該微生物能持續存在於製造環境中且方法可用時，在相鄰的區域中，應在製造期間與清潔去污染完成之後執行環境監測。在處理活微生物及/或產芽孢菌類的區域中，也應注意源自使用某些監測設備（例如，浮游微粒監測）的風險。	(e) Environmental monitoring, specific for the micro-organism being manufactured, where the micro-organisms are capable of persistence in the manufacturing environment and where methods are available, is conducted in adjacent areas during manufacture and after completion of cleaning and decontamination. Attention should also be given to risks arising with use of certain monitoring equipment (e.g. airborne particle monitoring) in areas handling live and/or spore forming organisms.
(f) 僅能使用防止其他區域、其他產品及不同產品階段受污染（例如，防止經去活化的產品或未去活化類毒素製品的污染）的方式，進行在區域內移動或移除產品、設備、輔助設備（例如，用於校正與確效）與拋棄式物品。	(f) Products, equipment, ancillary equipment (e.g. for calibration and validation) and disposable items are only moved within and removed from such areas in a manner that prevents contamination of other areas, other products and different product stages (e.g. prevent contamination of inactivated or toxoided products with non-inactivated products).
(g) 基於時段切換製造。	(g) Campaign based manufacturing.
9. 對於最終（二級）操作[12]，專用設施的需要性將取決於上述考慮事項並額外考慮例如：生物藥品之特定需求，且取決於在同一設施中其他產品的特性，包含任何非生物產品在內。對於最終操作的其他管制措施，可能包括需要特定的添加順序、混合速度、時間與溫度管制、暴露於光的限制，以及在溢出情況下的圍堵與清潔程序。	9. For finishing (secondary) operations[12], the need for dedicated facilities will depend on consideration of the above together with additional considerations such as the specific needs of the biological medicinal product and on the characteristics of other products, including any non-biological products, in the same facility. Other control measures for finishing operations may include the need for specific addition sequences, mixing speeds, time and temperature controls, limits on exposure to light and containment and cleaning procedures in the event of spillages.
[12] 配方調製、充填及分包裝	[12] Formulation, filling and packaging
10. 圍堵所需要的措施與程序（亦即，對環境與操作人員的安全性）不得與產品品質相衝突。	10. The measures and procedures necessary for containment (i.e. for environment and operator safety) should not conflict with those for product quality.
11. 空氣處理單元應經設計、建造與維護保養，以使在不同製造區域間之交叉污染的風險減到最低，而且，對某區域可能需要專用的。基於品質風險管理原則，應考慮使用單次通過（single pass）的空調系統。	11. Air handling units should be designed, constructed and maintained to minimise the risk of cross-contamination between different manufacturing areas and may need to be specific for an area. Consideration, based on QRM principles, should be given to the use of single pass air systems.

12. 對於操作無菌產品，應使用正壓區域，但是，為圍堵的原因，在病原體暴露的特定區域，負壓是可接受的。具有特定風險之物料（例如，病原菌）的無菌處理，使用負壓區域或安全櫃時，該等物料應由適當等級的正壓潔淨區域所包圍。這些壓力梯度應予以清楚地界定、連續監測並具適當警報裝置。	12. Positive pressure areas should be used to process sterile products but negative pressure in specific areas at the point of exposure of pathogens is acceptable for containment reasons. Where negative pressure areas or safety cabinets are used for aseptic processing of materials with particular risks (e.g. pathogens), they should be surrounded by a positive pressure clean zone of appropriate grade. These pressure cascades should be clearly defined and continuously monitored with appropriate alarm settings.
13. 在活有機體與細胞之處理所使用的設備，包括用於取樣的設備，應設計成在操作期間防止任何污染。	13. Equipment used during handling of live organisms and cells, including those for sampling, should be designed to prevent any contamination during processing.
14. 一級圍堵[13]應經設計並定期測試，以確保防止生物物質（biological agents）逸入直接的工作環境。	14. Primary containment[13] should be designed and periodically tested to ensure the prevention of escape of biological agents into the immediate working environment.
[13]詳 GMP 指引術語彙編之「圍堵」	[13]See main GMP Glossary on 'Containment'.
15. 可能時，應使用「原位清潔」與「原位蒸氣處理」(「原位滅菌」）系統。在醱酵容器上的閥門應為可以完全蒸氣滅菌的。	15. The use of 'clean in place' and 'steam in place' ('sterilisation in place') systems should be used where possible. Valves on fermentation vessels should be completely steam sterilisable.
16. 空氣通氣口濾器應為疏水性、應對其預定使用壽命確效，並根據適當的 QRM 原則，於適當的時間間隔進行完整性測試。	16. Air vent filters should be hydrophobic and validated for their scheduled life span with integrity testing at appropriate intervals based on appropriate QRM principles.
17. 排水系統必須設計成使排放物可被有效地中和或去污染，以使交叉污染的風險減到最低。必須遵守當地法規，依照與廢棄物之生物危害本質相關的風險，使外在環境污染的風險減到最小。	17. Drainage systems must be designed so that effluents can be effectively neutralised or decontaminated to minimise the risk of cross-contamination. Local regulation must be complied with to minimise the risk of contamination of the external environment according to the risk associated with the biohazardous nature of waste materials.
18. 由於生物產品或製程的變異性，相關的/關鍵的原料（例如，培養基與緩衝劑）可能必須在生產過程中，予以量測或秤重。在這些情況中，基於所界定的標準，例如，在該批次的製造或在時段切換製造的期間，這些原料可依所界定的時間少量保存在生產區中。	18. Due to the variability of biological products or manufacturing processes, relevant/critical raw materials (such as culture media and buffers) have to be measured or weighed during the production process. In these cases, small stocks of these raw materials may be kept in the production area for a specified duration based on defined criteria such as for the duration of manufacture of the batch or of the campaign.
動物（ANIMALS）	

19. 廣泛的動物物種被用來製造許多生物藥品。這些動物可以分成兩個廣泛的來源類型：	19. A wide range of animal species are used in the manufacture of a number of biological medicinal products. These can be divided into 2 broad types of sources:
(a) 活的動物群體：例如包括脊髓灰白質炎疫苗（猴子）、對蛇毒與破傷風的免疫血清（馬、綿羊與山羊）、過敏原（貓）、狂犬病疫苗（兔、小鼠與倉鼠）、基因轉殖產品（山羊、牛）。	(a) Live groups, herds, flocks: examples include polio vaccine (monkeys), immunosera to snake venoms and tetanus (horses, sheep and goats), allergens (cats), rabies vaccine (rabbits, mice and hamsters), transgenic products (goats, cattle).
(b) 在屍體剖檢後與來自例如屠宰場等機構衍生的動物性原料，實例包括來自屠宰場來源（羊與豬）的酵素、抗凝血劑與激素。	(b) Animal materials derived post-mortem and from establishments such as abattoirs: examples include, abattoir sources for enzymes, anticoagulants and hormones (sheep and pigs).
此外，動物也可用於品質管制中一般的測定，例如，熱原性，或特定的效價測定，例如，百日咳疫苗（小鼠）、熱原性（兔子）、卡介苗（豚鼠）。	In addition, animals may also be used in quality control either in generic assays, e.g. pyrogenicity, or specific potency assays, e.g. pertussis vaccine (mice), pyrogenicity (rabbits), BCG vaccine (guinea-pigs).
20. 除了符合 TSE 法規外，其他值得關注的外來病原（人畜共通傳染病、動物源疾病）應當由一個持續性的健康計畫予以監測之，並且加以記錄。在建立該等計畫時應納入專家建議。在來源動物/捐贈動物發生健康欠佳的情況，應進行其適用性的調查，而且與健康欠佳動物接觸之動物，對於持續使用之適用性（在製造上、作為起始物與原料的來源、在品質管制與安全性測試上）的決定，必須加以文件化。應具備回溯程序，通知關於已經使用或併入該動物來源起始物或原料之生物原料藥或藥品的持續適用性之決策過程。這個決策過程可能包括來自同一捐贈動物（如可適用時）之留存樣品的再測試，以確立最近一次的陰性捐贈。對於來源動物/捐贈動物使用治療劑治療的停用期間，必須加以文件化，並且用以決定那些動物在界定的期間從計畫中移除。	20. In addition to compliance with TSE regulations, other adventitious agents that are of concern (zoonotic diseases, diseases of source animals) should be monitored by an ongoing health programme and recorded. Specialist advice should be obtained in establishing such programmes. Instances of ill-health occurring in the source/donor animals should be investigated with respect to their suitability and the suitability of in-contact animals for continued use (in manufacture, as sources of starting and raw materials, in quality control and safety testing), the decisions must be documented. A look-back procedure should be in place which informs the decision making process on the continued suitability of the biological active substance or medicinal product in which the animal sourced starting or raw materials have been used or incorporated. This decision-making process may include the re-testing of retained samples from previous collections from the same donor animal (where applicable) to establish the last negative donation. The withdrawal period of therapeutic agents used to treat source/donor animals must be documented and used to determine the removal of those animals from the programme for defined periods.

21. 應特別注意防止並監測來源動物/捐贈動物的感染。其措施應包括來源、設施、飼養管理、生物安全性程序、檢驗制度、墊料與飼料的管制。這是與在藥典個論要求必須符合的無特定病原動物特別相關。對於其他動物類別（例如，健康的動物群體）之飼養設施與健康監測，應加以界定。	21. Particular care should be taken to prevent and monitor infections in the source / donor animals. Measures should include the sourcing, facilities, husbandry, biosecurity procedures, testing regimes, control of bedding and feed materials. This is of special relevance to specified pathogen free animals where pharmacopoeial monograph requirements must be met. Housing and health monitoring should be defined for other categories of animals (e.g. healthy flocks or herds).
22. 對於從基因轉殖動物所製造的產品，自來源動物產生該動物之過程的可追溯性，應當加以保存。	22. For products manufactured from transgenic animals, traceability should be maintained in the creation of such animals from the source animals.
23. 對於用於科學目的之動物保護的國家要求，應當加以注意。生物原料藥與藥品之生產與管制所使用的動物之飼養設施，應與生產區與管制區隔離。	23. Note should be taken of national requirements on the protection of animals used for scientific purposes[14]. Housing for animals used in production and control of biological active substances and medicinal products should be separated from production and control areas.
24. 對於不同的動物物種，其關鍵標準應當加以界定、監控並且記錄之。這些標準可能包括動物的年齡、體重與健康狀況。	24. For different animal species, key criteria should be defined, monitored, and recorded. These may include age, weight and health status of the animals.
25. 動物、生物物質與所執行的檢驗，應具備識別系統，以防止任何混淆的風險，並且管制所有已經識別的危害。	25. Animals, biological agents, and tests carried out should be the subject of an identification system to prevent any risk of confusion and to control all identified hazards.
文件製作（DOCUMENTATION）	
26. 起始物與原料可能需要就其來源、種源、運銷鏈、製造方法與管制予以額外的文件化，以確保適當的管制水準，包括其微生物學上的品質在內。	26. Starting and raw materials may need additional documentation on the source, origin, distribution chain, method of manufacture, and controls applied, to assure an appropriate level of control including their microbiological quality.
27. 某些產品類型可能需要特別界定其構成一個批次所需的材料，尤其是細胞。	27. Some product types may require specific definition of what materials constitutes a batch, particularly cells.

28. 當使用人類細胞或組織捐贈物時，在維持個人隱私與健康相關資訊之保密性的同時，應要求完整追溯，包含從接觸細胞或組織之所有物質在內的起始物與原料到在使用端產品之接收的確認。追溯紀錄必須保存到該藥品的末效日期後 30 年。對於特殊使用案例，例如，已捐贈配對之細胞，應特別注意維持產品的可追溯性。當成分血在藥品製造過程作為起始物或原料使用時，其可追溯性要求與嚴重不良反應及事件之通知，則適用國家要求。	28. Where human cell or tissue donors are used, full traceability is required from starting and raw materials, including all substances coming into contact with the cells or tissues through to confirmation of the receipt of the products at the point of use whilst maintaining the privacy of individuals and confidentiality of health related information[15]. Traceability records must be retained for 30 years after the expiry date of the medicinal product. Particular care should be taken to maintain the traceability of products for special use cases, such as donor-matched cells. National requirements[16] in regards to traceability requirements and notification of serious adverse reactions and events apply to blood components when they are used as starting or raw materials in the manufacturing process of medicinal products.
生產（PRODUCTION）	
29. 由於許多生物原料與藥品的固有變異性，應當在產品品質檢討時，對產品生命週期的不同階段加以再評估，以增加製程穩健性，因而減低製程變異性與提高再現性，例如，製程設計。	29. Given the variability inherent in many biological active substances and medicinal products, steps to increase process robustness thereby reducing process variability and enhancing reproducibility at the different stages of the product lifecycle such as process design should be reassessed during Product Quality Reviews.
30. 由於培養條件、培養基與試劑是設計來促進細胞或微生物有機體的生長，因此，典型上是在純培養物的狀態，在管制策略上，應特別注意，以確保具有穩健的步驟，防止非預期的負荷菌與相關代謝物及內毒素的產生或使其減到最少。對於生產批次經常是小批量之來自細胞與組織的藥品，其來自具有不同健康狀況之不同捐贈者的細胞製備間交叉污染的風險，應在所界定之程序與要求下加以管制。	30. Since cultivation conditions, media and reagents are designed to promote the growth of cells or microbial organisms, typically in an axenic state, particular attention should be paid in the control strategy to ensure there are robust steps that prevent or minimise the occurrence of unwanted bioburden and associated metabolites and endotoxins. For medicinal products from cells and tissues where production batches are frequently small the risk of cross-contamination between cell preparations from different donors with various health status should be controlled under defined procedures and requirements.
起始物與原料（STARTING AND RAW MATERIALS）	

31. 生物起始物與原料（例如，冷凍保護劑、餵養細胞、試劑、培養基、緩衝劑、血清、酵素、細胞激素、生長因子）之來源、種源與適用性應予明確界定。當所需檢驗耗時長時，可能可以允許在獲得檢驗結果前處理起始物，使用可能失敗的原料及其對其他批次之潛在影響的風險，應當清楚地瞭解，並且在品質風險管理的原則下加以評估。在該等情況中，最終產品係依該等測試的滿意結果，予以條件性放行。所有起始物的鑑別，應符合適其製造階段的要求。對於生物藥品可在第一部與附則 8 及在第二部的生物原料藥找到進一步指引。	31. The source, origin and suitability of biological starting and raw materials (e.g. cryoprotectants, feeder cells, reagents, culture media, buffers, serum, enzymes, cytokines, growth factors) should be clearly defined. Where the necessary tests take a long time, it may be permissible to process starting materials before the results of the tests are available, the risk of using a potentially failed material and its potential impact on other batches should be clearly understood and assessed under the principles of QRM. In such cases, release of a finished product is conditional on satisfactory results of these tests. The identification of all starting materials should be in compliance with the requirements appropriate to its stage of manufacture. For biological medicinal products further guidance can be found in Part I and Annex 8 and for biological active substances in Part II.
32. 起始物與原料在沿著供應鏈傳遞期間污染之風險，必須加以評估，特別是著重於 TSE。直接接觸製造設備或產品的原物料（例如，使用於培養基充填實驗的培養基與可能接觸產品之潤滑劑），也必須列入考慮。	32. The risk of contamination of starting and raw materials during their passage along the supply chain must be assessed, with particular emphasis on TSE. Materials that come into direct contact with manufacturing equipment or the product (such as media used in media fill experiments and lubricants that may contact the product) must also be taken into account.
33. 不論污染自何製造階段導入，其風險對於最終產品的後果是一樣的，因此，保護產品之管制策略的建立及對於溶液、緩衝劑與其他添加物的配製，應基於附則 1 中適當條項所包含的原則與指引。對於起始物與原料的品質與關於無菌製程所需要的管制，特別是對於不能最終滅菌的產品承擔了較大的重要性。當臨床試驗許可或上市許可規定可允許之負荷菌的類型與限量時，例如，在原料藥階段，該管制策略應提出維持負荷菌在所規定限度內的方法。	33. Given that the risks from the introduction of contamination and the consequences to the finished product is the same irrespective of the stage of manufacture, establishment of a control strategy to protect the product and the preparation of solutions, buffers and other additions should be based on the principles and guidance contained in the appropriate sections of Annex 1. The controls required for the quality of starting and raw materials and on the aseptic manufacturing process, assume greater importance particularly for products, in respect of which final sterilisation is not possible. Where a CTA or MA provides for an allowable type and level of bioburden, for example at active substance stage, the control strategy should address the means by which this is maintained within the specified limits.

34. 當起始物與原料應予滅菌時，可能時應使用熱處理法。當必要時，對於生物原料的去活化，也可使用其他適當方法（例如，輻射照射與過濾）。	34. Where sterilisation of starting and raw materials is required, it should be carried out where possible by heat. Where necessary, other appropriate methods may also be used for inactivation of biological materials (e.g. irradiation and filtration).
35. 減少採集活組織及活細胞作業相關之負荷菌，可能需要在早期製造階段中使用其他措施，例如，抗生素。這應該避免，但必要時，其使用應證明其合理性，且應在臨床試驗許可或在上市許可所界定的製程階段移除。	35. Reduction in bioburden associated with procurement of living tissues and cells may require the use of other measures such as antibiotics at early manufacturing stages. This should be avoided, but where it is necessary their use should be justified, they should be removed from the manufacturing process at the stage specified in the CTA or MA.
36. 用於生物藥品起始原料的人體組織與細胞，其捐贈、採集及測試應遵守國家法規要求。作為生物藥品起始原料之人體組織與細胞，應保持其從捐贈者至最終藥品批次之可追溯性。基於對製造之藥品的品質或安全會產生影響，製造廠與組織及細胞之供應商間，應就健康捐贈者資訊之移轉做出適當安排，該等資訊能於供應起始原料後取得。	36. The donation, procurement and testing of human tissues and cells used as starting materials for biological medicinal products should be in accordance with national law requirements.[17] Traceability for human tissues and cells used as starting materials for biological medicinal products should be maintained from the donor to the batch of a finished medicinal product. Appropriate arrangements should be made between the manufacturer and the supplier of tissues and cells regarding the transfer of health donor information that may become available after the supply of the starting material and which may have an impact on the quality or safety of the medicinal product manufactured therefrom.
(a) 其採集、捐贈與測試，在有些國家是受管制的。這樣的供應場所必須持有國家主管機關的適當核准，其應作為起始原料供應商管理的一部分加以確認之。	(a) Their procurement, donation and testing is regulated in some countries[18]. Such supply sites must hold appropriate approvals from the national competent authority(ies) which should be verified as part of starting material supplier management.
(b) 當該等人體細胞或組織是輸入時，必須符合品質與安全性之相等的國家標準。嚴重不良反應與嚴重不良事件及其可追溯性依國家法規通報。	(b) Where such human cells or tissues are imported, they must meet equivalent national standards of quality and safety[19]. The traceability and serious adverse reaction and serious adverse event notification requirements may be set out in national legislation[20].
(c) 可能有一些情況，將會在組織機構中進行作為生物藥品之起始原料使用的細胞與組織之處理。	(c) There may be some instances where processing of cells and tissues used as starting materials for biological medicinal products will be conducted at tissue establishments[21].

(d) 組織與細胞在裝運到藥品製造廠之前，是由組織機構中的權責人員（RP）放行，自此以後，適用正常的藥品起始原料管制。由組織機構所供給之所有組織/細胞的測試結果，應提供給藥品的製造廠，並須作為原料適當之隔離與儲存的決定。當必須在收到來自組織機構測試結果之前開始製造，倘若製造廠具備管制措施，以防止與已由組織機構中權責人員放行之組織與細胞的交叉污染，組織與細胞可以裝運到藥品製造廠。	(d) Tissue and cells are released by the Responsible Person (RP) in the tissue establishment before shipment to the medicinal product manufacturer, after which normal medicinal product starting material controls apply. The test results of all tissues / cells supplied by the tissue establishment should be available to the manufacturer of the medicinal product. Such information must be used to make appropriate material segregation and storage decisions. In cases where manufacturing must be initiated prior to receiving test results from the tissue establishment, tissue and cells may be shipped to the medicinal product manufacturer provided controls are in place to prevent cross-contamination with tissue and cells that have been released by the RP in the tissue establishment.
(e) 人體組織與細胞運輸到製造場所，必須由負責各方之間的書面協議加以管制。製造場所應有遵守規定之儲存與運輸條件的文件化證據。	(e) The transport of human tissues and cells to the manufacturing site must be controlled by a written agreement between the responsible parties. The manufacturing sites should have documentary evidence of adherence to the specified storage and transport conditions.
(f) 組織與細胞運輸到製造場所，必須由負責各方之間的書面協議加以管制。製造場所應有遵守規定之儲存與運輸條件的文件化證據。	(f) Continuation of traceability requirements started at tissue establishments through to the recipient(s), and vice versa, including materials in contact with the cells or tissues, should be maintained.
(g) 在各權責方（例如，製造廠、組織機構、發起者、上市許可持有者）之間應具備技術協議，其中界定包括權責人員與被授權人（AP）在內之各方的工作。	(g) A technical agreement should be in place between the responsible parties (e.g. manufacturers, tissue establishment, Sponsors, MA Holder) which defines the tasks of each party, including the RP and Authorised Person.
37. （…）不採用	37. (…)[22]
38. 當人體或動物細胞用於製造過程中作為餵養細胞時，對於來源尋求、測試、運輸與儲存等作業，應具備適當管制，包含符合國家要求對人體細胞之管制。	38. Where human or animal cells are used in the manufacturing process as feeder cells, appropriate controls over the sourcing, testing, transport and storage should be in place[23], including control of compliance with national requirements for human cells.
種批與細胞庫系統（SEED LOT AND CELL BANK SYSTEM）	

39. 為了防止重複的繼代培養或多代培養可能導致不需要的性質漂移，由微生物培養物、細胞培養物或在胚胎與動物的繁殖所獲得之生物原料藥及產品的生產，應以主病毒種批與工作病毒種批及/或主細胞庫與工作細胞庫系統為基礎。	39. In order to prevent the unwanted drift of properties which might ensue from repeated subcultures or multiple generations, the production of biological medicinal substances and products obtained by microbial culture, cell culture or propagation in embryos and animals should be based on a system of master and working virus seed lots and/or cell banks.
40. 種批或細胞庫、生物原料藥與最終產品之間的世代數目（倍增、繼代數目），應與臨床試驗許可或上市許可上的規格一致。	40. The number of generations (doublings, passages) between the seed lot or cell bank, the biological active substance and the finished product should be consistent with specifications in the CTA or MA.
41. 作為產品生命週期管理的一部分，種批與細胞庫，包括主世代與工作世代的建立在內，應在適當的 GMP 條件下執行。這應包括經適當管制的環境，以保護種批與細胞庫以及其處理的人員。在建立種批與細胞庫的期間，不得同時在相同區域或不得同時由同一組人處理其他活的或傳染性的物質（例如病毒、細胞株或細胞品系）。對於建立種批或細胞庫產生之前的所有階段，GMP 原則可能可以加以使用。對於建立主細胞庫之前（pre-master bank）的所有階段，應備有文件以支持可追溯性。在開發期間，所使用之組成物相關的所有問題，自最初來源尋求與基因開發對產品安全性（例如，生物來源的試劑）之潛在影響，應加以文件化。對於疫苗，適用藥典個論的規定。	41. As part of product lifecycle management, establishment of seed lots and cell banks, including master and working generations, should be performed under appropriate GMP conditions. This should include an appropriately controlled environment to protect the seed lot and the cell bank and the personnel handling it. During the establishment of the seed lot and cell bank, no other living or infectious material (e.g. virus, cell lines or cell strains) should be handled simultaneously in the same area or by the same persons. For all stages prior to the establishment of the master seed or cell bank generation, principles of GMP may be applied. For all pre-master bank stages, documentation should be available to support traceability. All issues related to components used during the development with potential impact on product safety (e.g. reagents of biological origin) from initial sourcing and genetic development should be documented. For vaccines the requirements of pharmacopoeial monographs will apply[24].
42. 在建立主細胞庫與工作細胞庫及主種批與工作種批之後，應遵循隔離與放行程序。這應該包括對污染物的充分特性描述與測試。其持續適用性應經由產品之後續生產批次的特性與品質之一致性予以進一步證實之。種批與細胞庫之安定性與復原（recovery）的證據應加以文件化，而且應以允許趨勢評估的方式保存紀錄。	42. Following the establishment of master and working cell banks and master and working seed lots, quarantine and release procedures should be followed. This should include adequate characterization and testing for contaminants. Their on-going suitability for use should be further demonstrated by the consistency of the characteristics and quality of the successive batches of product. Evidence of the stability and recovery of the seeds and banks should be documented and records should be kept in a manner permitting trend evaluation.

43. 種批與細胞庫應以使其污染或改變之風險減到最低的方式，予以儲存與使用（例如，儲存在密閉容器中之液態氮的氣相中）。確保遵循在相同區域或設備中儲存不同病毒種及/或細胞之防止混雜措施，並應考慮該原料的傳染本質，以防止交叉污染。	43. Seed lots and cell banks should be stored and used in such a way as to minimize the risks of contamination (e.g. stored in the vapour phase of liquid nitrogen in sealed containers) or alteration. Ensuring compliance with measures for the storage of different seeds and/or cells in the same area or equipment should prevent mix-up and take into account the infectious nature of the materials to prevent cross contamination.
44. （…）不採用	44. (…)[25]
45. 儲存容器應予密封、清楚地標示，並且保持在適當的溫度。應保存庫存品清單。儲存溫度應連續記錄，並且，如使用液態氮應監測其液位。偏離設定限值與所採取的矯正與預防行動，應加以記錄。	45. Storage containers should be sealed, clearly labelled and kept at an appropriate temperature. A stock inventory must be kept. The storage temperature should be recorded continuously and, where used, the liquid nitrogen level monitored. Deviation from set limits and corrective and preventive action taken should be recorded.
46. 將庫存分散並將其存放在不同的地點是必要的，以使全部損失的風險減到最低。在該等地點的管制應提供前段所述的保證。	46. It is desirable to split stocks and to store the split stocks at different locations so as to minimize the risks of total loss. The controls at such locations should provide the assurances outlined in the preceding paragraphs.
47. 對於庫存品的儲存與處理條件，應依相同的程序與參數予以管理。一旦容器從其種批/細胞庫管理系統中移出時，則該等容器應不得退回庫存。	47. The storage and handling conditions for stocks should be managed according to the same procedures and parameters. Once containers are removed from the seed lot / cell bank management system, the containers should not be returned to stock.
作業原則（OPERATING PRINCIPLES）	
48. 變更管理應定期考慮對最終產品品質、安全性與有效性的影響，包括所有變更（例如，對製程）所累積的影響在內。	48. Change management should, on a periodic basis, take into account the effects, including cumulative effects of changes (e.g. to the process) on the quality, safety and efficacy of the finished product.
49. 關鍵的操作（製程）參數，或影響產品品質之其他輸入參數需要加以識別、確效與文件化，且須顯示維持在要求範圍之內。	49. Critical operational (process) parameters, or other input parameters which affect product quality, need to be identified, validated, documented and be shown to be maintained within requirements.

50. 物品與物料進入生產區的管制策略，應基於品質風險管理原則。於無菌製程，對熱安定的物品與物料，進入潔淨區或潔淨/圍堵的區域時，最好應經由兩端開口之雙門高壓蒸氣滅菌器或乾熱滅菌器滅菌後進入。對熱不安定的物品與物料，應經由具有互鎖門的氣鎖室進入，使其在氣鎖室裡接受有效的表面滅菌程序。假如物品與物料的包裝層數是配合進入潔淨區之階段數目，並且在經由氣鎖室進入時，有適當的表面滅菌防範措施，則該物品與物料在其他地方預先滅菌，是可以接受的。	50. A control strategy for the entry of articles and materials into production areas should be based on QRM principles. For aseptic processes, heat stable articles and materials entering a clean area or clean/contained area should preferably do so through a double-ended autoclave or oven. Heat labile articles and materials should enter through an air lock with interlocked doors where they are subject to effective surface sanitisation procedures. Sterilisation of articles and materials elsewhere is acceptable provided that they are multiple wrappings, as appropriate to the number of stages of entry to the clean area, and enter through an airlock with the appropriate surface sanitisation precautions.
51. 培養基之促進生長性質應經證明適合其預定的用途。可行時，培養基應以原位滅菌，且氣體、培養基、酸或鹼溶液及抗發泡劑等例行添加到醱酵槽時，應盡可能使用線內滅菌過濾器。	51. The growth promoting properties of culture media should be demonstrated to be suitable for its intended use. If possible, media should be sterilized in situ. In-line sterilizing filters for routine addition of gases, media, acids or alkalis, anti-foaming agents etc. to fermenters should be used where possible.
52. 原料或培養物加入醱酵槽與其他桶槽以及取樣時，應在謹慎管制的條件下執行，以防止污染。當執行添加或取樣時，應注意確保該等桶槽正確連接。	52. Addition of materials or cultures to fermenters and other vessels and sampling should be carried out under carefully controlled conditions to prevent contamination. Care should be taken to ensure that vessels are correctly connected when addition or sampling takes place.
53. 某些生產過程（例如醱酵）必須連續監測，此等數據應涵蓋於批次紀錄中。採用連續培養方式進行生產時，應特別考慮源於此類型之生產方法所需的品質管制要求。	53. Continuous monitoring of some production processes (e.g. fermentation) may be necessary; such data should form part of the batch record. Where continuous culture is used, special consideration should be given to the quality control requirements arising from this type of production method.
54. 產品的離心及混合可能導致氣霧形成，因此圍堵該等作業以使交叉污染減到最低是必要的。	54. Centrifugation and blending of products can lead to aerosol formation and containment of such activities to minimise cross-contamination is necessary.

55. 意外的溢出，特別是活的有機體，必須快速而且安全地處理。對於各有機體或相關有機體群，應有經驗證的去污染措施。在涉及不同品系的單一菌種或非常相似的病毒時，除非有理由認為它們對所使用之去污劑的抗性可能顯著不同外，去污染程序可以用一個具代表性的品系進行確效。	55. Accidental spillages, especially of live organisms, must be dealt with quickly and safely. Qualified decontamination measures should be available for each organism or groups of related organisms. Where different strains of single bacteria species or very similar viruses are involved, the decontamination process may be validated with one representative strain, unless there is reason to believe that they may vary significantly in their resistance to the agent(s) involved.
56. 如有明顯污染時，諸如，經由溢出或氣霧，或者，如果涉及潛在有害有機體時，生產與管制用料，包括文件在內，必須充分地消毒，或須將該資訊經由其他方式轉出。	56. If obviously contaminated, such as by spills or aerosols, or if a potential hazardous organism is involved, production and control materials, including paperwork, must be adequately disinfected, or the information transferred out by other means.
57. 製造過程中，執行病毒之去活化或移除時，應採取措施以避免經處理之產品，被未經處理之產品再污染的風險。	57. In cases where a virus inactivation or removal process is performed during manufacture, measures should be taken to avoid the risk of recontamination of treated products by non-treated products.
58. 對於經由添加試劑所去活化的產品（例如，在疫苗製造過程中的微生物），其製程應確保活有機體的完全去活化。除了培養物與去活化劑的充分混合外，應考慮所有產品接觸表面與活培養物及去活化劑的接觸，並在需要時，移轉到第二個桶槽中。	58. For products that are inactivated by the addition of a reagent (e.g. micro-organisms in the course of vaccine manufacture) the process should ensure the complete inactivation of live organism. In addition to the thorough mixing of culture and inactivant, consideration should be given to contact of all product-contact surfaces exposed to live culture and, where required, the transfer to a second vessel.
59. 層析法使用了各種不同設備。當使用於時段切換製造與多種產品環境時，品質風險管理原則應用於設計關於層析裝置的基質、殼體與相關設備等的管制策略。在不同的操作階段應避免重複使用相同基質。層析管柱的允收標準、操作條件、再生方法、使用期限與滅菌或滅菌方法應予界定。	59. A wide variety of equipment is used for chromatography. QRM principles should be used to devise the control strategy on matrices, the housings and associated equipment when used in campaign manufacture and in multi-product environments. The re-use of the same matrix at different stages of processing is discouraged. Acceptance criteria, operating conditions, regeneration methods, life span and sanitization or sterilisation methods of columns should be defined.
60. 使用經輻射照射之設備與材料時，其進一步的指引應參考附則 12。	60. Where irradiated equipment and materials are used, Annex 12 should be consulted for further guidance.

61. 在最終產品或中間產品呈現特殊的風險時，應有系統確保充填後容器的完整性與密封，並有程序處理任何洩漏或溢出。充填與包裝作業需備有適當的程序，以維持產品在任何規定的條件範圍之內，例如，時間及/或溫度。	61. There should be a system to assure the integrity and closure of containers after filling where the final products or intermediates represent a special risk and procedures to deal with any leaks or spillages. Filling and packaging operations need to have procedures in place to maintain the product within any specified limits, e.g. time and/or temperature.
62. 處理含有活生物物質之小瓶的作業，必須以防止其他產品之污染或活生物物質流入工作環境或外部環境的方式予以執行之。該等有機體的存活力及其生物學上的分類應考慮作為此類風險管理的一部分。	62. Activities in handling vials containing live biological agents, must be performed in such a way to prevent the contamination of other products or egress of the live agents into the work environment or the external environment. The viability of such organisms and their biological classification should take into consideration as part of the management of such risks.
63. 在標籤的製作、印刷、儲存與應用上應當注意，包括在直接包裝與外包裝上對患者專一性之特定產品的任何特定內文。 在自體產品的情況，獨一的病人識別碼與「僅供自體使用」之陳述，應標示於外包裝上，或如無外包裝時則標示於直接包裝上。	63. Care should be taken in the preparation, printing, storage and application of labels, including any specific text for patient-specific product of the contents on the immediate and outer packaging. In the case of autologous products, the unique patient identifier and the statement “for autologous use only” should be indicated on the outer packaging or, where there is no outer packaging, on the immediate packaging.
64. 標籤與超低儲存溫度的相容性，應當在使用該等溫度時加以確認之。	64. The compatibility of labels with ultra-low storage temperatures, where such temperatures are used, should be verified.
65. 回收程序應考量當採集後獲知捐贈者（人類及/或動物的健康）資訊對產品品質有影響時之情形。	65. Where donor (human or animal health) information becomes available after procurement, which affects product quality, it should be taken into account in recall procedures.
品質管制（QUALITY CONTROL）	
66. 確保生物原料藥與藥品品質一致性之製程中管制較傳統產品者更為重要。製程中管制測試，應在生產的適當階段執行，以管制對最終產品品質之重要條件。	66. In-process controls have a greater importance in ensuring the consistency of the quality of biological active substance and medicinal products than for conventional products. In-process control testing should be performed at appropriate stages of production to control those conditions that are important for the quality of the finished product.
67. 在中間產品儲存時間可延長（數天、數週或更長）時，應於持續安定性計畫中，將中間產品使用最長儲存期間之批次所製成之最終產品納入考量。	67. Where intermediates can be stored for extended periods of time (days, weeks or longer), consideration should be given to the inclusion of finished product batches made from materials held for their maximum in-process periods in the on-going stability programme.

68. （…）不採用	68. (…) [26]
69. 對於細胞產品，無菌性試驗應以無抗生素之細胞或細胞庫的培養物執行，以提供無細菌與真菌污染的證據，並且，合適時，要能檢測苛養性有機體（fastidious organisms）。	69. For cellular products, sterility tests should be conducted on antibiotic-free cultures of cells or cell banks to provide evidence for absence of bacterial and fungal contamination and to be able to detection fastidious organisms where appropriate.
70. 就本附則之目的，短架儲期的生物藥品，意指於無菌性試驗結果於 14 天後提供或更短期間內不允許放行的藥品，該等藥品在完成所有最終產品品質管制檢驗（例如，無菌性試驗）之前需要批次核定，須具備適當的管制策略。該等管制需建立在加強產品與製程性能之瞭解上，並且考慮起始物與原料之管制與屬性。整個放行程序之正確與詳細的描述是必需的，包括涉及生產與分析數據之評估的不同人員之職責在內。必須具備品質保證系統有效性的持續評估，並包括以允許趨勢評估的方式保存其紀錄。 當最終產品檢驗報告由於其短架儲期而無法適時取得時，應考慮能獲得相等數據的替代方法（例如，快速微生物學方法），以允許批次核定。對於批次核定與放行的程序，可採兩個或多個階段執行：	70. For biological medicinal products with a short shelf life, which for the purposes of the annex is taken to mean a period that does not permit release when sterility testing results are provided after 14 days or less, and which need batch certification before completion of all end product quality control tests (e.g. sterility tests) a suitable control strategy must be in place. Such controls need to be built on enhanced understanding of product and process performance and take into account the controls and attributes of starting and raw materials. The exact and detailed description of the entire release procedure, including the responsibilities of the different personnel involved in assessment of production and analytical data is essential. A continuous assessment of the effectiveness of the quality assurance system must be in place including records kept in a manner which permit trend evaluation. Where end product tests are not available due to their short shelf life, alternative methods of obtaining equivalent data to permit batch certification should be considered (e.g. rapid microbiological methods). The procedure for batch certification and release may be carried out in two or more stages:
(a) 經由指定人員評估批次操作紀錄、涵蓋生產條件之環境監測結果（可取得時）、正常程序的所有偏差與可以獲得的分析結果，以用於供權責人員審查以準備初始核定。	(a) Assessment by designated person(s) of batch processing records, results from environmental monitoring (where available) which should cover production conditions, all deviations from normal procedures and the available analytical results for review in preparation for the initial certification by the Responsible Person.

(b) 由被授權人評估最後檢驗與其他可獲得的資訊，以供最終產品之核定。得到偏離規格檢驗結果時，應備有程序，以描述所要採取的措施（包括與臨床工作人員的聯繫在內）。該等事件應進行充分調查，並且採取相關防止重複發生的矯正與預防行動，予以文件化。	(b) Assessment of the final analytical tests and other information available for final certification by the Authorised Person. A procedure should be in place to describe the measures to be taken (including liaison with clinical staff) where out of specification test results are obtained. Such events should be fully investigated and the relevant corrective and preventive actions taken to prevent recurrence documented.
B 部：對特定產品類型的專用指引 （PART B: SPECIFIC GUIDANCE ON SELECTED PRODUCT TYPES）	
B1. 動物來源的產品（ANIMAL SOURCED PRODUCTS[27]）	
本指引適用於動物性原料，包括來自諸如屠宰場等機構的原料。由於供應鏈可能廣泛且複雜，所以，基於品質風險管理原則之管制需要加以應用，也參見適當藥典個論的要求，包括需要在所界定之階段的特定測試在內。應具備證明供應鏈可追溯性[28]與參與者在供應鏈中之明確角色的文件，典型上，包括詳盡且最新之流程圖（process map）在內。	This guidance applies to animal materials which includes materials from establishments such as abattoirs. Since the supply chains can be extensive and complex, controls based on QRM principles need to be applied, see also requirements of appropriate pharmacopoeial monographs, including the need for specific tests at defined stages. Documentation to demonstrate the supply chain traceability[28] and clear roles of participants in the supply chain, typically including a sufficiently detailed and current process map, should be in place.
[28] 詳第一部第 5 章	[28] See PIC/S GMP Chapter 5.
1. 對於人類健康須關注之動物疾病應具備監測計畫。當包括世界動物衛生組織等組織匯集其風險評估與風險降低因素時，應考慮來自值得信賴之國家疾病流行率來源的報告。這應藉由國家與地方層級關於衛生監測與管制計畫的資訊加以補充，地方層級之資訊要包括選取該等動物的來源處所（例如，養殖場或飼養場）與在運輸到屠宰場期間的管制措施。	1. Monitoring programmes should be in place for animal disease that are of concern to human health. Organisations should take into account reports from trustworthy sources on national disease prevalence when compiling their assessment of risk and mitigation factors. Such organisations include the World Organisation for Animal Health (OIE, Office International des Epizooties[29]). This should be supplemented by information on health monitoring and control programme(s) at national and local levels, the latter to include the sources (e.g. farm or feedlot) from which the animals are drawn and the control measures in place during transport to the abattoirs.
2. 當來源動物組織是來自屠宰場時，該等屠宰場應顯示依嚴格的標準運作。應考慮來自國家主管機關的報告，確認其符合食品安全與品質及動植物衛生法規。	2. Where abattoirs are used to source animal tissues, they should be shown to operate to stringent standards. Account should be taken of reports from national regulatory organisations[30] which verify compliance with the requirements of food safety and quality, veterinary and plant health legislation.

3.	在如屠宰場等之機構，起始物或原料的管制措施應包括品質管理系統的適當要素，以確保操作人員訓練、原料可追溯性、管制與一致性的滿意水準。這些措施可取自 GMP 以外的來源，但應顯示提供同等的管制水準。	3.	Control measures for starting or raw materials at establishments such as abattoirs should include appropriate elements of a Quality Management System to assure a satisfactory level of operator training, materials traceability, control and consistency. These measures may be drawn from sources outside PIC/S GMP but should be shown to provide equivalent levels of control.
4.	在其通過製造與供應鏈的進程中，應具備起始物或原料之管制措施，防止可能影響原料品質之因素的介入，或至少提供該等活動的證據。這包括在初始收集、部分純化與最終純化、儲存場所、轉運站、集貨商與仲介商之場所間的原料移動。可追溯性系統與任何違反紀錄、調查及應採取的行動均應記錄該等安排的細節。	4.	Control measures for starting or raw materials should be in place which prevent interventions which may affect the quality of materials, or which at least provides evidence of such activities, during their progression through the manufacturing and supply chain. This includes the movement of material between sites of initial collection, partial and final purification(s), storage sites, hubs, consolidators and brokers. Details of such arrangements should be recorded within the traceability system and any breaches recorded, investigated and actions taken.
5.	應執行起始物或原料供應商的定期稽查，以確認其在不同製造階段遵從原料的管制。依據問題決定調查的程度，並留有完整文件。也應具備確保採取有效之矯正與預防行動的系統。	5.	Regular audits of the starting or raw material supplier should be undertaken which verify compliance with controls for materials at the different stages of manufacture. Issues must be investigated to a depth appropriate to their significance, for which full documentation should be available. Systems should also be in place to ensure that effective corrective and preventive actions are taken.
B2. 過敏原產品（ALLERGEN PRODUCTS）			
	原料可以經由從天然來源萃取予以製造，或經由基因重組 DNA 技術予以製造。		Materials may be manufactured by extraction from natural sources or manufactured by recombinant DNA technology.
1.	來源原料應以足夠的細節予以描述，以確保在其供應上的一致性，例如：俗名與學名、種源、本質、污染物限量及收集方法。從動物所衍生的原料應該來自健康的來源。對於使用於過敏原之萃取的群落（例如蟎、動物）應具備適當的生物安全性管制。過敏原產品應儲存在所界定的條件下，以使品質惡化減到最低。	1.	Source materials should be described in sufficient detail to ensure consistency in their supply, e.g. common and scientific name, origin, nature, contaminant limits, method of collection. Those derived from animals should be from healthy sources. Appropriate biosecurity controls should be in place for colonies (e.g. mites, animals) used for the extraction of allergens. Allergen products should be stored under defined conditions to minimise deterioration.
2.	生產步驟，包括前處理、萃取、過濾、透析、濃縮或冷凍乾燥步驟在內，應詳細描述並經確效。	2.	The production process steps including pre-treatment, extraction, filtration, dialysis, concentration or freeze-drying steps should be described in detail and validated.

3. 對於製造經修飾之過敏原萃取物（例如類過敏原、接合物）的修飾製程應加以描述。在製造過程中的中間產物應加以識別並且進行管制。	3. The modification processes to manufacture modified allergen extracts (e.g. allergoids, conjugates) should be described. Intermediates in the manufacturing process should be identified and controlled.
4. 過敏原萃取混合物應以來自單一來源原料的個別萃取物製備之。每一個別萃取物應視為一個原料藥。	4. Allergen extract mixtures should be prepared from individual extracts from single source materials. Each individual extract should be considered as one active substance.
B3. 動物免疫血清產品（ANIMAL IMMUNOSERA PRODUCTS）	
1. 關於生物來源之抗原的管制應特別小心運用，以確保其品質、一致性且無外來病源。用於免疫接種來源動物之原料（例如，抗原、半抗原載體、佐劑、安定劑）的製備，在免疫接種之前該原料之儲存應依照文件化的程序。	1. Particular care should be exercised on the control of antigens of biological origin to assure their quality, consistency and freedom from adventitious agents. The preparation of materials used to immunise the source animals (e.g. antigens, hapten carriers, adjuvants, stabilising agents), the storage of such material immediately prior to immunisation should be in accordance with documented procedures.
2. 免疫接種、試血與採血時程表，應符合臨床試驗許可或上市許可所核准者。	2. The immunisation, test bleed and harvest bleed schedules should conform to those approved in the CTA or MA.
3. 對於抗體次片段（例如，Fab 或 $F(ab')_2$）之製備的製造條件與任何進一步修飾，必須依照經確效且核准的參數。當該等酵素是由幾個組成物所組成時，應確保其一致性。	3. The manufacturing conditions for the preparation of antibody sub-fragments (e.g. Fab or $F(ab')_2$) and any further modifications must be in accordance with validated and approved parameters. Where such enzymes are made up of several components, their consistency should be assured.
B4. 疫苗（VACCINES）	
1. 當使用雞蛋時，應確保用於生產雞蛋的所有來源雞群之健康狀況（是否無特定的病原體或是否為健康的雞群）。	1. Where eggs are used, the health status of all source flocks used in the production of eggs (whether specified pathogen free or healthy flocks) should be assured.
2. 對於儲存中間產品所使用之容器的完整性與保持時間必須加以確效。	2. The integrity of containers used to store intermediate products and the hold times must be validated.
3. 含有經去活化之產品的桶槽，不得在含有活生物物質的區域中開啟或抽樣。	3. Vessels containing inactivated products should not be opened or sampled in areas containing live biological agents.
4. 在中間產品或最終產品之配方調製的期間中，活性成分、佐劑與賦形劑之添加順序，必須遵循規格。	4. The sequence of addition of active ingredients, adjuvants and excipients during the formulation of an intermediate or final product must be in compliance with specifications.

5. 在製造或測試中，當要使用較高生物安全性等級的有機體時（例如，大流行疫苗株），必須具備適當的圍堵安排。該等安排應獲得適當國家機關的核准，且備有該核准文件以供確認。	5. Where organisms with a higher biological safety level (e.g. pandemic vaccine strains) are to be used in manufacture or testing, appropriate containment arrangements must be in place. The approval of such arrangements should be obtained from the appropriate national authority(ies) and the approval documents be available for verification.
B5. 基因重組產品（RECOMBINANT PRODUCTS）	
1. 在細胞增長、蛋白質表現與純化之期間的製程條件，必須維持在經確效的參數範圍內，以確保產品的一致性，且雜質在製程能力能減低至可接受水準之界定範圍內。視生產所使用之細胞類型，可能須要採取加強的措施以確保其無病毒。對於涉及多次收集的生產，其連續培養的期間應在所界定的範圍內。	1. Process condition during cell growth, protein expression and purification must be maintained within validated parameters to assure a consistent product with a defined range of impurities that is within the capability of the process to reduce to acceptable levels. The type of cell used in production may require increased measures to be taken to assure freedom from viruses. For production involving multiple harvest, the period of continuous cultivation should be within specified limits.
2. 對於移除不需要之宿主細胞蛋白質、核酸、碳水化合物、病毒與其他雜質的純化過程，應在所界定之經確效的範圍內。	2. The purification processes to remove unwanted host cell proteins, nucleic acids, carbohydrates, viruses and other impurities should be within defined validated limits.
B6. 單株抗體產品（MONOCLONAL ANTIBODY PRODUCTS）	
1. 單株抗體可從鼠融合瘤、人類融合瘤或經由基因重組 DNA 技術製造之。應具備適合使用於建立融合瘤/細胞株之不同來源細胞（倘有使用，包含餵養細胞在內）與原料的管制措施，以確保產品的安全性與品質。應確認這些都是在經核准的範圍之內。應特別重視無病毒。應注意到源自相同製造技術平台所產生之產品的數據，可能被接受用以證明其適用性。	1. Monoclonal antibodies may be manufactured from murine hybridomas, human hybridomas or by recombinant DNA technology. Control measures appropriate to the different source cells (including feeder cells if used) and materials used to establish the hybridoma / cell line should be in place to assure the safety and quality of the product. It should be verified that these are within approved limits. Freedom from viruses should be given particular emphasis. It should be noted that data originating from products generated by the same manufacturing technology platform may be acceptable to demonstrate suitability.
2. 生產週期之結束與提前終止所要監測的標準，應確認是在經核准的範圍內。	2. Criteria to be monitored at the end of a production cycle and for early termination of production cycles should be verified that these are within approved limits.
3. 抗體次片段（例如，Fab、$F(ab')_2$、scFv）製備的製造條件與任何進一步修飾（例如，放射性標識、接合、化學連結）必須依照經確效的參數。	3. The manufacturing conditions for the preparation of antibody sub-fragment (e.g. Fab, $F(ab')_2$, scFv) and any further modifications (e.g. radio labelling, conjugation, chemical linking) must be in accordance with validated parameters.

B7. 基因轉殖動物產品（TRANSGENIC ANIMAL PRODUCTS）	
來自基因轉殖來源之起始原料的一致性，通常可能比非基因轉殖生物技術學來源的原料情況更有問題。因此，在所有方面，對於證明產品批與批的一致性，有越來越多的要求。	Consistency of starting material from a transgenic source is likely to be more problematic than is normally the case for non-transgenic biotechnology sources. Consequently, there is an increased requirement to demonstrate batch-to-batch consistency of product in all respects.
1. 可用於生產生物藥品的品種範圍，可能表現於體液（例如，乳汁）以供收集與純化。動物應清楚且獨一地識別，而且，應當具備在主要標記喪失時的備案安排。	1. A range of species may be used to produce biological medicinal products, which may be expressed into body fluids (e.g. milk) for collection and purification. Animals should be clearly and uniquely identified and backup arrangements should be put in place in the event of loss of the primary marker.
2. 動物之飼養設施與照護安排應予界定，以使動物暴露於致病性病媒與人畜共通傳染病媒減到最少。應建立適當的措施，以保護外部環境。應建立健康監測計畫，並將所有結果文件化，任何事件都應加以調查，且其對動物之後續的影響與其對先前批次產品的影響應加以確定。應注意確保任何用於治療動物之產品不會污染該基因轉殖產品。	2. The arrangements for housing and care of the animals should be defined such that they minimise the exposure of the animals to pathogenic and zoonotic agents. Appropriate measures to protect the external environment should be established. A health-monitoring programme should be established and all results documented, any incident should be investigated and its impact on the continuation of the animal and on previous batches of product should be determined. Care should be taken to ensure that any therapeutic products used to treat the animals do not contaminate the product.
3. 從創始動物到生產動物之血緣系統必須加以文件化。因為一個基因轉殖株將會從一個單一的基因創始動物所衍生，因此，不得將來自不同基因轉殖株的原料混合。	3. The genealogy of the founder animals through to production animals must be documented. Since a transgenic line will be derived from a single genetic founder animal, materials from different transgenic lines should not be mixed.
4. 收集產品之條件應符合臨床試驗許可或上市許可條件。收集時程表與動物除役之條件，應依照經核准的程序與允收標準予以執行之。	4. The conditions under which the product is harvested should be in accordance with CTA or MA conditions. The harvest schedule and conditions under which animals may be removed from production should be performed according to approved procedures and acceptance limits.
B8. 基因轉殖植物產品（TRANSGENIC PLANT PRODUCTS）	
來自基因轉殖來源之起始原料的一致性，通常可能比非基因轉殖生物技術學來源的原料情況更有問題。因此，在所有方面，對於證明產品批與批的一致性，有越來越多的要求。	Consistency of starting material from a transgenic source is likely to be more problematic than is normally the case for non-transgenic biotechnology sources. Consequently, there is an increased requirement to demonstrate batch-to-batch consistency of product in all respects.

1. 可能需要追加措施(遠超過在 A 部所給予的措施)，以防止主基因轉殖庫與工作基因轉殖庫，被外來植物材料與相關的外來病原所污染。在所界定之世代數目內基因的穩定性，應加以監測。	1. Additional measures, over and above those given in Part A, may be required to prevent contamination of master and working transgenic banks by extraneous plant materials and relevant adventitious agents. The stability of the gene within defined generation numbers should be monitored.
2. 植物應清楚且獨一地識別，每次收成時，其關鍵植物特徵（包括健康狀況在內）的表現，應在整個培育期間依界定時間之間隔加以確認，以確保每次收成量之一致性。	2. Plants should be clearly and uniquely identified, the presence of key plant features, including health status, across the crop should be verified at defined intervals through the cultivation period to assure consistency of yield between crops.
3. 可能時，為保護作物的每次收成，其安全性安排應加以界定，以使暴露於微生物物質之污染及與非相關植物之交叉污染降至最低。應具備措施以避免例如殺蟲劑與肥料等物質污染產品。應建立監測計畫，並且將所有結果予以文件化，任何事件都應進行調查，且其對生產計畫中作物之持續收成的影響亦應加以確定。	3. Security arrangements for the protection of crops should be defined, wherever possible, such that they minimise the exposure to contamination by microbiological agents and cross-contamination with non-related plants. Measures should be in place to prevent materials such as pesticides and fertilisers from contaminating the product. A monitoring programme should be established and all results documented, any incident should be investigated and its impact on the continuation of the crop in the production programme should be determined.
4. 植物可以從生產中移出的條件應加以界定。對於可能干擾純化過程的物質（例如，宿主蛋白）應設定其允收標準。應確認該等結果是在經核准的範圍之內。	4. Conditions under which plants may be removed from production should be defined. Acceptance limits should be set for materials (e.g. host proteins) that may interfere with the purification process. It should be verified that the results are within approved limits.
5. 從種植、培育到收成期間及收成物之暫存，可能影響重組蛋白品質屬性及產量之環境條件（溫度、降雨），應加以文件化。擬定該標準時，可參照例如「Guideline on Good Agricultural and Collection Practice for Starting Materials of Herbal origin[31]」文件的原則。	5. Environmental conditions (temperature, rain), which may affect the quality attributes and yield of the recombinant protein from time of planting, through cultivation to harvest and interim storage of harvested materials should be documented. The principles in documents such as 'Guideline on Good Agricultural and Collection Practice for Starting Materials of Herbal Origin'[31] should be taken into account when drawing up such criteria.
[31]EMA, WHO 或同等標準	[31]EMA, WHO or equivalent
術語彙編（GLOSSARY）	
見附則 2A	See Annex 2A

1	In the EEA, this is Directive 2002/98/EC and its Commission Directives.
2	In the EEA, this is Directive 2009/41/EC on contained use of genetically modified micro-organisms.
5	In the EEA: HMPC guideline on Good Agricultural and Collection Practice - EMEA/HMPC/246816/2005 may be applied to growing, harvesting and initial processing in open fields.
7	In the EEA, human tissues and cells must comply with Directive 2004/23/EC and implementing Directives at these stages.
8	In the EEA, these are Directive 2004/23/EC and Directive 2006/17/EC.
9	In the EEA, this is the Commission Directive 2006/86/EC.
10	In the EEA, this is Directive 2006/86/EC.
14	In the EEA, this is Directive 2010/63/EC.
15	In the EEA, see Article 15 of Regulation 1394/ 2007.
16	In the EEA, these are Directives 2002/98/EC and 2005/61/EC.
17	In the EEA, this is Directive 2004/23/EC or for blood-derived cells, compliance with Directive 2002/98 regarding donation, procurement and testing.
18	In the EEA, this is Directive 2004/23/EC and its Commission directives.
19	In the EEA, they must be equivalent to those laid down in Directive 2004/23/EC.
20	In the EEA, this is Directive 2006/86/EC.
21	In the EEA, such processing steps, are under the scope of 2004/23/EC and the Responsible Person (RP).
22	This line has been intentionally left blank to harmonise with the formatting structure of the EU GMP Guide.
23	In the EEA, this includes compliance with Directive 2004/23 EC for human cells.
24	In the EEA, this is Ph Eur monograph 2005;153 “Vaccines for human use”.
25	This line has been intentionally left blank to harmonise with the formatting structure of the EU GMP Guide.
26	This line has been intentionally left blank to harmonise with the formatting structure of the EU GMP Guide.
27	In the EEA, see also PhEur monograph requirements, 0333
29	http://www.oie.int/eng/en_index.htm
30	In the EEA, this is the Food and Veterinary Office .

附則 3　放射性藥品的製造（MANUFACTURE OF RADIOPHARMACEUTICALS）

原則（PRINCIPLE）	
放射性藥品之製造應依照藥品GMP第一部及第二部所定原則執行。本附則特別針對放射性藥品特定的實務進行論述。	The manufacture of radiopharmaceuticals should be undertaken in accordance with the principles of Good Manufacturing Practice for Medicinal Products Part I and II. This annex specifically addresses some of the practices, which may be specific for radiopharmaceuticals.
註 i. 本指引未涵蓋在放射性藥品藥局 (醫院或特定藥局) 使用具有上市許可或國家執照之發生器及套組（Generators and Kits）製備放射性藥品。但國家有要求者，應予納入。	Note i. Preparation of radiopharmaceuticals in radiopharmacies (hospitals or certain pharmacies), using Generators and Kits with a marketing authorisation or a national licence, is not covered by this guideline, unless covered by national requirement.
註 ii. 依輻射防護法規，應確保任何醫療暴露皆在專門執業人員之臨床責任下執行。在執行診斷及治療之核子醫學業務時，應聘有一位醫學物理學專家。	Note ii. According to radiation protection regulations it should be ensured that any medical exposure is under the clinical responsibility of a practitioner. In diagnostic and therapeutic nuclear medicine practices a medical physics expert should be available.
註 iii. 本附則亦適用於臨床試驗使用之放射性藥品。	Note iii. This annex is also applicable to radiopharmaceuticals used in clinical trials.
註 iv. 放射性藥品的運送受國際原子能協會 (International Atomic Energy Association ，IAEA)及輻射防護要求之管制。	Note iv. Transport of radiopharmaceuticals is regulated by the International Atomic Energy Association (IAEA) and radiation protection requirements.
註 v. 除本附則中所描述之方法外，尚有其他能達到品質保證之可接受的方法，該等方法應經確效，並提供至少等同於本附則所訂之品質保證水準。	Note v. It is recognised that there are acceptable methods, other than those described in this annex, which are capable of achieving the principles of Quality Assurance. Other methods should be validated and provide a level of Quality Assurance at least equivalent to those set out in this annex.
前言（INTRODUCTION）	

1. 放射性藥品之製造與處理具有潛在的危害性。危險的程度特別取決於輻射的類型、輻射能及放射性同位素之半衰期。對於交叉污染的防止、放射性核種污染物的滯留，以及廢棄物的處置應特別注意。	1. The manufacturing and handling of radiopharmaceuticals is potentially hazardous. The level of risk depends in particular upon the types of radiation, the energy of radiation and the half-lives of radioactive isotopes. Particular attention must be paid to the prevention of cross-contamination, to the retention of radionuclide contaminants, and to waste disposal.
2. 由於放射性核種之架儲期短，故有些放射性藥品可能在其所有品管試驗完成前先予放行。於此情形下，整體放行程序之準確及詳細的描述是必要的，包含參與人員的責任及與品質保證系統之有效性的持續評估在內。	2. Due to short shelf-life of their radionuclides, some radiopharmaceuticals may be released before completion of all quality control tests. In this case, the exact and detailed description of the whole release procedure including the responsibilities of the involved personnel and the continuous assessment of the effectiveness of the quality assurance system is essential.
3. 本指引可適用於由工業製造廠、核醫中心/機構（Nuclear Centres/ Institutes）與正子斷層造影中心(positron emission tomography，PET Centres）使用於下列產品類型之生產及品質管制的製造程序：	3. This guideline is applicable to manufacturing procedures employed by industrial manufacturers, Nuclear Centres/Institutes and PET Centres for the production and quality control of the following types of products:
➢ 放射性藥品	➢ Radiopharmaceuticals
➢ 正子放射性藥品	➢ Positron Emitting (PET) Radiopharmaceuticals
➢ 生產放射性藥品之放射性前驅物	➢ Radioactive Precursors for radiopharmaceutical production
➢ 放射性核種發生器	➢ Radionuclide Generators

製造類型	**非 GMP***	**GMP第2部及第1部（漸增）包含相關附則在內**			
1. 放射性藥品 2. 正子放射性藥品 3.放射性藥品前驅物	**反應器/迴旋加速器生產**	**化學合成**	**純化步驟**	**操作，配方設計及調配**	**無菌製備或最終滅菌**
放射性核種發生器	**反應器/迴旋加速器生產**	**操作過程**			

Type of manufacture	Non - GMP *	GMP part II & I (Increasing) including relevant annexes			
Radiopharmaceuticals PET Radiopharmaceuticals Radioactive Precursors	**Reactor/Cyclotron Production**	**Chemical synthesis**	**Purification steps**	**Processing, formulation and dispensing**	**Aseptic or final sterilization**
Radionuclide Generators	**Reactor/Cyclotron Production**	**Processing**			

* 從迴旋加速器到合成裝置之標的物及傳送系統可認定為原料藥製造的第一步。	* Target and transfer system from cyclotron to synthesis rig may be considered as the first step of active substance manufacture.
4. 最終放射性藥品之製造廠應描述原料藥及最終藥品之製造步驟，並判斷該特定的製程/製造步驟所適用之 GMP 要求 (第 1 部或第 2 部)。	4. The manufacturer of the final radiopharmaceutical should describe and justify the steps for manufacture of the active substance and the final medicinal product and which GMP (part I or II) applies for the specific process/manufacturing steps.
5. 放射性藥品之製備包含遵守輻射防護法規。	5. Preparation of radiopharmaceuticals involves adherence to regulations on radiation protection.
6. 以注射投用的放射性藥品應符合注射劑之無菌性要求，而且相關時，應該遵守 PIC/S GMP 指引附則 1 所訂無菌藥品製造之無菌操作條件。	6. Radiopharmaceuticals to be administered parenterally should comply with sterility requirements for parenterals and, where relevant, aseptic working conditions for the manufacture of sterile medicinal products, which are covered in PIC/S GMP Guide, Annex 1.
7. 常用之放射性藥品的規格及品質管制測試程序規定在相關藥典或上市許可中。	7. Specifications and quality control testing procedures for the most commonly used radiopharmaceuticals are specified in the European (or other relevant) Pharmacopoeia or in the marketing authorisation.
臨床試驗（*Clinical Trials*）	
8. 預定在臨床試驗上用為研究用藥品之放射性藥品另應依照 PIC/S GMP 指引附則 13（研究用藥品的製造）所訂原則生產。	8. Radiopharmaceuticals intended for use in clinical trials as investigational medicinal products should in addition be produced in accordance with the principles in PIC/S GMP Guide, Annex 13.
品質保證（QUALITY ASSURANCE）	
9. 因為放射性藥品之特定特性、低容量而且在有些情形需要在完成測試前就投用該產品，所以，在放射性藥品的製造上，品質保證更加重要。	9. Quality assurance is of even greater importance in the manufacture of radiopharmaceuticals because of their particular characteristics, low volumes and

	in some circumstances the need to administer the product before testing is complete.
10. 如同所有藥品，本產品必須妥善保護以避免污染及交叉污染。然而，環境與操作者亦須防護輻射照射。這意指有效之品質保證系統的角色極具重要性。	10. As with all pharmaceuticals, the products must be well protected against contamination and cross-contamination. However, the environment and the operators must also be protected against radiation. This means that the role of an effective quality assurance system is of the utmost importance.
11. 精確地記錄監測廠房設施及製程所產生之數據，並作為放行過程的一部分予以評估，是重要的。	11. It is important that the data generated by the monitoring of premises and processes are rigorously recorded and evaluated as part of the release process.
12. 驗證及確效之原則應適用於放射性藥品的製造，驗證/確效之程度應使用風險管理方法決定，該方法之重點集中於結合優良製造規範與輻射防護。	12. The principles of qualification and validation should be applied to the manufacturing of radiopharmaceuticals and a risk management approach should be used to determine the extent of qualification/validation, focusing on a combination of Good Manufacturing Practice and Radiation Protection.
組織與人事（PERSONNEL）	
13. 所有製造作業皆應在額外配備具輻射防護能力之人員的負責下執行。參與放射性藥品之生產、分析管制及放行的人員，應經放射性藥品之品質管理體系的特定方面之適當訓練。被授權人員應具有產品放行的全部責任。	13. All manufacturing operations should be carried out under the responsibility of personnel with additional competence in radiation protection. Personnel involved in production, analytical control and release of radiopharmaceuticals should be appropriately trained in radiopharmaceutical specific aspects of the quality management system. The Authorised Person should have the overall responsibility for release of the products.
14. 放射性產品製造區域內的所有人員(包括與清潔及維護保養有關的人員)應接受配合此類產品之額外訓練。	14. All personnel (including those concerned with cleaning and maintenance) employed in areas where radioactive products are manufactured should receive additional training adapted to this class of products.

15. 生產設施/設備與研究機構共用者，研究人員應受過 GMP 法規的適當訓練，且 QA 的職責必須包括研究活動之檢討及核准，以確保該活動不對放射性藥品之製造引起任何危害。	15. Where production facilities are shared with research institutions, the research personnel must be adequately trained in GMP regulations and the QA function must review and approve the research activities to ensure that they do not pose any hazard to the manufacturing of radiopharmaceuticals.
廠房設施及設備（PREMISES AND EQUIPMENT）	
概述（General）	
16. 放射性產品應在受管制 (環境的及放射性) 的區域中製造。所有製造步驟應在專用於放射性藥品之自足圍堵的設施/設備中執行。	16. Radioactive products should be manufactured in controlled (environmental and radioactive) areas. All manufacturing steps should take place in self-contained facilities dedicated to radiopharmaceuticals.
17. 應建立並採取措施，以防止來自人員、原物料及放射性核種等之交叉污染。每當合適時，應使用密閉或圍堵的設備。使用開放設備，或開啟設備時，應採取防範措施，以將污染風險減到最低。風險評價應證明建議之環境潔淨度水準適合於擬製造的產品類型。	17. Measures should be established and implemented to prevent cross-contamination from personnel, materials, radionuclides etc. Closed or contained equipment should be used whenever appropriate. Where open equipment is used, or equipment is opened, precautions should be taken to minimize the risk of contamination. The risk assessment should demonstrate that the environmental cleanliness level proposed is suitable for the type of product being manufactured.
18. 進入製造區應經由更衣區，且應限於被授權的人員。	18. Access to the manufacturing areas should be via a gowning area and should be restricted to authorised personnel.
19. 關於在性能驗證期間中所建立之放射活性、微粒及微生物學上之品質，工作站及其環境應予監測。	19. Workstations and their environment should be monitored with respect to radioactivity, particulate and microbiological quality as established during performance qualification (PQ).

20. 預防性維護保養、校正及驗證計畫應予運作，以確保使用於放射性藥品之製造的所有設施與設備皆合適且經過驗證。這些活動應由有勝任能力之人員執行，且其記錄與日誌應予保存。	20. Preventive maintenance, calibration and qualification programmes should be operated to ensure that all facilities and equipment used in the manufacture of radiopharmaceutical are suitable and qualified. These activities should be carried out by competent personnel and records and logs should be maintained.
21. 應採取防範措施，以避免設施內之放射性污染。應備有適當的管制，以檢測任何放射性污染。這可直接透過輻射偵測儀的使用或間接透過例行的擦拭作業。	21. Precautions should be taken to avoid radioactive contamination within the facility. Appropriate controls should be in place to detect any radioactive contamination, either directly through the use of radiation detectors or indirectly through a swabbing routine.
22. 設備應經設計建造，使其與產品接觸之表面不具反應性、加成性或吸附性以避免改變放射性藥品之品質。	22. Equipment should be constructed so that surfaces that come into contact with the product are not reactive, additive or absorptive so as to alter the quality of the radiopharmaceutical.
23. 如無正當理由，應避免將從處理放射性產品之區域排出的空氣再循環。排風口應經設計，以將放射性微粒及氣體所致之環境污染減到最低；且應採取適當的措施，以防護管制區域受到微粒及微生物的污染。	23. Re-circulation of air extracted from area where radioactive products are handled should be avoided unless justified. Air outlets should be designed to minimize environmental contamination by radioactive particles and gases and appropriate measures should be taken to protect the controlled areas from particulate and microbial contamination.
24. 為圍堵放射性微粒，產品暴露之區域的空氣壓力可能有必要比其周圍區域的壓力為低。不過，仍然需要防護產品受到環境污染，例如可利用屏障技術或氣鎖室當成壓力沈槽（pressure sinks）來達成。	24. In order to contain radioactive particles, it may be necessary for the air pressure to be lower where products are exposed, compared with the surrounding areas. However, it is still necessary to protect the product from environmental contamination. This may be achieved by, for example, using barrier technology or airlocks, acting as pressure sinks.
無菌生產（Sterile production）	

25. 無菌放射性藥品可區分為以無菌製備的產品及以最終滅菌製造的產品。廠房/設施/設備應保持於執行中之作業類型的適當環境潔淨度水準。為無菌產品的製造，在產品或容器可能暴露於環境之作業區，其潔淨度應符合 PIC/S GMP 指引附則 1 所描述的要求。	25. Sterile radiopharmaceuticals may be divided into those, which are manufactured aseptically, and those, which are terminally sterilised. The facility should maintain the appropriate level of environmental cleanliness for the type of operation being performed. For manufacture of sterile products the working zone where products or containers may be exposed to the environment, the cleanliness requirements should comply with the requirements described in the PIC/S GMP Guide, Annex 1.
26. 對放射性藥品的製造，可應用風險評價，以決定其適當之壓差、氣流方向及空氣品質。	26. For manufacture of radiopharmaceuticals a risk assessment may be applied to determine the appropriate pressure differences, air flow direction and air quality.
27. 如使用密閉及自動化系統(化學合成、純化、線上無菌過濾)，C 級環境【通常是「鉛室/鉛櫃」(Hot-cell)】將是適當的。「鉛室/鉛櫃」應符合高度的空氣潔淨度，且當密閉時，應供應經過濾之空氣。無菌作業必須在 A 級區中執行。	27. In case of use of closed and automated systems (chemical synthesis, purification, on-line sterile filtration) a grade C environment (usually “Hot-cell”) will be suitable. Hot-cells should meet a high degree of air cleanliness, with filtered feed air, when closed. Aseptic activities must be carried out in a grade A area.
28. 製造開始前，經滅菌之設備及消耗品 (連接至密封之流體路徑的管線、經滅菌之過濾器、無菌密閉及密封的小瓶)的組裝必須在無菌條件下執行。	28. Prior to the start of manufacturing, assembly of sterilised equipment and consumables (tubing, sterilised filters and sterile closed and sealed vials to a sealed fluid path) must be performed under aseptic conditions
文件製作（DOCUMENTATION）	
29. 與放射性藥品製造有關之所有文件，皆應依書面程序製作、審查、核准及分發。	29. All documents related to the manufacture of radiopharmaceuticals should be prepared, reviewed, approved and distributed according to written procedures.

30. 原料、標示及包裝材料、關鍵中間體/中間產品及最終放射性藥品，皆應建立其規格並文件化。使用於製程中之任何其他關鍵品項，諸如，對品質可能會有關鍵性影響之製程助劑、墊圈、無菌過濾套組等，亦應備有規格。	30. Specifications should be established and documented for raw materials, labelling and packaging materials, critical intermediates and the finished radiopharmaceutical. Specifications should also be in place for any other critical items used in the manufacturing process, such as process aids, gaskets, sterile filtering kits, that could critically impact on quality.
31. 放射性藥品應建立其允收標準，包括放行標準及架儲期規格在內【例如，同位素之化學同一性（chemical identity）、放射性濃度、純度以及特定活性】。	31. Acceptance criteria should be established for the radiopharmaceutical including criteria for release and shelf life specifications (examples: chemical identity of the isotope, radioactive concentration, purity, and specific activity).
32. 主要設備之使用、清潔、滅菌處理/滅菌及維護保養的紀錄，除應顯示人員參與這類活動之日期、時間及簽名外，合適時，並應顯示該產品名稱及批號。	32. Records of major equipment use, cleaning, sanitisation or sterilisation and maintenance should show the product name and batch number, where appropriate, in addition to the date and time and signature for the persons involved in these activities.
33. 除了國家要求另有規定外，紀錄應保存至少三年。	33. Records should be retained for at least 3 years unless another timeframe is specified in national requirements.
生產（PRODUCTION）	
34. 為了將交叉污染或混雜的風險減到最低，應避免在相同作業區中【亦即，鉛室/鉛櫃、層流空氣單元】於相同時間生產不同的放射性產品。	34. Production of different radioactive products in the same working area (i.e. hotcell, LAF unit), at the same time should be avoided in order to minimise the risk of cross-contamination or mix-up.
35. 確效應予以特別注意，包含電腦化系統在內，該系統之確效應依照 PIC/S GMP 指引附則 11 執行。新製程應進行先期性確效。	35. Special attention should be paid to validation including validation of computerised systems which should be carried out in accordance in compliance PIC/S GMP Guide, Annex 11. New manufacturing processes should be validated prospectively.
36. 關鍵參數通常應在確效前或在確效期間予以確認，並應界定再現性操作所需的範圍。	36. The critical parameters should normally be identified before or during validation and the ranges necessary for reproducible operation should be defined.

37. 考慮輻射防護的需要及過濾器無菌性的維護，無菌充填的產品應執行濾膜過濾器的完整性測試。	37. Integrity testing of the membrane filter should be performed for aseptically filled products, taking into account the need for radiation protection and maintenance of filter sterility.
38. 由於輻射暴露，所以大部分直接容器的標示在製造前即已完成是可接受的。若該標示程序不損及無菌性或妨礙經充填小瓶的目視管制，則空的無菌密閉小瓶得在充填前標示部分資訊。	38. Due to radiation exposure it is accepted that most of the labelling of the direct container, is done prior to manufacturing. Sterile empty closed vials may be labelled with partial information prior to filling providing that this procedure does not compromise sterility or prevent visual control of the filled vial.
品質管制（QUALITY CONTROL）	
39. 有些放射性藥品可能必須在完成所有化學的與微生物學上的檢驗前，即依據批次文件之評估予以運銷及使用。	39. Some radiopharmaceuticals may have to be distributed and used on the basis of an assessment of batch documentation and before all chemical and microbiology tests have been completed.
放射性藥品之放行，得在完整分析檢驗前，以二或二個以上的階段執行：	Radiopharmaceutical product release may be carried out in two or more stages, before and after full analytical testing:
a) 在允許放射性藥品於隔離待驗狀態下運送至臨床部門前，經由指定人員對其批次操作紀錄之評估，應涵蓋至當時已執行之生產條件及分析檢驗。	a) Assessment by a designated person of batch processing records, which should cover production conditions and analytical testing performed thus far, before allowing transportation of the radiopharmaceutical under quarantine status to the clinical department.
b) 被授權人員出具書面證明前，應評估最終分析數據，以確保與正常程序之所有偏離業經文件化並證明其適當性，且適當地放行。在產品使用前無法獲得某些檢驗結果時，被授權人員應在其使用前有條件地證明該產品，並應在取得所有檢驗結果後，予以最終證明。	b) Assessment of the final analytical data, ensuring all deviations from normal procedures are documented, justified and appropriately released prior to documented certification by the Authorised Person. Where certain test results are not available before use of the product, the Authorised Person should conditionally certify the product before it is used and should finally certify the product after all the test results are obtained.

40. 大多數放射性藥品均預定在短時間內使用，關於放射性架儲有效期間必需清楚地陳述。	40. Most radiopharmaceuticals are intended for use within a short time and the period of validity with regard to the radioactive shelf-life, must be clearly stated.
41. 具有長半衰期之放射性核種的放射性藥品應經測試，以顯示其在由被授權人員放行及給予證明前，符合所有相關的允收標準。	41. Radiopharmaceuticals having radionuclides with long half-lives should be tested to show, that they meet all relevant acceptance criteria before release and certification by the Authorised Person.
42. 在執行檢驗前，得將樣品儲存，以允許足夠之放射活性衰變。所有檢驗，包括無菌試驗在內，應盡速執行。	42. Before testing is performed samples can be stored to allow sufficient radioactivity decay. All tests including the sterility test should be performed as soon as possible.
43. 應建立詳述生產與分析數據評估的書面程序。該評估在批次發送前即應考慮。	43. A written procedure detailing the assessment of production and analytical data, which should be considered before the batch is dispatched, should be established.
44. 不符合允收標準之產品應予拒用。若該物質經重處理應依循預先建立之程序，且最終產品在放行前應符合允收標準。退回之產品不能重處理，且必須視為放射性廢棄物予以儲存。	44. Products that fail to meet acceptance criteria should be rejected. If the material is reprocessed, pre-established procedures should be followed and the finished product should meet acceptance criteria before release. Returned products may not be reprocessed and must be stored as radioactive waste.
45. 產品若在發送後且末效日期屆滿前得到不滿意的試驗結果 (偏離規格) 時，程序亦應描述被授權人員所要採取之措施。該等事件應予調查，以包括防止未來類似事件所應採取之相關的矯正及預防措施。	45. A procedure should also describe the measures to be taken by Authorised Person if unsatisfactory test results (Out-of-Specification) are obtained after dispatch and before expiry. Such events should be investigated to include the relevant corrective and preventative actions taken to prevent future events.
這個過程應予以文件化。	This process must be documented.
46. 必要時，應將資訊提供臨床負責人員。為便利這種做法，應對放射性藥品實施一可追溯性系統。	46. Information should be given to the clinical responsible persons, if necessary. To facilitate this, a traceability system should be implemented for radiopharmaceuticals.

47. 應備有確認原料品質的系統。供應商之核准應包含提供該原料一致地符合規格之適當保證的評估。原料、包裝材料及關鍵製程助劑應購自經核准的供應商。	47. A system to verify the quality of starting materials should be in place. Supplier approval should include an evaluation that provides adequate assurance that the material consistently meets specifications. The starting materials, packaging materials and critical process aids should be purchased from approved suppliers.
對照樣品及留存樣品（REFERENCE AND RETENTION SAMPLES）	
48. 放射性藥品每批待分/包裝產品應留存足夠的樣品。除透過風險管理證明其適當性者外，該等樣品應保存到最終產品的末效日期後至少六個月。	48. For radiopharmaceuticals sufficient samples of each batch of bulk formulated product should be retained for at least six months after expiry of the finished medicinal product unless otherwise justified through risk management.
49. 使用於製造過程之原料的樣品，不屬於溶劑、氣體或水者，應留存至該產品放行後至少兩年。相關規格中所示之原料的安定性期間較短者，該期間得縮短之。	49. Samples of starting materials, other than solvents gases or water used in the manufacturing process should be retained for at least two years after the release of the product. That period may be shortened if the period of stability of the material as indicated in the relevant specification is shorter.
50. 原料及個別製造或小量製造、或其儲存可能引起特別問題之產品，其抽樣及留存得與主管機關以協議界定其他條件。	50. Other conditions may be defined by agreement with the competent authority, for the sampling and retaining of starting materials and products manufactured individually or in small quantities or when their storage could raise special problems.
運銷（DISTRIBUTION）	
51. 這些放射性藥品，直到獲得滿意的檢驗結果，並經指定的人員進行評估前不會被接收機構所投用，則在獲得所有適當檢驗結果前，最終產品在管制條件下的運銷是可以接受的。	51. Distribution of the finished product under controlled conditions, before all appropriate test results are available, is acceptable for radiopharmaceuticals, providing the product is not administered by the receiving institute until satisfactory test results has been received and assessed by a designated person.
術語彙編（GLOSSARY）	

製備： 自醫院內之發生器或放射性前驅物溶洗出具有放射性核種之套組的處理及輻射標示。套組、發生器及前驅物應有上市許可或國家執照。	**Preparation:** handling and radiolabelling of kits with radionuclide eluted from generators or radioactive precursors within a hospital. Kits, generators and precursors should have a marketing authorisation or a national licence.
製造： 放射性藥品從活性物質與原料之生產、品質管制、放行及送交。	**Manufacturing:** roduction, quality control and release and delivery of radiopharmaceuticals from the active substance and starting materials.
鉛室/鉛櫃： 為放射性物質之製造及處理的具有遮蔽之作業站。鉛室/鉛櫃未必需要設計成隔離裝置。	**Hot–cells:** shielded workstations for manufacture and handling of radioactive materials. Hot-cells are not necessarily designed as an isolator.
被授權人員： 經權責機關認定為具備必要之基礎科學與技術背景及經驗的人員。	**Authorised person:** Person recognised by the authority as having the necessary basic scientific and technical background and experience.

附則 6　醫用氣體的製造（MANUFACTURE OF MEDICINAL GASES）

原則（PRINCIPLE）	
本附則論述原料藥氣體的製造與醫用氣體的製造。	This Annex deals with the manufacture of active substance gases and the manufacture of medicinal gases.
原料藥的製造與藥品的製造，應在每一個上市許可文件檔案中加以清楚界定。通常，氣體的生產與純化步驟是屬於原料藥的製造領域。氣體從初始儲存預定供製劑使用起，即進入製劑的領域。	The delineation between the manufacture of the active substance and the manufacture of the medicinal product should be clearly defined in each Marketing Authorisation dossier. Normally, the production and purification steps of the gas belong to the field of manufacture of active substances. Gases enter the pharmaceutical field from the first storage of gas intended for such use.
原料藥氣體的製造應遵循 GMP 指引的基本要求（第二部）、本附則的相關部分以及 GMP 指引的其他附則（若相關時）。	Manufacture of active substance gases should comply with the Basic Requirements of this Guide (Part II), with the relevant part of this Annex, and with the other Annexes of the Guide if relevant.
醫用氣體的製造應遵循 GMP 指引的基本要求（第一部）、本附則的相關部分以及 GMP 指引的其他附則（若相關時）。	Manufacture of medicinal gases should comply with the basic requirements of this Guide (Part I), with the relevant part of this Annex and with the other Annexes of the Guide if relevant.
連續製程中在原料藥氣體的製造與藥品的製造之間，沒有中間儲存的例外情況是可能的。該完整過程（從原料藥起始物到最終產品）應認定為屬於製劑領域。這在上市許可文件檔案中應清楚地陳述。	In the exceptional cases of continuous processes where no intermediate storage of gas between the manufacture of the active substance and the manufacture of the medicinal product is possible, the whole process (from starting materials of active substance to medicinal finished product) should be considered as belonging to the pharmaceutical field. This should be clearly stated in the Marketing Authorisation dossier.

本附則不涵蓋醫院中之醫用氣體的製造與處理，除非被認定為工業製備或製造。然而，本附則之相關部分，可被用作對該等活動的基礎。	The Annex does not cover the manufacture and handling of medicinal gases in hospitals unless this is considered industrial preparation or manufacturing. However, relevant parts of this Annex may be used as a basis for such activities.
原料藥氣體的製造（Manufacture of Active Substance Gases）	
原料藥氣體可利用化學合成法製備或由天然來源所取得，必要時經純化步驟（例如空氣分離工廠）。	Active substance gases can be prepared by chemical synthesis or be obtained from natural sources followed by purification steps, if necessary (as for example in an air separation plant).
1. 對應於這兩種原料藥氣體製造方法的流程，應遵循 GMP 指引的基本要求（第二部），然而：	1. The processes corresponding to these two methods of manufacturing active substance gases should comply with Part II of the Basic Requirements. However:
(a) 關於第二部第七章對原料藥氣體之起始物的要求，並不適用於經由空氣分離之原料藥氣體的生產（然而，製造廠應確保週遭空氣的品質是適合所建立的製程，而且在週遭空氣品質的任何變化，不得影響原料藥氣體的品質）；	(a) the requirements regarding starting materials for active substances (Part II, Chapter 7) do not apply to the production of active substance gases by air separation (however, the manufacturer should ensure that the quality of ambient air is suitable for the established process and any changes in the quality of ambient air do not affect the quality of the active substance gas);
(b) 使用於確認儲存條件與末效日期/再驗日期（第二部，第 11.6 章）之關於持續安定性試驗的要求（第二部，第 11.5 章），不適用於初始安定性試驗已由參考書目/文獻數據取代的情況；	(b) the requirements regarding on-going stability studies (Part II, Chapter 11.5), which are used to confirm storage conditions and expiry/retest dates (Part II, Chapter 11.6), do not apply in case initial stability studies have been replaced by bibliographic data; and
(c) 除另有規定，留樣品/留存樣品的要求（第二部，第 11.7 章）不適用於原料藥氣體。	(c) the requirements regarding reserve/retention samples (Part II, Chapter 11.7) do not apply to active substance gases, unless otherwise specified.
2. 經由連續製程之原料藥氣體的生產（如：空氣分離），應持續監測其品質。此監測的結果應以允許趨勢評估的方式保存之。	2. The production of active substance gases through a continuous process (e.g. air separation) should be continuously monitored for quality. The results of this monitoring should be kept in a manner permitting trend evaluation.

3. 此外：	3. In addition:
a) 大宗原料藥氣體之輸送與交付應遵循下述對醫用氣體的要求（本附則第 19 至 21 條）；	a) transfers and deliveries of active substance gases in bulk should comply with the same requirements as those mentioned below for the medicinal gases (sections 19 to 21 of this Annex);
b) 原料藥氣體之灌充到鋼瓶，或灌充到移動式低溫容器應遵循下述對醫用氣體（本附則第 22 至 37 條）以及第二部第 9 章的要求。	b) filling of active substance gases into cylinders or into mobile cryogenic vessels should comply with the same requirements as those mentioned below for the medicinal gases (sections 22 to 37 of this Annex) as well as Part II Chapter 9.
醫用氣體的製造 Manufacture of Medicinal Gases	
通常，醫用氣體的製造是在密閉的設備中進行，因此，產品受環境污染是最少的。然而，污染（或與其它氣體的交叉污染）的風險可能會發生，特別是由於容器的重複使用。	Manufacture of medicinal gases is generally carried out in closed equipment. Consequently, environmental contamination of the product is minimal. However, risks of contamination (or cross contamination with other gases) may arise, in particular because of the reuse of containers.
4. 適用於鋼瓶的要求亦應適用於集束鋼瓶（儲存與運送有遮蓋者除外）。	4. Requirements applying to cylinders should also apply to cylinders bundles (except storage and transportation under cover).
組織與人事（PERSONNEL）	
5. 參與醫用氣體之生產與運銷的所有人員，應接受適用於這類產品的適當 GMP 訓練。他/她們應該知道關鍵性的重要層面，以及這些產品對患者的潛在危害。	5. All personnel involved in the manufacture and distribution of medicinal gases should receive an appropriate GMP training applying to this type of products. They should be aware of the critically important aspects and potential hazards for patients from these products.
6. 可能影響醫用氣體品質之轉包商的人員（如：負責鋼瓶或閥門維護保養的人員）應經適當訓練。	6. Personnel of subcontractors that could influence the quality of medicinal gases (such as personnel in charge of maintenance of cylinders or valves) should be appropriately trained.
廠房設施與設備（PREMISES AND EQUIPMENT）	
廠房設施（Premises）	

7. 鋼瓶與移動式低溫容器應在與非醫用氣體隔離的區域中進行檢查、準備、灌充與儲存，且在這些區域間的鋼瓶/移動式低溫容器不應交換。然而，假如它們符合醫用氣體的規格，且製造作業依照 GMP 標準執行時，則在同一區域中進行其他氣體的檢查、準備、灌充與儲存，可能可以被接受。	7. Cylinders and mobile cryogenic vessels should be checked, prepared, filled and stored in a separate area from non-medicinal gases, and there should be no exchange of cylinders/mobile cryogenic vessels between these areas. However, it could be accepted to check, prepare, fill and store other gases in the same areas, provided they comply with the specifications of medicinal gases and that the manufacturing operations are performed according to GMP standards.
8. 廠房設施應具備足夠的空間以供製造、測試與儲存作業，以避免混雜的風險。廠房設施應加以指定，以提供：	8. Premises should provide sufficient space for manufacturing, testing and storage operations to avoid the risk of mix-up. Premises should be designated to provide:
a) 不同氣體之各自標記區域；	a) separate marked areas for different gases;
b) 鋼瓶/移動式低溫容器在操作/加工的不同階段（如：「待檢查」、「待灌充」、「待驗」、「認可」、「拒用」、「準備交貨」） 之清楚識別與隔離。	b) clear identification and segregation of cylinders/mobile cryogenic vessels at various stages of processing (e.g. “waiting checking”, "awaiting filling", "quarantine", "certified", “rejected “,“prepared deliveries”).
達到這些不同層次所使用之隔離方法，取決於整體作業之本質、程度及複雜性，但可使用經標記之地板區域、隔板、柵欄、符號、標識或其他適當方法等。	The method used to achieve these various levels of segregation will depend on the nature, extent and complexity of the overall operation. Marked-out floor areas, partitions, barriers, signs, labels or other appropriate means could be used.
9. 經分類整理或維護保養後的空鋼瓶/家用低溫容器，與經灌充的鋼瓶/家用低溫容器應在遮蓋下儲存，以避免不良的天氣狀況。經灌充的鋼瓶/家用低溫容器的儲存方式，應確保其將以潔淨的狀態交貨，並與其將被使用之環境相容。	9. Empty cylinders/home cryogenic vessels after sorting or maintenance, and filled cylinders/home cryogenic vessels should be stored under cover, protected from adverse weather conditions. Filled cylinders/mobile cryogenic vessels should be stored in a manner that ensures that they will be delivered in a clean state, compatible with the environment in which they will be used.
10. 特定的儲存條件（如：冷凍時會發生相分離的氣體混合物）應依上市許可之要求。	10. Specific storage conditions should be provided as required by the Marketing Authorisation (e.g. for gas mixtures where phase separation occurs on freezing).
設備（Equipment）	

11. 設備應經設計，以確保正確的氣體灌充到正確的容器。通常輸送不同氣體之管線間應不得有交叉連接。如果需要交叉連接時（如：混合物的灌充設備），其驗證應確保不同氣體間沒有交叉污染的風險。此外，歧管應配備特定的接頭。這些接頭可能會受國際或國家標準所管制。符合不同標準之接頭在同一灌充場所的使用應予小心管制；在有些情況需要使用轉接器以繞過特定的灌充連接系統者，亦同。	11. Equipment should be designed to ensure the correct gas is filled into the correct container. There should normally be no cross connections between pipelines carrying different gases. If cross connections are needed (e.g. filling equipment of mixtures), qualification should ensure that there is no risk of cross contamination between the different gases. In addition, the manifolds should be equipped with specific connections. These connections may be subject to international or national standards. The use of connections meeting different standards at the same filling site should be carefully controlled, as well as the use of adaptors needed in some situations to bypass the specific fill connection systems.
12. 儲槽與槽車應專用於單一且經界定品質的氣體。然而，非醫用氣體品質至少等於醫用氣體，且維持 GMP 標準時，則醫用氣體可用該非醫用氣體的儲槽、其他中間產品儲存之容器或槽車來儲存或運送。在該等情況中，應執行品質風險管理並進行文件化。	12. Tanks and tankers should be dedicated to a single and defined quality of gas. However, medicinal gases may be stored or transported in the same tanks, other containers used for intermediate storage, or tankers, as the same non-medicinal gas, provided that the quality of the latter is at least equal to the quality of the medicinal gas and that GMP standards are maintained. In such cases, quality risk management should be performed and documented.
13. 供應氣體到醫用與非醫用氣體歧管的共通系統，僅在有經確效的方法以防止從非醫用氣體管線回流到醫用氣體管線時，方可接受。	13. A common system supplying gas to medicinal and non-medicinal gas manifolds is only acceptable if there is a validated method to prevent backflow from the non-medicinal gas line to the medicinal gas line.

14. 灌充歧管應專用於單一醫用氣體或特定的醫用氣體混合物。在例外情況下，如經證明其合理性並在管制下執行時，在專用於醫用氣體的歧管上灌充具其他醫療目的的氣體，是可接受的。在這些情況中，非醫用氣體的品質至少應等於醫用氣體所要求的品質，而且應維持 GMP 標準。然後，灌充應經由時段切換方式執行之。	14. Filling manifolds should be dedicated to a single medicinal gas or to a given mixture of medicinal gases. In exceptional cases, filling gases used for other medical purposes on manifolds dedicated to medicinal gases may be acceptable if justified and performed under control. In these cases, the quality of the non-medicinal gas should be at least equal to the required quality of the medicinal gas and GMP standards should be maintained. Filling should then be carried out by campaigns.
15. 設備的修理與維護保養作業（包括清潔與沖吹在內），不得影響醫用氣體的品質。特別是，對於損及該系統完整性的修理與維護保養作業後所要採取的措施，應描述於程序中。具體而言，它應證明該設備在放行使用之前，無任何可能對最終產品品質有不良影響的污染。該紀錄應予以保存。	15. Repair and maintenance operations (including cleaning and purging) of equipment, should not adversely affect the quality of the medicinal gases. In particular, procedures should describe the measures to be taken after repair and maintenance operations involving breaches of the system's integrity. Specifically it should be demonstrated that the equipment is free from any contamination that may adversely affect the quality of the finished product before releasing it for use. Records should be maintained.
16. 當槽車回到醫用氣體的使用時（在第 12 條所述條件中運送非醫用氣體後，或在維護保養操作後），其程序應描述所要採取的措施。這應包括分析測試。	16. A procedure should describe the measures to be taken when a tanker is back into medicinal gas service (after transporting non-medicinal gas in the conditions mentioned in section 12, or after a maintenance operation). This should include analytical testing.
文件製作（DOCUMENTATION）	
17. 對於每一批次之鋼瓶/移動式低溫容器的紀錄，所包含之數據必須確保每一灌充鋼瓶是可追溯到相關灌充作業的重要層面。合適時，應該登錄下列內容：	17. Data included in the records for each batch of cylinders/mobile cryogenic vessels must ensure that each filled cylinder is traceable to significant aspects of the relevant filling operations. As appropriate, the following should be entered:
a) 產品名稱；	a) the name of the product;
b) 批號；	b) batch number;
c) 灌充日期與時間；	c) the date and the time of the filling operations;

d) 執行每一重要步驟（例如：清線、接收、灌充前準備、灌充等）之人員的身分識別；	d) identification of the person(s) carrying out each significant step (e.g. line clearance, receipt, preparation before filling, filling etc.);
e) 使用於灌充操作之氣體的批次參考資料，如同第 22 條所述，包括其狀態在內；	e) batch(es) reference(s) for the gas(es) used for the filling operation as referred to in section 22, including status;
f) 所使用之設備（例如：灌充歧管）；	f) equipment used (e.g. filling manifold);
g) 在灌充之前，鋼瓶/移動式低溫容器的數量，包含個別識別參考資料與水容積在內；	g) quantity of cylinders/mobile cryogenic vessels before filling, including individual identification references and water capacity(ies);
h) 灌充前所執行的作業（參見第 30 條）;	h) pre-filling operations performed (see section 30);
i) 需要確保在標準條件下正確灌充之關鍵參數；	i) key parameters that are needed to ensure correct fill at standard conditions;
j) 確保容器已完成灌充之檢查結果；	j) results of appropriate checks to ensure the containers have been filled;
k) 批次標籤的樣品；	k) a sample of the batch label;
l) 最終產品的規格與品質管制測試的結果（包含測試設備校正狀態之參照）；	l) specification of the finished product and results of quality control tests (including reference to the calibration status of the test equipment);
m) 拒用之鋼瓶/移動式低溫容器的數量，並有個別的識別參考資料與拒用的原因；	m) quantity of rejected cylinders/mobile cryogenic vessels, with individual identification references and reasons for rejections;
n) 任何問題或異常事件之詳細資料，與灌充指令之任何偏差的簽章認可；	n) details of any problems or unusual events, and signed authorisation for any deviation from filling instructions; and
o) 由被授權人員的認可聲明、日期與簽章。	o) certification statement by the Authorised Person, date and signature.
18. 對於預定要送入醫院儲槽之每一批氣體之紀錄應該加以保存。合適時，這些紀錄應該包括下列內容：	18. Records should be maintained for each batch of gas intended to be delivered into hospital tanks. These records should, as appropriate, include the following:
a) 產品名稱；	a) name of the product;
b) 批號；	b) batch number;
c) 經認可之批次的儲槽（槽車）之識別參考資料；	c) identification reference for the tank (tanker) in which the batch is certified;
d) 灌充操作日期與時間；	d) date and time of the filling operation;
e) 執行儲槽（槽車）灌充之人員的身分識別；	e) identification of the person(s) carrying out the filling of the tank (tanker);

f) 供應槽車（儲槽）的參考資料，適用時，來源氣體的參考資料；	f) reference to the supplying tanker (tank), reference to the source gas as applicable;
g) 關於灌充操作的相關細節；	g) relevant details concerning the filling operation;
h) 最終產品的規格與品質管制測試的結果（包含測試設備校正狀態之參照）；	h) specification of the finished product and results of quality control tests (including reference to the calibration status of the test equipment);
i) 任何問題或異常事件的細節及與灌充指令之任何偏差的簽章認可；	i) details of any problems or unusual events, and signed authorisation for any deviation from filling instructions; and
j) 由被授權人員的認可聲明、日期與簽章。	j) certification statement by the Authorised Person, date and signature.
生產（PRODUCTION）	
低溫氣體與液化氣體的輸送與交付 （Transfers and deliveries of cryogenic and liquefied gas）	
19. 從主儲存槽之低溫氣體或液化氣體的輸送，包括輸送前的管制在內，應該依照經設計以避免任何污染之經過確效的程序。輸送管線應配備逆止閥或其他合適的替代品。伸縮連接裝置、耦合軟管及接頭應在使用前以相關的氣體進行沖吹。	19. The transfers of cryogenic or liquefied gases from primary storage, including controls before transfers, should be in accordance with validated procedures designed to avoid any contamination. Transfer lines should be equipped with non-return valves or other suitable alternatives. Flexible connections, and coupling hoses and connectors should be flushed with the relevant gas before use.
20. 使用於灌充儲槽與槽車的輸送軟管應配備產品專一性的連接頭。使用轉接器連接非該氣體之專用儲槽及槽車時，應予充分管制。	20. The transfer hoses used to fill tanks and tankers should be equipped with. The use of adaptors allowing the connection of tanks and tankers not dedicated to the same gases should be adequately controlled.
21. 氣體之交付，若其樣品經測試以確保所交付之氣體的品質可接受時，則可灌入含有相同品質氣體的儲槽中。這個樣品可以取自所要交付的氣體，或取自交付後的接收儲槽。	21. Deliveries of gas may be added to tanks containing the same quality of gas provided that a sample is tested to ensure that the quality of the delivered gas is acceptable. This sample may be taken from the gas to be delivered or from the receiving tank after delivery.
*注意：*對於由客戶保存於其處所之儲槽的灌充，請參見第 42 條的特定安排。	*Note:* See specific arrangements in section 42 for filling of tanks retained by customers at the customer's premises.
鋼瓶與移動式低溫容器的灌充與標示 （Filling and labelling of cylinders and mobile cryogenic vessels）	

22. 在灌充鋼瓶與移動式低溫容器之前，氣體之批次應予確定、依規格管制及核准以供灌充。	22. Before filling cylinders and mobile cryogenic vessels, a batch (batches) of gas(es) should be determined, controlled according to specifications and approved for filling.
23. 如同在「原則」中所述，在連續製程的情況，應有足夠的製程中管制，以確保該氣體符合規格。	23. In the case of continuous processes as those mentioned in 'Principle', there should be adequate in-process controls to ensure that the gas complies with specifications.
24. 鋼瓶、移動式低溫容器與閥門應符合適當的技術規格與上市許可的任何相關要求。它們應專用於單一醫用氣體或已知特定的醫用氣體的混合物。鋼瓶應依照相關標準編以顏色代碼。為適當的防止污染，最好應配備具有逆止機轉的最低壓力殘壓閥。	24. Cylinders, mobile cryogenic vessels and valves should conform to appropriate technical specifications and any relevant requirements of the Marketing Authorisation. They should be dedicated to a single medicinal gas or to a given mixture of medicinal gases. Cylinders should be colour-coded according to relevant standards. They should preferably be fitted with minimum pressure retention valves with non-return mechanism in order to get adequate protection against contamination.
25. 鋼瓶、移動式低溫容器與閥門，在第一次用於生產前應進行檢查，並且應適當地維護保養。醫療器材已經通過符合性評鑑[1]者，其維護保養應敘明醫療器材製造廠的維護保養指示。	25. Cylinders, mobile cryogenic vessels and valves should be checked before first use in production, and should be properly maintained. Where medical devices have gone through a conformity assessment procedure[1], the maintenance should address the medical device manufacturer's instructions.
26. 檢查與維護保養作業應不得影響藥品的品質與安全性。執行鋼瓶水壓試驗所使用的水應該至少符合飲用水品質。	26. Checks and maintenance operations should not affect the quality and the safety of the medicinal product. The water used for the hydrostatic pressure testing carried out on cylinders should be at least of drinking quality.
27. 鋼瓶在接上閥門之前應該進行內部目視檢查，作為操作之檢查與維護保養的一部分，以確保其未被水或其他污染物所污染。這個作業應在下列情況時完成：	27. As part of the checks and maintenance operations, cylinders should be subject to an internal visual inspection before fitting the valve, to make sure they are not contaminated with water or other contaminants. This should be done:
• 新的鋼瓶初次使用於醫用氣體時；	• when they are new and initially put into medicinal gas service;

• 在取下閥門以執行任何法定水壓試驗或等同的測試時；	• following any hydrostatic statutory pressure test or equivalent test where the valve is removed;
• 每次更換閥門時。	• whenever the valve is replaced.
在閥門套合後應保持關閉，以防止任何污染進入鋼瓶。如果對鋼瓶的內部狀況有任何疑問時，應將閥門移除，並且進行鋼瓶內部檢查，以確保其未被污染。	After fitting, the valve should be kept closed to prevent any contamination from entering the cylinder. If there is any doubt about the internal condition of the cylinder, the valve should be removed and the cylinder internally inspected to ensure it has not been contaminated.
28. 鋼瓶、移動式低溫容器與閥門之維護保養與修理作業是藥品製造廠的責任。如果轉包時，它們應該僅經由核准的轉包商執行，並應建立包含技術協議在內的合約。轉包商應經稽查，以確保其維持適當的標準。	28. Maintenance and repair operations of cylinders, mobile cryogenic vessels and valves are the responsibility of the manufacturer of the medicinal product. If subcontracted, they should only be carried out by approved subcontractors, and contracts including technical agreements should be established. Subcontractors should be audited to ensure that appropriate standards are maintained.
29. 應有一個適當的系統，以確保鋼瓶、移動式低溫容器與閥門的可追溯性。	29. There should be a system in place to ensure traceability of cylinders, mobile cryogenic vessels and valves.
30. 在灌充之前所要執行的檢查包括：	30. Checks to be performed before filling should include:
a) 鋼瓶：依照所界定的程序執行檢查，以確保每一個鋼瓶的殘壓為正壓;	a) in the case of cylinders, a check, carried out according to defined procedure, to ensure there is a positive residual pressure in each cylinder;
• 如鋼瓶有最低壓力殘壓閥，當沒有信號指出有正的殘壓時，應該檢查閥門的正確功能，且如果顯示閥門不能發揮正確功能時，鋼瓶應送維護保養，	• if the cylinder is fitted with a minimum pressure retention valve, when there is no signal indicating there is a positive residual pressure, the correct functioning of the valve should be checked, and if the valve is shown not to function properly the cylinder should be sent to maintenance,

• 如鋼瓶沒有最低壓力殘壓閥，當沒有正的殘壓時，該鋼瓶應另予存放，以執行追加措施，確認其未被水或其他污染物所污染；追加措施可包括內部目視檢查，並使用經確效的方法清潔；	• if the cylinder is not fitted with a minimum pressure retention valve, when there is no positive residual pressure the cylinder should be put aside for additional measures, to make sure it is not contaminated with water or other contaminants; additional measures could consist of internal visual inspection followed by cleaning using a validated method;
b) 確保所有先前批次之標籤已移除的檢查；	b) a check to ensure that all previous batch labels have been removed;
c) 任何損毀之產品標籤已移除並更換的檢查；	c) a check that any damaged product labels have been removed and replaced;
d) 外部目視檢查每一鋼瓶、移動式低溫容器與閥門之凹陷、電弧燒傷、破片、其他損害及油污污染，必要時應進行清潔；	d) a visual external inspection of each cylinder, mobile cryogenic vessel and valve for dents, arc burns, debris, other damage and contamination with oil or grease; cleaning should be done if necessary;
e) 檢查每一鋼瓶、移動式低溫容器出口連接頭，以確定其為特定氣體的正確類型；	e) a check of each cylinder or mobile cryogenic vessel outlet connection to determine that it is the proper type for the particular gas involved;
f) 檢查閥門下次執行測試的日期（對於需定期測試的閥門）；	f) a check of the date of the next test to be performed on the valve (in the case of valves that need to be periodically tested);
g) 檢查鋼瓶或移動式低溫容器，以確保已經執行任何由國家或國際法規所要求的測試（例如：鋼瓶的水壓試驗或同等的測試），而且仍然有效；	g) a check of the cylinders or mobile cryogenic vessels to ensure that any tests required by national or international regulations (e.g. hydrostatic pressure test or equivalent for cylinders) have been conducted and still is valid; and
h) 確定每一容器按上市許可規定編以色碼（相關國家/國際標準的顏色編碼）的檢查。	h) a check to determine that each container is colour-coded as specified in the Marketing Authorisation (colour-coding of the relevant national/international standards).
31. 灌充作業的批次應予定義。	31. A batch should be defined for filling operations.

32. 收回供再灌充之鋼瓶，應依據上市許可所界定的程序小心準備，以使污染的風險減到最低。抽氣排空及/或沖吹操作等程序應經確效。	32. Cylinders which have been returned for refilling should be prepared with care in order to minimise risks for contamination in line with the procedures defined in the Marketing Authorisation. These procedures, which should include evacuation and/or purging operations, should be validated.
*注意：*對於壓縮氣體，在 15 ºC、200 巴的灌充壓力下，其雜質理論上限為 500 ppm v/v（其他灌充壓力也相當）。	*Note:* For compressed gases a maximum theoretical impurity of 500 ppm v/v should be obtained for a filling pressure of 200 bar at 15 °C (and equivalent for other filling pressures).
33. 收回供再灌充之移動式低溫容器，應依據上市許可所界定的程序小心準備，以使污染的風險減到最低。尤其是無殘壓之移動式容器，應使用經確效的方法準備。	33. Mobile cryogenic vessels that have been returned for refilling should be prepared with care in order to minimise the risks of contamination, in line with the procedures defined in the Marketing Authorisation. In particular, mobile vessels with no residual pressure should be prepared using a validated method.
34. 應有適當檢查，以確保每一個鋼瓶/移動式低溫容器已經正確灌充。	34. There should be appropriate checks to ensure that each cylinder/mobile cryogenic vessel has been properly filled.
35. 每一經灌充的鋼瓶，在加裝防竄改易顯封緘或裝置之前，應使用適當的方法測試洩漏（參見第 36 條）。該測試方法應不得將任何污染物導入閥門出口，可行時，應在抽取任何品質樣品之後執行。	35. Each filled cylinder should be tested for leaks using an appropriate method, prior to fitting the tamper evident seal or device (see section 36). The test method should not introduce any contaminant into the valve outlet and, if applicable, should be performed after any quality sample is taken.
36. 灌充後，鋼瓶閥門應予加蓋，以保護出口免受污染。鋼瓶與移動式低溫容器應加裝防竄改易顯封緘或裝置。	36. After filling, cylinders valves should be fitted with covers to protect the outlets from contamination. Cylinders and mobile cryogenic vessels should be fitted with tamper-evident seals or devices.
37. 每一鋼瓶或移動式低溫容器應予標示。批號與末效日期可標示在另一標籤上。	37. Each cylinder or mobile cryogenic vessel should be labelled. The batch number and the expiry date may be on a separate label.

38. 將兩種或兩種以上不同氣體，在灌充前之管道上混合或直接灌入鋼瓶內混合以生產醫用氣體時，其混合過程應經確效，以確保每一鋼瓶氣體業經適當混合且為均質。	38. In the case of medicinal gases produced by mixing two or more different gases (in-line before filling or directly into the cylinders); the mixing process should be validated to ensure that the gases are properly mixed in every cylinder and that the mixture is homogeneous.
品質管制（QUALITY CONTROL）	
39. 每批次醫用氣體（鋼瓶、移動式低溫容器、醫院儲槽），應依上市許可的要求進行測試並經認可。	39. Each batch of medicinal gas (cylinders, mobile cryogenic vessels, hospital tanks) should be tested in accordance with the requirements of the Marketing Authorisation and certified.
40. 除非上市許可有要求不同的規定，否則鋼瓶所要執行的抽樣計畫與分析應符合下列的要求：	40. Unless different provisions are required in the Marketing Authorisation, the sampling plan and the analysis to be performed should comply, in the case of cylinders with the following requirements.
a) 在單一醫用氣體經由多鋼瓶歧管灌充的情況，每次在歧管上更換鋼瓶時，每一鋼瓶歧管灌充週期，至少應測試一個鋼瓶氣體之同一性與含量。	a) In the case of a single medicinal gas filled via a multi-cylinder manifold, the gas from at least one cylinder from each manifold filling cycle should be tested for identity and assay each time the cylinders are changed on the manifold.
b) 在單一醫用氣體每次灌入一鋼瓶的情況，每一未中斷灌充週期，至少應測試一個鋼瓶氣體之同一性與含量。未中斷灌充週期的實例，如同一工作班次使用相同之人員、設備與氣體批次。	b) In the case of a single medicinal gas filled put into cylinders one at a time, the gas from at least one cylinder of each uninterrupted filling cycle should be tested for identity and assay. An example of an uninterrupted filling cycle is one shift's production using the same personnel, equipment, and batch of gas to be filled.

c) 經由同一歧管灌充兩種或兩種以上氣體於同一鋼瓶中混合時，每一鋼瓶的氣體應測試其每一組成氣體的同一性與含量。對於平衡氣體（如果有的話），可以在每一個歧管灌充週期（或於每次灌充一鋼瓶的每一未中斷灌充週期）的一個鋼瓶進行同一性之測試。若使用經確效之自動灌充系統，可測試較少的鋼瓶。	c) In the case of a medicinal gas produced by mixing two or more gases in a cylinder from the same manifold, the gas from every cylinder should be tested for assay and identity of each component gas. For excipients, if any, testing on identity could be performed on one cylinder per manifold filling cycle (or per uninterrupted filling cycle in case of cylinders filled one at a time). Fewer cylinders may be tested in case of validated automated filling system.
d) 預混合氣體之灌充，若線上連續測試其混合物，應遵循單一氣體灌充之原則；若未線上連續測試其混合物，則應遵循將氣體於鋼瓶內混合以生產醫用氣體之原則。	d) Premixed gases should follow the same principles as single gases when continuous in-line testing of the mixture to be filled is performed. Premixed gases should follow the same principle as medicinal gases produced by mixing gases in the cylinders when there is no continuous inline testing of the mixture to be filled.
如無合理證明，應執行水分含量測試。	Testing for water content should be performed unless otherwise justified.
能提供至少具相等品質保證的其它抽樣與檢驗程序，可能可以證明其合理性。	Other sampling and testing procedures that provide at least equivalent level of quality assurance may be justified
41. 除非上市許可有要求不同的規定，否則移動式低溫容器最終測試應包括每一容器之含量及同一性。僅於每一容器被灌充前，其剩餘氣體被證明維持其關鍵屬性者，方可採行批次測試。	41. Unless different provisions are required in the Marketing Authorisation, final testing on mobile cryogenic vessels should include a test for assay and identity on each vessel. Testing by batches should only be carried out if it has been demonstrated that the critical attributes of the gas remaining in each vessel before refilling have been maintained.

42. 以專用槽車就地再灌充客戶所保管之低溫容器（醫院的儲槽或家用低溫容器）時，若隨交貨檢附槽車內容物之分析證明書，則灌充後無須抽樣，然而，應證明容器中的氣體在連續再灌充期間維持其規格。	42. Cryogenic vessels retained by customers (hospital tanks or home cryogenic vessels), which are refilled in place from dedicated tankers do not need to be sampled after filling, provided that a certificate of analysis on the contents of the tanker accompanies the delivery. However, it should be demonstrated that the specification of the gas in the vessels is maintained over the successive refillings.
43. 除另有規定，對照樣品與留存樣品是不需要的。	43. Reference and retention samples are not required, unless otherwise specified.
44. 以文獻資料取代初始安定性研究者，持續進行之安定性研究是不需要的。	44. On-going stability studies are not required in case initial stability studies have been replaced by bibliographic data.
包裝氣體的運送（TRANSPORTATION OF PACKAGED GASES）	
45. 經灌充之氣體鋼瓶與家用低溫容器，在運送期間應加以保護，特別是交付客戶時，其潔淨狀態能與將被使用的環境相符合。	45. Filled gas cylinders and home cryogenic vessels should be protected during transportation so that, in particular, they are delivered to customers in a clean state compatible with the environment in which they will be used.
術語彙編（GLOSSARY）	
原料藥氣體 預定作為藥品之活性物質的任何氣體。	**Active substance gas** Any gas intended to be an active substance for a medicinal product.
空氣分離 在低溫下使用分餾法將空氣組成成分分離。	**Air separation** Separation of atmospheric air into its constituent gases using fractional distillation at cryogenic temperatures.
壓縮氣體 在加壓下分裝的氣體，在所有高於 -50 ºC 的溫度下完全是氣態的。	**Compressed gas** Gas which, when packaged under pressure is entirely gaseous at all temperatures above –50 ºC.
容器 容器是指與氣體直接接觸的低溫容器（儲槽、槽車或其他類型的移動式低溫容器）、鋼瓶、集束鋼瓶或任何其它包裝形式。	**Container** A container is a cryogenic vessel (tank, tanker or other type of mobile cryogenic vessel), a cylinder, a cylinder bundle or any other package that is in direct contact with the gas.
低溫氣體 在 1.013 巴與溫度低於 -150 ºC 時液化的氣體。	**Cryogenic gas** Gas which liquefies at 1.013 bar at temperatures below –150 ºC.

鋼瓶 通常為圓筒形容器，適用於盛裝經壓縮、液化或溶解之氣體，配備有在大氣壓與室溫下調節氣體自發性流出的裝置。	**Cylinder** Container usually cylindrical suited for compressed, liquefied or dissolved gas, fitted with a device to regulate the spontaneous outflow of gas at atmospheric pressure and room temperature.
集束鋼瓶 為鋼瓶的組合，由歧管互連緊固在一起，作為一個單元供運輸與使用。	**Cylinder bundle** An assembly of cylinders, which are fastened together interconnected by a manifold, transported and used as a unit.
抽氣排空 使用抽真空系統，從容器/系統移除殘餘氣體使壓力低於 1.013 巴。	**Evacuate** To remove the residual gas from a container/system to a pressure less than 1.013 bar using a vacuum system.
氣體 在 1.013 巴與 20 ºC 是完全氣態，或在 50 ºC 時具有蒸氣壓力超過 3 巴的任何物質。	**Gas** Any substance that is completely gaseous at 1.013 bar and +20 ºC or has a vapour pressure exceeding 3 bar at + 50 ºC.
家用低溫容器 經設計以盛裝液態氧的移動式低溫容器，供患者居家使用氣態氧氣。	**Home cryogenic vessel** Mobile cryogenic vessel designed to hold liquid oxygen and dispense gaseous oxygen at patients' home.
水壓試驗 為確保壓力容器能夠承受所設計之壓力上限，依照國家或國際法規要求所執行的試驗。	**Hydrostatic pressure test** Test performed as required by national or international regulations in order to ensure that pressure containers are able to withstand pressures up to the container's design pressure.
液化氣體 經分裝以供運送，在高於 -50 ºC 時為部分液體（或固體）的氣體。	**Liquefied gas** A gas which, when packaged for transport, is partially liquid (or solid) at a temperature above –50ºC.
歧管 經設計能使一個或多個氣體容器在同一時間被排空與灌充的設備或裝置。	**Manifold** Equipment or apparatus designed to enable one or more gas containers to be emptied and filled at the same time.
最高理論殘留雜質 來自於可能之回流與灌充前對鋼瓶作預處理時的殘留污染所造成的氣態雜質。最高理論殘留雜質的計算只與壓縮氣體有關，且假設此氣體為理想氣體。	**Maximum theoretical residual impurity** Gaseous impurity coming from a possible backflow that remains after the cylinders pre-treatment before filling. The calculation of the maximum theoretical residual impurity is only relevant for compressed gases and supposes that these gases act as perfect gases.

醫用氣體 歸類為藥品之任何氣體或氣體的混合物。	**Medicinal gas** Any gas or mixture of gases classified as a medicinal product.
最低壓力殘壓閥 為了防止鋼瓶的內部污染，在氣體鋼瓶使用後，可保持高於大氣壓之正壓的鋼瓶閥。	**Minimum pressure retention valve** A cylinder valve, which maintains a positive pressure above atmospheric pressure in a gas cylinder after use, in order to prevent internal contamination of the cylinder.
移動式低溫容器 經設計之移動式絕熱的容器，以保持內容物在液體狀態。在本附則中，本術語不包括槽車。	**Mobile cryogenic vessel** Mobile thermally insulated container designed to maintain the contents in a liquid state. In the Annex, this term does not include the tankers.
逆止閥 只允許單向流動的閥門。	**Non-return valve** Valve which permits flow in one direction only.
沖吹 先經加壓，再排出該沖吹用氣體至 1.013 巴，以移除容器/系統中殘留的氣體。	**Purge** To remove the residual gas from a container/system by first pressurising and then venting the gas used for purging to 1.013 bar.
儲槽 經設計供液化氣體或低溫氣體儲存的靜態絕熱容器，又稱為「固定式低溫容器」。	**Tank** Static thermally insulated container designed for the storage of liquefied or cryogenic gas. They are also called “Fixed cryogenic vessels”.
槽車 在本附則中，係指固定在車輛上供用於液化氣體或低溫氣體運送的絕熱容器。	**Tanker** In the context of the Annex, thermally insulated container fixed on a vehicle for the transport of liquefied or cryogenic gas.
閥門 供開關容器用的裝置。	**Valve** Device for opening and closing containers.
排氣 在大氣下打開容器/系統，以將殘餘氣體從容器/系統中移出降至 1.013 巴。	**Vent** To remove the residual gas from a container/system down to 1.013 bar, by opening the container/system to atmosphere.
[1] 在 EU/EEA，這些裝置是標以«CE»標誌。	[1] In the EU/EEA, these devices are marked «CE».

附則 8　原料及包裝材料的抽樣（SAMPLING OF STARTING AND PACKAGING MATERIALS）

原則（PRINCIPLE）	
抽樣是一個重要的作業。抽樣係只抽取一個批次中的一小部分。整體而言，有效結論不能以不具代表性之樣品所執行的試驗為依據。因此，正確的抽樣是品質保證系統的必要部分。	Sampling is an important operation in which only a small fraction of a batch is taken. Valid conclusions on the whole cannot be based on tests which have been carried out on non-representative samples. Correct sampling is thus an essential part of a system of Quality Assurance.
註：抽樣規定於 GMP 總則中的第 6 章 6.11 到 6.14 條。本附則係就原料及包裝材料之抽樣提供附加的規定。	Note: Sampling is dealt with in Chapter 6 of the Guide to GMP, items 6.11 to 6.14. These supplementary guidelines give additional guidance on the sampling of starting and packaging materials.
組織與人事（PERSONNEL）	
1. 抽樣人員應接受與正確抽樣相關之職前及持續定期訓練。本訓練應包括：	1. Personnel who take samples should receive initial and on-going regular training in the disciplines relevant to correct sampling. This training should include:
➢ 抽樣計畫；	➢ sampling plans,
➢ 書面抽樣程序；	➢ written sampling procedures,
➢ 抽樣技術及設備；	➢ the techniques and equipment for sampling,
➢ 交叉污染的風險；	➢ the risks of cross-contamination,
➢ 關於不安定的及/或無菌的物質要採取的預防措施；	➢ the precautions to be taken with regard to unstable and/or sterile substances,
➢ 考慮原物料、容器及標籤之目視外觀的重要性；	➢ the importance of considering the visual appearance of materials, containers and labels,
➢ 記錄任何非預期或異常狀況的重要性。	➢ the importance of recording any unexpected or unusual circumstances.
原料（STARTING MATERIALS）	
2. 原料之完整批次的鑑識，通常只有在自全部容器中抽取個別樣品，並對每一樣品執行鑑別試驗時始能確保。已建立確效程序確保無任何原料容器會被不正確的標示者，可容許只對一定比例之容器抽樣。	2. The identity of a complete batch of starting materials can normally only be ensured if individual samples are taken from all the containers and an identity test performed on each sample. It is permissible to sample only a proportion of the containers where a validated procedure has been established to ensure that no single container of starting

	material will be incorrectly identified on its label.
3. 本確效應至少考慮下列項目：	3. This validation should take account of at least the following aspects:
➢ 製造商與供應商的本質與狀況及其對製藥工業 GMP 要求的瞭解；	➢ nature and status of the manufacturer and of the supplier and their understanding of the GMP requirements of the Pharmaceutical Industry;
➢ 原料製造商的品質保證系統；	➢ the Quality Assurance system of the manufacturer of the starting material;
➢ 原料之生產及管制所依循的製造條件；	➢ the manufacturing conditions under which the starting material is produced and controlled;
➢ 原料的特質及將使用該原料之藥品。	➢ the nature of the starting material and the medicinal products in which it will be used.
在上述安排下，一個經確效的程序，對於下列情形，可接受免除每一進廠容器中原料的鑑別試驗：	Under such arrangements, it is possible that a validated procedure exempting identity testing of each incoming container of starting material could be accepted for:
➢ 來自單一產品製造商或工廠的原料；	➢ starting materials coming from a single product manufacturer or plant;
➢ 直接來自於製造商的原料或源自製造商已封緘之容器中的原料，其製造商應具有可信賴的歷史紀錄及由買方(藥品的製造商或經由官方認證的團體)定期稽查製造商之品質保證系統。	➢ starting materials coming directly from a manufacturer or in the manufacturer's sealed container where there is a history of reliability and regular audits of the manufacturer's Quality Assurance system are conducted by the purchaser (the manufacturer of the medicinal products or by an officially accredited body.)
對於下列情形，上述程序欲達成滿意的確效是不可能的：	It is improbable that a procedure could be satisfactorily validated for:
➢ 由中間商，例如由仲介者所供應之原料，其製造來源不明或未經稽查者；	➢ starting materials supplied by intermediaries such as brokers where the source of manufacture is unknown or not audited;
➢ 供注射產品使用的原料。	➢ starting materials for use in parenteral products.

4. 原料批次的品質，可藉由抽取並測試具代表性的樣品予以評價。供鑑別試驗抽取之樣品，可供此目的使用。為製備代表性樣品所抽取的樣品數，應依統計學的方法決定，並規定於抽樣計畫書中。個別樣品可能可以混合以構成一個組合樣品，混合之樣品數應考量原料的特質、供應商的瞭解及組合樣品的均質性予以界定。	4. The quality of a batch of starting materials may be assessed by taking and testing a representative sample. The samples taken for identity testing could be used for this purpose. The number of samples taken for the preparation of a representative sample should be determined statistically and specified in a sampling plan. The number of individual samples which may be blended to form a composite sample should also be defined, taking into account the nature of the material, knowledge of the supplier and the homogeneity of the composite sample.
包裝材料（PACKAGING MATERIAL）	
5. 包裝材料的抽樣計畫應至少考量下列事項：接收的數量、要求的品質、物料的特質(例如，直接包裝材料及/或印刷的包裝材料)、生產方法及藉由稽查瞭解包裝材料製造商之品質保證系統。抽取之樣品數應依統計學的方法決定並規定在抽樣計畫書中。	5. The sampling plan for packaging materials should take account of at least the following: the quantity received, the quality required, the nature of the material (e.g. primary packaging materials and/or printed packaging materials), the production methods, and the knowledge of Quality Assurance system of the packaging materials manufacturer based on audits. The number of samples taken should be determined statistically and specified in a sampling plan.

附則 9　液劑、乳膏及軟膏的製造（MANUFACTURE OF LIQUIDS, CREAMS AND OINTMENTS）

原則（PRINCIPLE）	
製造過程中，液劑、乳膏及軟膏可能特別容易受到微生物及其他污染。因此，應採取特別措施，以防止任何污染。	Liquids, creams and ointments may be particularly susceptible to microbial and other contamination during manufacture. Therefore special measures must be taken to prevent any contamination.
註：液劑、乳膏劑和軟膏劑的製造，應依 GMP 之總則及其他適用的附則，本附則僅強調該類產品製造之重點。	Note: The manufacture of liquids, creams and ointments must be done in accordance with the GMP described in the PIC Guide to GMP and with the other supplementary guidelines, where applicable. The present guidelines only stress points which are specific to this manufacture.
廠房設施及設備（PREMISES AND EQUIPMENT）	
1. 為防止產品受到污染，建議使用密閉的作業及轉送系統。產品或未封口之潔淨容器所暴露的生產區，通常應以過濾空氣予以有效通風。	1. The use of closed systems of processing and transfer is recommended in order to protect the product from contamination. Production areas where the products or open clean containers are exposed should normally be effectively ventilated with filtered air.
2. 儲槽、容器、管路及幫浦應予設計及安裝，使其易於清潔，且必要時應予以滅菌處理。特別是設備的設計，應使可能積聚殘留物及可能促進微生物增殖的盲管或部位減至最小。	2. Tanks, containers, pipework and pumps should be designed and installed so that they may be readily cleaned and if necessary sanitised. In particular, equipment design should include a minimum of dead-legs or sites where residues can accumulate and promote microbial proliferation.
3. 應盡可能避免玻璃器具的使用。高品質的不銹鋼常是與產品接觸的首選材質。	3. The use of glass apparatus should be avoided wherever possible. High quality stainless steel is often the material of choice for product contact parts.
生產（PRODUCTION）	

4. 生產用水之化學與微生物學上的品質應予規定並監測。水系統的維護保養應予以注意，以避免微生物增殖的風險。水系統之任何化學滅菌處理後，接著應有經過確效的沖洗程序，以確保滅菌處理劑已有效移除。	4. The chemical and microbiological quality of water used in production should be specified and monitored. Care should be taken in the maintenance of water systems in order to avoid the risk of microbial proliferation. After any chemical sanitization of the water systems, a validated flushing procedure should be followed to ensure that the sanitising agent has been effectively removed.
5. 以大容量槽車接收之原料的品質，在被輸送到大容量儲槽前，應予以檢查。	5. The quality of materials received in bulk tankers should be checked before they are transferred to bulk storage tanks.
6. 經由管路輸送原料時應小心，以確保其送至正確的目的地。	6. Care should be taken when transferring materials via pipelines to ensure that they are delivered to their correct destination.
7. 易於釋出纖維或其他污染物的材料，例如厚紙板或木質棧板，不得進入產品或潔淨容器暴露所在的區域。	7. Materials likely to shed fibres or other contaminants, like cardboard or wooden pallets, should not enter the areas where products or clean containers are exposed.
8. 充填時應小心維持混合物或懸液劑等之均質性。混合及充填製程應予確效。充填製程開始時、暫停後及製程終了時，應予特別注意，以確保維持其均質性。	8. Care should be taken to maintain the homogeneity of mixtures, suspensions, etc. during filling. Mixing and filling processes should be validated. Special care should be taken at the beginning of a filling process, after stoppages and at the end of the process to ensure that homogeneity is maintained.
9. 最終產品不立即分/包裝者，應規定其最長的儲存期間及儲存條件並遵循之。	9. When the finished product is not immediately packaged, the maximum period of storage and the storage conditions should be specified and respected.

附則 10 加壓計量劑量之吸入用氣化噴霧劑的製造（MANUFACTURE OF PRESSURISED METERED DOSE AEROSOL PREPARATIONS FOR INHALATION）

原則（PRINCIPLE）	
附有計量閥之吸入用加壓氣化噴霧劑產品的製造，需要源自該藥劑劑型之特質的特別規定。其製造應在使微生物及微粒污染能減到最低的條件下進行。計量閥組件之品質的確保，以及，若為懸液劑，其均一性的確保均特別重要。	Manufacture of pressurised aerosol products for inhalation with metering valves requires some special provisions arising from the particular nature of this pharmaceutical form. It should occur under conditions which minimise microbial and particulate contamination. Assurance of the quality of the valve components and, in the case of suspensions, of uniformity is also of particular importance.
註：計量劑量氣化噴霧劑的製造必須依 PIC/S 指引所述之 GMP，及可行時，依其他補充指引執行。本附則僅強調針對本製造的重點。	Note: The manufacture of metered dose aerosols must be done in accordance with the GMP described in the PIC Guide to GMP and with the other supplementary guidelines, where applicable. The present guidelines only stress points which are specific to this manufacture.
概述（GENERAL）	
1. 目前，氣化噴霧劑有如下兩種通用的製造及灌充方法：	1. There are presently two common manufacturing and filling methods as follows:
a) 二次灌充系統（壓力灌充法）(Two-shot system)：先將有效成分懸浮於高沸點的推進劑中，再將該劑量充填到氣化噴霧劑的容器，後將計量閥捲縮於容器上，並透過計量閥桿將較低沸點的推進劑灌入，以製得最終產品。推進劑中之有效成分的懸浮液應保持低溫，以減少揮發損失。	a) Two-shot system (pressure filling). The active ingredient is suspended in a high boiling point propellant, the dose is filled into the container, the valve is crimped on and the lower boiling point propellant is injected through the valve stem to make up the finished product. The suspension of active ingredient in propellant is kept cool to reduce evaporation loss.
b) 一次灌充製程(One-shot process)（冷充填法）：將有效成分懸浮於推進劑的混合物中，並在高壓及/或在低溫下保存。後在一次灌充/充填中，將懸浮液直接注入容器中。	b) One-shot process (cold filling). The active ingredient is suspended in a mixture of propellants and held either under high pressure and/or at a low temperature. The suspension is then filled directly into the container in one shot.

廠房設施與設備（PREMISES AND EQUIPMENT）	
2. 製造與充填作業應盡可能在密閉系統中執行。	2. Manufacture and filling should be carried out as far as possible in a closed system.
3. 產品或潔淨的組件暴露之區域，應供應經過濾的空氣、至少符合 D 級環境的要求，且應通過氣鎖室進入。	3. Where products or clean components are exposed, the area should be fed with filtered air, should comply with the requirements of at least a Grade D environment and should be entered through airlocks.
生產與品質管制（PRODUCTION AND QUALITY CONTROL）	
4. 氣化噴霧劑之計量閥的設計是比大多數藥用組件更複雜，故規格、抽樣與測試應合適於此情況。稽查計量閥製造廠的品質保證系統特別重要。	4. Metering valves for aerosols are a more complex engineering article than most pharmaceutical components. Specifications, sampling and testing should be appropriate for this situation. Auditing the Quality Assurance system of the valve manufacturer is of particular importance.
5. 所有流體（例如液態或氣態推進劑）應經過濾，以除去大於 0.2 μm 的粒子。如有可能，緊臨充填前最好再次過濾。	5. All fluids (e.g. liquid or gaseous propellants) should be filtered to remove particles greater than 0.2 micron. An additional filtration where possible immediately before filling is desirable.
6. 容器與計量閥之清潔應使用適合於該產品且經確效的方法，以確保無任何污染物例如設備裝配助劑（例如潤滑油）或微生物學上的污染。在清潔之後，計量閥應保存在潔淨且密閉的容器中，並於後續處理，例如取樣，採取預防污染的措施。容器應以潔淨的狀態提供至充填線，或在緊臨充填前於線上清潔。	6. Containers and valves should be cleaned using a validated procedure appropriate to the use of the product to ensure the absence of any contaminants such as fabrication aids (e.g. lubricants) or undue microbiological contaminants. After cleaning, valves should be kept in clean, closed containers and precautions taken not to introduce contamination during subsequent handling, e.g. taking samples. Containers should be provided to the filling line in a clean condition or cleaned on line immediately before filling.
7. 在整個充填過程中應採取預防措施，以確保懸浮液在充填點的均一性。	7. Precautions should be taken to ensure uniformity of suspensions at the point of fill throughout the filling process.
8. 採用二次灌充製程者，為達到正確的組成，需要確保兩次充填皆有正確的重量。為此目的，最好在每一階段執行 100%的重量檢查。	8. When a two-shot filling process is used, it is necessary to ensure that both shots are of the correct weight in order to achieve the correct composition. For this purpose, 100% weight checking at each stage is often desirable.
9. 充填後的管制應確保無洩漏。任何洩漏試驗應以避免微生物污染或殘留水分的方式執行。	9. Controls after filling should ensure the absence of undue leakage. Any leakage test should be performed in a way which avoids microbial

	contamination or residual moisture.

附則 11 電腦化系統（COMPUTERISED SYSTEMS）

原則（PRINCIPLE）	
本附則適用於作為GMP管理活動使用之電腦化系統，電腦化系統是一套軟體與硬體組件，共同應用以完成某些功能。	This annex applies to all forms of computerised systems used as part of a GMP regulated activities. A computerised system is a set of software and hardware components which together fulfill certain functionalities.
該應用軟體應進行確效；資訊技術之基礎設施應該加以驗證。	The application should be validated; IT infrastructure should be qualified.
電腦化系統取代手工作業時，不得有降低產品品質、製程管制或品質保證之結果。不應增加該流程的整體風險。	Where a computerised system replaces a manual operation, there should be no resultant decrease in product quality, process control or quality assurance. There should be no increase in the overall risk of the process.
概述（GENERAL）	
1. ***風險管理（Risk Management）***	
在考慮病人安全性、數據完整性與產品品質下，風險管理應應用於電腦化系統的整個生命週期。作為風險管理系統之一部分，確效與數據完整性管制的程度之決定，應基於已證明其合理性並文件化之電腦化系統的風險評估。	Risk management should be applied throughout the lifecycle of the computerised system taking into account patient safety, data integrity and product quality. As part of a risk management system, decisions on the extent of validation and data integrity controls should be based on a justified and documented risk assessment of the computerised system.
2. ***組織與人事（Personnel）***	
所有相關人員如：流程權責人員、系統權責人員、被授權人員與資訊技術人員之間應有密切的合作。所有人員應具備適當的資格認可、可存取的層級及所界定的責任，以執行其所被指定的職務。	There should be close cooperation between all relevant personnel such as Process Owner, System Owner, Authorised Persons and IT. All personnel should have appropriate qualifications, level of access and defined responsibilities to carry out their assigned duties.
3. ***供應商與服務提供者（Suppliers and Service Providers）***	

3.1 當使用第三方（如：供應商、服務提供者），例如：提供、安裝、配置、整合、確效、維護（如：經由遠端存取）、修改或保存電腦化系統，或相關服務提供或為數據處理時，則在製藥廠與任何第三方之間必須具備正式協議，而且該等協議應包括第三方責任的明確聲明。資訊技術部門亦應有類似考量。	3.1 When third parties (e.g. suppliers, service providers) are used e.g. to provide, install, configure, integrate, validate, maintain (e.g. via remote access), modify or retain a computerised system or related service or for data processing, formal agreements must exist between the manufacturer and any third parties, and these agreements should include clear statements of the responsibilities of the third party. IT-departments should be considered analogous.
3.2 當選擇電腦化系統相關產品或服務的提供者時，供應商的能力與可靠性是關鍵因素。稽查的需要性應基於風險評估。	3.2 The competence and reliability of a supplier are key factors when selecting a product or service provider. The need for an audit should be based on a risk assessment.
3.3 商業上現成之套裝產品所附的文件，應經由使用者進行審核，以核對符合使用者要求。	3.3 Documentation supplied with commercial off-the-shelf products should be reviewed by regulated users to check that user requirements are fulfilled.
3.4 與軟體供應商或開發者及其所實施之系統有關的品質系統及其稽核資訊，當稽查員要求時應可隨時提供。	3.4 Quality system and audit information relating to suppliers or developers of software and implemented systems should be made available to inspectors on request.
計畫階段（PROJECT PHASE）	
4. *確效（Validation）*	
4.1 確效文件與報告應包括生命週期的相關步驟。製造業者應能基於風險評估證明其標準、計畫書、允收標準、程序與紀錄的正當性。	4.1 The validation documentation and reports should cover the relevant steps of the life cycle. Manufacturers should be able to justify their standards, protocols, acceptance criteria, procedures and records based on their risk assessment.
4.2 確效文件應包括在確效過程中，所觀察到之任何偏差的變更管制紀錄（適用時）與報告。	4.2 Validation documentation should include change control records (if applicable) and reports on any deviations observed during the validation process.
4.3 應具備所有相關系統及其GMP功能性的最新清單。	4.3 An up to date listing of all relevant systems and their GMP functionality (inventory) should be available.

	對於關鍵性系統，應具備詳述其實體與邏輯的安排、數據流及其與其它系統或程序的連結、任何硬體與軟體的先決條件及安全措施的最新系統描述。		For critical systems an up to date system description detailing the physical and logical arrangements, data flows and interfaces with other systems or processes, any hardware and software pre-requisites, and security measures should be available.
4.4	使用者要求規格應基於書面的風險評估與GMP的影響，並描述電腦化系統所需要的功能。使用者之要求應在整個生命週期是可以追溯的。	4.4	User Requirements Specifications should describe the required functions of the computerised system and be based on documented risk assessment and GMP impact. User requirements should be traceable throughout the life-cycle.
4.5	使用者應採取所有合理的步驟，以確保該系統已依適當的品質管理系統開發。應對供應商進行適當的評估。	4.5	The regulated user should take all reasonable steps, to ensure that the system has been developed in accordance with an appropriate quality management system. The supplier should be assessed appropriately.
4.6	對於訂製/客製化之電腦化系統的確效，應備有過程，以確保系統之所有生命週期階段的品質與性能措施經正式評估與提報。	4.6	For the validation of bespoke or customised computerised systems there should be a process in place that ensures the formal assessment and reporting of quality and performance measures for all the life-cycle stages of the system.
4.7	應呈現適當測試方法與測試方案的證據。特別是，應考慮系統（流程）參數限度、數據限度與錯誤處理。自動化測試工具與試驗環境的適當性應有書面化評估。	4.7	Evidence of appropriate test methods and test scenarios should be demonstrated. Particularly, system (process) parameter limits, data limits and error handling should be considered. Automated testing tools and test environments should have documented assessments for their adequacy.
4.8	如果數據轉換到另一種數據格式或系統時，確效應該包括在此轉移過程中，核對其數值及/或意義並未改變。	4.8	If data are transferred to another data format or system, validation should include checks that data are not altered in value and/or meaning during this migration process.
操作階段（OPERATIONAL PHASE）			
5.	***數據（Data）***		
	為了將風險減到最低，與其他系統以電子方式交換數據之電腦化系統，對於數據的正確與安全登入及處理應包括適當之內建核對。		Computerised systems exchanging data electronically with other systems should include appropriate built-in checks for the correct and secure entry and processing of data, in order to minimize the risks.
6.	***準確性核對（Accuracy Checks）***		

	關鍵資料以手工輸入者，應就其數據的準確性再次核對。該核對得由第二位操作者，或由已確效的電子方法執行。對系統輸入錯誤或不正確之數據的嚴重性與潛在後果應涵蓋於風險管理中。		For critical data entered manually, there should be an additional check on the accuracy of the data. This check may be done by a second operator or by validated electronic means. The criticality and the potential consequences of erroneous or incorrectly entered data to a system should be covered by risk management.
7.	***數據儲存（Data Storage）***		
7.1	數據應經由防止損壞的實體與電子方法以維護其安全。所儲存的數據應對其可存取性、可讀性與準確性進行核對。保留期間，應確保數據可存取。	7.1	Data should be secured by both physical and electronic means against damage. Stored data should be checked for accessibility, readability and accuracy. Access to data should be ensured throughout the retention period.
7.2	所有相關數據應定期備份。備份數據的完整性、準確性及回復該數據的能力，應在確效期間加以核對，並應定期監測。	7.2	Regular back-ups of all relevant data should be done. Integrity and accuracy of backup data and the ability to restore the data should be checked during validation and monitored periodically.
8.	***列印本（Printouts）***		
8.1	以電子方式儲存的數據，應能獲得清晰列印的複本。	8.1	It should be possible to obtain clear printed copies of electronically stored data.
8.2	對於支持批次放行的紀錄，應能產生顯示任何原始輸入數據是否已被變更之列印本。	8.2	For records supporting batch release it should be possible to generate printouts indicating if any of the data has been changed since the original entry.
9.	***追蹤稽核（Audit Trails）***		
	基於風險評估，所有GMP相關變更與刪除之紀錄的產生，應考慮內建於此系統中（系統產生的「追蹤稽核」）。對於GMP相關數據之變更或刪除，應將其原因加以文件化。追蹤稽核需能取得並能轉換成一般可理解的形式，且需定期檢討。		Consideration should be given, based on a risk assessment, to building into the system the creation of a record of all GMP-relevant changes and deletions (a system generated "audit trail"). For change or deletion of GMP-relevant data the reason should be documented. Audit trails need to be available and convertible to a generally intelligible form and regularly reviewed.
10.	***變更與組態管理（Change and Configuration Management）***		
	對於電腦化系統的任何變更，包括系統組態在內，應以受管控的方式依界定的程序進行。		Any changes to a computerised system including system configurations should only be made in a controlled manner in accordance with a defined procedure.
11.	***定期評估（Periodic evaluation）***		

電腦化系統應進行定期評估，以確認其保持於有效的狀態並符合GMP。合適時，該等評估應包括現行功能性的範圍、偏差紀錄、偶發事件、問題、升級歷程、性能、可靠性、安全性以及確效狀態報告。	Computerised systems should be periodically evaluated to confirm that they remain in a valid state and are compliant with GMP. Such evaluations should include, where appropriate, the current range of functionality, deviation records, incidents, problems, upgrade history, performance, reliability, security and validation status reports.
12. *安全性（Security）*	
12.1 應備有實體及/或邏輯管控，以限制僅被授權人員進入電腦化系統。防止未被授權進入該系統的適當方法，可能包括使用鑰匙、通行卡、個人密碼、生物識別技術及限制進入電腦設備與數據儲存區。	12.1 Physical and/or logical controls should be in place to restrict access to computerized system to authorised persons. Suitable methods of preventing unauthorised entry to the system may include the use of keys, pass cards, personal codes with passwords, biometrics, restricted access to computer equipment and data storage areas.
12.2 安全管控的程度依電腦化系統的重要性而定。	12.2 The extent of security controls depends on the criticality of the computerised system.
12.3 進入電腦化系統之授權的建立、變更與取消應加以記錄。	12.3 Creation, change, and cancellation of access authorisations should be recorded.
12.4 對於數據及文件的管理系統應加以設計，以記錄登入、變更、確認或刪除數據之操作人員的身分，包含日期與時間在內。	12.4 Management systems for data and for documents should be designed to record the identity of operators entering, changing, confirming or deleting data including date and time.
13. *偶發事件管理（Incident Management）*	
所有偶發事件皆應提報與評估，包括系統失效及數據錯誤。關鍵事件的根本原因應加以鑑別，以作為矯正與預防措施的基礎。	All incidents, not only system failures and data errors, should be reported and assessed. The root cause of a critical incident should be identified and should form the basis of corrective and preventive actions.
14. *電子簽章（Electronic Signature）*	
電子紀錄可以電子方式簽署。電子簽章應：	Electronic records may be signed electronically. Electronic signatures are expected to:
a. 與公司內部的手寫簽名具有相同的效力，	a. have the same impact as hand-written signatures within the boundaries of the company,
b. 與其各自的紀錄永久連結，	b. be permanently linked to their respective record,
c. 包括其使用的日期與時間。	c. include the time and date that they were applied.
15. *批次放行（Batch release）*	

當電腦化系統使用於記錄批次認可與放行時，應只允許被授權人員認可批次放行，且應清楚辨識並記錄放行或認可該等批次的人員。這應使用電子簽章執行之。	When a computerised system is used for recording certification and batch release, the system should allow only Authorised Persons to certify the release of the batches and it should clearly identify and record the person releasing or certifying the batches. This should be performed using an electronic signature.
16. ***作業連續性（Business Continuity）***	
對於支持關鍵過程之電腦化系統的可用性，應提供確保系統當機時，能支持關鍵過程的連續性之措施（如：手動或替代系統）。基於風險，導入使用替代系統所需的時間，應適合特定的系統及其支持的作業過程。前述之安排應加以充分文件化及測試。	For the availability of computerised systems supporting critical processes, provisions should be made to ensure continuity of support for those processes in the event of a system breakdown (e.g. a manual or alternative system). The time required to bring the alternative arrangements into use should be based on risk and appropriate for a particular system and the business process it supports. These arrangements should be adequately documented and tested.
17. ***存檔（Archiving）***	
數據得進行存檔。該存檔數據應核對其可存取性、可讀性與完整性。若該系統（如：電腦設備或程式）進行相關的變更時，則應確保並測試其擷取數據的能力。	Data may be archived. This data should be checked for accessibility, readability and integrity.If relevant changes are to be made to the system (e.g. computer equipment or programs), then the ability to retrieve the data should be ensured and tested.
術語彙編（GLOSSARY）	
應用軟體 安裝於界定的平台/硬體上，提供特定功能的軟體。	**Application** Software installed on a defined platform/hardware providing specific functionality.
訂製/客製化的電腦化系統 個別設計以適合特定之作業過程的電腦化系統。	**Bespoke/Customized computerised system** A computerised system individually designed to suit a specific business process.
商業套裝軟體 市售的軟體，其適用性已經過廣泛的使用者所證明。	**Commercial of the shelf software** Software commercially available, whose fitness for use is demonstrated by a broad spectrum of users.
資訊技術之基礎設施 硬體與軟體（如：網路軟體與作業系統），可使應用軟體發揮功能。	**IT Infrastructure** The hardware and software such as networking software and operation systems, which makes it possible for the application to function.

生命週期 係指系統從初始需求到退役之生命中的所有階段，包括設計、規格、程式設計、測試、安裝、操作與維護保養在內。	**Life cycle** All phases in the life of the system from initial requirements until retirement including design, specification, programming, testing, installation, operation, and maintenance.
流程權責人員 作業流程的負責人員。	**Process owner** The person responsible for the business process.
系統權責人員 對於電腦化系統之可用性與維護保養，以及對於留存在該系統之數據安全性的負責人員。	**System owner** The person responsible for the availability, and maintenance of a computerised system and for the security of the data residing on that system.
第三方 非由製造許可及/或輸入許可持有者直接管理的各方。	**Third Party** Parties not directly managed by the holder of the manufacturing and/or import authorisation.

附則 12 游離輻射在藥品製造上的應用（USE OF IONISING RADIATION IN THE MANUFACTURE OF MEDICINAL PRODUCTS）

前言（INTRODUCTION）	
游離輻射可因應不同目的，使用在製造過程中，包括負荷菌的減少與原料、包材或產品的滅菌及血液產品之處理等。	Ionising radiation may be used during the manufacturing process for various purposes including the reduction of bioburden and the sterilisation of starting materials, packaging components or products and the treatment of blood products.
有兩種類型的輻射照射程序：一為來自放射源的加馬輻射照射，二為來自加速器的高能電子輻射照射（貝他輻射）。	There are two types of irradiation process: Gamma irradiation from a radioactive source and high energy Electron irradiation (Beta radiation) from an accelerator.
加馬輻射照射：有兩種不同的操作模式可供使用：	Gamma irradiation: two different processing modes may be employed:
(i) 批次模式：指將產品放置在環繞於放射源的固定位置上，且在放射源暴露時，不能進行裝載或卸載。	(i) Batch mode: the products is arranged at fixed locations around the radiation source and cannot be loaded or unloaded while the radiation source is exposed.
(ii) 連續模式：指自動化系統將產品輸送到照射室中，沿著經界定的路徑並以適當的速度通過暴露的放射源後，離開照射室。	(ii) Continuous mode: an automatic system conveys the products into the radiation cell, past the exposed radiation source along a defined path and at an appropriate speed, and out of the cell.
電子輻射照射：指將產品輸送通過一連續式或脈衝式高能電子束(貝他輻射)，並將該電子束來回掃描該產品的穿越路徑。	Electron irradiation: the product is conveyed past a continuous or pulsed beam of high energy electrons (Beta radiation) which is scanned back and forth across the product pathway.
責任（RESPONSIBILITIES）	
1. 輻射照射處理得由藥廠或根據合約由輻射照射廠(受託製造者)的操作者執行。兩者皆應持有製造許可。	1. Treatment by irradiation may be carried out by the pharmaceutical manufacturer or by an operator of a radiation facility under contract (a "contract manufacturer"), both of whom must hold an appropriate manufacturing authorization.

2. 藥廠承擔產品品質的責任，包含達成輻射照射的目標。輻射照射廠的受託操作者所負擔的責任是確保將藥廠要求的輻射劑量傳送到照射容器(亦即，產品受照射時最外側的容器)。	2. The pharmaceutical manufacturer bears responsibility for the quality of the product including the attainment of the objective of irradiation. The contract operator of the radiation facility bears responsibility for ensuring that the dose of radiation required by the manufacturer is delivered to the irradiation container (i.e. the outermost container in which the products are irradiated).
3. 載明所要求的輻射劑量於該產品的上市許可申請中，包括經證明為合理的限量。	3. The required dose including justified limits will be stated in the marketing authorization for the product.
劑量測定法（DOSIMETRY）	
4. 劑量測定法，係界定為使用劑量計量測所吸收的劑量。對此技術之瞭解及正確使用，對該過程的確效、試運轉及管制是必需的。	4. Dosimetry is defined as the measurement of the absorbed dose by the use of dosimeters. Both understanding and correct use of the technique is essential for the validation, commissioning and control of the process.
5. 每批例行劑量計之校正，應可追溯至國家標準或國際標準。校正的有效期間應予載明、經證明為合理並應遵守。	5. The calibration of each batch of routine dosimeters should be traceable to a national or international standard. The period of validity of the calibration should be stated, justified and adhered to.
6. 通常，應使用同一儀器來建立例行劑量計之校正曲線，並用來量測輻射照射後，劑量計之吸收度的變異。使用不同儀器者，應建立各儀器之絕對吸收度。	6. The same instrument should normally be used to establish the calibration curve of the routine dosimeters and to measure the change in their absorbance after irradiation. If a different instrument is used, the absolute absorbance of each instrument should be established.
7. 隨使用之劑量計的類型，應注意其不精確的可能原因，包括水分含量的改變、溫度的改變、照射與量測間所經歷的時間及劑量率等。	7. Depending on the type of dosimeter used, due account should be taken of possible causes of inaccuracy including the change in moisture content, change in temperature, time elapsed between irradiation and measurement, and the dose rate.
8. 用來量測劑量計吸收度變化之儀器的波長及用來量測劑量計厚度之儀器，應根據其穩定性、目的與用途所建立之時間間隔，進行定期檢查其校正狀態。	8. The wavelength of the instrument used to measure the change in absorbance of dosimeters and the instrument used to measure their thickness should be subject to regular checks of calibration at intervals established on the basis of stability, purpose and usage.

過程確效（VALIDATION OF THE PROCESS）	
9. 確效是證實把預定被吸收之劑量傳送到產品的過程，將會達到預期之結果的行動。關於確效之要求，在「游離輻射在藥品製造上之應用」的指引中有更充分說明。	9. Validation is the action of proving that the process, i.e. the delivery of the intended absorbed dose to the product, will achieve the expected results. The requirements for validation are given more fully in the note for guidance on "the use of ionising radiation in the manufacture of medicinal products"
10. 確效應包含劑量分佈圖之繪製，以建立照射容器內經界定之產品裝載型式時，其吸收劑量的分佈。	10. Validation should include dose mapping to establish the distribution of absorbed dose within the irradiation container when packed with product in a defined configuration.
11. 輻射照射過程的規格至少應包括下列各項：	11. An irradiation process specification should include at least the following:
a) 產品分/包裝的細節；	a) details of the packaging of the product;
b) 產品在照射容器內之裝載型式。照射容器中允許不同產品之混合裝載時，應特別注意，不使其發生高密度產品之劑量不足，或其他產品被高密度產品遮蔽的情形。每一混裝產品的安排皆應予以規定與確效；	b) the loading pattern(s) of product within the irradiation container. Particular care needs to be taken, when a mixture of products is allowed in the irradiation container, that there is no underdosing of dense product or shadowing of other products by dense product. Each mixed product arrangement must be specified and validated;
c) 環繞放射源(批次模式)或通過照射室的路徑(連續模式)之照射容器的裝載型式；	c) the loading pattern of irradiation containers around the source (batch mode) or the pathway through the cell (continuous mode);
d) 產品之最大及最小的吸收劑量限量【以及相關的例行劑量量測法】；	d) maximum and minimum limits of absorbed dose to the product [and associated routine dosimetry];
e) 照射容器之最大及最小的吸收劑量限量及監測該吸收劑量之相關的例行劑量量測法；	e) maximum and minimum limits of absorbed dose to the irradiation container and associated routine dosimetry to monitor this absorbed dose;
f) 其他過程參數，包括劑量率、最長暴露時間、暴露次數等。	f) other process parameters, including dose rate, maximum time of exposure, number of exposures, etc.
依契約提供輻射照射時，至少照射過程規格中之(d)及(e)兩個項目應明列於契約中。	When irradiation is supplied under contract at least parts (d) and (e) of the irradiation process specification should form part of that contract.
輻射照射廠的試運轉（COMMISSIONING OF THE PLANT）	
概述（General）	

12. 試運轉是取得並作成文件證據的作業，以證明輻射照射廠在依過程規格操作時，將會持續一致地在預定限量內運轉。本附則中，預定限量指設計將為被照射容器吸收之最大及最小劑量。工廠的運轉不應在操作者不知悉的情形下，發生供應照射容器之劑量超出限量的變異。	12. Commissioning is the exercise of obtaining and documenting evidence that the irradiation plant will perform consistently within predetermined limits when operated according to the process specification. In the context of this annex, predetermined limits are the maximum and minimum doses designed to be absorbed by the irradiation container. It must not be possible for variations to occur in the operation of the plant which give a dose to the container outside these limits without the knowledge of the operator.
13. 試運轉應包括下列的基本要件：	13. Commissioning should include the following elements:
a. 設計	a. Design;
b. 繪製劑量分佈圖	b. Dose mapping;
c. 文件製作	c. Documentation;
d. 重新試運轉之要求	d. Requirement for re-commissioning.
加馬照射器（Gamma irradiators）	
設計 （Design）	
14. 在加馬照射器內之任一特定點上，由照射容器的特定位置接受之吸收劑量，主要取決於下列因素：	14. The absorbed dose received by a particular part of an irradiation container at any specific point in the irradiator depends primarily on the following factors:
a) 放射源的活性與幾何形狀；	a) the activity and geometry of the source;
b) 放射源到容器的距離；	b) the distance from source to container;
c) 由計時器設定或輸送帶速度所控制之輻射照射的期間；	c) the duration of irradiation controlled by the timer setting or conveyor speed;
d) 放射源與照射容器之特定位置間，材料(包含其他產品在內) 的組成與密度。	d) the composition and density of material, including other products, between the source and the particular part of the container.
15. 總吸收劑量還將取決於照射容器通過連續照射器之路徑或在批次照射器中的裝載型式及暴露週期的次數。	15. The total absorbed dose will in addition depend on the path of containers through a continuous irradiator or the loading pattern in a batch irradiator, and on the number of exposure cycles.
16. 具有固定路徑的連續性照射器，或具有固定裝載型式的批次照射器，如具有一定之放射源強度與產品類型，則由操作者控制之關鍵參數即為輸送帶的速度或計時器的設定。	16. For a continuous irradiator with a fixed path or a batch irradiator with a fixed loading pattern, and with a given source strength and type of product, the key plant parameter controlled by the operator is conveyor speed or timer setting.

繪製劑量分佈圖 （Dose Mapping）	
17. 為劑量分佈圖之繪製程序，該照射器應滿載裝有模擬產品或裝有均勻密度之代表性產品。通過照射器之裝載的輻射照射容器，至少三個容器應遍及放置劑量計，且為相似容器或模擬產品所圍繞。產品非均一包裝者，應將劑量計置於更多的照射容器中。	17. For the dose mapping procedure, the irradiator should be filled with irradiation containers packed with dummy products or a representative product of uniform density. Dosimeters should be placed throughout a minimum of three loaded irradiation containers which are passed through the irradiator, surrounded by similar containers or dummy products. If the product is not uniformly packed, dosimeters should be placed in a larger number of containers.
18. 劑量計放置的位置取決於照射容器的大小。例如照射容器大小在 1× 1 × 0.5 公尺以下者，一個遍及該容器及該容器外部表面之每邊 20 公分三度空間的格子可能是適當的。從先前照射器表現之特性已知悉其最小及最大劑量之預期的位置者，有些劑量計可以從平均劑量區移出，並將之放置在極端劑量區，以形成一個每邊 10 公分格子的佈置。	18. The positioning of dosimeters will depend on the size of the irradiation container. For example, for containers up to 1 x 1 x 0.5 m, a three-dimensional 20 cm grid throughout the container including the outside surfaces might be suitable. If the expected positions of the minimum and maximum dose are known from a previous irradiator performance characterisation, some dosimeters could be removed from regions of average dose and replaced to form a 10 cm grid in the regions of extreme dose.
19. 對於已知的工廠參數、產品密度及裝載型式，該劑量分佈圖繪製的結果將可提供在產品中及在容器表面之最大及最小吸收劑量。	19. The results of this procedure will give minimum and maximum absorbed doses in the product and on the container surface for a given set of plant parameters, product density and loading pattern.
20. 對照劑量計由於其較佳的精密度，理想上應使用在劑量分佈圖繪製作業上。雖可使用例行劑量計，但建議在預計會有最大及最小劑量的位置邊及在每一受重複照射容器的例行監測位置放置對照劑量計。該測得的劑量值將會有相關的隨機不確定值。該不確定值可從重複量測中之變異進行估算。	20. Ideally, reference dosimeters should be used for the dose mapping exercise because of their greater precision. Routine dosimeters are permissible but it is advisable to place reference dosimeters beside them at the expected positions of minimum and maximum dose and at the routine monitoring position in each of the replicate irradiation containers. The observed values of dose will have an associated random uncertainty which can be estimated from the variations in replicate measurements.
21. 為確保所有照射容器接收之最低要求劑量，例行劑量計所測得之最小劑量，將依該使用之例行劑量計隨機變異性的了解予	21. The minimum observed dose, as measured by the routine dosimeters, necessary to ensure that all irradiation containers receive the

以設定。	minimum required dose will be set in the knowledge of the random variability of the routine dosimeters used.
22. 繪製劑量分佈圖時，照射器參數應維持恆定，並予以監測及記錄。該紀錄應連同劑量測定的結果及其他產生的紀錄一併保存。	22. Irradiator parameters should be kept constant, monitored and recorded during dose mapping. The records, together with the dosimetry results and all other records generated, should be retained.
電子束照射器（Electron Beam Irradiators）	
設計 （Design）	
23. 受照射產品之特定位置所接收到的吸收劑量，主要取決於下列因素：	23. The absorbed dose received by a particular portion of an irradiated product depends primarily on the following factors:
a) 電子束的特性，亦即：電子能量、平均電子束電流、掃描寬度及掃描均勻性；	a) the characteristics of the beam, which are: electron energy, average beam current, scan width and scan uniformity;
b) 輸送帶速度；	b) the conveyor speed;
c) 產品組成與密度；	c) the product composition and density;
d) 介於輸出窗口與產品之特定位置間的材料之組成、密度與厚度；	d) the composition, density and thickness of material between the output window and the particular portion of product;
e) 輸出窗口到照射容器的距離。	e) the output window to container distance.
24. 由操作者控制之關鍵參數為電子束的特性及輸送帶的速度。	24. Key parameters controlled by the operator are the characteristics of the beam and the conveyor speed.
繪製劑量分佈圖 （Dose Mapping）	
25. 為繪製劑量分佈圖，劑量計應放置在具均質吸收之模擬產品的層與層之間，或放置在具均質密度之代表性產品的層與層之間，以便在電子束的最大照射範圍內，至少可作出十個量測。並參考本附則第 18 至第 21 條。	25. For the dose mapping procedure, dosimeters should be placed between layers of homogeneous absorber sheets making up a dummy product, or between layers of representative products of uniform density, such that at least ten measurements can be made within the maximum range of the electrons. Reference should also be made to sections 18 to 21.
26. 繪製劑量分佈圖時，照射器參數應保持恆定，並予以監測及記錄。該紀錄應連同劑量計的量測結果及其他產生的紀錄一併保存。	26. Irradiator parameters should be kept constant, monitored and recorded during dose mapping. The records, together with the dosimetry results and all other records generated, should be retained.
重新試運轉（Re-commissioning）	

27. 過程或照射器的變更(例如，放射源的改變)如會影響照射器之劑量分佈時，應重新執行試運轉。重新執行試運轉的程度，取決於照射器或裝載經改變的程度。如有任何懷疑，則應重新執行試運轉。	27. Commissioning should be repeated if there is a change to the process or the irradiator which could affect the dose distribution to the irradiation container (e.g. change of source pencils). The extent to re-commissioning depends on the extent of the change in the irradiator or the load that has taken place. If in doubt, re-commission.
廠房設施（PREMISES）	
28. 廠房設施應經設計與運作，以將已照射與未經照射的容器隔離，避免其交叉污染/混雜。原物料在密閉的照射容器內處理時，若藥用原物料無被非藥用原物料污染的風險，則兩者不須隔離。	28. Premises should be designed and operated to segregate irradiated from non-irradiated containers to avoid their cross-contamination. Where materials are handled within closed irradiation containers, it may not be necessary to segregate pharmaceutical from non-pharmaceutical materials, provided there is no risk of the former being contaminated by the latter.
任何來自放射源之放射核種對產品污染的可能性皆應予以排除。	Any possibility of contamination of the products by radionuclide from the source must be excluded.
照射處理/加工處理（PROCESSING）	
29. 照射容器應依確效時所建立之特定型式予以裝載。	29. Irradiation containers should be packed in accordance with the specified loading pattern(s) established during validation.
30. 照射過程中，應使用經確效的劑量偵測程序，監測照射容器所受輻射劑量。製程確效及工廠試運轉期間該劑量與照射容器內之產品所吸收劑量間的關係應已建立完成。	30. During the process, the radiation dose to the irradiation containers should be monitored using validated dosimetry procedures. The relationship between this dose and the dose absorbed by the product inside the container must have been established during process validation and plant commissioning.
31. 已照射與未照射的容器應使用輻射指示劑做為輔助的區分方法。輻射指示劑不得用作區分的唯一方法，或作為完成照射處理的指標。	31. Radiation indicators should be used as an aid to differentiating irradiated from non-irradiated containers. They should not be used as the sole means of differentiation or as an indication of satisfactory processing.
32. 從試運轉試驗或其他證據，已知個別容器接收之照射劑量維持在特定的限量之內者，始得在照射室內照射處理混合裝載的容器。	32. Processing of mixed loads of containers within the irradiation cell should only be done when it is known from commissioning trials or other evidence that the radiation dose received by individual containers remains within the limits specified.

33. 所需之輻射劑量係由照射工廠設計利用多次暴露或多次通過照射源所達成者，應有上市許可持有者的同意，並在預定的期間內完成。因照射期間非計畫性之中斷導致延長照射過程超過先前同意的期間者，應通知上市許可持有者。	33. When the required radiation dose is by design given during more than one exposure or passage through the plant, this should be with the agreement of the holder of the marketing authorization and occur within a predetermined time period. Unplanned interruptions during irradiation should be notified to the holder of the marketing authorization if this extends the irradiation process beyond a previously agreed period.
34. 任何時候，未經照射的產品應與已照射的產品隔離，其作法包括輻射指示劑的使用(31 條)及廠房設施的適當設計(28 條)。	34. Non-irradiated products must be segregated from irradiated products at all times. Methods or doing this include the use of radiation indicators (31.) and appropriate design of premises (28.).
加馬照射器（Gamma irradiators）	
35. 連續式照射處理模式，其劑量計之放置至少應使兩個劑量計全程暴露於照射中。	35. For continuous processing modes, dosimeters should be placed so that at least two are exposed in the irradiation at all times.
36. 批次式模式，至少有兩個劑量計應暴露於與最低照射劑量相關的位置。	36. For batch modes, at least two dosimeters should be exposed in positions related to the minimum dose position.
37. 連續式照射處理模式，應有放射源之正確位置的明確指標，且在放射源位置與輸送帶移動間應有互鎖裝置。輸送帶的速度應予以連續監測並記錄。	37. For continuous process modes, there should be a positive indication of the correct position of the source and an interlock between source position and conveyor movement. Conveyor speed should be monitored continuously and recorded.
38. 批次式照射處理模式，放射源的移動及每批次的暴露時間應予以監測並記錄。	38. For batch process modes source movement and exposure times for each batch should be monitored and recorded.
39. 對某一期望劑量，其計時器的設定或輸送帶的速度需依放射源的衰變及放射源的添加予以調整。該設定或速度的有效期間應予以記錄並且遵循。	39. For a given desired dose, the timer setting or conveyor speed requires adjustment for source decay and source additions. The period of validity of the setting or speed should be recorded and adhered to.
電子束照射器（Electron Beam Irradiators）	
40. 每一容器上應放置一個劑量計。	40. A dosimeter should be placed on every container.
41. 平均電子束電流、電子能量、掃描寬度及輸送帶速度應予以連續記錄。輸送帶速度以外的上述變數，因易發生瞬間性變化，必須將其控制於試運轉期間所界定之限量內。	41. There should be continuous recording of average beam current, electron energy, scan-width and conveyor speed. These variables, other than conveyor speed, need to be controlled within the defined limits

	established during commissioning since they are liable to instantaneous change.
文件製作（DOCUMENTATION）	
42. 接收、照射及送出的容器數目應調和一致並符合相關文件。任何差異均應提出報告並解決。	42. The numbers of containers received, irradiated and dispatched should be reconciled with each other and with the associated documentation. Any discrepancy should be reported and resolved.
43. 照射廠的操作者，應以書面方式證明於批次或交貨中的每一照射容器所接受的劑量範圍。	43. The irradiation plant operator should certify in writing the range of doses received by each irradiated container within a batch or delivery.
44. 每一照射批次之照射處理與管制紀錄應由指定的負責人員核對、簽章並予以保存。其保存的方法與場所應由照射廠操作者與上市許可持有者進行協議。	44. Process and control records for each irradiation batch should be checked and signed by a nominated responsible person and retained. The method and place of retention should be agreed between the plant operator and the holder of the marketing authorization.
45. 與照射廠的確效及試運轉有關的文件應保存至產品的末效日後一年，或自照射廠照射處理之最後產品放行後至少五年。兩者中取其較長者。	45. The documentation associated with the validation and commissioning of the plant should be retained for one year after the expiry date or at least five years after the release of the last product processed by the plant, whichever is the longer.
微生物的監測（MICROBIOLOGICAL MONITORING）	
46. 微生物的監測係藥廠的責任。可能包括產品製造場所之環境及上市許可中所規定該產品之輻射照射前的監測。	46. Microbiological monitoring is the responsibility of the pharmaceutical manufacturer. It may include environmental monitoring where product is manufactured and pre-irradiation monitoring of the product as specified in the marketing authorisation.

附則 13 研究用藥品的製造（MANUFACTURE OF INVESTIGATIONAL MEDICINAL PRODUCTS）

前言（INTRODUCTION）	
本指引明定解決關於研究用藥品 GMP 之特定問題的適當工具。該工具具有彈性，以供製程知識增加時之變更，並適合於產品開發階段。	These guidelines lay down appropriate tools to address specific issues concerning investigational medicinal products with regard to good manufacturing practice. The tools are flexible to provide for changes as knowledge of the process increases and appropriate to the stage of development of the product.
研究用藥品係指在臨床試驗中，被用來試驗或當做對照之活性成分藥品或安慰劑，包括已上市藥品使用於與其核准內容不同的用途、配方、分/包裝、適應症，或用於獲得有關核准用途之進一步資料。	An investigational medicinal product is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.
除在國家法律另有界定外，製造是界定為全程與部分製造，以及各種分裝、包裝與標示（包括盲性）。	Unless otherwise defined in national law, manufacturing is defined as total and partial manufacture, as well as the various processes of dividing up, packaging and labelling (including blinding).
研究用藥品須應用可確保該藥品品質之製造規範進行製造，以保障受試者安全與臨床試驗中產生之臨床數據的可靠性及穩健性（「優良製造規範」）。	Investigational medicinal products shall be manufactured by applying manufacturing practices which ensure the quality of such medicinal products in order to safeguard the safety of the subject and the reliability and robustness of clinical data generated in the clinical trial ("good manufacturing practice").
研究用藥品之優良製造規範要求明訂於本指引中。本規範之其他不同部分亦提供有助益的指引，應予以考慮。	The good manufacturing practice requirements for investigational medicinal products are set out in these guidelines. Various other parts of the PIC/S GMP Guide provide useful guidance also and they should be considered.
製造程序需要有彈性，以供製程知識增加時之變更，並適合於產品開發階段。	Procedures need to be flexible to provide for changes as knowledge of the process increases

	and appropriate to the stage of development of the products.
相較於使用經許可之藥品治療的病人，臨床試驗受試者可能會有較多的風險。將優良製造規範應用於研究用藥品的製造與輸入上，係要確保受試者不會處於不當的風險中，及臨床試驗結果不會受到由不符合要求之製造或輸入導致的不適當品質、安全性或療效所影響。（注意：此處與本附則中提及之「輸入」係指輸入作業至相關國家，該等作業應依照適當之國家法律/規定執行。）同樣地，亦要確保用於相同或不同臨床試驗之相同研究用藥品的批次間具有一致性，以及確保將研究用藥品在開發期間的變更充分文件化，並證明其合理性。	In clinical trials there may be added risk to the subjects compared to patients treated with authorised medicinal products. The application of good manufacturing practice for the manufacture and import of investigational medicinal products is intended to ensure that subjects are not placed at undue risk, and that the results of clinical trials are unaffected by inadequate quality, safety or efficacy arising from unsatisfactory manufacture or import. (Note: the reference to 'Import' here and in other parts of this annex refers to importation activities into the relevant country, which should be performed in accordance with applicable national laws/requirements.) Equally, it is intended to ensure that there is consistency between batches of the same investigational medicinal product used in the same or different clinical trials and that changes during the development of an investigational medicinal product are adequately documented and justified.
與經許可之藥品相較，研究用藥品之生產由於固定例行程序的欠缺、臨床試驗設計的多樣性與後續的包裝設計，因此會涉及附加的複雜性。隨機與盲性試驗之附加的複雜性，使藥品交叉污染與混雜之風險增加。此外，還可能對該研究用藥品之效價與毒性的知識不足及欠缺完整的製程確效。另外可能將經許可產品已經重新包裝或經以某種方式修改過。這些挑戰需要對優良製造規範應用於研究用藥品有充分瞭解並受過訓練的人員。因製造作業複雜性的增加，需有高度有效的品質系統。	The production of investigational medicinal products involves added complexity in comparison with authorised medicinal products by virtue of lack of fixed routines, variety of clinical trial designs and consequent packaging designs. Randomisation and blinding add to that complexity an increased risk of product cross-contamination and mix-up. Furthermore, there may be incomplete knowledge of the potency and toxicity of the product and a lack of full process validation. Moreover, authorised products may be used which have been re-packaged or modified in some way. These challenges require personnel with a thorough understanding of and training in the application of good manufacturing practice to investigational medicinal products. The increased complexity in

	manufacturing operations requires a highly effective quality system.
為使製造廠能應用與符合研究用藥品之優良製造規範，製造廠與臨床試驗委託者間之合作是必須的。該合作應描述於試驗委託者與製造廠間之技術協議中。	For manufacturers to be able to apply and comply with good manufacturing practice for investigational medicinal products, co-operation between manufacturers and sponsors of clinical trials is required. This co-operation should be described in a technical agreement between the sponsor and manufacturer.
1. 範圍（SCOPE）	
本指引適用於人用研究用藥品之製造或輸入。	These guidelines apply to manufacture or import of investigational medicinal products for human use.
除非國家法律另有規定，研究用藥品之重組不被認為是製造，因此本指引未將此涵蓋在內。	Reconstitution of investigational medicinal products is not considered manufacturing, unless otherwise subject to national law, and therefore is not covered by this guideline.
重組被理解為將研究用藥品進行溶解或分散過程的簡單過程，以投用於受試者，或使用一些其它物質作為載體，將研究用藥品進行稀釋或混合，以投用於受試者。	The reconstitution is understood as the simple process of dissolving or dispersing the investigational medicinal product for administration of the product to a trial subject, or diluting or mixing the investigation medicinal product with some other substance(s) used as a vehicle for the purpose of administering it to a trial subject.
重組並非將包括活性物質在內的幾種成分混合在一起，以生產研究用藥品。在一過程可被界定為重組之前，研究用藥品就必須存在。	Reconstitution is not mixing several ingredients, including the active substance, together to produce the investigational medicinal product. An investigational medicinal product must exist before a process can be defined as reconstitution.
重組的過程必須儘可能於接近給藥時進行，且必須要界定於臨床試驗申請文件檔案與文件中，該等文件可在臨床試驗現場取得。	The process of reconstitution has to be undertaken as close in time as possible to administration and has to be defined in the clinical trial application dossier and document available at the clinical trial site.
本指引不適用於下列活動，應依國家法律使這些過程符合適當且相稱之要求，以確保受試者安全與臨床試驗中產生之數據的可靠性及穩健性：	While these guidelines do not apply to the activities listed below, PIC/S Participating Authorities should, in accordance with national law, make those processes subject to appropriate

	and proportionate requirements to ensure subject safety and robustness of the data generated in the clinical trial:
• 由藥師或國家其他法定授權人員，於醫院、健康照護中心或診所內執行之重標示或重包裝作業，且該研究用藥品只被預訂用於同一國家之同一臨床試驗的醫院、健康照護中心或診所；	• Re-labelling or re-packaging, where those processes are carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the country concerned to carry out such processes, and if the investigational medicinal products are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the same country;
• 由藥師或國家其他法定授權人員，於醫院、健康照護中心或診所內製備診斷用放射性研究用藥品之作業，且該研究用藥品只被預訂用於同一國家之同一臨床試驗的醫院、健康照護中心或診所；	• The preparation of radiopharmaceuticals used as diagnostic investigational medicinal products where this process is carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the country concerned to carry out such processes, and where the investigational medicinal products are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the same country;
• 由藥師或國家其他法定授權人員，於醫院、健康照護中心或診所內製備研究用藥品之作業，且該研究用藥品只被預訂用於同一國家之同一臨床試驗的醫院、健康照護中心或診所。	• The preparation of medicinal products for use as investigational medicinal products, where this process is carried out in hospitals, health centres or clinics legally authorised in the country concerned to carry out such process and where the investigational medicinal products are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the same country.
2. 製藥品質系統（PHARMACEUTICAL QUALITY SYSTEM）	

製造廠應考量應用本規範第一部第一章之指引於研究用藥品，其設計、建立及確認之製藥品質系統，應以書面程序描述。	The pharmaceutical quality system which is designed, set-up and verified by the manufacturer should be described in written procedures, taking into account the guidance in Chapter 1 of Part 1 of the PIC/S GMP Guide, as applicable, to investigational medicinal products.
研究用藥品之規格及製造指令於開發期間得以變更。該變更的完整管制與可追溯性應予以文件化及保存。來自任何預先定義之規格與指令之偏差，應予立案、調查與合適時啟動矯正預防行動措施。	The product specifications and manufacturing instructions may be changed during development, but full control and traceability of the changes should be documented and maintained. Deviations from any predefined specifications and instructions should be registered, investigated and corrective and preventive action measures initiated as appropriate.
原料供應商的選擇、資格認可、核准及維護以及其原料之採購與接受，應作為製藥品質系統文件化的一部分，以確保供應鏈完整性及防範偽造產品。監督程度應該與由個別原料所呈現之風險成正比，考量它們的來源、製造過程、供應鏈的複雜性以及原料在研究用藥品中的最終用途。每一供應商及原料核准的支持性證據應予文件化並保存。	The selection, qualification, approval and maintenance of suppliers of starting materials, together with their purchase and acceptance, should be documented as part of the pharmaceutical quality system to ensure the integrity of the supply chain and protect against falsified products. The level of supervision should be proportionate to the risks posed by the individual materials, taking into account their source, manufacturing process, supply chain complexity and the final use to which the material is put in the investigational medicinal product. The supporting evidence for each supplier approval and material approval should be documented and maintained.
2.1 產品規格檔案（Product specification file）	
1. 產品規格檔案彙集並包含所有必要參考文件，以確保研究用藥品依其優良製造規範與臨床試驗許可進行製造。產品規格檔案為製藥品質系統要件之一。	1. The product specification file brings together and contains all of the essential reference documents to ensure that investigational medicinal products are manufactured according to good manufacturing practice for investigational medicinal products and the clinical trial authorisation. The product specification file is one of the essential elements of the pharmaceutical quality

	system.
2. 產品規格檔案之適用條項，於首批次用於臨床試驗之研究用藥品開始生產時應可取得。	2. Applicable sections of the product specification file should be available at the start of manufacturing of the first batch of the investigational medicinal product for use in a clinical trial.
3. 產品規格檔案應隨產品開發持續更新，並確保適當可追溯性至先前版本。該檔案應包含或引述至少下列文件：	3. The product specification file should be continually updated as development of the product proceeds, ensuring appropriate traceability to the previous versions. It should include, or refer to, at least the following documents:
i. 起始原料、包裝材料、中間產品、待分/包裝產品及最終產品的規格與分析方法；	i. Specifications and analytical methods for starting materials, packaging materials, intermediate product, bulk product and finished product;
ii. 製造方法；	ii. Manufacturing methods;
iii. 製程中測試與方法；	iii. In-process testing and methods;
iv. 核准的標籤複印本；	iv. Approved label copy;
v. 相關臨床試驗許可與其修訂、臨床試驗計畫書及隨機化編碼（合適時）；	v. Relevant clinical trial authorisations and amendments thereof, clinical trial protocol and randomisation codes, as appropriate;
vi. 與委託者及受託者相關之技術協議書（合適時）；	vi. Relevant technical agreements with contract givers and acceptors, as appropriate;
vii. 安定性計畫與報告；	vii. Stability plan and reports;
viii. 對照樣品與留存樣品之計畫與安排的細節；	viii. Details of plans and arrangements for reference and retention samples;
ix. 儲存及運輸條件；以及	ix. Storage and transport conditions; and
x. 供應鏈的細節，包括研究用藥品之製造、分/包裝、標示與試驗場所，儘可能使用詳盡的圖表格式。	x. Details of the supply chain including manufacturing, packaging, labelling and testing sites for the investigational medicinal products, preferably in the format of a comprehensive diagram.
4. 上列文件項目並非完整且無遺漏的。	4. This list of documents is neither exhaustive nor exclusive.
5. 產品規格檔案內容會依產品及開發階段而改變。	5. The contents of the product specification file will vary depending on the product and the

	stage of development.
6. 不同的製造步驟在不同場所進行時，於不同被授權人的權責下，以個別檔案保存限於各場所之相關活動的資訊，是可以接受的。製造場所應可取得必要的產品規格檔案文件，包括變更文件，以便於進行相關作業。	6. Where different manufacturing steps are carried out at different locations under the responsibility of different Authorised Persons, it is acceptable to maintain separate files limited to information of relevance to the activities at the respective locations. The manufacturing site should have access to the necessary documentation of the product specification file, including changes, to enable the relevant activities to be performed.
3. 組織與人事（PERSONNEL）	
1. 合適時，本規範第一部第二章中，與研究用藥品相關之指引應納入考慮。	1. The guidance in Chapter 2 of Part 1 of the PIC/S GMP Guide should be taken into account, as appropriate, in relation to the manufacture of investigational medicinal products.
2. 所有參與研究用藥品之製造、輸入、儲存或處理的人員，應經這類藥品特定要求之適當訓練。	2. All personnel involved with the manufacture, import, storage or handling of investigational medicinal products should be appropriately trained in the requirements specific to these types of product.
3. 即使參與研究用藥品之製造或輸入的人數不多，對於每個批次仍應有人員分別負責生產與品質管制。	3. Even where the number of staff involved in the manufacturing or import of investigational medicinal products is small, there should be, for each batch, separate people responsible for production and quality control.
4. 負責認可用於臨床試驗之研究用藥品最終批次的被授權人，應確保備有符合優良製造規範之要求的系統，且應具有藥品開發、臨床試驗過程及相關批次之供應鏈的廣博知識。	4. The Authorised Person who certifies the finished batch of investigational medicinal products for use in the clinical trial should ensure that there are systems in place that meet the requirements of good manufacturing practice and should have a broad knowledge of pharmaceutical development, clinical trial processes and supply chain of the batch concerned.
4. 廠房設施與設備（PREMISES AND EQUIPMENT）	
1. 由於可能無法充分瞭解研究用藥品之毒	1. The toxicity, potency or sensitising potential

性、效價或潛在致敏性，更須強調將所有交叉污染之風險減至最低。設備與廠房之設計、清潔後之檢查/測試方法及允收限值，應反應這些風險的本質，並考慮詳述於本規範第一部第三章與第五章中之品質風險管理原則。	may not be fully understood for investigational medicinal products and this reinforces the need to minimise all risks of cross-contamination. The design of equipment and premises, inspection/test methods and acceptance limits to be used after cleaning should reflect the nature of these risks and take account of the quality risk management principles detailed in Chapters 3 and 5 of Part 1 of the PIC/S GMP Guide.
2. 合適時，應考慮時段切換製造。在清潔溶劑的選定上，應考量藥品的溶解度。	2. Consideration should be given to campaign manufacturing, where appropriate. Account should be taken of the solubility of the product in decisions about the choice of cleaning solvent.
3. 品質風險管理過程（包括效價及毒理學評估）應加以使用，以評估及管制由所製造之研究用藥品呈現的交叉污染風險。應考慮的因素包括：	3. A quality risk management process, which includes a potency and toxicological evaluation, should be used to assess and control the cross-contamination risks presented by the investigational medicinal products manufactured. Factors that should be taken into account include:
i. 設施/設備的設計與使用；	i. facility/equipment design and use;
ii. 人流及物流；	ii. personnel and material flow;
iii. 微生物學上的管制；	iii. microbiological controls;
iv. 原料藥之理化特性；	iv. physio-chemical characteristics of the active substance;
v. 製程特性；	v. process characteristics;
vi. 清潔程序；	vi. cleaning processes;
vii. 由產品評估中所建立關於相關限量之分析能力。	vii. analytical capabilities relative to the relevant limits established from the evaluation of the investigational medicinal products.
4. 廠房設施與設備依照本規範附則 15 予以驗證是被期望的。	4. Premises and equipment are expected to be qualified in accordance with Annex 15 to the PIC/S GMP Guide.
5. 文件（DOCUMENTATION）	
1. 文件應根據詳述於本規範第一部第四章	1. Documentation should be generated and

之原則製作與管制。證明符合優良製造規範所需要之指令與紀錄的保存期間，應根據文件類別界定而符合任何相關的國家法律。文件應與產品規格檔案一致。除另於相關之國家法律中明訂，屬於產品規格檔案之文件應保存至少五年。	controlled in line with the principles detailed in the PIC/S GMP Guide, Part I, Chapter 4. The retention period for instructions and records required to demonstrate compliance with good manufacturing practice should be defined according to the type of document while complying with any relevant national laws. The documentation shall be consistent with the Product Specification File. Documents which are part of the Product Specification File shall be retained for the period of at least 5 years, unless otherwise specified in relevant national laws.
2. 依據相關之國家法律，試驗委託者可能有臨床試驗主檔案文件留存之特定責任，但除另於國家法律中明訂，該些文件應留存至試驗後至少 25 年。若試驗委託者與製造廠為不同機構，試驗委託者需與製造廠制定適當協議以達成試驗委託者對於留存臨床試驗主檔案之要求。該些文件留存之管理與所留存文件之類別，應於試驗委託者與製造廠間協議中界定。	2. The sponsor may have specific responsibilities for document retention of the clinical trial master file according to relevant national laws but unless otherwise specified in national laws, should retain such documentation for at least 25 years after the end of the trial. If the sponsor and the manufacturer are not the same entity, the sponsor has to make appropriate arrangements with the manufacturer to fulfil the sponsor's requirement to retain the clinical trial master file. Arrangement for retention of such documents and the type of documents to be retained should be defined in an agreement between the sponsor and manufacturer.
5.1 規格與指令（Specification and instructions）	
1. 規格（起始原料、直接包裝材料、中間產品/半製品、待分/包裝產品與最終產品）、製造配方及製造與分/包裝指令，應依現有知識盡可能完善，且在開發期間，應定期再予以評估，並視需要更新。每一新版本應考量最新之數據、所使用之現行技術、法規與藥典的開發，且應容許可追溯到先前的文件。任何變更應依書面程序執行。該變更程序應提及例如安定性及生體相	1. Specifications for starting materials, immediate packaging materials, intermediate products, bulk products and finished products, manufacturing formulae and processing and packing instructions should be as comprehensive as possible given the current state of knowledge. They should be re-assessed during development and updated as necessary. Each new version should take

等性等任何對產品品質的連帶影響。指令與變更之核准程序應包括製造廠的負責人員。	into account the latest data, current technology used, regulatory and pharmacopoeial developments and should allow traceability to the previous document. Any changes should be carried out according to a written procedure which should address any implications for product quality such as stability and bioequivalence. The approval process for instructions and changes thereof shall include responsible personnel at the manufacturing site.
2. 變更的理論基礎應予以記錄。一有變更，對於藥品品質及任何持續之臨床試驗的結果，應予以調查並充分文件化。	2. Rationales for changes should be recorded and the consequences of a change on product quality and on any on-going clinical trials should be investigated and fully documented.
5.2 研究用藥品訂單（Order）	
製造廠應將研究用藥品訂單作為批次文件的一部分保存之。研究用藥品訂單應要求一定單位數之製造、及/或分/包裝、及/或其運銷，並由試驗委託者或其代表交予研究用藥品的製造廠。該訂單應為書面（亦可經由電子方法傳送）且足夠精確，以避免任何模糊不清。這應經試驗委託者或其代表正式的授權，並應引述產品規格檔案，及合適時，引述相關的臨床試驗計畫書。	The manufacturer should retain the order for the investigational medicinal product as part of the batch documentation. The order should request the processing and/or packaging of a certain number of units and/or their distribution and be given by or on behalf of the sponsor to the manufacturer. The order should be in writing, though it may be transmitted by electronic means, and be precise enough to avoid any ambiguity. It should be formally authorised by the sponsor or his representative and refer to the product specification file and the relevant clinical trial protocol as appropriate.
5.3 製造配方及操作指令（Manufacturing formulae and processing instructions）	
1. 每一製造作業或供應，應使用產品規格檔案中詳述特定臨床研究資訊，準備清楚且適當之書面指令與紀錄。一旦獲得上市許可時，該紀錄對將用於例行製造文件最終版本的制作是特別重要。	1. For every manufacturing operation or supply there should be clear and adequate written instructions and written records which are prepared using the specific clinical study information detailed in the product specification file. Records are particularly important for the preparation of the final version of the documents to be used in routine manufacture once the marketing

	authorisation is granted.
2. 產品規格檔案之資訊應使用於草擬有關製造、分/包裝、品質管制測試及儲存（包括儲存條件）的詳細書面指令。	2. The relevant information in the product specification file should be used to draft the detailed written instructions on processing, packaging, quality control testing, and storage, including storage conditions.
5.4 分/包裝指令（Packaging instructions）	
1. 研究用藥品通常是為包含在臨床試驗中的每一位受試者以個別方式包裝。要包裝之單位數目，包含為執行品質管制及要保存的任何留存樣品在內，應在包裝操作開始前加以規定。為確保在每一製造階段，所需每一藥品之正確數量皆已計算過，應執行充分的數量調和。	1. Investigational medicinal products are normally packed in an individual way for each subject included in the clinical trial. The number of units to be packaged should be specified prior to the start of the packaging operations, including units necessary for carrying out quality control and for any retention samples to be kept. Sufficient reconciliations should take place to ensure that the correct quantity of each product required has been accounted for at each stage of processing.
2. 應說明使用於分/包裝研究用藥品之任何隨機化編碼的規格、產生、測試、保全、分配、處理與保存之作業程序，以及其解碼機制。適當的紀錄應予以保存。	2. Procedures should describe the specification, generation, testing, security, distribution, handling and retention of any randomisation code used for packaging investigational medicinal products as well as code-break mechanism. Appropriate records should be maintained.
5.5 批次紀錄（Batch records）	
1. 為準確訂定操作順序，批次紀錄應保持足夠的細節。這些紀錄應包含任何相關的註記，用以證明所使用之程序及所做任何變更的正當性，並增進對該產品的瞭解、開發其製造作業，及將與預定要求不符之偏差予以文件化。	1. Batch records should be kept in sufficient detail for the sequence of operations to be accurately determined. These records should contain any relevant remarks which justify procedures used and any changes made, enhance knowledge of the product, develop the manufacturing operations and document deviations from predefined requirements.
2. 批次製造紀錄應由製造廠保存至完成或正式停止使用該批次之最後一次臨床試驗後至少五年，或依國家法律要求為之。	2. Batch manufacturing records should be retained by the manufacturer for at least 5 years after the completion or formal discontinuation of the last clinical trial in

	which the batch was used, or in accordance with the requirements of national laws.
6. 生產（PRODUCTION）	
6.1 分/包裝材料（Packaging materials）	
規格與品質管制檢查應包括防範措施，以防止由於不同批次之分/包裝材料間之外觀上的變更所引起之無意解盲。	Specifications and quality control checks should include measures to guard against unintentional unblinding due to changes in appearance between different batches of packaging materials.
6.2 製造操作（Manufacturing operations）	
1. 開發期間，關鍵參數應予以確定，且製程中管制應主要作為製程管控之用。暫定的操作參數與製程中管制，可從先前的經驗推論，包含由早期開發工作中所獲得者。隨著所獲得之製程經驗，必要之指令需持續調適，並要求關鍵人員規劃其指令時應謹慎考量。已確定及管制的參數，應以當時可獲得的知識為基礎證明其合理性。	1. During development critical parameters should be identified and in-process controls primarily used to control the process. Provisional production parameters and in-process controls may be deduced from prior experience, including that gained from earlier development work. Careful consideration by key personnel is called for in order to formulate the necessary instructions and to adapt them continually to the experience gained in production. Parameters identified and controlled should be justifiable based on knowledge available at the time.
2. 製造過程雖不需確效到例行生產所需要的程度，但應考慮產品之開發階段，進行不同程度合適的確效。確效應依詳述於GMP附則15中之要求文件化。製造廠應識別保護受試者安全性之流程步驟，與臨床研究中產生之臨床試驗數據的可靠性及穩健性。	2. The manufacturing process is not required to be validated to the extent necessary for routine production but shall be validated in its entirety, as far as is appropriate, taking into account the stage of product development. The validation should be documented in accordance with the requirements detailed in Annex 15 of the PIC/S GMP Guide. The manufacturer shall identify the process steps that safeguard the safety of the subject and the reliability and robustness of the clinical trial data generated in the clinical study.
3. 為避免交叉污染，應有書面清潔程序與分析方法以確認清潔過程。	3. To avoid cross-contamination, written cleaning procedures and analytical methods to verify the cleaning process should be

	available.
4. 對於無菌產品，與無菌性保證相關之管制與製程的確效應與經許可之藥品達到相同的標準，並考量本規範附則1中關於無菌藥品製造之細節。同樣地，必要時，應證明已依循在本領域中既有之指引所界定的科學原理與技術將病毒去活化/移除，以及除去其他起源於生物的雜質，以確保利用生物技術衍生之產品的安全性。	4. For sterile products, the validation of controls and processes related to assurance of sterillity should be of the same standards as for authorised medicinal products and take account of the principles for the manufacture of sterile medicinal products as detailed in Annex 1 to the PIC/S GMP Guide. Likewise, when required, virus inactivation/removal and removal of other impurities of biological origin should be demonstrated, to assure the safety of biotechnologically derived and biological products by following the scientific principles and techniques defined in the available guidance in this area.
5. 當批量小時，無菌操作的確效會出現特別的問題。在這些狀況中，充填之單元數目可能是在生產中充填之最大的數目。如果可行，及除與該過程之模擬一致外，應以充填較多單元數目的培養基，以對結果取得較大的信心。充填與密封常常是以人工或半自動操作，這對無菌性呈現很大的挑戰，因此，對操作人員的訓練，以及個別操作者無菌技術的確效應特別注意。	5. Validation of aseptic processes presents special problems where the batch size is small; in these cases, the number of units filled may be the maximum number filled in production. If practicable, and otherwise consistent with simulating the process, a larger number of units should be filled with media to provide greater confidence in the results obtained. Filling and sealing is often a manual or semi-automated operation presenting great challenges to sterility, so enhanced attention should be given to operator training and validating the aseptic technique of individual operators.
6.3 比對用產品之修改（Modification of comparator products）	
1. 如果產品經過修改，應可取得其資料（例如：安定性、溶離度比對、生體可用率），以證明這些變更無顯著地改變該產品的原始品質特性。	1. If a product is modified, data should be available (e.g. stability, comparative dissolution or bioavailability) to demonstrate that these changes do not significantly alter the original quality characteristics of the product.
2. 比對用產品經重新包裝在不同容器中，可能不再提供相等的保護，或可能與該產品不相容，而使該比對用產品原始包裝上所	2. The expiry date stated for the comparator product in its original packaging might not be applicable to the product where it has been

載之末效日期可能不再適用。考慮該產品的本質、容器的特徵及該產品可能受制的儲存條件，試驗委託者或其代表應決定適當的再驗日期。該日期必須證明其正當性，且不得晚於原始包裝的末效日期。末效日期與臨床試驗期間應具相容性。	repackaged in a different container that may not offer equivalent protection, or be compatible with the product. A suitable retest date, taking into account the nature of the product, the characteristics of the container and the storage conditions to which the product may be subjected, should be determined by or on behalf of the sponsor. Such a date should be justified and must not be later than the expiry date of the original package. There should be compatibility of expiry dating and clinical trial duration.
3. 為盲性目的經重包裝或外加膠囊封裝之比對用產品的對照樣品，應於執行上述作業時點收集並保留，因為追加處理步驟可能對安定性具有影響，或於品質缺陷調查事件時為辨識目的之需求，不能以上市產品之留存樣品代表。	3. A reference sample of comparator product, which has been repackaged or over encapsulated for blinding purposes, should be taken at a point representative of the additional processing and retained, as the additional processing step could have an impact on stability or be needed for identification purposes in the event of a quality defect investigation, which would not be covered by the commercial retained sample.
6.4 盲性作業（Blinding operations）	
1. 經盲性化之產品，雖然容許「盲性」產品於必要時之識別，包含在盲性作業前該產品的批號在內，但應有系統確保該盲性之達成與維持，且緊急時亦能快速識別該產品。當製造廠被委託負責隨機化編碼之產生，於研究用藥品供貨前，製造廠應向負責試驗之場所的適當人員提供解盲資訊。	1. Where products are blinded, systems should be in place to ensure that the blind is achieved and maintained while allowing for identification of "blinded" products, when necessary, including batch numbers of the products before the blinding operation. Rapid identification of product should also be possible in an emergency. Where the manufacturer has been delegated the responsibility for generation of randomisation codes, the manufacturer should enable that unblinding information is available to the appropriate responsible investigator site personnel before investigational medicinal products are

	supplied.
2. 經盲性化之產品，所有產品所指定之末效日期應依最短效期者之末效日期載明，以保持其盲性。	2. Where products are blinded, the expiry date assigned to all products should be stated at the expiry of the shortest dated product so that the blinding is maintained.
6.5 分/包裝（Packaging）	
1. 研究用藥品的分/包裝期間，可能必須於相同時間在相同分/包裝線上，處理不同的藥品。應利用適當的程序及/或特別的設備（合適時）及相關人員的訓練，將產品意外混入（混雜）之風險減到最低。文件必須足以證明任何分/包裝作業過程中保持適當之隔離。	1. During packaging of investigational medicinal products, it may be necessary to handle different products on the same packaging line at the same time. The risk of product unintentional mixing (mix-ups) must be minimised by using appropriate procedures and/or specialised equipment as appropriate and relevant staff training. Documentation must be sufficient to demonstrate that appropriate segregation has been maintained during any packaging operations.
2. 研究用藥品之分/包裝與標示較經許可之藥品可能更為複雜及更易出差錯（該差錯也較難以檢測），尤其是當使用有相似外觀之盲性產品時。為防範錯標，諸如強調由經適當訓練之人員從事標籤數量的調和、清線、製程中管制檢查。	2. Packaging and labelling of investigational medicinal products are likely to be more complex and more liable to errors which are also harder to detect than for authorised medicinal products, particularly when blinded products with similar appearance are used. Precautions against mislabelling such as reconciliation, line clearance, in-process

	control checks by appropriately trained staff should accordingly be intensified.
3. 包裝必須確保研究用藥品在運輸及在中間目的地之儲存期間維持於良好的狀態中。運輸期間，其外包裝的開啟或竄改應易於識別。	3. The packaging must ensure that the investigational medicinal product remains in good condition during transport and storage at intermediate destinations. Any opening or tampering of the outer packaging during transport should be readily discernible.
4. 重包裝作業可能由被授權人員於符合相關之要求（國家法律或規定）的醫院、健康照護中心或診所中執行（亦即，於非受制於優良製造規範之健康照護機構中）。	4. Re-packaging operations may be performed by authorised personnel at a hospital, health centre or clinic that meet the requirements of relevant national laws or requirements (i.e. in healthcare establishments that are not otherwise subject to good manufacturing practices).
6.6 標示作業（Labelling）	
1. 研究用藥品之標示應符合相關之國家法律或規定的要求，若無此類要求存在，則至少應包含以下要素，除非可證明其不標示的合理性，例如，使用中央電子隨機系統：	1. The labelling of investigational medicinal products shall comply with the requirements of relevant national laws or requirements, and where no such requirements exist, it should address at least the following elements, unless their absence can be justified, e.g. use of a centralised electronic randomisation system:
i. 試驗委託者、受託研究機構或試驗主持人的姓名/名稱、地址及電話號碼（關於藥品、臨床試驗及緊急解盲之資訊的主要接洽對象）；	i. name, address and telephone number of the sponsor, contract research organisation or investigator (the main contact for information on the product, clinical trial and emergency unblinding);
ii. 名稱/識別符號及強度/效價，且於盲性試驗的情況，所有產品標示應標明「安慰劑/比對產品或[名稱/識別符號]及[強度/效價]」	ii. the name/identifier and strength/potency, and in the case of blinded trials, all product labelling should indicate “placebo/comparator or [name/identifier] + [strength/potency]”
iii. 藥品劑型、給藥途徑與劑型單元數；	iii. pharmaceutical dosage form, route of administration and quantity of dosage units;
iv. 用以識別內容物與分/包裝作業之批	iv. the batch and/or code number to identify

號及/或代碼；	the contents and packaging operation;
v. 他處未提供者，應有能夠識別該試驗、場所、試驗主持人及試驗委託者之試驗對照代碼；	v. a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;
vi. 試驗受試者之識別號碼、試驗/治療號碼及訪視號碼（合適時）；	vi. the trial subject identification number/treatment number and where relevant, the visit number;
vii. 試驗主持人之姓名（如果未包含在(i)或(v)中）；	vii. the name of the investigator (if not included in (i) or (v));
viii. 使用說明（可參考供受試者或給藥者所製作之說明書或其他解釋文件）；	viii. directions for use (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product);
ix. 「僅供臨床試驗使用」或相似措辭；	ix. “For clinical trial use only” or similar wording;
x. 儲存條件；	x. the storage conditions;
xi. 使用期間【使用期限、末效日期或再驗日期（合適時）】，以年/月之格式及避免任何不明確的方式；以及	xi. period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity; and
xii. 「避免孩童觸及」，除非該產品是使用於非由受試者帶回家裡投用的試驗。	xii. “keep out of reach of children” except when the product is for use in trials where the product is not taken home by subjects.
2. 須出現於標示上之資訊應符合任何相關的國家法律與要求。標示作業應依相關的國家法律與要求，於經許可之製造場所為之。	2. The information which shall appear on the labelling should comply with any relevant national laws or requirements. The labelling operation should be performed at an authorised manufacturing site in accordance with relevant national laws or requirements.
3. 有變更末效日期之必要者，應對研究用藥品貼上附加標籤。該附加標籤應載明新的末效日期，並重複該批號與臨床試驗參考編號。這可覆蓋貼在原末效日期上，但為品管的理由，不可貼在原批號上。	3. If it becomes necessary to change the expiry date, an additional label should be affixed to the investigational medicinal product. This additional label should state the new expiry date and repeat the batch number and clinical trial reference number. It may be superimposed on the old expiry date, but for quality control reasons, not on the original

	batch number.
4. 重標示作業應依優良製造規範原則與特定標準作業程序由經適當訓練人員為之，並應由第二者核對。該附加標籤的標示，應於批次紀錄上適當記載。為了避免錯誤，附加標籤的標示作業應於與其他作業區隔之區域執行。應於該作業開始與結束執行清線及標籤數量調和。數量調和時發現任何差異應於放行前調查與核算。	4. The re-labelling operation should be performed by appropriately trained staff in accordance with good manufacturing practice principles and specific standard operating procedures and should be checked by a second person. This additional labelling should be properly documented in the batch records. To avoid mistakes the additional labelling activity should be carried out in an area which is partitioned or separated from other activities. A line clearance at the start and end of activity should be carried out and label reconciliation performed. Any discrepancies observed during reconciliation should be investigated and accounted for before release.
5. 重標示作業可能由被授權人員於符合相關之要求（國家法律或規定）的醫院、健康照護中心或診所中執行（亦即，於非受制於優良製造規範之健康照護機構中）。	5. The re-labelling operation may be performed by authorised personnel at a hospital, health centre or clinic that meet the requirements of relevant national laws or requirements (i.e. in healthcare establishments that are not otherwise subject to good manufacturing practices).
7. 品質管制（QUALITY CONTROL）	
1. 製造廠應建立並維持品質管制系統，該系統由具備必要資格且獨立於生產之人員所負責。	1. The manufacturer should establish and maintain a quality control system placed under the authority of a person who has the requisite qualifications and is independent of production.
2. 由於製程可能無法標準化或完全確效，測試作業擔負重責，以確保每批產品在該測試時皆符合經核准之規格。	2. As processes may not be standardised or fully validated, testing takes on more importance in ensuring that each batch meets the approved specification at the time of testing.
3. 研究用藥品之品質管制，包括比對產品，應依所提交經相關之國家授權的臨床試驗申請資訊執行。	3. Quality control of the investigational medicinal product, including that of the comparator product, should be performed in accordance with the information submitted in

	the application for the clinical trial, as authorised by the relevant country.
4. 盲性有效性之確認應執行並記錄。	4. Verification of the effectiveness of blinding should be performed and recorded.
5. 研究用藥品之樣品的保存期限應符合相關的國家法律或其他要求。	5. Retention periods for samples of investigational medicinal products should comply with the relevant national laws or other requirements.
6. 樣品的留存是為了達成兩個目的：第一，為提供未來分析測試的樣品，第二，為提供可能用於產品品質瑕疵調查之最終研究用藥品的樣本。	6. Samples are retained to fulfil two purposes: firstly, to provide a sample for future analytical testing, and secondly, to provide a specimen of the finished investigational medicinal product which may be used in the investigation of a product quality defect.
7. 因此，樣品可以歸納成兩個類別：	7. Samples may therefore fall into two categories:
對照樣品：在相關批次之架儲期間中倘若發生分析需要時，為分析目的而儲存之一個批次的原料、包裝材料或最終產品的樣品。在安定性允許時，應保存來自關鍵中間階段（例如需要分析測試與放行）的對照樣品，或運送到製造者控管外之中間產品的對照樣品。	• Reference sample: a sample of a batch of starting material, packaging material or finished product which is stored for the purpose of being analysed should the need arise. Where stability permits, reference samples from critical intermediate stages, e.g. those requiring analytical testing and release, or intermediates which are transported outside of the manufacturer's control, should be kept.
留存樣品：每一分/包裝操作/試驗期間，來自一批次之最終產品的完整包裝單元之樣品。這是為識別目的而儲存。例如，倘若關注批次於架儲期內發生需要時，用以辨識其外觀、包裝、標示、包裝說明書、批號、末效日期等。	• Retention sample: a sample of a fully packaged unit from a batch of finished product. It is stored for identification purposes. For example, presentation, packaging, labelling, package leaflet, batch number, expiry date should the need arise during the shelf life of the batch concerned.
8. 可能有例外情形，即使未留存完全相同的樣品亦能符合本要求。例如，為不同市場，包裝一個批次中之小數量或製造極為昂貴之藥品。	8. There may be exceptional circumstances where this requirement can be met without retention of duplicate samples, e.g. where small amounts of a batch are packaged for different markets or in the production of very expensive medicinal products.

9. 如為留存樣品，若其紀錄提供足夠資訊時，可接受以書面、照相或電子紀錄儲存有關最終包裝的資訊，例如包裝樣品、標籤樣品及任何伴隨文件，以利與產品使用相關之調查。若為電子紀錄，該系統應符合本規範附則11之要求。	9. For retention samples it is acceptable to store information related to the final packaging as written, photographic or electronic records, if such records provide sufficient information, e.g. examples of packaging, labelling and any accompanying documentation to permit investigations associated with the use of the product. In case of electronic records, the system should comply with the requirements of Annex 11 of the PIC/S GMP Guide.
10. 當對照樣品與留存樣品以完全相同的型態（亦即，按完整包裝單元）呈現時，對照樣品及留存樣品可視為得以互換。	10. Where reference samples and retention samples are presented identically, i.e. as fully packaged units, the samples may be regarded as interchangeable.
11. 於原始包裝中非盲性比對之研究用藥品，且來自預定執行臨床試驗所在國家中被授權的供應鏈，或持有執行臨床試驗所在國家主管機關所核准之上市許可的產品時，得免留樣。	11. Samples are not expected of an investigational medicinal product which is an unblinded comparator in its original packaging and sourced from the authorised supply chain in the country in which the clinical trial is intended to occur or of a product which holds a marketing authorisation granted by the national competent authority of the country in which the clinical trial occurs. (Note: In the EU, it might be the European Commission that has granted the marketing authorisation.)
12. 樣品的儲存場所，應界定於試驗委託者與製造廠之間的技術協議中，並允許主管機關隨時取得。	12. The storage location of samples should be defined in a technical agreement between the sponsor and the manufacturer(s) and should allow timely access by the competent authorities.
13. 最終產品之對照樣品應於經界定的條件下被存放於製造廠所在國家，或當與所在國家間（或代表）作出適當安排之另一國家，以確保研究用藥品製造廠適用優良製造規範之標準至少等同於優良製造規範所規定之標準。例外的情況下，最終產品之對照樣品可能被製造廠儲存於其他國家，該情況下應證明其合理性並於試驗委	13. Reference samples of finished product should be stored under defined storage conditions in the country in which the manufacturer is located or in another country where appropriate arrangements have been made between (or on behalf of) the two countries to ensure that the manufacturer of the investigational medicinal product applies

託者、製造廠與儲存場所間之技術協議中予以文件化。	standards of good manufacturing practice at least equivalent to those laid down by the PIC/S GMP Guide. In exceptional circumstances, the reference samples of the finished product may be stored by the manufacturer in another country, in which case this should be justified and documented in a technical agreement between the sponsor, the manufacturer and the storage site.
14. 對照樣品應有足夠數量，以允許至少在兩個時機，執行定義於由相關國家核准之研究用藥品文件檔案中，所有關鍵品質屬性之測試。任何例外都應得到國家主管機關之認可與同意。	14. The reference sample should be of sufficient size to perform, on at least two occasions, all critical quality attribute tests as defined in the investigational medicinal product dossier authorised by the relevant country. Any exception to this should be justified to, and agreed with, the national competent authority.
8. 批次放行（RELEASE OF BATCHES）	
1. 於被授權人認可相關的要求已符合前，不得放行研究用藥品。合適時，被授權人應考量以下所列之要項。	1. Release of investigational medicinal products should not occur until after the Authorised Person has certified that the relevant requirements have been met. The Authorised Person should take into account the elements listed below, as appropriate.
2. 認可之範圍可能侷限於確保該產品依照臨床試驗許可，與製造廠為盲性、試驗特定性包裝及標示之目的所執行的任何後續處理。	2. The scope of the certification can be limited to assuring that the products are in accordance with the authorisation of the clinical trial and any subsequent processing carried out by the manufacturer for the purpose of blinding, trial-specific packaging and labelling.
3. 產品規格檔案中之資訊應作為被授權人認可與放行一特定批次之適當性的評估基礎，且應可被其取得。	3. The information in the product specification file should form the basis for assessment of the suitability for certification and release of a particular batch by the Authorised Person and should therefore be accessible to him or her.
4. 於放行前，每一批次經被授權人之認可評	4. Assessment by the Authorised Person of each

估應考量詳述於本規範附則16之原則，合適時，可包括：	batch for certification prior to release should take account of the principles detailed in Annex 16 of the PIC/S GMP Guide and may include as appropriate;
i. 批次紀錄，包含品管報告、製程中測試報告及放行報告，以證明符合產品規格檔案、訂單、計畫書及隨機編碼。這些紀錄應包括所有偏差或經計畫的變更，以及任何隨後附加的核對與測試，且應由依品質系統授權之人員完成與背書；	i. Batch records, including control reports, in-process test reports and release reports demonstrating compliance with the product specification file, the order, protocol and randomisation code. These records should include all deviations or planned changes, and any consequent additional checks and tests, and should be completed and endorsed by the staff authorised to do so according to the quality system;
ii. 生產條件；	ii. Production conditions;
iii. 清潔紀錄；	iii. Cleaning records;
iv. 廠房設施的驗證狀態與製程及方法的確效狀態；	iv. The qualification status of facilities, validation status of processes and methods;
v. 最終包裝品的檢查；	v. Examination of finished packs;
vi. 合適時，在輸入後所執行之所有分析或測試的結果；	vi. The results of any analyses or tests performed after importation, where relevant;
vii. 安定性計畫與報告；	vii. Stability plan and reports;
viii. 來源及儲存與裝運條件之確認；	viii. The source and verification of conditions of storage and shipment;
ix. 關於製造廠品質系統之稽查報告；	ix. Audit reports concerning the quality system of the manufacturer;
x. 相關國家的主管機關證明該製造廠係經授權，以製造供輸出之研究用藥品（適用國家法律）的文件；	x. Documents certifying that the manufacturer is authorised to manufacture investigational medicinal product for export (as applicable under national law); by the appropriate authorities in the relevant country;
xi. 合適時，上市許可的法規要求、適用之優良製造規範標準及任何遵循優良製造規範之官方證明；	xi. Where relevant, regulatory requirements for marketing authorisation, good manufacturing practice standards applicable and any official verification

	of compliance with good manufacturing practice;
xii. 供應鏈確認，包括研究用藥品之製造、分/包裝、標示與測試場所；	xii. Verification of the supply chain including manufacturing, packaging, labelling and testing sites for the investigational medicinal products;
xiii. 被授權人所知悉與該批次品質有關的所有因素。	xiii. All factors of which the Authorised Person is aware that are relevant to the quality of the batch.
5. 上述因素的關聯性受該產品的原產地、製造廠、該產品之狀態，例如，是否具有經相關主管機關批准之上市許可及其開發階段的影響。	5. The relevance of the above elements is affected by the country of origin of the product, the manufacturer, the status of the product, i.e. with or without a marketing authorisation granted by the relevant competent authority, and the phase of development of the product.
6. 如研究用藥品於不同的場所生產與分/包裝時，在不同的被授權人監督下，關於批次符合性，被授權人間分擔責任必須於各方正式同意之文件中加以界定。	6. Where investigational medicinal products are produced and packaged at different sites under the supervision of different Authorised Persons, sharing of responsibilities amongst the Authorised Persons in relation to compliance of a batch must be defined in a document formally agreed by all parties.
7. 被授權人必須確保研究用藥品於維持產品品質與供應鏈安全之條件下被儲存及運送。需要支持認可之相關情況可能包括短效期產品於被授權人最終認可之前放行，或研究用藥品退回至被授權製造廠供重標示與重包裝存在可能性。	7. Where required to support certification, the Authorised Person has to ensure that the investigational medicinal product has been stored and transported under conditions that maintain product quality and supply chain security. Relevant situations may include short expiry date products released prior to final Authorised Person certification, or where return of investigational medicinal products to an authorised manufacturer for re-labelling and re-packaging remains a possibility.
8. 製造廠受試驗委託者委託，執行除了經被授權人認可外之法規放行時，該安排亦須於試驗委託者與製造廠間協議中界定。於產品規格檔案中應備有相關臨床試驗許	8. Where the manufacturer is delegated by the sponsor to perform the regulatory release in addition to certification by the Authorised Person, the arrangements should be defined

可與修訂資訊以供參考，且製造廠應確保於裝運產品前所需之臨床試驗許可已具備，以用於該試驗。	in an agreement between the sponsor and the manufacturer. Relevant clinical trial authorisation and amendment information should be available for reference in the product specification file and the manufacturer should ensure the necessary clinical trial authorisations are in place and prior to shipping product for use in the trial.
9. 經被授權人認可後，研究用藥品應於維持產品品質與供應鏈安全之條件下被儲存及運送。	9. After certification by the Authorised Person, the investigational medicinal product should be stored and transported under conditions that maintain product quality and supply chain security.
10. 在符合相關之要求（國家法律或規定）下，被授權人不需認可由被授權之人員於醫院、健康照護中心或診所中所執行的重包裝（6.5條）或重標示（6.6條）。	10. The Authorised Person is not required to certify re-packaging (section 6.5) or re-labelling (section 6.6) performed by authorised personnel at a hospital, health centre or clinic that meet the requirements of relevant national laws or requirements.
9. 委外作業（OUTSOURCED OPERATIONS）	
委外活動應依詳述於本規範第一部第七章之原則，經由委託者與受託者間之書面契約界定、協議與管制。	Activities which are outsourced should be defined, agreed and controlled by written contracts between the contract giver and the party to whom the operations are outsourced in accordance with the principles detailed in Part I, Chapter 7 of the PIC/S GMP Guide.
10. 申訴（COMPLAINTS）	
1. 應有書面程序說明接獲申訴時，於製造、儲存或輸入等現場所要採取之行動。所有申訴應加以文件化與評估，以確定是否代表潛在的品質缺陷或其他問題。該程序應確保試驗委託者可以評估申訴，以證明決定是否向相關主管機關提報嚴重違反之合理性。	1. There should be written procedures describing the actions to be taken upon receipt of a complaint at the manufacturing, storage or importation site. All complaints should be documented and assessed to establish if they represent a potential quality defect or other issue. The procedures should ensure that the sponsor is able to assess the complaints to determine if they justify the reporting of a serious breach to the relevant competent authority.
2. 品質缺陷調查應依詳述於本規範第八章	2. The investigation of quality defect should be

之原則執行。	performed in accordance with the principles detailed in Part I, Chapter 8 of the PIC/S GMP Guide.
3. 完成調查後之結論，應及時在製造廠與試驗委託者間（若兩者不同時）討論。這應有被授權人及為相關臨床試驗負責的人員參與，以評估其對該臨床試驗、藥品開發及受試者之任何潛在影響。	3. The conclusions of the investigation should be discussed between the manufacturer and the sponsor, if different, in a timely manner. This should involve the Authorised Person and those responsible for the relevant clinical trial in order to assess any potential impact on the trial, product development and on subjects.
11. 回收和退回（RECALLS AND RETURNS）	
11.1 回收（Recalls）	
1. 取回研究用藥品之程序及其文件化應符合相關的國家法律與指引，並應經試驗委託者與製造廠（若兩者不同時）同意。製造廠、試驗主持人及試驗委託者代表需瞭解於該取回程序中之義務。研究用藥品取回程序應依照詳述於本規範第八章之原則。	1. Procedures for retrieving investigational medicinal products and documenting such retrievals should be in line with relevant national laws and guidelines, and be agreed by the sponsor in cooperation with the manufacturer, where different. The manufacturer, investigator and the sponsor's representative need to understand their obligations under the retrieval procedure. The procedures for retrieval of investigational medicinal products should be in accordance with the principles detailed in Chapter 8 of the PIC/S GMP Guide.
2. 為了便於回收，由製造廠製作之裝運藥品的詳細清單應予以保存。	2. To facilitate recall, a detailed inventory of the shipments made by the manufacturer should be maintained.
11.2 退回（Returns）	
退回的研究用藥品應予以清楚識別並儲存於適當管控之專屬區域中。退回之研究用藥品的庫存紀錄應予以保存。	Returned investigational medicinal products should be clearly identified and stored in an appropriately controlled, dedicated area. Inventory records of returned products should be kept.
11.3 銷毀（Destruction）	
1. 製造廠或試驗委託者之代表應僅在有試驗委託者之事先書面授權下銷毀研究用藥品。研究用藥品銷毀之安排必須於計畫	1. The manufacturer or sponsor’s representative should destroy investigational medicinal products only with prior written authorisation

書中描述。試驗委託者與製造廠間之任何此方面的安排應於彼此技術協議中加以界定。	by the sponsor. The arrangements for destruction of investigational medicinal products have to be described in the protocol. Any arrangement between sponsor and manufacturer in this regard should be defined in their technical agreement.
2. 未使用之研究用藥品的銷毀，應僅於產品之交付、使用與回收的數量調和之後，及任何差異皆已調查並滿意地解釋，且其數量調和已被接受後，才可執行。	2. Destruction of unused investigational medicinal products should be carried out only after reconciliation of delivered, used and recovered products and after investigation and satisfactory explanation of any discrepancies upon which the reconciliation has been accepted.
3. 銷毀作業之紀錄應予保存，包括給試驗委託者之載明日期的銷毀證明書或收據。這些文件應清楚地識別或允許對所涉批次及/或病人代碼及銷毀之實際數量的可追溯性。	3. Records of destruction operations should be retained, including a dated certificate of destruction or a receipt for destruction to the sponsor. These documents should clearly identify or allow traceability to the batches and/or patient numbers involved and the actual quantities destroyed.
附則 13 的術語彙編（GLOSSARY TO ANNEX 13）	
盲性 使參與試驗之一方或多方不知試驗治療分配之方式。單盲係指受試者不知治療分配之方式，雙盲是指受試者、試驗主持人、監測者，及在某些情況下，數據分析者亦不清楚治療分配之方式。關於一件研究用藥品，盲性意指依試驗委託者的指示刻意偽裝藥品的識別性。解盲意指揭露盲性藥品的識別性。	**Blinding** A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s). In relation to an investigational medicinal product, blinding shall mean the deliberate disguising of the identity of the product in accordance with the instructions of the sponsor. Unblinding shall mean the disclosure of the identity of blinded products.
時段切換製造 相同產品之一系列批次依序在一定期間內製造，而後進行適當的（經確效的）清潔程序。	**Campaign manufacturing** Manufacturing a series of batches of the same product in sequence in a given period of time followed by an appropriate (validated) cleaning procedure.

臨床試驗 指在受試者人體上執行的任何試驗。該試驗意在發現或確認研究用藥品之臨床、藥理及/或其他藥效學效應，及/或意在辨識研究用藥品的任何不良反應，及/或意在研究一種或一種以上研究用藥品的吸收、分佈、代謝及排泄，以確認研究用藥品之安全性及/或療效為目的。	**Clinical trial** Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s) and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of one or more investigational medicinal product(s) with the object of ascertaining its/their safety and/or efficacy.
比對用產品 在臨床試驗上作為比對使用的研究用藥品，包括安慰劑。	**Comparator product** An investigational medicinal product used as a reference, including as a placebo, in a clinical trial.
末效日期 在研究用藥品之容器/標籤上所載之日期，指定該研究用藥品於所指定期間內，如儲存於所界定之條件下，可期待維持在既定架儲期規格內，並且於該日期之後不得使用。	**Expiry date** The date placed on the container/labels of an investigational medicinal products designating the time during which the investigational medicinal products is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used.
研究用藥品 指在臨床試驗中，被用來試驗或當作對照之活性成分藥品或安慰劑，包括已上市藥品使用於與其核准內容不同的用途、配方、分/包裝、適應症，或用於獲得有關核准用途之進一步資料。	**Investigational medicinal product** A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.
試驗主持人 指在試驗場所負責從事臨床試驗的人。若試驗是在試驗場所由一個團隊執行時，試驗主持人是該團隊的主導負責人，亦可稱為總主持人。	**Investigator** A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
研究用藥品的製造廠/進口商 指製造/輸入研究用藥品之許可的持有者。	**Manufacturer/importer of Investigational Medicinal Products**

	Any holder of the authorisation to manufacture/import.
製造 為研究用藥品的原物料與物品的採購、生產、品質管制、放行、儲存、運銷以及相關管制的所有作業。注意本附則所用「製備」一詞應視為「製造」之同意詞。	**Manufacture** All operations of purchase of materials and products, production, quality control, release, storage, distribution of investigational medicinal products and the related controls. Note that the word 'preparation' as used in this Annex should be taken as synonymous with the word 'manufacture'.
訂單 研究用藥品訂單應要求一定單元數量之製造、及/或分/包裝、及/或其裝運，並由試驗委託者或其代表交予研究用藥品之製造廠。	**Order** The order should request the processing and/or packaging of a certain number of units and/or their shipment and be given by or on behalf of the sponsor to the manufacturer.
製備 參見上述「製造」。	**Preparation** See 'Manufacture' above.
產品規格檔案 指參考檔案或所引述的檔案，包含所有必需資料，用以草擬關於研究用藥品之製造、分/包裝、品質管制測試、批次放行及裝運的詳細書面指令。	**Product Specification File** A reference file containing, or referring to files containing, all the information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release and shipping of an investigational medicinal product.
隨機化 指為了減少偏差，使用機會因素以決定受試者指派至試驗組或對照組的指派過程。	**Randomisation** The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.
隨機化編碼 指用來辨識每一受試者按隨機化過程的試驗/治療指派清單。	**Randomisation Code** A listing in which the treatment assigned to each subject from the randomisation process is identified.
再驗日期（6.3 第 2 條） 當一材料（本附則中係指比對用產品）應當再度檢驗，以確保其仍然適合使用的日期。	**Retest date** The date when a material should be re-examined to ensure that it is still suitable for use.
法規放行 確認批次認可，且確認臨床試驗場所（其人員）業經訓練、合格並獲得所需之核准，從而準備	**Regulatory Release** The verification of batch certification and that the clinical trial site is trained, qualified and has the

好接收研究用藥品。	necessary approvals, thus is ready to receive investigational medicinal product.
裝運 指依訂單分/包裝及寄送臨床試驗用藥品的作業。	**Shipping** The operation of packaging for and sending of ordered medicinal products for clinical trials.
試驗委託者 指負責臨床試驗之發起、管理及/或財務的個人、公司、機構或組織。	**Sponsor** An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial.

附則 14 人類血液或血漿衍生之藥品的製造（MANUFACTURE OF MEDICINAL PRODUCTS DERIVED FROM HUMAN BLOOD OR PLASMA）

目錄（CONTENTS）	
術語彙編	**Glossary**
1. 範圍	1. Scope
2. 原則	2. Principles
3. 品質管理	3. Quality Management
4. 可追溯性與收集後措施	4. Traceability and Post Collection Measures
5. 廠房設施與設備	5. Premises and equipment
6. 製造	6. Manufacturing
7. 品質管制	7. Quality Control
8. 中間產品與最終產品的放行	8. Release of intermediate and finished products
9. 混合血漿樣品的留存	9. Retention of plasma pool samples
10. 廢棄物的處置	10. Disposal of waste
術語彙編（GLOSSARY）	
血液 血液意指自單一（人）捐血者所收集並經處理以供輸血或進一步製造的全血。	**Blood** Blood[1] means whole blood collected from a single (human) donor and processed either for transfusion or for further manufacturing.
成分血 成分血意指使用傳統血庫方法（例如，離心、過濾、冷凍），經由各種步驟製備之血液的治療成分（紅血球、白血球、血漿、血小板）。這不包括造血母細胞（haematopoietic progenitor cells）。	**Blood component** A blood component[2] means a therapeutic constituent of blood (red cells, white cells, platelets and plasma) that can be prepared by various methods, using conventional blood bank methodology (e.g. centrifugation, filtration, freezing). This does not include haematopoietic progenitor cells.
血液機構 血液機構，無論其預定的目的，負責任何方面之人類血液與成分血的收集與測試，以及當預定供作輸血使用時，負責其處理、儲存與運銷的任何組織或團體。	**Blood establishment** A blood establishment[3] is any structure or body that is responsible for any aspect of the collection and testing of human blood and blood components, whatever their intended purpose, and their processing, storage and distribution when intended for transfusion.

血液製劑 血液製劑意指從人類血液或血漿所衍生的任何治療產品。	**Blood products** A blood product[4] means any therapeutic product derived from human blood or plasma.
分離，分離工廠 分離是在一個工廠（分離工廠）的製造過程，在該期間，血漿成分是經由各種物理與化學方法進行分離/純化，例如，沉澱法、層析法。	**Fractionation, fractionation plant** Fractionation is the manufacturing process in a plant (fractionation plant) during which plasma components are separated/purified by various physical and chemical methods such as e.g. precipitation, chromatography.
優良規範指引 優良規範指引是對血液機構中之品質系統提供關於所界定的國家標準與規格之解釋。	**Good Practice guidelines** Good practice guidelines give interpretation on the national standards and specifications defined for quality systems in blood establishments[5].
人類血液或人類血漿衍生之藥品 人類血液或人類血漿衍生之藥品是指基於血液成分的藥品，是由公共機構或私人機構進行工業化製備。	**Medicinal products derived from human blood or human plasma** Medicinal products derived from human blood or human plasma [6] are medicinal products based on blood constituents which are prepared industrially by public or private establishments.
分離用血漿 分離用血漿，是從收集在含有抗凝血劑之容器中的血液，在細胞成分分離後，或以分離術（apheresis procedure）將經抗凝化之血液經由連續過濾或離心分離後，所剩餘的人類血液之液體部分；是預定使用於血漿衍生之藥品的製造，特別是人類來源的白蛋白、凝血因子與免疫球蛋白，並且規定於歐洲藥典（或其他相關藥典）「人類分離用血漿」的個論（0853）中。	**Plasma for fractionation** Plasma for fractionation is the liquid part of human blood remaining after separation of the cellular elements from blood collected in a container containing an anticoagulant, or separated by continuous filtration or centrifugation of anti-coagulated blood in an apheresis procedure; it is intended for the manufacture of plasma derived medicinal products, in particular albumin, coagulation factors and immunoglobulins of human origin and specified in the European (or other relevant) Pharmacopoeia (Ph. Eur.) monograph “Human Plasma for fractionation” (0853).

血漿管制標準書 血漿管制標準書是與上市許可檔案文件分開的一個獨立文件。它是提供關於整個人類血漿特徵的所有相關詳細資訊。該人類血漿是作為次分離物/中間分離物（sub/intermediate fractions）、賦形劑與活性物質組成物之製造的起始物及/或原料使用，該等物質是血漿、衍生的藥品或醫療器材的一部分。	**Plasma Master File (PMF)** A Plasma Master File[7] is a stand-alone document, which is separate from the dossier for marketing authorisation. It provides all relevant detailed information on the characteristics of the entire human plasma used as a starting material and/or a raw material for the manufacture of sub/intermediate fractions, constituents of the excipients and active substances, which are part of plasma, derived medicinal products or medical devices.
處理 處理是意指在血液成分之製備的任何步驟。它是在血液收集與成分血發出之間執行，例如，成分血的分離與冷凍。此外，在本附則中，處理是指針對所要使用於分離之血漿在血液機構所執行的製程。	**Processing** Processing[8] means any step in the preparation of blood component that is carried out between the collection of blood and the issuing of a blood component, e.g. separation and freezing of blood components. In this Annex, processing in addition refers to those operations performed at the blood establishment that are specific to plasma to be used for fractionation.
權責人員 是負責確保每一批次的（生物）活性物質或藥品已經遵守現行有效法律，並且，依照上市許可規格及/或要求進行製造與檢查的人。權責人員是等同於歐盟術語「Qualified Person」。	**Responsible Person (RP)** A person responsible for securing that each batch of (biological) active substance or medicinal product has been manufactured and checked in compliance with the laws in force and in accordance with the specifications and/or requirements of the marketing authorisation. The RP is equivalent to the EU term "Qualified Person"[9].
血液機構權責人員 是負責確保每一單元的血液或成分血已經遵守現行有效法律進行收集測試、處理、儲存與運銷的人。這個術語是等同於歐盟術語「權責人員（Responsible Person）」。	**Responsible Person (RP) for blood establishment** A person responsible for ensuring that every unit of blood or blood components has been collected and tested, processed, stored and distributed in compliance with the laws in force. This term is equivalent to the EU term "Responsible Person"[10].

委受託分離計畫 這是使用來自其他國家之原料，在國內的分離工廠/製造廠（fractionator/manufacturer）的一個委受託分離，且所製造之產品非預定用於國內市場。	**Contract fractionation program** This is a contract fractionation in a national plant of a fractionator/manufacturer, using starting material from other countries and manufacturing products not intended for the national market.
1. 範圍（SCOPE）	
1.1 本附則之規定適用於人類血液或血漿衍生之藥品，該藥品是在國內分離或進口到國內。本附則也適用於這些產品的原料（例如，人類血漿）。根據國家法規，這些要求可能也適用於納入醫療器材之人類血液或人類血漿的安定衍生物（例如，白蛋白）。	1.1 The provisions of this Annex apply to medicinal products derived from human blood or plasma, fractionated in or imported into the country. The Annex applies also to the starting material (e.g. human plasma) for these products. In line with national legislation[11] the requirements may apply also for stable derivatives of human blood or human plasma (e.g. Albumin) incorporated into medical devices.
1.2 本附則是對用於分離之人類血漿的收集、處理、儲存與輸送，以及人類血液或血漿衍生之藥品的製造，界定其特定之優良製造規範（GMP）要求。	1.2 This Annex defines specific Good Manufacturing Practices (GMP) requirements for collection, processing, storage and transport of human plasma used for fractionation and for the manufacture of medicinal products derived from human blood or plasma.
1.3 本附則是對用於原料從其他國家進口時與對其他國家的委受託分離計畫之特定規定。	1.3 The Annex addresses specific provisions for when starting material is imported from other countries and for contract fractionation programs for other countries.
1.4 本附則不適用於預定供輸血用的成分血。	1.4 The Annex does not apply to blood components intended for transfusion.
2. 原則（PRINCIPLES）	

2.1	人類血液或血漿衍生之藥品（及其作為原料使用的活性物質）必須遵守西藥藥品優良製造規範與相關的上市許可。它們被認定為是生物藥品，而且，原料是包括生物性物質，例如，人類來源的細胞或流體（包含血液或血漿在內）。某些特別的特徵是源自來源物質（source materials）之生物本質，例如，疾病傳染原，特別是病毒，可能會污染來源物質。因此，這些產品的品質與安全性是依賴來源物質及其來源的管制，而且也依賴後續製造程序，包含傳染性標記測試（marker testing）、病毒去除與病毒去活化在內。	2.1	Medicinal products derived from human blood or plasma (and their active substances which are used as starting materials) must comply with the principles and guidelines of Good Manufacturing Practice[12] as well as the relevant marketing authorisation. They are considered to be biological medicinal products and the starting materials include biological substances, such as cells or fluids (including blood or plasma) of human origin. Certain special features arise from the biological nature of the source material. For example, disease-transmitting agents, especially viruses, may contaminate the source material. The quality and safety of these products relies therefore on the control of source materials and their origin as well as on the subsequent manufacturing procedures, including infectious marker testing, virus removal and virus inactivation.

2.2	原則上，作為對於藥品之原料使用的活性物質，必須遵守西藥藥品優良製造規範（參見第 2.1 條）。對於人類血液與血漿衍生之起始原料，參與收集、製備與檢驗的血液機構須遵循國家或國際要求。收集、製備與檢驗必須依照適當的品質系統執行，並且界定其標準與規格。此外，關於從捐血者到接受者之可追溯性與嚴重不良反應及嚴重不良事件通知，應適用國家或國際要求。本附則提出如同在附錄中所界定的國際指引。此外，相關藥典的個論也要遵守。	2.2	In principle active substances used as starting material for medicinal products must comply with the principles and guidelines of Good Manufacturing Practice (see 2.1). For starting materials derived from human blood and plasma national[13] or international requirements for blood establishments involved in the collection, preparation and testing are to be followed. Collection, preparation and testing must be performed in accordance with an appropriate quality system[14] and for which standards and specifications are defined. Furthermore, the national[15] or international requirements on traceability and serious adverse reactions and serious adverse event notifications from the donor to the recipient should be applied. Reference is hereby made to international guidelines as defined in the addendum. In addition the monographs of the relevant Pharmacopoeia[16] are to be observed.
2.3	供製造人類血液或血漿衍生之藥品的原料，從其他國家進口並且預定在國內使用或運銷者，必須符合國家標準。	2.3	Starting material for the manufacture of medicinal products derived from human blood or plasma imported from other countries and intended for use or distribution within the country must meet the national[17]standards.

2.4	在委受託分離計畫之情況，從其他國家進口的原料，必須符合該國成分血之國家或等同的品質與安全性要求。在國內執行的活動，必須完全遵守 GMP。對於與血液機構之品質系統有關的國家標準與規格、可追溯性要求及嚴重不良反應與事件的通知以及如同在附錄中所列舉之相關世界衛生組織指引與建議，應當納入考慮。	2.4	In the case of contract fractionation programs the starting material imported from other countries must comply with the national or equivalent[18] quality and safety requirements for blood components. The activities conducted within the country must fully comply with GMP. Consideration should be given to national[19] standards and specifications relating to a quality system for blood establishments, the traceability requirements and notification of serious adverse reactions and events and the relevant WHO guidelines and recommendations as listed in the addendum.

2.5	因此，在收集與測試後的所有後續步驟【例如，處理（包含分離「separation」在內）、冷凍、儲存與運送至製造廠】必須依照西藥藥品優良製造規範完成。通常，這些活動都在具有製造許可之機構的權責人員之職責下執行。但是，在與分離用血漿有關之特定處理步驟在血液機構進行時，血液機構權責人員的存在與職責，及權責人員的指定任命，可能不相稱。為了確保法規遵從性（compliance），分離工廠/製造廠應依照 GMP 第 7 章與血液機構建立合約，界定各自責任與詳細的要求，以解決這種特殊情況並且確保適當地解決權責人員的法律責任。血液機構的權責人員與分離工廠/製造廠（參見第 3.5 條）的權責人員應參與合約之草擬。權責人員應確保稽查之執行，以確認該血液機構遵守合約。	2.5	All subsequent steps after collection and testing (e.g. processing (including separation), freezing, storage and transport to the manufacturer) must therefore be done in accordance with the principles and guidelines of Good Manufacturing Practice[20]. Normally, these activities would be carried out under the responsibility of a Responsible Person in an establishment with a manufacturing authorisation. Where specific processing steps in relation to plasma for fractionation take place in a blood establishment, the specific appointment of a Responsible Person may, however, not be proportionate given the presence and responsibility of a Responsible Person of the blood establishment. To address this particular situation and to ensure the legal responsibilities of the Responsible Person are properly addressed, the fractionation plant/manufacturer should establish a contract in accordance with Chapter 7 of the GMP Guide with the blood establishment that defines respective responsibilities and the detailed requirements in order to ensure compliance. The Responsible Person of the blood establishment and the Responsible Person of the fractionation/manufacturing plant (see 3.5) should be involved in drawing up this contract. The Responsible Person should ensure that audits are performed to confirm that the blood establishment complies with the contract.

2.6	依國家法規而定，與血漿衍生之藥品的原料有關之文件的特定要求與其他安排是界定於血漿管制標準書中。	2.6	Depending on national legislation, specific requirements for documentation and other arrangements relating to the starting material of plasma-derived medicinal products are defined in the Plasma Master File.
3.	**品質管理（QUALITY MANAGEMENT）**		
3.1	品質管理應管制從血液機構選擇捐血者至產品製造廠運送最終產品之所有階段。每一個捐血至（且包含）血漿之運送到分離工廠的可追溯性，應依照國家或國際要求，透過準確的鑑別程序、紀錄保存與適當標示系統，由血液機構加以確保之，而且，在最終產品經由製造廠進一步製造與運銷期間，應當加以維持。	3.1	Quality management should govern all stages from donor selection in the blood establishment up to delivery of the finished product by the finished product manufacturer. Traceability of each donation up to and including the delivery of plasma to the fractionation plant should be ensured by the blood establishment through accurate identification procedures, record maintenance and an appropriate labelling system according to national [21] or international requirements, and should be maintained during further manufacturing and distribution of final products by the manufacturer.
3.2	對於藥品之製造，作為來源物質所使用的血液或血漿，必須依照國家或國際標準由血液機構進行收集與處理，並且應在具品質系統之實驗室中進行檢驗。其文件所應具備項目可參考附錄。血液機構必須經由國家主管機關核准並接受定期檢查。委受託分離計畫應由製造廠通知主管機關。	3.2	Blood or plasma used as source material for the manufacture of medicinal products must be collected and processed by blood establishments and be tested in laboratories which apply quality systems in accordance with national[22]or international standards. Reference is made to documents listed in the addendum. The blood establishments have to be authorised and subject to regular inspections by a national competent authority[23]. Contract fractionation programs have to be notified to the competent authority by the manufacturer[24].

3.3	如果血漿是從其他國家進口時，該血漿應僅從認可的供應商（例如，血液機構，包含外部倉庫在內）購買。該等供應商應於分離工廠/製造廠所界定之原料的規格中指定，而且，應被輸入國的主管機關接受（例如，在檢查之後），並且也被輸入之分離工廠的權責人員接受。作為原料之血漿（分離用血漿）的認可與放行訂於第 6.8 條中。	3.3	If plasma is imported from other countries it should only be purchased from approved suppliers (e.g. blood establishments, including external warehouses). They should be named in the specifications for starting materials as defined by the fractionation plant/manufacturer, and be accepted by the competent authority (e.g. following an inspection) of the importing country and by the Responsible Person of the importing fractionation plant. Certification and release of plasma (plasma for fractionation) as starting material is mentioned in section 6.8.
3.4	供應商資格認可，包括稽查在內，應依照書面程序由最終產品的分離工廠/製造廠執行，包含檢驗實驗室在內。供應商的資格再認可應定期執行，並以風險考量訂定間隔時間。	3.4	Supplier qualification, including audits, should be performed by the fractionation plant/manufacturer of the finished product including test laboratory according to written procedures. Re-qualification of suppliers should be performed at regular intervals taking a risk-based approach into account.
3.5	最終產品的分離工廠/製造廠應與供應血液的機構建立書面合約。至少應提出下列關鍵層面：	3.5	The fractionation plant/manufacturer of the finished product should establish written contracts with the supplying blood establishments. As a minimum the following key aspects should be addressed:
	- 職責與各自責任的界定		- definition of duties and respective responsibilities
	- 品質系統與文件要求		- quality system and documentation requirements
	- 捐血者篩選標準與測試		- donor selection criteria and testing
	- 對於血液分離為成分血/血漿的要求		- requirements for the separation of blood into blood components/plasma
	- 血漿的冷凍		- freezing of plasma
	- 血漿的儲存與運送		- storage and transport of plasma

- 可追溯性與捐贈/收集後的資訊（包含不良事件在內）。	- traceability and post donation/collection information (including adverse events).
3.6 應具備正式的變更管制系統，以規劃、評估與文件化所有可能影響產品之品質或安全性或可追溯性的變更。所提出之變更的潛在影響應加以評估。對於追加之檢驗與確效的需要性應加以確定，特別是病毒去活化與移除的步驟。	3.6 A formal change control system should be in place to plan, evaluate and document all changes that may affect the quality or safety of the products, or traceability. The potential impact of proposed changes should be evaluated. The need for additional testing and validation, especially viral inactivation and removal steps, should be determined.
3.7 應具備足夠的安全性策略，以將來自傳染原與新興傳染原的風險減到最低。這項策略應包括下列的風險評估：	3.7 An adequate safety strategy should be in place to minimise the risk from infectious agents and emerging infectious agents. This strategy should involve a risk assessment that:
- 界定在處理庫存血漿之前的留置時間（內部隔離時間），亦即，移除回溯單元（look back units）[註]。	- defines an inventory holding time (internal quarantine time) before processing the plasma i.e. to remove look back units[25].
[25] 在所界定的期間（按照國家界定），由捐血者所捐出的血漿單元在發現來自一個高風險捐血者的捐贈之前，應已被排除處理，例如，由於陽性測試結果。	[25] Plasma units donated by donors during a defined period (as defined on a national / EU basis) before it is found that a donation from a high-risk donor should have been excluded from processing, e.g. due to a positive test result.
- 考慮病毒減量及/或傳染原或其替代物（surrogates）之檢驗的所有層面。	- considers all aspects of virus reduction and/or testing for infectious agents or surrogates.
- 考慮病毒減量能力、合併量（pool size）與製造過程的其他相關層面。	- considers the virus reduction capabilities, the pool size and other relevant aspects of the manufacturing processes.
4. 可追溯性與收集後措施（TRACEABILITY AND POST COLLECTION MEASURES）	
4.1 必須有一個適當的系統使得每次捐血，從捐血者及經由血液機構之採集到藥品的批次，都能被追溯，反之亦然。	4.1 There must be a system in place that enables each donation to be traced, from the donor and the donation via the blood establishment through to the batch of medicinal product and vice versa.

4.2 對於產品之可追溯性的責任應加以界定（不得有間斷）：	4.2 Responsibilities for traceability of the product should be defined (there should be no gaps):
- 從捐血者與在血液機構的採集到分離工廠（這是血液機構權責人員的責任）；	- from the donor and the donation in the blood establishment to the fractionation plant (this is the responsibility of the RP of the blood establishment);
- 從分離工廠到藥品製造廠與任何附屬設施，不論是否為藥品或醫療器材的製造廠（這是權責人員的責任）。	- from the fractionation plant to the manufacturer of the medicinal product and any secondary facility, whether a manufacturer of a medicinal product or of a medical device (this is the responsibility of the RP). [25]
4.3 對於需要完全追溯的數據，必須依照國家法規儲存。	4.3 Data needed for full traceability must be stored according to national legislation[26].
4.4 在血液機構（包括測試實驗室在內）與分離工廠/製造廠之間的合約（如同在第 3.5 條所述），應確保可追溯性與收集後措施，涵蓋從血漿收集到負責最終產品放行的所有製造廠之完整鏈。	4.4 The contracts (as mentioned in 3.5) between the blood establishments (including testing laboratories) and the fractionation plant/manufacturer should ensure that traceability and post collection measures cover the complete chain from the collection of the plasma to all manufacturers responsible for release of the final products.

4.5	血液機構應通知分離工廠/製造廠有關任何可能影響產品品質或安全性的事件，包括嚴重不良事件與反應以及對捐血者適當性或血漿之放行之後續發現的其他相關資訊，例如，回溯資訊（收集後的資訊）在內。當分離工廠/製造廠位於另外一個國家時，該資訊應轉送給以前述血漿所製造的任何產品之他國負責放行製造廠。在這兩種情況中，涉及最終產品的品質或安全性時，這些資訊應依照國家法規所要求轉送給負責分離工廠/製造廠的主管機關。	4.5	The blood establishments should notify the fractionating plant/manufacturer of any event which may affect the quality or safety of the product including serious adverse events and reactions[27] and other relevant information found subsequent to donor acceptance or release of the plasma, e.g. look back information[28] (post-collection information). Where the fractionation plant/manufacturer is located in another country, the information should be forwarded to the manufacturer responsible for release in the country of any product manufactured from the plasma concerned. In both cases, if relevant for the quality or safety of the final product, this information should be forwarded to the competent authority[29] responsible for the fractionation plant/manufacturer as required by national legislation.
4.6	當血液機構經主管機關檢查導致所持有許可證/證明書/許可之撤銷時，亦適用第 4.5 條所描述的通知程序。	4.6	The notification procedure as described in 4.5 also applies when an inspection of a blood establishment by a competent authority leads to a withdrawal of an existing licence/certificate/approval.
4.7	血漿收集後資訊的管理，應在標準作業程序中描述，並且應考量通知主管機關的義務與程序。如同在國家或相關國際的建議所界定，收集後措施應當可以取得。捐血後如有下列情況時，血液機構與分離工廠/製造廠，應彼此通知對方：	4.7	The management of post-collection information should be described in standard operating procedures and taking into account obligations and procedures for informing the competent authorities. Post-collection measures should be available as defined in national or relevant international recommendations[30]. The blood establishment and the fractionation/ manufacturer should inform each other if, following donation:

- 發現捐血者不符合相關的捐血者健康標準；	- It is found that the donor did not meet the relevant donor health criteria;
- 先前對病毒標記呈現陰性反應之捐血者，而後續捐血發現對任何病毒標記呈現陽性反應；	- A subsequent donation from a donor previously found negative for viral markers is found positive for any of the viral markers;
- 發現對病毒標記的測試未依所訂定的程序執行；	- It is discovered that testing for viral markers has not been carried out according to agreed procedures;
- 捐血者已罹患由某種病原體引起的傳染病，該等病原體（B 型肝炎、C 型肝炎、A 型肝炎及其他非 A 型、非 B 型、非 C 型等肝炎病毒、後天人類免疫缺乏病毒第 I 和第 II 型，及依現今知識已知的其他病原體）可能藉由自血漿衍生的產品傳染；	- The donor has developed an infectious disease caused by an agent potentially transmissible by plasma-derived products (HBV, HCV, HAV and other non-A, non-B, non-C hepatitis viruses, HIV-1 and 2 and other agents in the light of current knowledge);
- 捐血者罹患庫賈氏症（CJD 或 vCJD）；	- The donor develops Creutzfeldt-Jakob disease (CJD or vCJD);
- 血液或成分血的受血者發生輸血後的感染，且該感染牽涉或可追溯至該捐血者。	- The recipient of blood or a blood component develops post-transfusion infection which implicates or can be traced back to the donor.
如果發生上述任何一種狀況時，則應執行批次文件的再評估。執行該批次收回之必要性，應就所涉及的傳染病原體、合併量的大小、捐血與血清陽轉期間之時間、產品本質及其製造方法等因素謹慎考量。	In the event of any of the above, a re-assessment of the batch documentation should always be carried out. The need for withdrawal of the given batch should be carefully considered, taking into account criteria such as the transmissible agent involved, the size of the pool, the time period between donation and seroconversion, the nature of the product and its manufacturing method.
5. 廠房設施與設備（PREMISES AND EQUIPMENT）	

5.1	為使混合血漿遭受微生物或外來異物的污染減到最少，血漿單元的解凍與合併，應在PIC/S GMP附則1所界定之至少D級潔淨區中執行，而且，操作者須穿戴適當的服裝，包含面罩與手套在內。在製造過程中的所有其他開放性操作，應在符合PIC/S GMP附則1的適當要求下完成。	5.1	In order to minimise microbiological contamination or the introduction of foreign material into the plasma pool, thawing and pooling of plasma units should be performed in an area conforming at least to the Grade D requirements defined in Annex 1 of the PIC/S GMP Guide. Appropriate clothing should be worn including face masks and gloves. All other open manipulations during the manufacturing process should be done under conditions conforming to the appropriate requirements of Annex 1 of the PIC/S GMP Guide.
5.2	環境監測應依照PIC/S GMP附則1定期執行，尤其是在打開血漿容器與後來解凍及合併過程的期間。	5.2	Environmental monitoring should be performed regularly, especially during the 'opening' of plasma containers, and during subsequent thawing and pooling processes in accordance with Annex 1 of the PIC/S GMP Guide.
5.3	生產自血漿衍生之藥品時，應使用適當之病毒去活化或移除程序，而且應採取步驟，以防止經處理的產品與未經處理之產品的交叉污染。對於在病毒去活化處理之前與處理之後的製造步驟，應使用專用且區隔的廠房設施與設備。	5.3	In the production of plasma-derived medicinal products, appropriate viral inactivation or removal procedures are used and steps should be taken to prevent cross contamination of treated with untreated products. Dedicated and distinct premises and equipment should be used for manufacturing steps before and after viral inactivation treatment.
5.4	為避免例行製造受確效研究所用病毒污染的風險，不得在生產設施中執行病毒減量之方法確效。確效應依照國際的建議執行之。	5.4	To avoid placing routine manufacture at risk of contamination from viruses used during validation studies, the validation of methods for virus reduction should not be conducted in production facilities. Validation should be performed according to international recommendations[31].
6.	**製造（MANUFACTURING）**		
原料（Starting material）			

6.1	原料應符合相關藥典之所有相關個論的要求與在各自上市許可檔案文件所明定的條件（包括血漿管制標準書，如可適用時)。這些要求應於血液機構與分離工廠/製造廠之間的書面合約中界定（參見第3.5條)，並且透過品質系統予以管制。	6.1	The starting material should comply with the requirements of all relevant monographs of the relevant Pharmacopoeia and of the conditions laid down in the respective marketing authorisation dossier (including the Plasma Master File if applicable). These requirements should be defined in the written contract (see 3.5) between the blood establishment and the fractionating plant/manufacturer and controlled through the quality system.
6.2	為委受託分離計畫所進口的原料應符合第 2.4 條所規定的要求。	6.2	Starting material imported for contract fractionation programs should comply with the requirements as specified in 2.4.
6.3	依收集的類型而定（亦即全血收集或自動分離術）可能需要不同的處理步驟。所有處理步驟（例如，離心及/或分離、抽樣、標示、冷凍）應在書面程序中界定。	6.3	Depending on the type of collection (i.e. either whole blood collection or automated apheresis) different processing steps may be required. All processing steps (e.g. centrifugation and/or separation, sampling, labelling, freezing) should be defined in written procedures.
6.4	應避免血漿袋與樣品的任何混雜（特別是在標示時）及污染（例如，切割管段/密封容器時)。	6.4	Any mix-ups of units and of samples, especially during labelling, as well as any contamination, e.g. when cutting the tube segments/sealing the containers, must be avoided.

6.5	冷凍對於血漿中不安定之蛋白質（例如，凝血因子）的回收是一個關鍵步驟。因此，冷凍應依循經確效的方法並在收集後儘早執行（參見歐洲藥典個論 No 0853「分離用人類血漿」以及，相關時，個論 No 1646 「為病毒去活化經合併與處理的人類血漿」，或其他相關的藥典）。	6.5	Freezing is a critical step for the recovery of proteins that are labile in plasma, e.g. clotting factors. Freezing should therefore be performed as soon as possible after collection (see the European Pharmacopoeia monograph No 0853 "Human Plasma for Fractionation" and where relevant, monograph No 1646 "Human Plasma pooled and treated for virus inactivation", or other relevant Pharmacopoeia), following a validated method.
6.6	對於分離工廠，在運輸鏈的任何階段，血液與血漿的儲存與運送應加以界定並且記錄。任何與所界定溫度之偏離應通知分離工廠。應使用驗證合格的設備與經確效的程序。	6.6	The storage and transport of blood or plasma at any stage in the transport chain to the fractionation plant should be defined and recorded. Any deviation from the defined temperature should be notified to the fractionation plant. Qualified equipment and validated procedures should be used.
作為原料之分離用血漿的認可/放行 （Certification/release of plasma for fractionation as starting material）			

6.7	分離用血漿應僅透過確保最終產品之製造所需要的品質之系統與程序予以放行，亦即，從一個待驗狀態放行。它應僅在其已由血液機構的權責人員（或者在其他國家血液/血漿收集時，應由具有同等責任與資格認定的人）經文件證明該分離用血漿確實符合相應的書面合約所界定之要求與規格，而且合適時，所有步驟都依照優良規範與相關 GMP 指引執行後才運送到血漿分離工廠/製造廠。	6.7	Plasma for fractionation should only be released, i.e. from a quarantine status, through systems and procedures that assure the quality needed for the manufacture of the finished product. It should only be distributed to the plasma fractionation plant/ manufacturer after it has been documented by the Responsible Person of the blood establishment (or in case of blood/plasma collection in other countries by a person with equivalent responsibilities and qualifications) that the plasma for fractionation does comply with the requirements and specifications defined in the respective written contracts and that all steps have been performed in accordance with Good Practice and GMP Guidelines, as appropriate.
6.8	在進入分離工廠時，該血漿單元應在權責人員的職責下放行以供分離。權責人員應確認該血漿符合所有相關個論之要求與在各自上市許可檔案（包括血漿管制標準書在內，如可適用時）中所明定的條件，或在血漿要使用於委受託分離計畫時，應確保符合第 2.4 條分離用血漿的處理中所規定的要求。	6.8	On entering the fractionation plant, the plasma units should be released for fractionation under the responsibility of the Responsible Person. The Responsible Person should confirm that the plasma complies with the requirements of all relevant monographs and the conditions laid down in the respective marketing authorisation dossier (including the Plasma Master File if applicable) or, in case of plasma to be used for contract fractionation programs,with the requirements as specified in 2.4. Processing of plasma for fractionation.

6.9	在分離過程中所使用的步驟，因產品與製造廠而異，而且通常包括幾個分離/純化程序，其中的一些程序可能有助於潛在污染的去活化及/或移除。	6.9	The steps used in the fractionation process vary according to product and manufacturer and usually include several fractionation/purification procedures, some of which may contribute to the inactivation and/or removal of potential contamination.
6.10	對於合併的過程、合併後取樣與分離/純化及病毒去活化/移除的要求應加以界定，並且徹底遵循。	6.10	Requirements for the processes of pooling, pool sampling and fractionation/purification and virus inactivation/removal should be defined and followed thoroughly.
6.11	在病毒去活化過程所使用的方法，應嚴格遵守經確效的程序並且符合在病毒確效研究上所使用的方法進行。應執行病毒去活化程序失敗的詳細調查。在病毒減量程序上，遵守經確效的生產過程特別重要，因為任何的偏離對最終產品都可能導致安全性風險。應具備考量這個風險的程序。	6.11	The methods used in the viral inactivation process should be undertaken with strict adherence to validated procedures and in compliance with the methods used in the virus validation studies. Detailed investigation of failures in virus inactivation procedures should be performed. Adherence to the validated production process is especially important in the virus reduction procedures as any deviation could result in a safety risk for the final product. Procedures which take this risk into consideration should be in place.
6.12	任何重處理或再加工可能僅在已經執行品質風險管理運作之後，並且使用相關上市許可所界定的處理步驟進行。	6.12	Any reprocessing or reworking may only be performed after a quality risk management exercise has been performed and using processing steps as defined in the relevant marketing authorisation.
6.13	在已進行與未進行病毒減量處理之產品或中間產品之間，應具備清楚地隔離/區別的系統。	6.13	A system for clearly segregating/distinguishing between products or intermediates which have undergone a process of virus reduction, from those which have not, should be in place.

6.14	依全面之風險管理的結果而定（考慮到在流行病學上的可能差異），當不同來源的血漿/中間產品在同一工廠進行處理時，應採取時段切換生產，包括清楚隔離與已確效的清潔程序在內。對於該等措施的要求，可參考國際建議。在委受託分離計畫的情況中，風險管理過程應考慮對於使用專用設備是否必要。	6.14	Depending on the outcome of a thorough risk management process (taking into consideration possible differences in epidemiology) production in campaigns including clear segregation and defined validated cleaning procedures should be adopted when plasma/intermediates of different origins is processed at the same plant. The requirement for such measures should be based on international recommendations[32]. The risk management process should consider whether it is necessary to use dedicated equipment in the case of contract fractionation programs.
6.15	對於預定進行儲存的中間產品，應依據安定性數據界定一個架儲期。	6.15	For intermediate products intended to be stored, a shelf-life should be defined based on stability data.
6.16	中間產品與最終藥品在運輸鏈之任何階段的儲存與運送，應加以規定並且記錄。應使用驗證合格的設備與經確效的程序。	6.16	The storage and transport of intermediate and finished medicinal products at any stage of the transport chain should be specified and recorded. Qualified equipment and validated procedures should be used.
7.	**品質管制（QUALITY CONTROL）**		
7.1	對於病毒或其他傳染原的測試要求，應根據傳染原的最新知識並考慮適當且經確效之測試方法的可得性。	7.1	Testing requirements for viruses or other infectious agents should be considered in the light of knowledge emerging on infectious agents and on the availability of appropriate, validated test methods.
7.2	首次均質之混合血漿（例如，從混合血漿冷凍沉澱物分離之後），應依照相關藥典個論，使用經確效且具適當靈敏度與專一性的試驗方法進行測試。	7.2	The first homogeneous plasma pool (e.g. after separation of the cryoprecipitate from the plasma pool) should be tested using validated test methods of suitable sensitivity and specificity, according to the relevant Pharmacopoeia monographs[33].
8.	**中間產品與最終產品的放行（RELEASE OF INTERMEDIATE AND FINISHED PRODUCTS）**		

8.1	僅可放行經測試，並且對於病毒標記/抗體呈現陰性反應，而且符合相關藥典個論，包括任何特定病毒限量（cut-off limits）在內，以及具有經核准的規格（例如，血漿管制標準書，如可適用時）之混合血漿所衍生的批次產品。	8.1	Only batches derived from plasma pools tested and found negative for virus markers/ antibodies and found in compliance with the relevant Pharmacopoeia monographs, including any specific virus cut-off limits, and with the approved specifications (e.g. Plasma Master File if applicable), should be released.
8.2	預定進一步在廠內處理或遞送到不同場所之中間產品的放行與最終產品之放行，應由權責人員依核准的上市許可執行。	8.2	The release of intermediates intended for further in-house processing or delivery to a different site and the release of finished products should be performed by the Responsible Person and in accordance with the approved marketing authorisation.
8.3	在委受託分離計畫中所使用之中間產品與最終產品的放行，應由權責人員依據委託者所同意的標準並且遵循 PIC/S GMP 標準執行。	8.3	The release of intermediates and final products used in contract fractionation programs should be performed by the Responsible Person on the basis of standards agreed with the contract giver and compliance with PIC/S GMP standards.
9.	**混合血漿樣品的留存（RETENTION OF PLASMA POOL SAMPLES）**		
	一混合血漿可以使用於製造多個批次及/或產品。從每一個混合血漿的留存樣品與相應的紀錄，應保存到自該混合血漿所衍生之具有最長架儲期的最終藥品之末效日期後至少一年。		One plasma pool may be used to manufacture more than one batch and/or product. Retention samples and corresponding records from every pool should be kept for at least one year after the expiry date of the finished medicinal product with the longest shelf-life derived from the pool.
10.	**廢棄物的處置（DISPOSAL OF WASTE）**		

廢棄物、拋棄式與拒用之物品（例如，受污染、來自受感染之捐血者與過期的血液、血漿、中間產品或最終產品）之安全與文件化儲存應有書面程序規範。	There should be written procedures for the safe and documented storage and disposal of waste, disposable and rejected items (e.g. contaminated units, units from infected donors, out of date blood, plasma, intermediate or finished products).
附錄（ADDENDUM）	
（以下供參考）附錄列舉關於特定主題的進一步指引或必須由歐盟/歐洲經濟區成員國實施的歐盟特定指令與指引。	The Addendum lists EU-specific directives and guidelines which give further guidance on specific topics or must be implemented by EU/EEA Member States.

附錄（Addendum）

A) EU/EEA Member States have been obliged to implement the following Directives and guidelines:		
1. for collection and testing of blood and blood components:		
Directive/Guidelines	**Title**	**Scope**
Directive 2002/98/EC of the European Parliament and of the Council	Setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components, amending Directive 2001/83/EC.	Art.2 Defines standards of quality and safety for the collection and testing of human blood and blood components, whatever their intended purpose, and for their processing, storage and distribution when intended for transfusion.
Commission Directive 2004/33/EC	Implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components	Defines the provision of information to prospective donors and information required from donors (Part A and B, Annex II), eligibility of donors (Annex III), storage, transport and distribution conditions for blood and blood components (Annex IV), as well as quality and safety requirements for blood and blood components (Annex V).

Commission Directive 2005/61/EC	Implementing Directive 2002/98/EC of the European Parliament and of the Council as regards traceability requirements and notification of serious adverse reactions and events.	Defines traceability requirements for blood establishments, donors, blood and blood components, and for the final destination of each unit, whatever the intended purpose. It further defines the reporting requirements in the event of serious adverse events and reactions.
Commission Directive 2005/62/EC	Implementing Directive 2002/98/EC of the European Parliament and of the Council as regards Community standards and specifications relating to a quality system for blood establishments.	Defines the implementation of quality system standards and specifications as referred to in article 47 of Directive 2001/83/EC.
2. for collection and regulatory submission of data/information for plasma for fractionation:		
Directive/ Guidelines	Title	Scope
Directive 2001/83/EC of the European Parliament and the Council	On the Community Code relating to medicinal products for human use.	Art. 2 Medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process, covering medicinal products derived from human blood or human plasma.
Commission Directive 2003/63/EC	Amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use; Amending the Annex on documentation of medicinal products	
Commission Directive 2003/94/EC	Laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use	Art. 1 Principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use
EU Guidelines to Good Manufacturing Practice	Giving interpretation on the principles and guidelines on GMP	
EMEA/CHMP/BWP/3794/03 Rev.1, 15. Nov. 2006	Guideline on the Scientific data requirements for a Plasma Master File (PMF) Revision 1	
EMEA/CPMP/BWP/125/04 EMEA Guideline	Guideline on Epidemiological Data on Blood Transmissible Infections	
B. Other relevant documents		

PE 005 PE005	PIC/S GMP Guide for blood Establishments	Guidance for GMP for blood establishments
Recommendation No. R (95) 15 (Council of Europe)	Guide to the Preparation, use and quality assurance of blood components	
World Health Organization WHO Technical Report Series No 941, 2007; Annex 4	WHO Recommendations for the production, control and regulation of human plasma for fractionation	Guidance on the production, control and regulation of human plasma for fractionation, adopted by the 56th meeting of the WHO Expert Committee on Biological Standardiz
World Health Organization, WHO Technical Report Series, No. 961, 2011; Annex 4	WHO guidelines on Good Manufacturing Practices for blood establishments	
Reference should be made to the latest revisions of these documents for current guidance.		

[1] For EU/EEA as referred to in Directive 2002/98/EC (Art. 3a)

[2] For EU/EEA as referred to in Directive 2002/98/EC (Art. 3b)

[3] For EU/EEA as referred to in Directive 2002/98/EC (Art. 3e)

[4] For EU/EEA as referred to in Directive 2002/98/EC (Art. 3c)

[5] For EU/EEA as established in the Annex of Directive 2005/62/EC

[6] For EU/EEA as referred to as referred to in Directive 2001/83/EC (Art. 1 No. 10)

[7] For EU/EEA as referred to in Directive 2001/83/EC (Annex I, Part III, No. 1.1.a)

[8] For EU/EEA as according to the terminology of directive 2005/62/EC

[9] For EU/EEA, see Article 48 of Directive 2001/83/EC and Article 52 of Directive 2001/82/EC.

[10] For EU/EEA, see Article 9 of Directive 2002/98/EC.

[11] For EU/EEA as set out in Directive 2003/63/EC

[12] For EU/EEA this is laid down in Commission Directive 2003/94/EC and the EU Guidelines on GMP published by the European Commission.

[13] For EU/EEA requirement for the collection and testing are defined in Directive 2002/98/EC.

[14] For EU/EEA standards and specifications for quality systems are defined in the Annex of Directive 2005/62/EC and interpreted in the Good Practice guidelines referred to in Article 2 (2) of Directive 2005/62/EC.

[15] For EU/EEA requirements on traceability and serious adverse reactions and serious adverse event notifications are defined in Directive 2005/61/EC.

[16] For EU/EEA this is the European Pharmacopoeia as defined in Directive 2002/98/EC.

[17] For EU/EEA these standards are equivalent to Community Standards and specifications relating to a quality system for blood establishments as set out in Commission Directive 2005/62/EC (Recital 6; Article 2(3)), the traceability and serious adverse reaction and serious adverse event notification requirements as set out in Commission Directive 2005/61/EC (Recital 5; Article 7), and the technical requirements for blood and blood components as set out in Commission Directive 2004/33/EC (Recital 4; point 2.3 of Annex V).

[18] For EU/EEA reference is made to the quality and safety requirements as laid down in Directive 2002/98/EC and in

Annex V of Directive 2004/33/EC.

[19] For EU/EEA considerations should be given to the Community standards and specifications relating to a quality system for blood establishments set out in Commission Directive 2005/62/EC and the traceability requirements and notification of serious adverse reactions and events as set out in Commission Directive 2005/61/EC.

[20] For EU/EEA the requirements of Directive 2001/83/EC apply.

[21] For EU/EEA reference is made to Directive 2005/61/EC and to Directive 2005/62/EC.

[22] For EU/EEA reference is made to Directive 2005/62/EC.

[23] For EU/EEA as referred to in Directive 2002/98/EC

[24] For EU/EEA it is the competent authority as referred to in Directive 2001/83/EC.

[26] For EU/EEA this is for at least 30 years according to Article 4 of Directive 2005/61/EC and Article 14 of Directive 2002/98/EC. Both Directives are linked to Article 109 of Directive 2001/83/EC by defining specific rules for medicinal products derived from human blood or plasma.

[27] For EU/EEA reference is made to in Annex II part A and Annex III part A of Directive 2005/61/EC.

[28] Information that appears if a subsequent donation from a donor previously found negative for viral markers is found positive for any of the viral markers or any other risk factors which may induce a viral infection.

[29] For EU/EEA this is the competent authority as referred to in Directive 2001/83/EC.

[30] For EU/EEA referene is made to the “Note for Guidance on Plasma Derived Medicinal Products" in its current version as adopted by the Committee for Medicinal Products for Human Use (CHMP) andpublished by the European Medicines Agency. Current version at date of publication:CPMP/BWP/269/95.

[31] For EU/EEA reference is made to the "Note for Guidance on Virus Validation Studies: The Design, Contribution and Interpretation of Studies validating the Inactivation and Removal of Viruses" in its current version as adopted by the Committee for Medicinal Products for Human Use (CHMP) and published by the European Medicines Agency. Current version at date of publication: CHMP/BWP/268/95.

[32] For EU/EEA, see Guideline on Epidemiological Data on Blood Transmissible Infections, EMEA/CPMP/BWP/125/04.

[33] For EU/EEA reference is made to the relevant European Pharmacopoeia monographs (e.g. No 0853).

附則 15 驗證與確效（QUALIFICATION AND VALIDATION）

原則（PRINCIPLE）	
本附則是描述驗證與確效的原則，該原則可適用於藥品製造所使用的廠房設施、設備、公用設施與製程，對 PIC/S GMP 第二部沒有導入追加的要求，也可作為原料藥的補充選用指引。在產品與製程的整個生命週期中，製藥廠透過驗證與確效管制其特殊操作的關鍵層面是 GMP 的要求。對可能影響產品品質之廠房設施、設備、公用設施與製程等的任何計畫性變更，應予正式文件化，並且評估其對於已確效之狀態或管制策略的影響。使用於藥品之製造的電腦化系統也應當依照附則 11 的要求予以確效。在 ICH Q8、Q9、Q10 與 Q11 所呈現的相關概念與指引也應當納入考慮。	This Annex describes the principles of qualification and validation which are applicable to the facilities, equipment, utilities and processes used for the manufacture of medicinal products and may also be used as supplementary optional guidance for active substances without introduction of additional requirements to Part II. It is a GMP requirement that manufacturers control the critical aspects of their particular operations through qualification and validation over the life cycle of the product and process. Any planned changes to the facilities, equipment, utilities and processes, which may affect the quality of the product, should be formally documented and the impact on the validated status or control strategy assessed. Computerised systems used for the manufacture of medicinal products should also be validated according to the requirements of Annex 11. The relevant concepts and guidance presented in ICH Q8, Q9, Q10 and Q11 should also be taken into account.
概述（GENERAL）	

	品質風險管理方法應當在藥品的整個生命週期中加以應用。作為品質風險管理系統之一部分，關於驗證與確效的範圍與程度之決定，應以廠房設施、設備、公用設施與製程經證明其合理性且經文件化的風險評估為基礎。回溯性確效不再被認為是可以接受的方法。		A quality risk management approach should be applied throughout the lifecycle of a medicinal product. As part of a quality risk management system, decisions on the scope and extent of qualification and validation should be based on a justified and documented risk assessment of the facilities, equipment, utilities and processes. Retrospective validation is no longer considered an acceptable approach.
	源自於製藥廠自身計畫外的支持驗證及/或確效試驗之數據，若其作法經證明其合理性，且充分保證該等數據之獲得的整個過程中具適當之管制，則該等數據可加以使用。		Data supporting qualification and/or validation studies which were obtained from sources outside of the manufacturers own programmes may be used provided that this approach has been justified and that there is adequate assurance that controls were in place throughout the acquisition of such data.
1.	**驗證與確效的籌組與規劃（ORGANISING AND PLANNING FOR QUALIFICATION AND VALIDATION）**		
1.1	所有驗證與確效活動應加以規劃，並將廠房設施、設備、公用設施、製程與產品之生命週期納入考慮。	1.1	All qualification and validation activities should be planned and take the life cycle of facilities, equipment, utilities, process and product into consideration.
1.2	驗證與確效活動應僅由受過適當訓練的人員並遵循已核准的程序執行。	1.2	Qualification and validation activities should only be performed by suitably trained personnel who follow approved procedures.
1.3	如同製藥品質系統中所界定，驗證/確效人員應進行提報，雖然並非必需向品質管理或品質保證功能單位報告；但是，在整個確效生命週期中應有適當的品質監督。	1.3	Qualification/validation personnel should report as defined in the pharmaceutical quality system although this may not necessarily be to a quality management or a quality assurance function. However, there should be appropriate quality oversight over the whole validation life cycle.

1.4 製藥工廠之驗證及確效計畫的關鍵要項應在確效主計畫書或等同的文件中加以清楚地界定，並予以文件化。	1.4 The key elements of the site qualification and validation programme should be clearly defined and documented in a validation master plan (VMP) or equivalent document.
1.5 確效主計畫書或等同的文件應界定驗證/確效系統，且應包含或引述資訊至少如下：	1.5 The VMP or equivalent document should define the qualification/validation system and include or reference information on at least the following:
i. 驗證與確效政策；	i. Qualification and Validation policy;
ii. 組織架構，包含對於驗證與確效活動的角色與職責在內；	ii. The organisational structure including roles and responsibilities for qualification and validation activities;
iii. 廠房設施、設備、系統、製程與其驗證及確效狀態的摘要；	iii. Summary of the facilities, equipment, systems, processes on site and the qualification and validation status;
iv. 對於驗證與確效的變更管制與偏差管理；	iv. Change control and deviation management for qualification and validation;
v. 關於開發允收標準的指引；	v. Guidance on developing acceptance criteria;
vi. 引述現有文件；	vi. References to existing documents;
vii. 驗證與確效策略，適用時，包含再驗證在內。	vii. The qualification and validation strategy, including requalification, where applicable.
1.6 對於大型與複雜的計畫，規劃顯得額外重要，且分開的確效計畫可以提升清晰度。	1.6 For large and complex projects, planning takes on added importance and separate validation plans may enhance clarity.
1.7 驗證與確效活動應運用品質風險管理方法。根據來自計畫階段中或商業生產中之任何變更所增加的知識與理解，需要時，應再次執行風險評估。使用風險評估以支持驗證與確效活動的方式，應清楚地文件化。	1.7 A quality risk management approach should be used for qualification and validation activities. In light of increased knowledge and understanding from any changes during the project phase or during commercial production, the risk assessments should be repeated, as required. The way in which risk assessments are used to support qualification and validation activities should be clearly documented.

1.8	適當的檢查應納入驗證與確效工作中，以確保所獲得之所有數據的完整性。	1.8	Appropriate checks should be incorporated into qualification and validation work to ensure the integrity of all data obtained.
2.	**文件製作，包括確效主計畫書在內（DOCUMENTATION, INCLUDING VMP）**		
2.1	優良文件製作規範對於支持整個產品生命週期的知識管理，是很重要的。	2.1	Good documentation practices are important to support knowledge management throughout the product lifecycle.
2.2	在驗證與確效中所產生的所有文件，應由製藥品質系統中所界定的適當人員予以核准與授權。	2.2	All documents generated during qualification and validation should be approved and authorised by appropriate personnel as defined in the pharmaceutical quality system.
2.3	在複雜的確效計畫中，文件之間的相互關係應清楚地界定。	2.3	The inter-relationship between documents in complex validation projects should be clearly defined.
2.4	應製作確效計畫書，以界定關鍵之系統、屬性與參數及其相關的允收標準。	2.4	Validation protocols should be prepared which defines the critical systems, attributes and parameters and the associated acceptance criteria.
2.5	合適時，驗證文件可以合併在一起，例如，安裝驗證與操作驗證。	2.5	Qualification documents may be combined together, where appropriate, e.g. installation qualification (IQ) and operational qualification (OQ).
2.6	經由第三方提供確效計畫書與其他文件製作等確效服務時，在核准前，廠內的適當人員應確認其適用性，並且遵從內部程序。使用供應商的計畫書前，可經由追加的文件/測試計畫書加以補充。	2.6	Where validation protocols and other documentation are supplied by a third party providing validation services, appropriate personnel at the manufacturing site should confirm suitability and compliance with internal procedures before approval. Vendor protocols may be supplemented by additional documentation/test protocols before use.

2.7	在執行期間，對於已核准之確效計畫書的任何重要變更，例如，允收標準、操作參數等，應記錄為偏差且有科學性的證明。	2.7	Any significant changes to the approved protocol during execution, e.g. acceptance criteria, operating parameters etc., should be documented as a deviation and be scientifically justified.
2.8	不符合預先界定之允收標準的結果應記錄為偏差，並應依廠內程序予以全面地調查。對確效之任何可能的影響應在報告中加以討論。	2.8	Results which fail to meet the pre-defined acceptance criteria should be recorded as a deviation, and be fully investigated according to local procedures. Any implications for the validation should be discussed in the report.
2.9	確效的檢討與結論應予以提報，並且所得結果應對照允收標準加以概述。對於允收標準之任何後續變更，應在科學上證明其合理性，並且作出關於該確效結果的最後建議。	2.9	The review and conclusions of the validation should be reported and the results obtained summarised against the acceptance criteria. Any subsequent changes to acceptance criteria should be scientifically justified and a final recommendation made as to the outcome of the validation.
2.10	可進入下一階段驗證與確效過程的正式放行，應經由相關負責人員核准，作為確效報告核准的一部分或個別的摘要文件。在某些允收標準或偏差尚未完全解決，且已有文件化評估證明其對下一個活動沒有顯著影響時，則對於進入下一個驗證階段可給予有條件的核准。	2.10	A formal release for the next stage in the qualification and validation process should be authorised by the relevant responsible personnel either as part of the validation report approval or as a separate summary document. Conditional approval to proceed to the next qualification stage can be given where certain acceptance criteria or deviations have not been fully addressed and there is a documented assessment that there is no significant impact on the next activity.
3.	**設備、廠房設施、公用設施與系統的驗證階段（QUALIFICATION STAGES FOR EQUIPMENT, FACILITIES, UTILITIES AND SYSTEMS.）**		

3.1 設備、廠房設施、公用設施或系統的驗證活動，應考慮從使用者需求規格之初始開發至其終止使用的所有階段。主要階段與包含在各階段之某些建議標準（雖然這些標準是取決於個別計畫情況，而且可能不同），如下所示：	3.1 Qualification activities should consider all stages from initial development of the user requirements specification through to the end of use of the equipment, facility, utility or system. The main stages and some suggested criteria (although this depends on individual project circumstances and may be different) which could be included in each stage are indicated below:
使用者需求規格【User requirements specification (URS)】	
3.2 對於設備、廠房設施、公用設施或系統的規格，應在使用者需求規格及/或在功能規格中加以界定。基本的品質要件需要在此階段予以建立，並且將任何 GMP 風險降到可接受的程度。使用者需求規格應當是整個確效生命週期的一個參考點。	3.2 The specification for equipment, facilities, utilities or systems should be defined in a URS and/or a functional specification. The essential elements of quality need to be built in at this stage and any GMP risks mitigated to an acceptable level. The URS should be a point of reference throughout the validation life cycle.
設計驗證【Design qualification (DQ)】	
3.3 在設備、廠房設施、公用設施或系統之驗證的下一個要件，就是設計驗證，在該驗證中應證明其設計遵循 GMP 並且加以文件化。在設計驗證中應確認使用者需求規格的要求。	3.3 The next element in the qualification of equipment, facilities, utilities, or systems is DQ where the compliance of the design with GMP should be demonstrated and documented. The requirements of the user requirements specification should be verified during the design qualification.
工廠驗收測試（FAT）/現場驗收測試（SAT）【Factory acceptance testing (FAT) /Site acceptance testing (SAT)】	
3.4 若適用時，設備可於交貨前在供應商處進行評估，尤其是有新穎或複雜技術時。	3.4 Equipment, especially if incorporating novel or complex technology, may be evaluated, if applicable, at the vendor prior to delivery.
3.5 若適用時，設備在安裝前，應在供應商的場所確認符合使用者需求規格/功能規格。	3.5 Prior to installation, equipment should be confirmed to comply with the URS/ functional specification at the vendor site, if applicable.

3.6 當合適並證明合理時，文件審查與一些測試可在工廠驗收測試或其他階段執行，如果可以顯示其功能不受運輸與安裝影響時，則該等審查與測試在安裝驗證/操作驗證時不需於現場重複。	3.6 Where appropriate and justified, documentation review and some tests could be performed at the FAT or other stages without the need to repeat on site at IQ/OQ if it can be shown that the functionality is not affected by the transport and installation.
3.7 工廠驗收測試可由製藥工廠接收設備後，執行現場驗收測試予以補充。	3.7 FAT may be supplemented by the execution of a SAT following the receipt of equipment at the manufacturing site.
安裝驗證【Installation qualification (IQ)】	
3.8 對於設備、廠房設施、公用設施或系統應執行安裝驗證。	3.8 IQ should be performed on equipment, facilities, utilities, or systems.
3.9 安裝驗證應包括但不侷限於下列各項：	3.9 IQ should include, but is not limited to the following:
i. 對照工程圖及規格，確認組件、儀器儀表、設備、管路工程與公用設施的正確安裝；	i. Verification of the correct installation of components, instrumentation, equipment, pipe work and services against the engineering drawings and specifications;
ii. 對照預先界定之標準，確認正確安裝；	ii. Verification of the correct installation against pre-defined criteria;
iii. 收集與整理供應商之操作指令與工作指令及維護保養要求；	iii. Collection and collation of supplier operating and working instructions and maintenance requirements;
iv. 儀器儀表的校正；	iv. Calibration of instrumentation;
v. 建造材質的確認。	v. Verification of the materials of construction.
操作驗證【Operational qualification (OQ)】	
3.10 操作驗證通常是在安裝驗證之後進行，但視設備的複雜性，得以合併的安裝驗證/操作驗證（IOQ）方式執行。	3.10 OQ normally follows IQ but depending on the complexity of the equipment, it may be performed as a combined Installation/Operation Qualification (IOQ).
3.11 操作驗證應包括但不侷限於下列各項：	3.11 OQ should include but is not limited to the following:

i. 已從製程、系統與設備之知識開發的測試，以確保系統可按原設計運作；	i. Tests that have been developed from the knowledge of processes, systems and equipment to ensure the system is operating as designed;
ii. 能確認操作限度之上下限及/或「最差狀況」條件的測試。	ii. Tests to confirm upper and lower operating limits, and/or “worst case” conditions.
3.12 成功之操作驗證的完成，應允許標準作業程序、清潔程序、操作者訓練及預防性維護保養等要求之最終確定。	3.12 The completion of a successful OQ should allow the finalisation of standard operating and cleaning procedures, operator training and preventative maintenance requirements.
性能驗證【Performance qualification (PQ)】	
3.13 性能驗證通常應在安裝驗證與操作驗證成功完成後執行。但在有些情況，與操作驗證或製程確效合併執行可能是合適的。	3.13 PQ should normally follow the successful completion of IQ and OQ. However, it may in some cases be appropriate to perform it in conjunction with OQ or Process Validation.
3.14 性能驗證應包括但不侷限於下列各項：	3.14 PQ should include, but is not limited to the following:
i. 使用生產原料、合格替代品，或經證明在正常操作條件下具有等同之特性的模擬產品，以最差狀況之批量測試。用於確認製程管制之抽樣頻率，應證明其合理性。	i. Tests, using production materials, qualified substitutes or simulated product proven to have equivalent behaviour under normal operating conditions with worst case batch sizes. The frequency of sampling used to confirm process control should be justified;
ii. 除非來自開發階段之文件化證據可確認操作範圍，否則，測試應涵蓋預期的製程操作範圍。	ii. Tests should cover the operating range of the intended process, unless documented evidence from the development phases confirming the operational ranges is available.
4. 再驗證（RE-QUALIFICATION）	
4.1 設備、廠房設施、公用設施與系統應以適當的頻率加以評估，以確認其維持在管制狀態中。	4.1 Equipment, facilities, utilities and systems should be evaluated at an appropriate frequency to confirm that they remain in a state of control.

4.2 當再驗證為必要且要在規範期間執行時，應證明該期間的合理性，並且對於評估的標準應加以界定；此外，可能隨時間而產生之小變更，應加以評估。	4.2 Where re-qualification is necessary and performed at a specific time period, the period should be justified and the criteria for evaluation defined. Furthermore, the possibility of small changes over time should be assessed.
5. 製程確效（PROCESS VALIDATION）	
概述（General）	
5.1 在本節中所概述的要求與原則，可適用於所有藥品劑型的製造。該要求與原則涵蓋新製程的初始確效、經修改之製程的後續確效、場所移轉與持續進行的製程確認。在本附則中，意指具備穩健的產品開發過程，即能達成成功的製程確效。	5.1 The requirements and principles outlined in this section are applicable to the manufacture of all pharmaceutical dosage forms. They cover the initial validation of new processes, subsequent validation of modified processes, site transfers and ongoing process verification. It is implicit in this annex that a robust product development process is in place to enable successful process validation.
5.2 第 5 節應與涉及製程確效之相關指引合併使用[1]。	5.2 Section 5 should be used in conjunction with relevant guidelines on Process Validation[1].
[1] 在 EU/ EEA，參見：EMA/CHMP/CVMP/QWP/BWP/70278/2012	[1] In the EU/EEA, see EMA/CHMP/CVMP/QWP/BWP/70278/2012
5.2.1 製程確效指引是預定提供關於僅在法規送件中所要提供之資訊與數據的指導。但是，GMP 對製程確效的要求是涵蓋整個製程生命週期。	5.2.1 A guideline on Process Validation is intended to provide guidance on the information and data to be provided in the regulatory submission only. However GMP requirements for process validation continue throughout the lifecycle of the process.
5.2.2 這種方法應應用於聯結產品與製程開發。它將確保商業製程的確效，以及確保該製程在例行商業生產，維持在管制狀態中。	5.2.2 This approach should be applied to link product and process development. It will ensure validation of the commercial manufacturing process and maintenance of the process in a state of control during routine commercial production.

5.3	製造過程可以使用傳統方法或連續確認方法予以開發之，但是，不管所使用的方法為何，製程必須顯示為穩健的，並且在任何產品放行到市場前能確保一致的產品品質。使用傳統方法的製造過程，當可能時，在產品認可前應進行先期性確效計畫。回溯性確效不再是可接受的方法。	5.3	Manufacturing processes may be developed using a traditional approach or a continuous verification approach. However, irrespective of the approach used, processes must be shown to be robust and ensure consistent product quality before any product is released to the market. Manufacturing processes using the traditional approach should undergo a prospective validation programme wherever possible prior to certification of the product. Retrospective validation is no longer an acceptable approach.
5.4	對於新產品之製程確效，應涵蓋所有預定上市的強度（含量）及製造的場所。對於新產品，基於來自開發階段之廣泛的製程知識，且與適當之持續進行的確認計畫合併，涵括法（Bracketing）可證明是合理的。	5.4	Process validation of new products should cover all intended marketed strengths and sites of manufacture. Bracketing could be justified for new products based on extensive process knowledge from the development stage in conjunction with an appropriate ongoing verification programme.
5.5	對於產品從一個場所到另一場所或在同一場所內移轉的製程確效，其確效批數可經由使用涵括法（Bracketing）予以減少之，但應能取得包含先前確效內容在內的既有產品知識。對於不同強度（含量）、批量與包裝大小/容器類型，如經證明其合理時，涵括法（Bracketing）也可使用。	5.5	For the process validation of products, which are transferred from one site to another or within the same site, the number of validation batches could be reduced by the use of a bracketing approach. However, existing product knowledge, including the content of the previous validation, should be available. Different strengths, batch sizes and pack sizes/ container types may also use a bracketing approach if justified.

5.6	對於老舊產品的場所移轉，其製造過程與管制必須遵循其上市許可，且須符合該產品類型之上市許可的現行標準。必要時，應提交對該上市許可的變更申請。	5.6	For the site transfer of legacy products, the manufacturing process and controls must comply with the marketing authorisation and meet current standards for marketing authorisation for that product type. If necessary, variations to the marketing authorisation should be submitted.
5.7	為確保製程的確效狀態及產品可接受的品質，製程確效應確立被認為是重要的所有品質屬性與製程參數能一致地符合。考慮任何風險評估活動的結果，製程參數與品質屬性經確認為關鍵性與否的基礎，應予清楚地文件化。	5.7	Process validation should establish whether all quality attributes and process parameters, which are considered important for ensuring the validated state and acceptable product quality, can be consistently met by the process. The basis by which process parameters and quality attributes were identified as being critical or non-critical should be clearly documented, taking into account the results of any risk assessment activities.
5.8	通常，用於製程確效所製造之批次的批量與預定商業規模批次之批量應相同，且任何其他批量的使用應證明其合理性，或應在 GMP 指引的其他部分中有所規定。	5.8	Normally batches manufactured for process validation should be the same size as the intended commercial scale batches and the use of any other batch sizes should be justified or specified in other sections of the GMP guide.
5.9	使用於製程確效的設備、廠房設施、公用設施與系統應經驗證。對其預定用途之測試方法應經確效。	5.9	Equipment, facilities, utilities and systems used for process validation should be qualified. Test methods should be validated for their intended use.
5.10	對於所有產品，不論其使用的方法為何，除非另有合理性證明，否則來自開發研究與其它來源的製程知識，應可在廠內被取得，且應為確效活動的基礎。	5.10	For all products irrespective of the approach used, process knowledge from development studies or other sources should be accessible to the manufacturing site, unless otherwise justified, and be the basis for validation activities.

5.11 對於製程確效批次，生產、開發或其他場所移轉等人員可能會參與；確效批次應僅由受過訓練的人員使用經核准的文件依照 GMP 進行製造。期望生產人員參與確效批次的製造，以利產品瞭解。	5.11 For process validation batches, production, development, or other site transfer personnel may be involved. Batches should only be manufactured by trained personnel in accordance with GMP using approved documentation. It is expected that production personnel are involved in the manufacture of validation batches to facilitate product understanding.
5.12 在確效批次製造之前，關鍵起始物與包裝材料的供應商應經資格認可。否則，基於品質風險管理原則之應用，證明該供應商之資格的合理性，應加以文件化。	5.12 The suppliers of critical starting and packaging materials should be qualified prior to the manufacture of validation batches; otherwise a justification based on the application of quality risk management principles should be documented.
5.13 尤其重要的是，應可取得證明設計空間合理性（如有使用），與任何數學模式開發（如有使用）的基本製程知識，以確認製程管制策略。	5.13 It is especially important that the underlying process knowledge for the design space justification (if used) and for development of any mathematical models (if used) to confirm a process control strategy should be available.
5.14 在確效批次放行到市場時，該放行應預先加以界定。其所據以生產的條件應完全遵循 GMP，並符合確效允收標準、任何連續製程確認標準（如有使用）以及上市許可或臨床試驗許可等。	5.14 Where validation batches are released to the market, this should be pre-defined. The conditions under which they are produced should fully comply with GMP, with the validation acceptance criteria, with any continuous process verification criteria (if used) and with the marketing authorisation or clinical trial authorisation.
5.15 對於研究用藥品的製程確效，請參照附則 13。	5.15 For the process validation of investigational medicinal products (IMP), please refer to Annex 13.
併行性確效（Concurrent validation）	

5.16	例外情況下，對病人有強烈的效益-風險比值時，例行生產開始前未完成確效計畫並使用併行性確效，是可接受的。但是，對於執行併行性確效的決定，必須證明其合理性，並在確效主計畫書中加以文件化以清楚表明，而且，必須經由被授權人員核准。	5.16	In exceptional circumstances, where there is a strong benefit-risk ratio for the patient, it may be acceptable not to complete a validation programme before routine production starts and concurrent validation could be used. However, the decision to carry out concurrent validation must be justified, documented in the VMP for visibility and approved by authorised personnel.
5.17	在已採用併行性確效方法時，應有足夠數據以支持任何特定產品批次是均一的，且符合所界定之允收標準的結論。該等結果與結論應加以正式文件化，並應在該批次認可前，可為被授權人員取得。	5.17	Where a concurrent validation approach has been adopted, there should be sufficient data to support a conclusion that any given batch of product is uniform and meets the defined acceptance criteria. The results and conclusion should be formally documented and available to the Authorised Person prior to certification of the batch.
傳統製程確效（Traditional process validation）			
5.18	在傳統方法上，若干批次的最終產品是在例行條件下製造，以確認其再現性。	5.18	In the traditional approach, a number of batches of the finished product are manufactured under routine conditions to confirm reproducibility.
5.19	製造的批次數目與取樣的樣品數目，應基於品質風險管理原則，以建立允許變異的正常範圍與趨勢及提供足夠的評估數據。各製造廠必須確定所需批次數目並證明其合理性，以顯示該製程能高度保證一致地生產出符合品質之產品。	5.19	The number of batches manufactured and the number of samples taken should be based on quality risk management principles, allow the normal range of variation and trends to be established and provide sufficient data for evaluation. Each manufacturer must determine and justify the number of batches necessary to demonstrate a high level of assurance that the process is capable of consistently delivering quality product.

5.20 在不影響第 5.19 條下，於例行條件下製造至少須執行三個連續批次的確效，通常認為是可接受的。考量是否使用標準製造方法，以及類似產品或製程是否已在廠內使用，一替代批次數目也許可證明為合理。以三個批次的初始確效運作，可能需要以後續批次的進一步數據予以補充，作為持續進行之製程確認運作的一部分。	5.20 Without prejudice to 5.19, it is generally considered acceptable that a minimum of three consecutive batches manufactured under routine conditions could constitute a validation of the process. An alternative number of batches may be justified taking into account whether standard methods of manufacture are used and whether similar products or processes are already used at the site. An initial validation exercise with three batches may need to be supplemented with further data obtained from subsequent batches as part of an on-going process verification exercise.
5.21 應制訂製程確效計畫書。該計畫書係根據開發數據或文件化之製程知識，界定其關鍵製程參數（CPP）、關鍵品質屬性（CQA）與相關允收標準。	5.21 A process validation protocol should be prepared which defines the critical process parameters (CPP), critical quality attributes (CQA) and the associated acceptance criteria which should be based on development data or documented process knowledge.
5.22 確效計畫書應包括但不侷限於下列各項：	5.22 Process validation protocols should include, but are not limited to the following:
i. 製程的簡短描述並引述各自的主批次紀錄；	i. A short description of the process and a reference to the respective Master Batch Record;
ii. 功能與職責；	ii. Functions and responsibilities;
iii. 所要探討之關鍵品質屬性的摘要；	iii. Summary of the CQAs to be investigated;
iv. 關鍵製程參數及其關聯限度的摘要；	iv. Summary of CPPs and their associated limits;
v. 在確效活動期間，將進行探討或監測之其它（非關鍵）屬性與參數的摘要及其納入的理由；	v. Summary of other (non-critical) attributes and parameters which will be investigated or monitored during the validation activity, and the reasons for their inclusion;

vi. 所要使用的設備/廠房設施（包括量測/監測/記錄設備在內）連同其校正狀態的清單；	vi. List of the equipment/facilities to be used (including measuring/monitoring/recording equipment) together with the calibration status;
vii. 分析方法與方法確效（合適時）的清單；	vii. List of analytical methods and method validation, as appropriate;
viii. 建議的製程中管制與允收標準及每一製程中管制被挑選的原因；	viii. Proposed in-process controls with acceptance criteria and the reason(s) why each in-process control is selected;
ix. 所要執行的追加測試與允收標準；	ix. Additional testing to be carried out, with acceptance criteria;
x. 抽樣計畫及其理論基礎；	x. Sampling plan and the rationale behind it;
xi. 記錄與評估結果的方法；	xi. Methods for recording and evaluating results;
xii. 批次放行與認可的過程（適用時）。	xii. Process for release and certification of batches (if applicable).
連續製程確認（Continuous process verification）	
5.23 對於品質源於設計（quality by design）方法開發的產品，在開發期間於科學上已確立能提供高度產品品質保證之既定管制策略時，則連續製程確認可被用作傳統製程確效的替代方法。	5.23 For products developed by a quality by design approach, where it has been scientifically established during development that the established control strategy provides a high degree of assurance of product quality, then continuous process verification can be used as an alternative to traditional process validation.

5.24 用於確認製程的方法應加以界定。對於進料所要求的屬性、關鍵品質屬性與關鍵製程參數應有基於科學的管制策略，以確認產品實現。此亦應包括該管制策略的定期評估。製程分析技術與多變項統計製程管制可作為工具使用。各製藥廠須確定所必需之批次數目並證明其合理性，以顯示該製程能高度保證一致地生產出符合品質之產品。	5.24 The method by which the process will be verified should be defined. There should be a science based control strategy for the required attributes for incoming materials, critical quality attributes and critical process parameters to confirm product realisation. This should also include regular evaluation of the control strategy. Process Analytical Technology and multivariate statistical process control may be used as tools. Each manufacturer must determine and justify the number of batches necessary to demonstrate a high level of assurance that the process is capable of consistently delivering quality product.
5.25 在上述 5.1 至 5.14 條中所規定的一般原則仍然適用。	5.25 The general principles laid down in 5.1 – 5.14 above still apply.
混合的方法（Hybrid approach）	
5.26 已有從製造經驗與歷史批次數據得到大量的產品與製程知識及瞭解時，就可使用混合傳統方法與連續製程確認的方法。	5.26 A hybrid of the traditional approach and continuous process verification could be used where there is a substantial amount of product and process knowledge and understanding which has been gained from manufacturing experience and historical batch data.
5.27 即使該產品已經用傳統方法初始確效過，混合的方法也可用於變更後的任何確效活動，或在持續進行的製程確認期間中使用。	5.27 This approach may also be used for any validation activities after changes or during ongoing process verification even though the product was initially validated using a traditional approach.
在生命週期中持續進行的製程確認（Ongoing Process Verification during Lifecycle）	
5.28 5.28 至 5.32 條可適用於上述製程確效的所有三種方法，亦即，傳統方法、連續製程確認方法與混合的方法。	5.28 Paragraphs 5.28-5.32 are applicable to all three approaches to process validation mentioned above, i.e. traditional, continuous and hybrid.

5.29	製藥廠應監測產品品質，以確保在整個產品的生命週期中均維持於管制狀態，並有相關製程趨勢的評估。	5.29	Manufacturers should monitor product quality to ensure that a state of control is maintained throughout the product lifecycle with the relevant process trends evaluated.
5.30	應定期檢討持續進行之製程確認的程度與頻率。在整個產品生命週期中之任何時間點，考慮現行的製程瞭解程度與製程性能水準後，修改該等要求可能是合適的。	5.30	The extent and frequency of ongoing process verification should be reviewed periodically. At any point throughout the product lifecycle, it may be appropriate to modify the requirements taking into account the current level of process understanding and process performance.
5.31	持續進行的製程確認應在核准的計畫書或等同的文件下執行，並製作相對應的報告，以將所得結果予以文件化。合適時，統計工具應予以使用，以支持關於特定製程之變異性及能力的任何結論，並且確保在管制的狀態中。	5.31	Ongoing process verification should be conducted under an approved protocol or equivalent documents and a corresponding report should be prepared to document the results obtained. Statistical tools should be used, where appropriate, to support any conclusions with regard to the variability and capability of a given process and ensure a state of control.
5.32	應在整個產品生命週期中使用持續進行的製程確認，以支持如同在產品品質檢討中文件化之產品確效狀態。隨著時間遞增的變更也應加以考慮，並且對於任何追加行動的需求也應加以評估，例如，增加抽樣。	5.32	Ongoing process verification should be used throughout the product lifecycle to support the validated status of the product as documented in the Product Quality Review. Incremental changes over time should also be considered and the need for any additional actions, e.g. enhanced sampling, should be assessed.
6.	**運輸的確認（VERIFICATION OF TRANSPORTATION）**		
6.1	最終藥品、研究用藥品、待分/包裝產品與樣品，從製造場所之運輸應依照上市許可、核准標籤、產品規格檔案或經製藥廠證明合理等所界定的條件執行。	6.1	Finished medicinal products, investigational medicinal products, bulk product and samples should be transported from manufacturing sites in accordance with the conditions defined in the marketing authorisation, the approved label, product specification file or as justified by the manufacturer.

6.2	一般認知，由於所涉及的可變因素，運輸的確認可能具挑戰性，但是，運輸路線應加以清楚界定；在運輸的確認中，季節上的變動或其他變動也應加以考慮。	6.2	It is recognised that verification of transportation may be challenging due to the variable factors involved however, transportation routes should be clearly defined. Seasonal and other variations should also be considered during verification of transport
6.3	應執行風險評估，以考慮在運輸過程中持續管制與監測以外之變數的影響，例如，運輸期間的延遲、監測裝置失效、補足液態氮、產品敏感性以及任何其它相關因素。	6.3	A risk assessment should be performed to consider the impact of variables in the transportation process other than those conditions which are continuously controlled or monitored, e.g. delays during transportation, failure of monitoring devices, topping up liquid nitrogen, product susceptibility and any other relevant factors.
6.4	因為在運輸期間會有預期之可變條件，除另有合理性證明外，應連續監測與記錄該產品可能遭遇之任何關鍵環境條件。	6.4	Due to the variable conditions expected during transportation, continuous monitoring and recording of any critical environmental conditions to which the product may be subjected should be performed, unless otherwise justified.
7.	**包裝的確效（VALIDATION OF PACKAGING）**		
7.1	設備操作參數上的變異，尤其在直接包裝期間，對包裝（例如，泡殼/條形、小袋與無菌組件）的完整性與發揮正確功能可能具有顯著的影響，因此，對於最終產品與待分/包裝產品的直接與間接包裝設備應加以驗證。	7.1	Variation in equipment processing parameters especially during primary packaging may have a significant impact on the integrity and correct functioning of the pack, e.g. blister strips, sachets and sterile components; therefore primary and secondary packaging equipment for finished and bulk products should be qualified.
7.2	使用於直接包裝之設備的驗證，應對該關鍵製程參數，諸如，溫度、機器速度與密封壓力，或任何其它因素等，所界定之最小與最大操作範圍執行之。	7.2	Qualification of the equipment used for primary packing should be carried out at the minimum and maximum operating ranges defined for the critical process parameters such as temperature, machine speed and sealing pressure or for any other factors.

8.	**公用設施的驗證（QUALIFICATION OF UTILITIES）**		
8.1	蒸汽、水、空氣、其他氣體等的品質，應在安裝後使用上述第 3 節（設備、廠房設施、公用設施與系統的驗證階段）所描述的驗證步驟加以確認之。	8.1	The quality of steam, water, air, other gases etc. should be confirmed following installation using the qualification steps described in section 3 above.
8.2	驗證的期間長短與程度，應能反映任何季節上的變動（合適時），並能反映該公用設施之預定用途。	8.2	The period and extent of qualification should reflect any seasonal variations, if applicable, and the intended use of the utility.
8.3	在與產品可能有直接接觸，例如，加熱、通風與空調（HVAC）系統，或間接接觸，例如，有通過熱交換器時，應執行風險評估，以減少任何失敗的風險。	8.3	A risk assessment should be carried out where there may be direct contact with the product, e.g. heating, ventilation and air-conditioning (HVAC) systems, or indirect contact such as through heat exchangers to mitigate any risks of failure.
9.	**測試方法的確效（VALIDATION OF TEST METHODS）**		
9.1	必要時，所有使用於驗證、確效或清潔作業中的分析試驗方法，應按照 PIC/S GMP 第一部第 6 章所界定，以適當的檢測限量與定量限量加以確效。	9.1	All analytical test methods used in qualification, validation or cleaning exercises should be validated with an appropriate detection and quantification limit, where necessary, as defined in Chapter 6 of the PIC/S GMP guide Part I.
9.2	在執行產品微生物測試時，其方法應加以確效，以確認該產品不會影響微生物的回收率。	9.2	Where microbial testing of product is carried out, the method should be validated to confirm that the product does not influence the recovery of microorganisms.
9.3	在潔淨室中執行表面微生物測試時，應對該測試方法執行確效，以確認滅菌劑不會影響微生物的回收率。	9.3	Where microbial testing of surfaces in clean rooms is carried out, validation should be performed on the test method to confirm that sanitising agents do not influence the recovery of microorganisms.
10.	**清潔確效（CLEANING VALIDATION）**		

10.1	為了確認對於所有產品接觸設備之任何清潔程序的有效性，應執行清潔確效。可以使用具有適當科學合理性證明的模擬劑。在將相似設備類型分在同一群組時，證明選取清潔確效之特定設備的合理性，是被預期的。	10.1	Cleaning validation should be performed in order to confirm the effectiveness of any cleaning procedure for all product contact equipment. Simulating agents may be used with appropriate scientific justification. Where similar types of equipment are grouped together, a justification of the specific equipment selected for cleaning validation is expected.
10.2	對於潔淨度之目視檢查，是清潔確效允收標準的重要部分，但是，單獨使用該允收標準通常是不被接受的。重複清潔與再測試直到獲得可接受之殘留結果，並不被認為是可接受的方法。	10.2	A visual check for cleanliness is an important part of the acceptance criteria for cleaning validation. It is not generally acceptable for this criterion alone to be used. Repeated cleaning and retesting until acceptable residue results are obtained is not considered an acceptable approach.
10.3	一般認知，清潔確效計畫可能需要花費一些時間來完成，而對於有些產品，例如，研究用藥品，可能需要經由在每一批次生產後的確認來確效。應有來自該確認的充份數據，以支持設備是潔淨並可供進一步使用的結論。	10.3	It is recognised that a cleaning validation programme may take some time to complete and validation with verification after each batch may be required for some products e.g. investigational medicinal products. There should be sufficient data from the verification to support a conclusion that the equipment is clean and available for further use.
10.4	確效應考慮清潔過程中的自動化程度。當使用自動化程序時，其公用設施與設備所規定之正常操作範圍應加以確效。	10.4	Validation should consider the level of automation in the cleaning process. Where an automatic process is used, the specified normal operating range of the utilities and equipment should be validated.

10.5 對於所有清潔過程應執行評估，以確定影響清潔有效性與效能的可變因素，例如，操作者、程序的詳細程度（如沖洗次數）等。如果可變因素已經識別時，則應將最差狀況作為清潔確效研究的基礎。	10.5 For all cleaning processes an assessment should be performed to determine the variable factors which influence cleaning effectiveness and performance, e.g. operators, the level of detail in procedures such as rinsing times etc. If variable factors have been identified, the worst case situations should be used as the basis for cleaning validation studies.
10.6 產品殘留物之殘轉限量（carryover），應以毒理學的評估為基礎[2]。對於所選擇之限量的合理性證明，應在風險評估中加以文件化，該風險評估應包含所有的支持文獻。對於移除所使用之任何清潔劑，也應建立限量。允收標準應考慮在製程設備序列中多項設備的潛在累積效應。	10.6 Limits for the carryover of product residues should be based on a toxicological evaluation[2]. The justification for the selected limits should be documented in a risk assessment which includes all the supporting references. Limits should be established for the removal of any cleaning agents used. Acceptance criteria should consider the potential cumulative effect of multiple items of equipment in the process equipment train.
[2] 在 EU/EEA，這是 EMA 關於 Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities	[2] In the EU/EEA, this is the EMA Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities
10.6.1 已知治療用大分子與胜肽暴露於極端 pH 及/或熱時會降解與變性，並且可能變成不具藥理活性。因此，在這些情況中，毒理學評估可能是不適用的。	10.6.1 Therapeutic macromolecules and peptides are known to degrade and denature when exposed to pH extremes and/or heat, and may become pharmacologically inactive. A toxicological evaluation may therefore not be applicable in these circumstances.
10.6.2 如果對特定產品殘留物的測試不可行時，則可選擇其他代表性的參數，例如，總有機碳（TOC）與導電度。	10.6.2 If it is not feasible to test for specific product residues, other representative parameters may be selected, e.g. total organic carbon (TOC) and conductivity.
10.7 在清潔確效計畫書制訂時，應考慮微生物與內毒素污染的風險。	10.7 The risk presented by microbial and endotoxin contamination should be considered during the development of cleaning validation protocols.

10.8 清潔程序之髒污留置時間與潔淨保持時間的界定，應考慮在製造與清潔之間的時間以及在清潔與使用之間的時間之影響。	10.8 The influence of the time between manufacture and cleaning and the time between cleaning and use should be taken into account to define dirty and clean hold times for the cleaning process.
10.9 當執行時段切換製造時，應考慮在時段切換結束時對清潔容易性的影響，而且，時段切換的最長時間及/或最多批數應是清潔確效作業的基礎。	10.9 Where campaign manufacture is carried out, the impact on the ease of cleaning at the end of the campaign should be considered and the maximum length of a campaign (in time and/or number of batches) should be the basis for cleaning validation exercises.
10.10 用最差狀況產品方法作為清潔確效模式時，應對該最差狀況產品之選擇以及新產品對所評估之場所的影響，提供科學的理論基礎。對於訂定最差狀況的標準可能包括溶解度、可清潔性、毒性與效價等。	10.10 Where a worst case product approach is used as a cleaning validation model, a scientific rationale should be provided for the selection of the worst case product and the impact of new products to the site assessed. Criteria for determining the worst case may include solubility, cleanability, toxicity, and potency.
10.11 清潔確效計畫書應規定或提及所要取樣的位置、位置選擇之理論基礎，並且界定其允收標準。	10.11 Cleaning validation protocols should specify or reference the locations to be sampled, the rationale for the selection of these locations and define the acceptance criteria.
10.12 取樣應經由擦拭及/或潤洗或以其他方式執行，依生產設備而定。取樣的材料與方法不應影響其結果。以所使用之所有取樣方法，從所有產品接觸材質（設備表面）取得之樣品，應顯示其回收率為合理的。	10.12 Sampling should be carried out by swabbing and/or rinsing or by other means depending on the production equipment. The sampling materials and method should not influence the result. Recovery should be shown to be possible from all product contact materials sampled in the equipment with all the sampling methods used.
10.13 為了證明清潔方法是經過確效的，清潔程序應以風險評估為基礎執行適當的次數，並且符合允收標準。	10.13 The cleaning procedure should be performed an appropriate number of times based on a risk assessment and meet the acceptance criteria in order to prove that the cleaning method is validated.

10.14 在清潔過程對於有些設備為無效或不適合時，則對於各產品應當按照 PIC/S GMP 規範第一部第 3 章與第 5 章所指示，使用專用的設備或採取其它適當的措施。	10.14 Where a cleaning process is ineffective or is not appropriate for some equipment, dedicated equipment or other appropriate measures should be used for each product as indicated in chapters 3 and 5 of the PIC/S GMP Guide.
10.15 在執行設備的人工清潔時，尤其重要的是，該人工清潔過程的有效性，應以經證明合理的頻率加以確認。	10.15 Where manual cleaning of equipment is performed, it is especially important that the effectiveness of the manual process should be confirmed at a justified frequency.
11. 變更管制（CHANGE CONTROL）	
11.1 變更管制是知識管理重要的一部分，且應在製藥品質系統內管控。	11.1 The control of change is an important part of knowledge management and should be handled within the pharmaceutical quality system.
11.2 如果在產品生命週期中提出對起始原料、產品組成物、製程、設備、廠房設施、產品範圍、生產或測試的方法、批量、設計空間可能影響產品品質或再現性之計畫性的變更或任何其它變更時，應具備書面程序，以描述所要採取的行動。	11.2 Written procedures should be in place to describe the actions to be taken if a planned change is proposed to a starting material, product component, process, equipment, premises, product range, method of production or testing, batch size, design space or any other change during the lifecycle that may affect product quality or reproducibility.
11.3 在使用設計空間時，變更對於設計空間之影響，應針對在上市許可內登記的設計空間加以考慮，並評估任何法規行動的必要性。	11.3 Where design space is used, the impact on changes to the design space should be considered against the registered design space within the marketing authorisation and the need for any regulatory actions assessed.

11.4	對於評估計畫性的變更應使用品質風險管理，以確定對於產品品質、製藥品質系統、文件系統、確效、法規狀態、校正、維護保養以及任何其他系統的潛在影響，以避免非預期的後果，並規劃必要的製程確效、確認或再驗證工作。	11.4	Quality risk management should be used to evaluate planned changes to determine the potential impact on product quality, pharmaceutical quality systems, documentation, validation, regulatory status, calibration, maintenance and on any other system to avoid unintended consequences and to plan for any necessary process validation, verification or requalification efforts.
11.5	變更應依照製藥品質系統，經由權責人員或相關的職能人員予以授權與核准。	11.5	Changes should be authorised and approved by the responsible persons or relevant functional personnel in accordance with the pharmaceutical quality system.
11.6	支持性數據，例如，文件複印本，在最終核准之前，應加以檢討以證明該變更之影響已經確認。	11.6	Supporting data, e.g. copies of documents, should be reviewed to confirm that the impact of the change has been demonstrated prior to final approval.
11.7	在變更執行之後，及合適時，應執行變更之有效性評估，以確認該變更已成功完成。	11.7	Following implementation, and where appropriate, an evaluation of the effectiveness of change should be carried out to confirm that the change has been successful.
12.	**術語彙編（GLOSSARY）**		
	與驗證及確效有關之術語的定義，在現行 PIC/S GMP 規範之其他章節未規定者，規定如下。		Definitions of terms relating to qualification and validation which are not given in other sections of the current PIC/S Guide to GMP are given below.

涵括法： 一種基於科學與風險之確效方法，使其在製程確效的期間中，僅對某些預先確定並經證明合理之設計因素，例如，強度（含量）、批量及/或包裝量的極端之批次予以測試。這種設計是假設任何中間層級的確效，是由該等極端的確效予以代表。在一強度（含量）範圍內要進行確效時，如果該強度（含量）在組成上相同或有非常密切地相關時，例如，以類似/同一基礎顆粒之不同壓錠重量所製成的一個錠劑含量範圍，或將相同基礎組成以不同柱塞充填重量，充填到不同大小的膠囊殼所製成之膠囊劑含量範圍時，則可適用涵括法。涵括法可適用於相同容器封蓋系統中之不同大小的容器，或相同容器之不同充填量。	**Bracketing approach:** A science and risk based validation approach such that only batches on the extremes of certain predetermined and justified design factors, e.g. strength, batch size, and/or pack size, are tested during process validation. The design assumes that validation of any intermediate levels is represented by validation of the extremes. Where a range of strengths is to be validated, bracketing could be applicable if the strengths are identical or very closely related in composition, e.g. for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells. Bracketing can be applied to different container sizes or different fills in the same container closure system.
（參考 ICH Q1D 2.3.1.2 Container Closure Sizes and/or Fills）	
變更管制： 變更管制是一個正式系統，由適當學科領域之合格代表人員藉該系統審核所提議的變更或實際的變更。該等變更可能影響廠房設施、系統、設備或製程的確效狀態。變更管制之目的是要確定需採取的行動，以確保該系統維持在已確效的狀態中，並予以文件化。	**Change Control:** A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect the validated status of facilities, systems, equipment or processes. The intent is to determine the need for action to ensure and document that the system is maintained in a validated state.
清潔確效： 清潔確效是一個經核准之清潔程序，可再現地移除設備上的先前產品或使用之清潔劑，達到低於科學上設定之最大允許殘轉量（carryover level）的文件化證據。	**Cleaning Validation:** Cleaning validation is documented evidence that an approved cleaning procedure will reproducibly remove the previous product or cleaning agents used in the equipment below the scientifically set maximum allowable carryover level.

清潔確認： 在每一批次/每一時段切換後透過化學分析收集證據，以顯示先前產品或清潔劑的殘留已經降低到低於科學上設定之最大允許殘轉量。	**Cleaning verification:** The gathering of evidence through chemical analysis after each batch/campaign to show that the residues of the previous product or cleaning agents have been reduced below the scientifically set maximum allowable carryover level.
併行性確效： 於例外情況下，基於對病人顯著利益所執行的確效，其確效計畫書是與商業化生產之確效批次同時執行。	**Concurrent Validation:** Validation carried out in exceptional circumstances, justified on the basis of significant patient benefit, where the validation protocol is executed concurrently with commercialisation of the validation batches.
連續的製程確認： 對製程確效的一種替代方法，藉此方法連續地監測與評估製造過程的效能。（ICH Q8）	**Continuous process verification:** An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated. (ICH Q8)
管制策略： 源自對現行產品與製程理解之一套經規劃的管制，以確保製程性能與產品品質。該等管制可包括與原料藥及製劑原料與包裝組件相關的參數與屬性、設施與設備操作條件、製程中管制、最終產品規格以及管制與監測相關的方法與頻率。（ICH Q10）	**Control Strategy:** A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10)
關鍵製程參數（CPP）： 為一個製程參數，其變異性對關鍵品質屬性具有影響，因此應加以監測或管制，以確保該製程產生所預期的品質。（ICH Q8）	**Critical process parameter (CPP):** A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality. (ICH Q8)

關鍵品質屬性（CQA）： 為物理、化學、生物或微生物學的性質或特性，其應在核可的限值、範圍或分佈內，以確保所預期的產品品質。（ICH Q8）	**Critical quality attribute (CQA):** A physical, chemical, biological or microbiological property or characteristic that should be within an approved limit, range or distribution to ensure the desired product quality. (ICH Q8)
設計驗證（DQ）： 所提出之廠房設施、系統及設備的設計是適合預定目的之文件化的確認作業。	**Design qualification (DQ):** The documented verification that the proposed design of the facilities, systems and equipment is suitable for the intended purpose.
設計空間： 已經證明能提供品質保證之投入變數（例如，原物料屬性）與製程參數的多層面組合與相互作用，在設計空間內的作業不認為是變更，在設計空間外者則視為變更，而且，通常會啓動法規上的核准後變更過程。設計空間是由申請人提出，且受制於法規的評估與核准。（ICH Q8）	**Design Space:** The multidimensional combination and interaction of input variables, e.g. material attributes, and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval. (ICH Q8)
安裝驗證（IQ）： 廠房設施、系統及設備經安裝或修改時，其符合核准的設計及製造廠的建議之文件化的確認作業。	**Installation Qualification (IQ):** The documented verification that the facilities, systems and equipment, as installed or modified, comply with the approved design and the manufacturer's recommendations.
知識管理： 對於獲得、分析、儲存及傳播資訊的系統性方法。（ICH Q10）	**Knowledge management:** A systematic approach to acquire, analyse, store and disseminate information. (ICH Q10)

生命週期： 產品、設備或廠房設施從初始開發或使用，直到停止使用之生命中的所有階段。	**Lifecycle:** All phases in the life of a product, equipment or facility from initial development or use through to discontinuation of use.
持續進行的製程確認（也稱為後續製程確認）： 製程在商業製造的期間，保持在管制狀態之文件化的證據。	**Ongoing Process Verification (also known as continued process verification):** Documented evidence that the process remains in a state of control during commercial manufacture.
操作驗證（OQ）： 廠房設施、系統及設備於安裝或修改時，在整個預期之操作範圍內，依照期望執行之文件化的確認作業。	**Operational Qualification (OQ):** The documented verification that the facilities, systems and equipment, as installed or modified, perform as intended throughout the anticipated operating ranges.
性能驗證（PQ）： 在核准的製程方法及產品規格的基礎上，系統及設備能有效執行並具再現性之文件化的確認作業。	**Performance Qualification (PQ):** The documented verification that systems and equipment can perform effectively and reproducibly based on the approved process method and product specification.
製程確效： 製程在已建立之參數內操作時，能有效且再現地生產符合其預定規格及品質屬性的藥品之文件化的證據。	**Process Validation:** The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.
產品實現： 具有適當符合病患、健康照護專業人員之需求，並且符合主管機關與公司內部單位要求之品質屬性的產品之達成。（ICH Q10）	**Product realization:** Achievement of a product with the quality attributes to meet the needs of patients, health care professionals and regulatory authorities and internal customer requirements. (ICH Q10)
先期性確效： 預定販售之產品例行生產前所執行的確效。	**Prospective Validation:** Validation carried out before routine production of products intended for sale.

品質源於設計： 以健全的科學與品質風險管理為基礎，始於預先界定的目標，並強調產品理解與製程理解及製程管制的一個系統性方法。	**Quality by design:** A systematic approach that begins with predefined objectives and emphasises product and process understanding and process control, based on sound science and quality risk management.
品質風險管理： 為對跨越生命週期之品質的風險，評價、管制、溝通及檢討之系統性的過程。（ICH Q9）	**Quality risk management:** A systematic process for the assessment, control, communication and review of risks to quality across the lifecycle. (ICH Q9)
模擬劑： 一種與確效中產品之物理及可行時化學的特性非常接近的物質，例如黏度、粒子大小、pH 等。	**Simulated agents:** A material that closely approximates the physical and, where practical, the chemical characteristics, e.g. viscosity, particle size, pH etc., of the product under validation.
管制狀態： 以整套的管制，一致地提供可接受的製程性能與產品品質保證之狀態。	**State of control:** A condition in which the set of controls consistently provides assurance of acceptable process performance and product quality.
傳統方法： 界定製程參數之設定點與操作範圍，以確保再現性的一種產品開發方法。	**Traditional approach:** A product development approach where set points and operating ranges for process parameters are defined to ensure reproducibility.
使用者需求規格（URS）： 必需且足以創造符合系統之預定目的的可行設計之所有者、使用者與工程的整套要求。	**User requirements Specification (URS):** The set of owner, user, and engineering requirements necessary and sufficient to create a feasible design meeting the intended purpose of the system.

最差狀況： 包含在標準作業程序內之上限及下限作業極限及環境的一個或一套條件，當其與理想條件相比時，有最大之產品或製程失敗的機會，然該條件未必引起產品或製程之失敗。	**Worst Case:** A condition or set of conditions encompassing upper and lower processing limits and circumstances, within standard operating procedures, which pose the greatest chance of product or process failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure.

附則 16 由被授權人認可與批次放行（CERTIFICATION BY THE AUTHORISED PERSON AND BATCH RELEASE）

範圍（SCOPE）	
本附則提供被授權人認可與批次放行國內用或輸出之人用藥品的指引。本指引之原則亦適用於人用研究用藥品。（依照我國法律發布之法律規定與特別指引中任何差異所規範）	This Annex provides guidance on the certification by an Authorised Person and on batch release of medicinal products for human or veterinary use within a Pharmaceutical Inspection Co-operation Scheme (PIC/S) Participating Authority or made for export. The principles of this guidance also apply to investigational medicinal products (IMP) for human use, subject to any difference in the legal provisions and more specific guidance published by PIC/S Participating Authorities under national law.
本附則中對於藥品製造廠之批次認可的指引是涵蓋於 PIC/S 範圍內。然而，本附則中「與輸入藥品批次認可」相關的指引，採自願性符合。	Guidance in this Annex on the certification of batches by a manufacturer of a medicinal product is within the scope of the Pharmaceutical Inspection Co-operation Scheme. However, each PIC/S Participating Authority may decide whether guidance expressed in this Annex should become a legally-binding standard in relation to imported medicinal products.
本附則未涉及國家法律下對藥品放行之任何管制（例如某些血液與免疫學產品）；然而，本附則適用於該等批次之被授權人認可及後續放行。	This Annex does not address any controls on release of medicinal products by a National Competent Authority under national law (e.g. certain blood and immunological products); however, this Annex does apply to the Authorised Person certification and subsequent release of such batches.
藥品批次放行的基本安排是由其上市許可（MA）所界定；本附則中的任何內容都不應凌駕於該些安排之上。	The basic arrangements for batch release for a medicinal product are defined by its marketing authorisation (MA). Nothing in this Annex should be taken as overriding those arrangements.
一般原則（GENERAL PRINCIPLES）	
藥品於其生命週期內之安全、品質與療效之表現的最終責任在於上市許可持有者（MAH）。	The ultimate responsibility for the performance of a medicinal product over its lifetime, its safety, quality and efficacy, lies with the marketing authorisation holder (MAH).
但被授權人有責任確保每一個別批次之製造與檢查符合國家的上市許可與 GMP 要求。	However, the Authorised Person is responsible for ensuring that each individual batch has been manufactured and checked in compliance with national requirements in accordance with the requirements of the marketing authorisation

	(MA) and with Good Manufacturing Practice (GMP).
批次放行流程包括：	The process of batch release comprises of:
依所界定之放行程序進行批次製造與檢驗之核對。	The checking of the manufacture and testing of the batch in accordance with defined release procedures.
由被授權人對最終產品批次之認可，表示該批次符合 GMP 及其上市許可之要求；此代表批次之品質放行。	The certification of the finished product batch performed by an Authorised Person signifying that the batch is in compliance with GMP and the requirements of its MA. This represents the quality release of the batch.
產品最終批次移轉至可銷售庫存及/或出口應有由被授權人執行之認可；若此移轉發生於認可場所外之其他場所時，場所間應有文件化之書面協議。	The transfer to saleable stock, and/or export of the finished batch of product which should take into account the certification performed by the Authorised Person. If this transfer is performed at a site other than that where certification takes place, then the arrangement should be documented in a written agreement between the sites.
管制批次放行之目的係確保：	The purpose of controlling batch release is notably to ensure that:
1. 批次製造與檢查符合上市許可之要求。	The batch has been manufactured and checked in accordance with the requirements of its MA.
2. 批次製造與檢查符合 GMP 之原則與指引。	The batch has been manufactured and checked in accordance with the principles and guidelines of GMP.
3. 任何其他相關法律要求已列入考慮。	Any other relevant legal requirements are taken into account.
4. 當發生本規範第一部第八章所述之品質缺陷事件需經調查或有批次回收時，確保有任何被授權人參與認可或確認[1]，且相關紀錄皆易於辨識。	In the event that a quality defect as referred to in Chapter 8 of PIC/S GMP Guide, Part I, needs to be investigated or a batch recalled, to ensure that any Authorised Persons involved in the certification or confirmation[1] and any relevant records are readily identifiable.
[1.] 當被授權人負責之批次於場所間移轉時，其需確認之資訊，建議於本附則之附錄 1 中。	[1.] Information required for the confirmation, where Authorised Person responsibilities for the batch are being transferred between sites, is recommended in Appendix I to this Annex.
1. 認可流程（THE PROCESS OF CERTIFICATION）	
1.1 每一最終產品批次於放行銷售、供應或輸出前必須經被授權人認可[2]。認可僅能由製造廠及/或輸入商的被授權人為之。	1.1 Each batch of finished product must be certified[2] by an Authorised Person before being released for sale, supply or export. Certification can only be performed by an Authorised Person of the manufacturer and/or importer which are described in the MA.
[2.] 藥品批次認可之建議內容詳本附則的附錄 2。當國家法律另有要求或當國家主管機關間另有便利安排之要求，批次認可的內容可能與附錄 2 不同。	[2.] The contents of a batch certificate for medicinal products are recommended in Appendix II to this Annex. The content of a batch certification may differ from Appendix II as required under national law or as required to facilitate arrangements between National Competent Authorities.

1.2	涉及批次認可或確認之任何被授權人，必須對其所負責之階段具備足夠知識。被授權人必須能證明其持續接受對於產品類別、製程、技術提升及 GMP 變更之訓練。	1.2	Any Authorised Person involved in the certification or confirmation of a batch must have detailed knowledge of the steps for which they are taking responsibility. The Authorised Persons should be able to prove their continuous training regarding the product type, production processes, technical advances and changes to GMP.
1.3	批次通過認可前之製造、輸入、檢驗與儲存之多個階段可能涉及多個場所。無論涉及幾個場所，對最終產品進行認可之被授權人必須確保所有所需步驟於被接受之製藥品質系統下完成，以確保該批次符合 GMP、上市許可以及認可執行所在國家的其他要求。	1.3	There may be several sites involved in the various stages of manufacture, importation, testing and storage of a batch before it undergoes certification. Regardless of how many sites are involved, the Authorised Person performing certification of the finished product must ensure that all necessary steps have been completed under accepted pharmaceutical quality systems to assure compliance of the batch with GMP, the MA and any other national requirements where certification is taking place.
1.4	各製造場所必須至少有一名被授權人。	1.4	Each manufacturing site must have at least one Authorised Person.
1.4.1	對於僅進行某批次產品部分製造作業之場所，該場所之被授權人必須至少確認於該場所進行之作業符合 GMP 及各方間書面協議條款（詳述該場所負責之作業）。若被授權人負責提供該等作業符合相關上市許可之確認，則被授權人應可取得所需部分之上市許可細節。	1.4.1	Where the site only undertakes partial manufacturing operations in relation to a batch, then an Authorised Person at that site must at least confirm that the operations undertaken by the site have been performed in accordance with GMP and the terms of the written agreement detailing the operations for which the site is responsible. If the Authorised Person is responsible for providing confirmation of compliance for those operations with the relevant MA, then the Authorised Person should have access to the necessary details of the MA.
1.4.2	對最終產品批次進行認可之被授權人，可承擔對該批次製造之所有階段的全部責任，或可與其他對該批次製造與管制之特定步驟提供確認的被授權人分擔此責任。該些被授權人可能為其他被授權人於相同製造許可持有者下作業，或於不同製造許可持有者下作業。	1.4.2	The Authorised Person who performs certification of the finished product batch should assume full responsibility for all stages of manufacture of the batch or this responsibility may be shared with other Authorised Persons who have provided confirmation for specified steps in the manufacture and control of a batch. These could be other Authorised Persons who are operating under the same manufacturing authorisation holder or operating under different MIA holders.

1.4.3	被授權人間關於批次符合性之責任分擔必須界定於書面協議中。該文件需詳述關於評估任何偏差對批次符合 GMP 與上市許可影響之責任。	1.4.3	Any sharing of responsibilities amongst Authorised Persons in relation to compliance of a batch must be defined in a written agreement. This document should detail responsibility for assessment of the impact any deviation(s) has/have on compliance of the batch with GMP and the MA.
1.5	依國家法律，於國家主管機關管轄區域外製造之藥品，該批次移轉至可銷售庫存前之實際輸入與認可為製造的最後階段。	1.5	For medicinal products manufactured outside the jurisdiction of a National Competent Authority, physical importation and certification are the final stages of manufacturing which precede the transfer to saleable stock of the batch, depending on national law.
1.5.1	於本附則第 1 條規定之認可流程，適用預定於國內市場放行或出口之所有藥品，無論其供應鏈之複雜性及所涉及製造場所之全球位置。	1.5.1	The process of certification as described in Section 1 of this Annex, applies to all medicinal products intended to be released within domestic markets, or for export, irrespective of the complexity of the supply chain and the global locations of manufacturing sites involved.
1.5.2	依據描述於本附則 1.4 條之原則與各管轄區域內之法律，被授權人認可最終藥品批次可能考慮其他被授權人之確認及與其分擔所界定之責任；該其他被授權人係涉及發生於同一管轄區域之其他場所的任何製造及輸入作業，及相關上市許可中界定之其他製造廠。	1.5.2	In accordance with the principles described in Section 1.4 of this Annex and the law in each jurisdiction, the Authorised Person certifying the finished medicinal product batch may take account of the confirmation by, and share defined responsibilities with, other Authorised Persons in relation to any manufacturing or importation operations taking place at other sites in the same jurisdiction and other manufacturing authorisation holders defined in the relevant MA.
1.5.3	若產品批次與樣品分開運送時，於批次認可前，被授權人應考量產品與樣品之儲存及運輸條件。	1.5.3	Conditions of storage and transport for the batch and the sample, if sent separately, should be taken into account by the Authorised Person before certification of a batch.
1.5.4	認可最終產品之被授權人，負責確保每一最終藥品批次之製造符合 GMP 與上市許可。 被授權人亦有責任確保最終藥品批次已依照國家法律完成輸入時所需之檢驗。	1.5.4	The Authorised Person certifying the finished product is responsible for ensuring that each finished medicinal product batch has been manufactured in accordance with GMP and the MA. The Authorised Person is also responsible for ensuring that the finished medicinal product batch has undergone testing required upon importation in accordance with national law.
1.5.5	若輸入產品之抽樣為必要，必須具該批次	1.5.5	If sampling of imported product is

之完整代表性。樣品可能於抵達我國主管機關管轄區域後抽取，或依照國家法律與依製藥廠品質系統內經文件化之技術上證明其合理性的方法，於他國管轄區域之製造場所抽取。關於抽樣之責任應界定於場所間之書面協議中。於我國主管機關管轄區域外抽取之任何樣品，應在與其代表之批次相同之運輸條件下運輸。	necessary, it should be fully representative of the batch. Samples may either be taken after arrival in the jurisdiction of the National Competent Authority, or be taken at the manufacturing site located in another jurisdicion in accordance with national law and a technically justified approach which is documented within the company's quality system. Responsibilities in relation to the sampling should be defined in a written agreement between the sites. Any samples taken outside the National Competent Authority jurisdiction should be shipped under equivalent transport conditions as the batch that they represent.
1.5.6 於他國管轄區域之製造場所執行之抽樣，技術合理性證明應包含正式品質風險管理過程，以辨識及管理任何與此方法有關之風險。應充分文件化並包括至少下列要件：	1.5.6 Where sampling is performed at a manufacturing site located in another jurisdiction, the technical justification should include a formal Quality Risk Management process to identify and manage any risks associated with this approach. This should be fully documented and include at least the following elements:
i. 製造活動之稽查包括於該國管轄區域場所之任何抽樣活動，並評估批次及樣品之後續運輸步驟，以確保輸入批次之樣品具代表性。	i. Audit of the manufacturing activity including any sampling activity in the other jurisdiction and evaluation of subsequent transportation steps of both the batch and samples to ensure that the samples are representative of the imported batch.
ii. 全面之科學研究，數據包括佐證於該國管轄區域所抽取之樣品可代表輸入後之批次的任何結論。該研究應至少包括：	ii. A comprehensive scientific study, including data to support any conclusions that samples taken in the other jurisdiction are representative of the batch after importation. This study should at least include:
i) 於該國管轄區域抽樣過程之描述；	i) description of the sampling process in the other jurisdiction;
ii) 樣品與輸入批次之運輸條件的描述。任何差異應證明其合理性；	ii) description of the transported conditions of the sample and the imported batch. Any differences should be justified;
iii) 樣品於該國管轄區域抽取及輸入後抽取之比較分析；以及	iii) comparative analysis of samples taken in the other jurisdiction and samples taken after importation; and
iv) 考慮抽樣與批次輸入之時間間	iv) consideration of the time interval

隔，並以數據證明該時限之合理性。	between sampling and importation of the batch and generation of data to support appropriate defined limits.
iii. 對輸入後抽取之樣品進行隨機定期分析的規定，以證明持續信賴於該國管轄區域抽取之樣本的合理性。	iii. Provision for random periodic analysis of samples taken after importation to justify ongoing reliance on samples taken in another jurisdiction.
iv. 任何非預期結果或經確認偏離規格結果之檢討。其可能對信賴於該國管轄區域製造場所進行之抽樣產生影響，並應通知進行認可之場所的國家主管機關。此類情形發生應被視為潛在品質缺陷，並應依據本規範第一部第八章進行調查。	iv. A review of any unexpected result or confirmed out of specification result. These may have implications for reliance on sampling performed at a manufacturing site located in another jurisdiction and should be notified to the National Competent Authority for the site where certification is performed. Such an occurrence should be regarded as a potential quality defect and investigated in line with the guidance in Chapter 8 of the PIC/S GMP Guide, Part I.
1.5.7 不同之輸入最終產品批次，可能源自於相同之待分/包裝產品批次。若需於輸入時進行檢驗（見 1.5.4），認可不同最終產品批次之被授權人，可基於其對於初次輸入最終批次之品質管制檢驗做出決定，前提為其合理性證明已根據品質風險管理原則文件化。應考慮與 1.5.6 段落關於信賴於他國管轄區域執行之任何抽樣之條文。應備有證據確保輸入之最終產品批次至少透過以下文件化確認作業建立其完整性及識別：	1.5.7 Different imported finished product batches may originate from the same bulk product batch. If testing upon importation is required (see 1.5.4), the Authorised Person(s) certifying the different finished product batches may base their decision on the quality control testing of the first imported finished batch provided that a justification has been documented based on Quality Risk Management principles. This should take into account the provisions of paragraph 1.5.6 in relation to reliance on any samples taken in another jurisdiction. Evidence should be available to ensure that the integrity and identity of the imported finished product batch has been established through documented verification of at least the following:
i. 待分/包裝產品於分/包裝前已滿足其儲存之相關要求；	i. relevant requirements for storage of the bulk product prior to packaging have been satisfied;
ii. 最終產品批次於所需條件下儲存及運輸；	ii. the finished product batch has been stored and transported under the required conditions;
iii. 託運物維持安全，且未有於儲存或運輸期間遭竄改之跡象；	iii. the consignment has remained secure and there is no evidence of tampering during storage or

	transportation;
iv. 已建立產品之正確識別；以及	iv. correct identification of the product has been established; and
v. 所檢驗之樣品代表來自待/分包裝批次之所有最終產品批次。	v. the sample(s) tested are representative of all finished product batches derived from the bulk batch.
1.6 批次認可前，被授權人必須確保履行下列業務責任：	1.6 The Authorised Person must ensure that the following operational responsibilities are fulfilled prior to certification of a batch :
i. 依經由國家主管機關許可之條款進行認可。	i. Certification is permitted under the terms of any authorisation by the national competent authority.
ii. 符合國家法律之任何追加職責與要求。	ii. Any additional duties and requirements of national law are complied with.
iii. 認可係依照本附則與依照國家法律記錄。	iii. Certification is recorded in accordance with this annex and in accordance to national law.
1.7 此外，被授權人有責任確保下列 1.7.1 至 1.7.21 項被確實遵循。該等工作可委任給受過適當訓練之人員或第三方。一般認知係被授權人將需要倚賴製藥品質系統，且被授權人應持續確保此倚賴具有完善根據。	1.7 In addition, the Authorised Person has responsibility for ensuring points 1.7.1 to 1.7.21 are secured. These tasks may be delegated to appropriately trained personnel or third parties. It is recognised that the Authorised Person will need to rely on the pharmaceutical quality system and the Authorised Person should have on-going assurance that this reliance is well founded.
1.7.1 與藥品之製造及檢驗相關的所有活動已依照 GMP 與其原則執行。	1.7.1 All activities associated with manufacture and testing of the medicinal product have been conducted in accordance with the principles and guidelines of GMP.
1.7.2 原料藥與藥品直到認可階段，其整個供應鏈業經文件化且可供被授權人取得。其應包括藥品之起始原料與包裝材料的製造場所，以及透過製程風險評估被認為關鍵之任何其他原物料。該文件最好應以包含相關廠商之綜合圖表格式呈現，包括關鍵步驟的轉包商在內，例如對於無菌操作之組件與設備的滅菌。	1.7.2 The entire supply chain of the active substance and medicinal product up to the stage of certification is documented and available for the Authorised Person. This should include the manufacturing sites of the starting materials and packaging materials for the medicinal product and any other materials deemed critical through a risk assessment of the manufacturing process. The document should preferably be in the format of a comprehensive diagram, where each party, including subcontractors of critical steps such as the sterilisation of components and equipment for aseptic processing, are included.
1.7.3 已執行涉及藥品製造與檢驗及原料藥製造之場所的所有稽查，且該稽查報告可供	1.7.3 All audits of sites involved in the manufacture and the testing of the

	被授權人取得以執行認可。		medicinal products and in the manufacture of the active substance have been carried out and that the audit reports are available to the Authorised Person performing the certification.
1.7.4	所有製造、分析與認可之場所均符合對於預定管轄區域之上市許可的條款。	1.7.4	All sites of manufacture, analysis and certification are compliant with the terms of the MA for the intended jurisdiction.
1.7.5	所有製造活動與檢驗活動均與上市許可中所描述的活動一致。	1.7.5	All manufacturing activities and testing activities are consistent with those described in the MA.
1.7.6	批次所使用之起始原料及包裝材料的來源與規格符合上市許可。具備供應商品質管理系統以確保僅有符合品質之原物料被供應。	1.7.6	The source and specifications of starting materials and packaging materials used in the batch are compliant with the MA. Supplier quality management systems are in place that ensures only materials of the required quality have been supplied.
1.7.7	對於藥品，其原料藥已依照 GMP 製造，且必要時，依照原料藥 GDP 運銷。	1.7.7	For medicinal products, the active substances have been manufactured in accordance with GMP and, where required, distributed in accordance with Good Distribution Practice (GDP) for Active Substances.
1.7.8	用於製造人用藥品之原料藥原則上於符合下列兩項要求時輸入：	1.7.8	Active substances used in the manufacture of medicinal products for human use shall only be imported if the active substances comply with the following requirements:
	i. 該原料藥已依照 GMP 標準製造，且合適時，已依照國家法律以原料藥 GDP 運銷；並且		i. the active substances have been manufactured in accordance with standards of GMP and, where applicable, distributed in accordance with Good Distribution Practice according to national law; and
	ii. 該原料藥製造廠依照國家法律有符合 GMP 之證據。		ii. there is evidence of GMP compliance of the manufacturer of the active substance in accordance to national law.
1.7.9	用於製造藥品之賦形劑已以適當之優良製造規範製造。適用時應依照 PIC/S 文件：PI 045-1「適用於人用藥品賦形劑之適當優良製造規範的正式風險評估指導原則」。	1.7.9	The excipients used to manufacture a medicinal product have been manufactured with an appropriate good manufacturing practice. Where applicable, this shall be in accordance with PI 045-1: Guidelines on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use.
1.7.10	合適時，用於批次製造之所有原物料的 TSE（傳播性海綿樣腦症）狀態符合上市許可之條款。	1.7.10	When relevant, the TSE (Transmissible Spongiform Encephalopathy) status of all materials used in batch manufacture is

	compliant with the terms of the MA.
1.7.11 所有紀錄由適當人員完成與簽署。所有要求之製程中管制及檢查已執行。	1.7.11 All records are complete and endorsed by appropriate personnel. All required in-process controls and checks have been made.
1.7.12 所有製造與檢驗過程維持在確效的狀態。人員經適當訓練及資格檢定。	1.7.12 All manufacturing and testing processes remain in the validated state. Personnel are trained and qualified as appropriate.
1.7.13 最終產品品質管制檢驗數據符合上市許可中描述之最終產品規格，或經許可時，符合即時放行檢驗計畫。	1.7.13 Finished product quality control (QC) test data complies with the Finished Product Specification described in the MA, or where authorised, the Real Time Release Testing programme.
1.7.14 與產品製造或檢驗相關之任何法規上市後許諾已完成。持續進行之安定性試驗數據持續支持認可。	1.7.14 Any regulatory post-marketing commitments relating to manufacture or testing of the product have been addressed. On-going stability data continues to support certification.
1.7.15 已評估對產品製造與檢驗之任何變更的影響，且已完成任何附加檢查與檢驗。	1.7.15 The impact of any change to product manufacturing or testing has been evaluated and any additional checks and tests are complete.
1.7.16 與批次認可相關之所有調查(包括偏離規格及偏離趨勢之調查)已充分完成以支持認可。	1.7.16 All investigations pertaining to the batch being certified (including out of specification and out of trend investigations) have been completed to a sufficient level to support certification.
1.7.17 如有對於批次可能有影響之任何持續進行的申訴、調查或回收，該批次不應被認可。	1.7.17 A batch should not be certified if there are any on-going complaints, investigations or recalls that may have impact on the batch.
1.7.18 備有所需之技術協議。	1.7.18 The required technical agreements are in place.
1.7.19 自我查核計畫是有效的且為現行的。	1.7.19 The self-inspection programme is active and current.
1.7.20 備有運銷與裝運之適當協議。	1.7.20 The appropriate arrangements for distribution and shipment are in place.
1.7.21 國家法律要求時，包裝已貼上安全性特徵，使批發運銷商及被授權或具資格人員向大眾供應藥品時，可：	1.7.21 Where required in national law, safety features have been affixed to the packaging enabling wholesale distributors and persons authorised or entitled to supply medicinal products to the public to:
i. 確認該藥品之真實性；	i. verify the authenticity of the medicinal product;
ii. 辨識個別包裝；及	ii. identify individual packs; and
iii. 經由檢查裝置確認外包裝是否被竄改。	iii. verify, via a device, of whether the outer packaging has been tampered with.
1.8 對於某些產品，可能適用特殊指引，例如本規範附則 2A「人用再生醫療製劑之製	1.8 For certain products, special guidance may apply, such as PIC/S GMP Guide

	造」與附則 2B「人用生物原料藥及產品的製造」,及附則 3「放射性藥品的製造」。		Annex 2: Manufacture of Biological active substances and Medicinal Products for Human Use, and Annex 3: Manufacture of Radiopharmaceuticals.
1.9	平行輸入與平行運銷之情況,且合適時根據國家法規,已放行之批次所執行之任何重新包裝操作,必須由預訂上市之主管機關核准。	1.9	In the case of parallel importation and parallel distribution, any repackaging operation carried out on a batch which has already been released, must be approved by the competent authority of the intended market, as applicable under national law.
1.9.1	重新包裝批次認可前,被授權人應確認符合關於平行輸入之國家要求及關於平行運銷之規則。	1.9.1	Prior to certification of a repacked batch the Authorised Person should confirm compliance with national requirements for parallel importation and rules for parallel distribution.
1.9.2	於重新包裝最終產品之上市許可中,被指定負責批次認可之製造許可持有者的被授權人,依照與重新包裝產品及 GMP 有關之相關許可執行重新包裝之認可。	1.9.2	The Authorised Person, who is responsible for the certification of the batch in the MA of the repackaged finished product, certifies that the repackaging has been performed in accordance with the relevant authorisation pertaining to the repackaged product and GMP.
1.10	被授權人認可之紀錄:	1.10	Recording of Authorised Person certification:
1.10.1	藥品認可由被授權人記錄於為此目的提供之文件中。該紀錄應顯示各生產批次滿足下列規定:	1.10.1	The certification of a medicinal product is recorded by the Authorised Person in the document provided for that purpose. The record should show that each production batch satisfies the following provisions:
	i. 藥品各批次符合國家法律並依照上市許可之需求製造與檢查。		i. Each batch of medicinal products has been manufactured and checked in compliance with national law and in accordance with the requirements of the marketing authorisation.
	ii. 藥品來自其他管轄區域之情況,依照上市許可要求,各生產批次具有完整定性分析、至少所有原料藥之定量分析、及所有其他確保藥品品質之必須的檢驗或檢查。於國家法律要求時,該等檢驗亦於輸入國執行。		ii. In the case of medicinal products coming from another jurisdiction, each production batch has a full qualitative analysis, a quantitative analysis of at least all the active substances and all the other tests or checks necessary to ensure the quality of medicinal products in accordance with the requirements of the marketing authorisation. Such testing is also performed in the importing country where required in national law.
	iii. 藥品自其他管轄區域輸入之情況,當		iii. In the case of medicinal products

已與輸出管轄區域進行適當安排，以確保藥品製造廠應用至少等同於由國家主管機關所規定之 GMP 標準，並確保於輸出國已執行第 ii 點之管制時，被授權人可免除執行該等管制之責任。	imported from another jurisdiction, where appropriate arrangements have been made with the exporting jurisdiction to ensure that the manufacturer of the medicinal product applies standards of good manufacturing practice at least equivalent to those laid down by the national competent authority, and to ensure that the controls referred to under point (ii) have been carried out in the exporting country, the authorised person may be relieved of responsibility for carrying out those controls.
iv. 除非國家法律另有規定，否則紀錄必須在執行操作時保持更新，而且必須保存到批次末效日期後一年或放行後五年（取其較長者）。	iv. The record must be kept up to date as operations are carried out and must remain at the disposal of the agents of the National Competent Authority the longer of one year after expiry of the batch or five years unless otherwise specified in national law.
1.10.2 為了在進入另一個國家主管機關管轄區域免於進一步的管制，應為該批次提供 1.10.1 中所提及的管制報告或基於等同系統為銷售、供應或輸出之另外的放行證明。	1.10.2 The control report referred to in 1.10.1 or another proof for release for sale, supply, or export, based on an equivalent system, should be made available for the batch in order to be exempted from further controls when entering another National Competent Authority jurisdiction.
2. 倚賴由第三方之 GMP 評估，例如稽核（RELYING ON GMP ASSESSMENTS BY THIRD PARTIES, E.G. AUDITS）	
在有些情況，被授權人將倚賴產品製造中所涉及場所的製藥品質系統之正確運作，而且這可能經由從第三方所執行的稽核衍生。	In some cases the Authorised Person will rely on the correct functioning of the pharmaceutical quality system of sites involved in the manufacture of the product and this may be derived from audits conducted by third parties.
2.1 倚賴第三方評估（例如稽核）必須符合本規範第七章之規定，以適當界定、同意及管制任何委外活動。	2.1 Relying on assessment by third parties, e.g. audits should be in accordance with Chapter 7 of the PIC/S GMP Guide in order to appropriately define, agree and control any outsourced activity.
2.2 稽核報告之核准應予特別注意：	2.2 Special focus should be given to the approval of audit reports:
i. 稽核報告應敘明一般 GMP 要求，例如品質管理系統，與所供應產品之所有相關生產與品質管制程序，例如原料藥製造、品質管制檢驗、直接包裝等。產出的詳細稽核報告應準確地描	i. The audit report should address general GMP requirements, as for example the quality management system, all relevant production and quality control procedures related to

述所有受稽核範圍。	the supplied product, e.g. active substance manufacturing, quality control testing, primary packaging, etc. All audited areas should be accurately described resulting in a detailed report of the audit.
ii. 應確定原料藥與藥品之製造及品質管制是否符合 GMP，或如於其他管轄區域製造時，其 GMP 至少等同於各國家主管機關之 GMP。	ii. It should be determined whether the manufacture and quality control of the active substance and medicinal product complies with GMP or in case of manufacture in another jurisdiction, GMP at least equivalent to that of each National Competent Authority.
iii. 若有委外活動時，應確認符合上市許可。	iii. In case of outsourced activities compliance with the MA should be verified.
iv. 被授權人應確保已對第三方稽核報告進行書面之最終評估與核准。被授權人應可取得有利於審查稽核結果及持續倚賴委外活動之所有文件。	iv. The Authorised Person should ensure that a written final assessment and approval of third party audit reports have been made. The Authorised Person should have access to all documentation which facilitates review of the audit outcome and continued reliance on the outsourced activity.
v. 對產品品質有關鍵影響的委外活動，應依照本規範附則 20 所描述之品質風險管理原則界定。故被授權人於認可相關批次前，應瞭解對產品品質有關鍵影響之稽核結果。	v. Outsourced activities with critical impact on product quality should be defined in accordance with the principles of Quality Risk Management as described in Annex 20 of the PIC/S GMP Guide. According to this, the Authorised Person should be aware of the outcome of an audit with critical impact on the product quality before certifying the relevant batches.
vi. 再稽核應依照品質風險管理原則執行。	vi. Repeated audits should be performed in accordance with the principles of Quality Risk Management.
3. 非預期偏差的處理（HANDLING OF UNEXPECTED DEVIATIONS）	
當關於製造過程及/或分析管制方法與上市許可內所包含的細節及/或 GMP 發生非預期的偏差時，倘原料藥、賦形劑、包裝材料與藥品符合查驗登記規格，則被授權人可考慮確認符合性或者認可此一批次。該偏差應進行徹底調查並且矯正根本原因。為了該產品的持續生產，這可能需要提交上市許可變更申請。	Provided registered specifications for active substances, excipients, packaging materials and medicinal products are met, an Authorised Person may consider confirming compliance or certifying a batch where an unexpected deviation concerning the manufacturing process and/or the analytical control methods from details contained within the MA and/or GMP has occurred. The deviation should be thoroughly investigated and the root cause corrected. This

	may require the submission of a variation to the MA for the continued manufacture of the product.
3.1 偏差之影響應根據品質風險管理過程，使用例如本規範附則 20 中所述之適當方法進行評估。品質風險管理過程應包括下列內容：	3.1 The impact of the deviation should be assessed in accordance with a quality risk management process using an appropriate approach such as described in Annex 20 of the PIC/S GMP Guide. The quality risk management process should include the following;
i. 偏差對所關注之批次的品質、安全性或有效性之潛在影響的評估與該影響可忽略不計的結論。	i. Evaluation of the potential impact of the deviation on quality, safety or efficacy of the batch(es) concerned and conclusion that the impact is negligible.
ii. 考慮將受影響批次納入持續進行之安定性計畫中的需要。	ii. Consideration of the need to include the affected batch(es) in the ongoing stability programme.
iii. 關於生物藥品，考慮與核准過程的任何偏差對安全性與有效性可能會有非預期的影響。	iii. In the case of biological medicinal products, consideration that any deviations from the approved process can have an unexpected impact on safety and efficacy.
考量於單一批次製造與管制中可能由一位以上的被授權人分擔責任，執行藥品批次認可之被授權人應了解並考慮潛在影響符合 GMP 及/或上市許可之任何偏差。	Taking account that responsibilities may be shared between more than one Authorized Person involved in the manufacture and control of a batch, the Authorized Person performing certification of a batch of medicinal product should be aware of and take into consideration any deviations which have the potential to impact compliance with GMP and/or compliance with the MA.
4. 批次的放行（THE RELEASE OF A BATCH）	
4.1 藥品批次應如上述僅由被授權人認可後放行銷售或供應於市場。批次被認可前，藥品應保存於製造場所。或以隔離狀態裝運至獲得相關國家主管機關核准為此目的之其他場所。	4.1 Batches of medicinal products should only be released for sale or supply to the market after certification by an Authorised Person as described above. Until a batch is certified, it should remain at the site of manufacture or be shipped under quarantine to another site which has been approved for that purpose by the relevant National Competent Authority.
4.2 應具備安全措施確保未經認可之批次不被移轉至可銷售庫存中，其可能為實體措施（例如使用隔離與標示），或電子措施（例如使用經確效之電腦化系統）。未經認可之批次由一核准場所移至另一核准場所時，應維持防止提前放行之安全措施。	4.2 Safeguards to ensure that uncertified batches are not transferred to saleable stock should be in place and may be physical in nature, e.g. the use of segregation and labelling or electronic in nature, e.g. the use of validated computerised systems. When uncertified batches are moved from one authorised site to another, the safeguards to prevent

	premature release should remain.
將被授權人的認可通知予進行移轉至可銷售庫存之場所，應於技術協議中界定該通知之必要步驟。由被授權人對此場所的此類通知應當是正式的而且明確的，並且應受本規範第一部第四章的要求所管制。	The steps necessary to notify Authorised Person certification to the site where the transfer to saleable stock is to take place should be defined within a technical agreement. Such notification by an Authorised Person to the site should be formal and unambiguous and should be subject to the requirements of Chapter 4 of the PIC/S GMP Guide, Part I.
4.3 考慮製造廠對最終產品之認可，國家法律可能要求上市許可持有者對當地市場進行特定放行（market release）。	4.3 National law may require a specific release for the local market (market release) by the MAH which takes into consideration the certification of the finished product by the manufacturer.
附則 16 的術語彙編（GLOSSARY TO ANNEX 16）	
本附則中某些文字與用語，使用時有下列特定意義；本規範主要部分之術語彙編亦應參考。	Certain words and phrases in this Annex are used with the particular meanings defined below. Reference should also be made to the Glossary in the main part of the PIC/S GMP Guide.
最終產品批次的認可 按本附則中所界定，這是在一份文件中經由被授權人的認可，而且是代表批次在放行銷售或運銷之前的批次品質放行。	**Certification of the finished product batch** The certification in a document by an Authorised Person, as defined in this Annex, and represents the quality release of the batch before the batch is released for sale or distribution.
確認 按照與負責認可最終產品批次的被授權人在放行前的書面同意，由被授權人所簽署的聲明用以說明製程或檢驗已依照 GMP 與相關上市許可或臨床試驗許可、產品規格檔案及/或技術協議（如適用）執行。提供確認的被授權人對該確認的活動負責。	**Confirmation (Confirm and confirmed have equivalent meanings)** A signed statement by an Authorised Person that a process or test has been conducted in accordance with GMP and the relevant marketing authorisation or clinical trial authorisation, product specification file and/or technical agreement, as applicable, as agreed in writing with the Authorised Person responsible for certifying the finished product batch before release. The Authorised Person providing a confirmation takes responsibility for those activities being confirmed.
最終產品批次 關於最終產品的管制或檢驗，一個最終藥品批次是一個實體，包括由相同初始數量的原物料所製成並且已經過相同系列之製造及/或滅菌作業的所有劑型單元，或者，在連續生產過程的情況，在既定期間中所製造的所有單元。本附則中，本術語尤其是指在其最終包裝中供放行到市場的產品批次。	**Finished product batch** With reference to the control or test of the finished product, a finished medicinal product batch is an entity which comprises all the units of a pharmaceutical form which are made from the same initial quantity of material and have undergone the same series of manufacturing and/or sterilisation operations or, in the case of a continuous production process, all the units manufactured in a given period of time. In the context of this Annex the term in particular denotes the batch of product in its final pack for release to the market.

輸入者 根據國家法律要求之任何輸入藥品許可證持有者。	**Importer** Any holder of the authorisation to import as required by national law.
管轄區域 係指法院或政府機構行使其權力之領土。管轄區域可以是，例如，一個國家（無論國際上被承認與否）或一個地區。	**Jurisdiction** A jurisdiction is a territory within which a court or government agency is exercising its power. A jurisdiction can be e.g. a State (whether internationally recognised or not) or a region.

附錄 1（APPENDIX I）
確認藥品部分製造的建議內容
（Recommended content of the confirmation of the partial manufacturing of a medicinal product）

[執行製造活動之製藥廠的信頭（全銜與地址等）]	[LETTER HEAD OF MANUFACTURER WHO CARRIED OUT THE MANUFACTURING ACTIVITY]
1. 產品名稱與製造階段的描述（例如，乙醯胺酚 500 mg 錠，分裝成泡殼包裝）。	1. Name of the product and description of the manufacturing stage (e.g. paracetamol 500 mg tablets, primary packaging into blister packs).
2. 批號。	2. Batch number.
3. 執行部分製造之場所的名稱與地址。	3. Name and address of the site carrying out the partial manufacturing.
4. 技術品質協議之引述(依照 GMP 指引第七章)。	4. Reference to the Technical Quality Agreement (in accordance with Chapter 7 of the PIC/S GMP Guide).
5. 確認聲明	5. Confirmation statement.
本人茲確認在技術品質協議中所提及之製造階段已完全符合[插入管轄區域]的 GMP 要求並且按照由[認可與放行此批次的委託者/廠]所提供之確保符合上市許可要求的協議中所描述之條款執行。	I hereby confirm that the manufacturing stages referred to in the Technical Quality Agreement have been carried out in full compliance with the GMP requirements of the [insert jurisdiction] and the terms described in the Agreement for ensuring compliance with the requirements of the Marketing Authorisation(s) as provided by [Contract Giver/manufacturer certifying and releasing the batch].
6. 確認部分製造之被授權人的姓名。	6. Name of the Authorised Person confirming the partial manufacturing.
7. 確認部分製造之被授權人的簽章。	7. Signature of Authorised Person confirming the partial manufacturing.
8. 簽章日期。	8. Date of signature.

附錄 2（APPENDIX II）
藥品批次認可的建議內容
（Recommended content of the Batch Certificate for Medicinal Products）

[批次認可與放行製造廠的信頭（全銜與地址等）]	[LETTER HEAD OF THE BATCH CERTIFYING AND RELEASING MANUFACTURER]
1. 品名、強度/效價、劑型與包裝尺寸（與最終產品包裝上的文字一致）。	1. Name, strength/potency, dosage form and package size (identical to the text on the finished product package).
2. 最終產品批號。	2. Batch number of the finished product.
3. 批次目的地之國家名稱。	3. Name of the destination country/countries of the batch.
4. 認可聲明	4. Certification statement.
本人茲認可本批最終產品之所有製造階段已完全符合[插入管轄區域]的 GMP 要求並且[適用時]符合目的地國家之上市許可的要求執行。	I hereby certify that all the manufacturing stages of this batch of finished product have been carried out in full compliance with the GMP requirements of the [insert jurisdiction] and [as applicable] with the requirements of the Marketing Authorisation(s) of the destination country/countries.
5. 認可批次之被授權人的姓名。	5. Name of the Authorised Person certifying the batch.
6. 認可批次之被授權人的簽章。	6. Signature of the Authorised Person certifying the batch.
7. 簽章日期。	7. Date of signature.

附則 19 對照樣品與留存樣品（REFERENCE AND RETENTION SAMPLES）

1. 範圍（SCOPE）	
1.1 藥品 GMP 指引（本指引）之本附則規定關於原料、包裝材料或最終產品之對照樣品，以及最終產品之留存樣品的取樣與保存的指導。	1.1 This Annex to the Guide to Good Manufacturing Practice for Medicinal Products (“the GMP Guide”) gives guidance on the taking and holding of reference samples of starting materials, packaging materials or finished products and retention samples of finished products.
1.2 關於研究用藥品之特別要求規定於本指引的附則 13。	1.2 Specific requirements for investigational medicinal products are given in Annex 13 to the Guide.
1.3 本附則亦包含關於平行輸入/運銷藥品的留存樣品之取樣指導。	1.3 This annex also includes guidance on the taking of retention samples for parallel imported / distributed medicinal products.
2.原則（PRINCIPLE）	
2.1 樣品的留存是為了達成兩個目的：第一，為提供分析檢驗的樣品，第二，為提供完整最終產品的樣本。因此，樣品可以歸納成兩個類別：	2.1 Samples are retained to fulfil two purposes; firstly to provide a sample for analytical testing and secondly to provide a specimen of the fully finished product. Samples may therefore fall into two categories:
對照樣品（Reference sample）：在相關批次之架儲期間中倘若發生分析需要時，為分析目的而儲存之一個批次的原料、包裝材料或最終產品的樣品。	Reference sample: a sample of a batch of starting material, packaging material or finished product which is stored for the purpose of being analyzed should the need arise during the shelf life of the batch concerned.
在安定性允許時，應保存來自關鍵中間階段（例如需要分析測試與放行）的對照樣品，或運送到製造者控管外之中間產品的對照樣品。	Where stability permits, reference samples from critical intermediate stages (e.g. those requiring analytical testing and release) or intermediates that are transported outside of the manufacturer’s control should be kept.
留存樣品（Retention sample）：來自一個批次之最終產品的完整包裝單元之樣品。這是為識別目的而儲存。例如，在相關批次之架儲期間中倘若發生需要時，用以辨識其外觀、包裝、標示、病人用說明書、批號、末效日期等。	Retention sample: a sample of a fully packaged unit from a batch of finished product. It is stored for identification purposes. For example, presentation, packaging, labelling, patient information leaflet, batch number, expiry date should the need arise during the shelf life of the batch concerned.
可能有例外情形，即使未留存完全相同的樣	There may be exceptional circumstances where

品亦能符合本要求。例如，為不同市場，包裝一個批次中之小數量或製造極為昂貴之藥品。	this requirement can be met without retention of duplicate samples e.g. where small amounts of a batch are packaged for different markets or in the production of very expensive medicinal products.
在許多情況中，最終產品之對照樣品與留存樣品會以完全相同的，亦即，以完整包裝單元的型態呈現。在此種情形中，對照樣品及留存樣品可視為得以互換。	For finished products, in many instances the reference and retention samples will be presented identically, i.e. as fully packaged units. In such circumstances, reference and retention samples may be regarded as interchangeable.
2.2 依第 7 與 8 節之規定，製造者、輸入者或批次放行者必須保存來自每批次之最終產品的對照及/或留存樣品；製造者並必須保存來自一個批次之原料（會有某些例外，參見下面 3.2 節）及/或中間產品的對照樣品。包裝廠應保存每批次之直接包裝材料及業經印刷之包裝材料的對照樣品。	2.2 It is necessary for the manufacturer, importer or site of batch release, as specified under section 7 and 8, to keep reference and/or retention samples from each batch of finished product and, for the manufacturer to keep a reference sample from a batch of starting material (subject to certain exceptions – see 3.2 below) and/or intermediate product. Each packaging site should keep reference samples of each batch of primary and printed packaging materials.
印刷之包裝材料作為最終產品之對照及/或留存樣品的一部分是可接受的。	Availability of printed materials as part of the reference and/or retention sample of the finished product can be accepted.
2.3 對照樣品及/或留存樣品可作為最終產品或原料批次的紀錄，例如當有劑型品質申訴、有關上市許可符合性的質疑、標示/包裝的質疑或藥品監視報告等情形時，可據以評定。	2.3 The reference and/or retention samples serve as a record of the batch of finished product or starting material and can be assessed in the event of, for example, a dosage form quality complaint, a query relating to compliance with the marketing authorization, a labelling/packaging query or a pharmacovigilance report.
2.4 樣品之可追溯性的紀錄應予以保存，並可供主管機關審閱。	2.4 Records of traceability of samples should be maintained and be available for review by competent authorities.
3.儲存期間（DURATION OF STORAGE）	

3.1 來自每一最終產品批次的對照樣品與留存樣品應保存至末效日期後至少一年。該對照樣品應裝在其最終直接包裝中或在與其上市產品直接容器相同材質所組成的包裝中【對於免疫製劑之外的動物用藥品，參見附則 4，第 8 及 9 段落】。	3.1 Reference and retention samples from each batch of finished product should be retained for at least one year after the expiry date. The reference sample should be contained in its finished primary packaging or in packaging composed of the same material as the primary container in which the product is marketed (for veterinary medicinal products other than immunologicals, see also Annex 4, paragraphs 8 & 9).
3.2 除非製造國（其主管機關是 PIC/S 會員）的法律要求一段較長的期間，原料樣品（製程中使用的溶劑、氣體或水除外），應保存至產品放行後至少兩年。依相關規格之記載原料之安定性期間較短者，該期間得以縮短。	3.2 Unless a longer period is required under the law of the country of manufacture (whose competent authority is a PIC/S Member), samples of starting materials (other than solvents, gases or water used in the manufacturing process) shall be retained for at least two years after the release of product. That period may be shortened if the period of stability of the material, as indicated in the relevant specification, is shorter.
包裝材料應保存至相關最終產品之架儲期間屆滿。	Packaging materials should be retained for the duration of the shelf life of the finished product concerned.
4.對照樣品與留存樣品的量 （SIZE OF REFERENCE AND RETENTION SAMPLES）	
4.1 對照樣品應有足夠數量，至少在兩種時機，可依照經相關主管機關評估與核准的上市許可檔案，對該批次從事全項分析對照（analytical controls）。	4.1 The reference sample should be of sufficient size to permit the carrying out, on, at least, two occasions, of the full analytical controls on the batch in accordance with the Marketing Authorisation File which has been assessed and approved by the relevant Competent Authority / Authorities.
當需要這樣做時，在從事每套分析對照時，應使用沒有打開的包裝品。	Where it is necessary to do so, unopened packs should be used when carrying out each set of analytical controls.
對此要求提出的任何例外，皆應向相關主管機關證明其正當性，並為其同意。	Any proposed exception to this should be justified to, and agreed with, the relevant competent authority.
4.2 適用時，應遵循國家關於對照樣品之量的要求；必要時，留存樣品，亦同。	4.2 Where applicable, national requirements relating to the size of reference samples and, if necessary, retention samples, should be followed.

4.3 對照樣品對於從其抽樣之原料、中間產品或最終產品的批次應具有代表性。亦可以抽取其他樣品，用以監測製程中最易發生偏差的部份（例如，製程的起始與終端）。一個批次在兩個以上不同包裝作業包裝者，應從每一個個別包裝作業抽取至少一個留存樣品。對此要求建議之任何例外，應向相關主管機關證明其正當性並為其同意。	4.3 Reference samples should be representative of the batch of starting material, intermediate product or finished product from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g. beginning or end of a process). Where a batch is packaged in two, or more, distinct packaging operations, at least one retention sample should be taken from each individual packaging operation. Any proposed exception to this should be justified to, and agreed with, the relevant competent authority.
4.4 最後製造批次的末效期後一年內，可從事規格中規定之所有試驗，應確保所有必要的分析材料及設備仍然具備，或是容易獲得。	4.4 It should be ensured that all necessary analytical materials and equipment are still available, or are readily obtainable, in order to carry out all tests given in the specification until one year after expiry of the last batch manufactured.
5.儲存條件（STORAGE CONDITIONS）	
5.1 …	5.1…
5.2 儲存條件應依照上市許可規定（例如，視情形，以冷藏儲存）。	5.2 Storage conditions should be in accordance with the marketing authorisation (e.g. refrigerated storage where relevant)
6.書面協議（WRITTEN AGREEMENTS）	
6.1 上市許可之持有者與負責批次放行場所之法律主體不相同時，對照樣品/留存樣品之取樣及儲存的責任，應依照本指引第七章，在雙方的書面協議中界定。這也適用於，任何製造或批次放行活動非在對該批次負全部責任之場所從事的情形。且每個不同場所間關於對照樣品與留存樣品之抽取與保存的安排，應於書面協議中界定。	6.1 Where the marketing authorization holder is not the same legal entity as the site(s) responsible for batch release, the responsibility for taking and storage of reference/retention samples should be defined in a written agreement between the two parties in accordance with Chapter 7 of the PIC/S Guide to Good Manufacturing Practice. This applies also where any manufacturing or batch release activity is carried out at a site other than that with overall responsibility for the batch and the arrangements between each different site for the taking and keeping of reference and retention samples should be defined in a written agreement.

6.2 負責簽署放行一個批次供銷售之被授權人員，應確保能在所有合理的時間取得所有相關對照樣品與留存樣品。必要時，對於該取得之安排應以書面協議界定。	6.2 The Authorised Person who certifies a batch for sale should ensure that all relevant reference and retention samples are accessible at all reasonable times. Where necessary, the arrangements for such access should be defined in a written agreement.
6.3 最終產品之製造涉及一個以上廠區者，對於對照樣品與留存樣品之取用與存放位置的管制，備妥書面協議至關重要。	6.3 Where more than one site is involved in the manufacture of a finished product, the availability of written agreements is key to controlling the taking and location of reference and retention samples.
7.對照樣品－一般考量要點 （REFERENCE SAMPLES－ GENERAL POINTS）	
7.1 對照樣品是為了分析目的，因此，應可為具有確效方法之實驗室方便獲得。對使用於藥品之原料及包裝材料，是指最終產品之原製造場所。對於最終產品，是指原製造場所。	7.1 Reference samples are for the purpose of analysis and, therefore, should be conveniently available to a laboratory with validated methodology. For starting materials and packaging materials used for medicinal products, this is the original site of manufacture of the finished product. For finished products, this is the original site of manufacture.
8. 留存樣品－一般考量要點 （RETENTION SAMPLES－GENERAL POINTS）	
8.1 為確認非技術性屬性符合上市許可或國家法律，留存樣品應代表一個批次如其在運銷時之狀態的最終產品，並可能需要被檢查。留存樣品最好應儲存於負責簽署該最終產品批次之被授權人員所在的處所。	8.1 A retention sample should represent a batch of finished products as distributed and may need to be examined in order to confirm non-technical attributes for compliance with the marketing authorization or national legislation. The retention samples should preferably be stored at the site where the Authorised Person (AP) certifying the finished product batch is located.
8.2 …	8.2…
8.3 為使主管機關能隨時取得，留存樣品應儲存在被授權之製造者的廠房。	8.3 Retention samples should be stored at the premises of an authorised manufacturer in order to permit ready access by the Competent Authority.
8.4 當一個產品涉及一個以上的製造場所時，考量產品特性，製造/輸入/包裝/檢驗/批次放行其留存樣品之取用及儲存的責任，應界定於所涉各方間的書面協議中。	8.4 Where more than one manufacturing site is involved in the manufacture/importation/ packaging/testing/batch release, as appropriate of a product, the responsibility for taking and storage of retention samples should be defined

	in a written agreement(s) between the parties concerned.
9.平行輸入/平行運銷產品的對照樣品及留存樣品（REFERENCE AND RETENTION SAMPLES FOR PARALLEL IMPORTED / PARALLEL DISTRIBUTED PRODUCTS）	
附註:本節僅在國家法律規範平行輸入/平行運銷之產品時適用。	Note: This section is only applicable if the national legislation deals with parallel imported / parallel distributed products.
9.1 未打開間接包裝時，因無或少有產品混雜的風險，只需要留存所使用的包裝材料。	9.1 Where the secondary packaging is not opened, only the packaging material used needs to be retained, as there is no, or little, risk of product mix up.
9.2 打開間接包裝時，例如，置換紙盒或病人用說明書時，因為在組裝過程中有產品混雜的風險，所以在每一包裝作業，應抽取一件含該產品之留存樣品。當有混雜發生時，能夠迅速識別誰應負責（原始製造者或是平行輸入組裝者）是重要的，因為這會影響任何衍生之回收程度。	9.2 Where the secondary packaging is opened, for example, to replace the carton or patient information leaflet, then one retention sample, per packaging operation, containing the product should be taken, as there is a risk of product mix-up during the assembly process. It is important to be able to identify quickly who is responsible in the event of a mix-up (original manufacturer or parallel import assembler), as it would affect the extent of any resulting recall.
10. 製造者關廠時之對照樣品及留存樣品（REFERENCE AND RETENTION SAMPLES IN THE CASE OF CLOSEDOWN OF A MANUFACTURER）	
10.1 製造者關廠，而讓與、吊銷或廢止其製造許可時，由該製造者製造之許多未屆效期批次之藥品可能還在市場上。為使該等批次繼續留在市場上，製造者應做出詳細的安排，將對照樣品及留存樣品(及相關的 GMP 文件）移轉到一個被授權的儲存場所。製造者應做到，使主管機關滿意該儲存的安排；必要時，該樣品並能夠易於取得及分析。	10.1 Where a manufacturer closes down and the manufacturing authorisation is surrendered, revoked, or ceases to exist, it is probable that many unexpired batches of medicinal products manufactured by that manufacturer remain on the market. In order for those batches to remain on the market, the manufacturer should make detailed arrangements for transfer of reference and retention samples (and relevant GMP documentation) to an authorised storage site. The manufacturer should satisfy the Competent Authority that the arrangements for storage are satisfactory and that the

	samples can, if necessary, be readily accessed and analysed.
10.2 製造者不能從事該必要安排者，得委任其他製造者。上市許可之持有者應負起對該委任及對主管機關提供所有必要資訊之責任。此外，有關提議之對照樣品與留存樣品的儲存安排之適當性，上市許可持有者應與任何未逾效期批次所在市場之每一國家的主管機關協商。	10.2 If the manufacturer is not in a position to make the necessary arrangements this may be delegated to another manufacturer. The Marketing Authorisation holder (MAH) is responsible for such delegation and for the provision of all necessary information to the Competent Authority. In addition, the MAH should, in relation to the suitability of the proposed arrangements for storage of reference and retention samples, consult with the competent authority of each country in which any unexpired batch has been placed on the market.

附則 20 品質風險管理（QUALITY RISK MANAGEMENT）

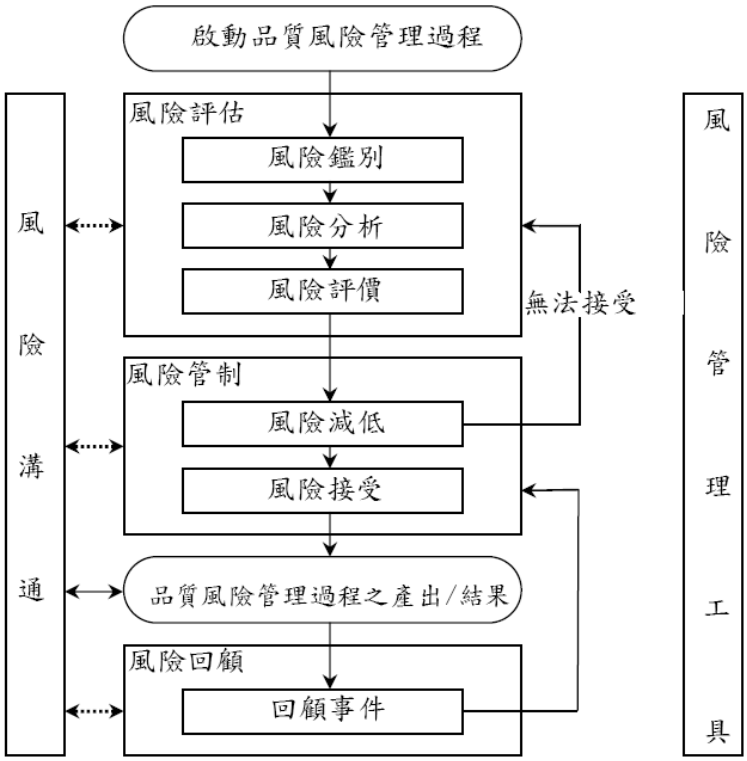
*本附則為自願性的/非強制性的。	* This Annex is voluntary.
序文和適用範圍 （FOREWORD AND SCOPE OF APPLICATION）	
1. 新的 GMP 附則 20 相當於 ICH Q9 關於品質風險管理的指引。它對於品質風險管理提供系統性方法之指引，以利遵守從 GMP 及其他品質之要求。當應用正式的品質風險管理方法時，它包括要使用之原理及可能使用之過程、方法和工具的選項。	1. The new GMP Annex 20 corresponds to ICH Q9 guideline on Quality Risk Management. It provides guidance on a systematic approach to quality risk management facilitating compliance with GMP and other quality requirements. It includes principles to be used and options for processes, methods and tools which may be used when applying a formal quality risk management approach.
2. 為確保其連貫性，已經修訂 GMP 第一部第一章關於品質管理之規定，以將品質風險管理的層面包含在品質系統架構內。計劃對本指引之第二部進行一個類似的修訂。GMP 指引之其他章節可能加以調整，以將品質風險管理的層面包含在將來那些章節之更為寬廣的修訂中。	2. To ensure coherence, GMP Part I, Chapter 1 on Quality Management, has been revised to include aspects of quality risk management within the quality system framework. A similar revision is planned for Part II of the Guide. Other sections of the GMP Guide may be adjusted to include aspects of quality risk management in future broader revisions of those sections.
3. 隨著在 GMP 第一部及第二部中之品質管理章節的修訂，品質風險管理變成製造廠品質系統之不可或缺的一部分。惟附則 20 本身並不意圖創造任何新的法規預期效果；它只是提供一份國際公認之風險管理方法及工具的清單，連同一份得由製造廠自由裁量其潛在應用的清單。	3. With the revision of the chapters on quality management in GMP Parts I and II quality risk management becomes an integral part of a manufacturer’s quality system. Annex 20 itself is not intended, however, to create any new regulatory expectations; it provides an inventory of internationally acknowledged risk management methods and tools together with a list of potential applications at the discretion of manufacturers.
4. 據瞭解，ICH Q9 指引最初是為人用醫藥產品之品質風險管理而開發。隨著附則 20 的實施，指引之效益，諸如對品質風險管理之過程、方法及工具，亦可使用於動物用藥領域。	4. It is understood that the ICH Q9 guideline was primarily developed for quality risk management of medicinal products for human use. With the implementation in Annex 20 benefits of the guideline, such as processes, methods and tools for quality risk management are also made available to the veterinary sector.
5. GMP 指引主要係針對製造廠，而 ICH Q9 指引則與其他品質指引具有關聯，並包括對主管機關之特定部門。	5. While the GMP guide is primarily addressed to manufacturers, the ICH Q9 guideline, has relevance for other quality guidelines and

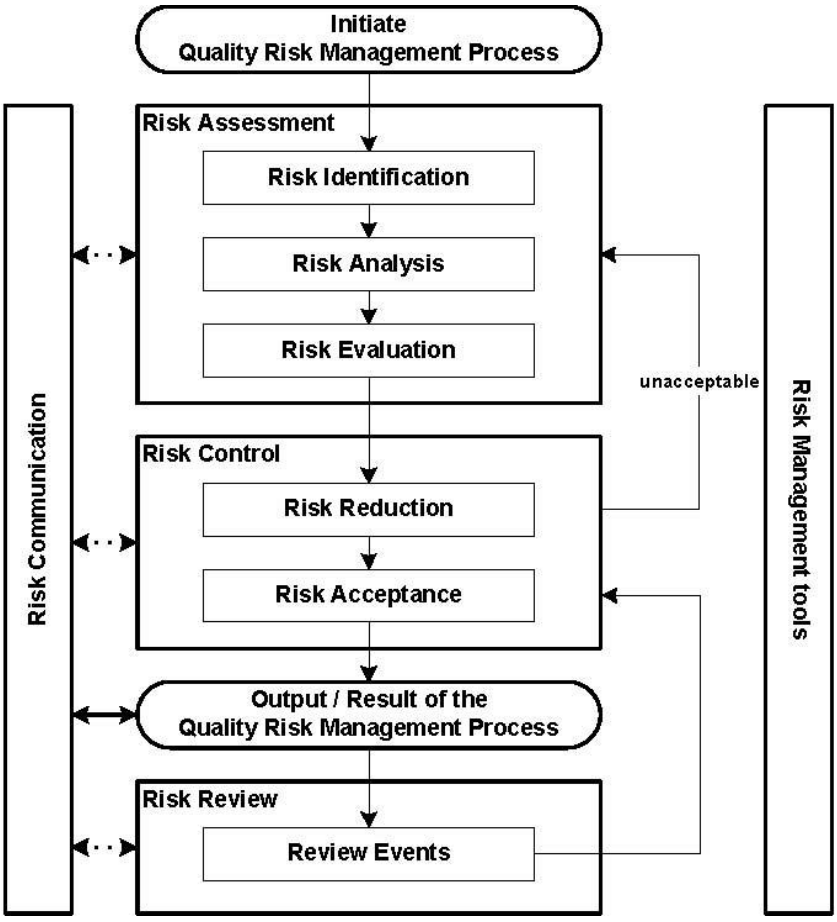
	includes specific sections for regulatory agencies.
6. 然而，為了連貫性及完整性，已將 ICH Q9 指引完全轉為 GMP 附則 20。	6. However, for reasons of coherence and completeness, the ICH Q9 guideline has been transferred completely into GMP Annex 20.
前言（Introduction）	
7. 風險管理原則，除有效地被利用在包括財政、保險、職業安全、公共衛生、藥物監視在內之許多商業及政府的領域外，亦被管理這些產業的主管機關有效地利用。雖然目前在製藥產業有一些*品質風險管理*之使用的實例，但他們是有限的，而且尚未代表風險管理應提供之全部的貢獻。此外，製藥產業中已經認知品質系統的重要性，而且變得越來越明顯的是，品質風險管理是一個有效品質系統之重要構成要素。	7. *Risk management* principles are effectively utilized in many areas of business and government including finance, insurance, occupational safety, public health, pharmacovigilance, and by agencies regulating these industries. Although there are some examples of the use of *quality risk management* in the pharmaceutical industry today, they are limited and do not represent the full contributions that risk management has to offer. In addition, the importance of *quality systems* has been recognized in the pharmaceutical industry and it is becoming evident that quality risk management is a valuable component of an effective quality system.
8. 普遍瞭解的是，風險經界定為損害之發生機率及該損害之嚴重度的結合。然而，因為每一位利害關係人可能感受不同的潛在損害，可能將不同的機率置於每一損害的發生上，並且將不同的嚴重度歸屬於每一種損害上，所以在不同利害關係人（stakeholders）間難以達成風險管理之應用的共識。關於醫藥產品，雖然有各種不同的利害關係人，包含病人和執業醫師以及政府與產業在內，但經由品質風險管理以保護病人應被視為最重要。	8. It is commonly understood that *risk* is defined as the combination of the probability of occurrence of *harm* and the *severity* of that harm. However, achieving a shared understanding of the application of risk management among diverse *stakeholders* is difficult because each stakeholder might perceive different potential harms, place a different probability on each harm occurring and attribute different severities to each harm. In relation to pharmaceuticals, although there are a variety of stakeholders, including patients and medical practitioners as well as government and industry, the protection of the patient by managing the risk to quality should be considered of prime importance.
9. 藥品(醫藥製品)之製造及使用，包含其組成物在內，必定伴隨著若干程度的風險。其品質之風險只是其整體風險的一個構成部分而已。重要的是，要瞭解在產品的整個	9. The manufacturing and use of a drug (medicinal) product, including its components, necessarily entail some degree of risk. The risk to its quality is just one

生命週期皆應維持產品品質，以將對於藥品(醫藥製品)之品質具有重要性的屬性，保持與臨床研究上所使用藥品的那些屬性一致。一個有效的品質風險管理方法，可以經由提供一個洞燭機先的方法，去確認和管制在開發及製造期間之潛在品質問題，以對病人進一步確保藥品的高度品質。此外，品質風險管理的使用，可以在品質問題發生時，改善其決策。有效的品質風險管理，可以幫助更好及具有更多情報的決策，可以就一個公司處理潛在風險的能力提供主管機關更大的保證，而且有利於影響主管機關監督的程度及等級。	component of the overall risk. It is important to understand that product *quality* should be maintained throughout the *product lifecycle* such that the attributes that are important to the quality of the drug (medicinal) product remain consistent with those used in the clinical studies. An effective quality risk management approach can further ensure the high quality of the drug (medicinal) product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing. Additionally, use of quality risk management can improve the decision making if a quality problem arises. Effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks and can beneficially affect the extent and level of direct regulatory oversight.
10. 本文件之目的是要對品質風險管理提供一個系統性的方法。它當作一個基礎文件或資源文件，獨立但支持其他 ICH 品質文件，並補充製藥產業及管制環境內既存的品管慣例、要求、標準及指引。它具體地提供關於品質風險管理原則及一些工具的指引。該指引能使主管機關及產業二者基於風險，對於跨越產品生命週期之藥物和醫藥產品的品質所作的決策更為有效且一致。它無意創造超過當前法規要求之任何新的期望。	10. The purpose of this document is to offer a systematic approach to quality risk management. It serves as a foundation or resource document that is independent of, yet supports, other ICH Quality documents and complements existing quality practices, requirements, standards, and guidelines within the pharmaceutical industry and regulatory environment. It specifically provides guidance on the principles and some of the tools of quality risk management that can enable more effective and consistent risk based decisions, both by regulators and industry, regarding the quality of drug substances and drug (medicinal) products across the product lifecycle. It is not intended to create any new expectations beyond the current regulatory requirements.
11. 使用一個正式的風險管理程序（使用受承認的工具及/或內部程序，例如，標準作業程序）既非總是適合的，也非總是必需的。使用非正式的風險管理程序（使用經驗上的工具及/或內部程序）亦得認定為可接	11. It is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/ or internal procedures e.g. standard operating procedures). The use of informal risk

受。	management processes (using empirical tools and/ or internal procedures) can also be considered acceptable.
12. 品質風險管理之適當的使用，可以是有幫助的，但不得排除產業需遵守法規要求的義務，也不取代產業與主管機關間之適當溝通。	12. Appropriate use of quality risk management can facilitate but does not obviate industry's obligation to comply with regulatory requirements and does not replace appropriate communications between industry and regulators.
範圍（Scope）	
13. 本指引提供可適用於製藥品質之不同層面的品質風險管理之原則及工具範例。這些層面涵蓋藥物、藥品、生物產品及生技產品（包含藥品、生物產品及生技產品之原料、溶媒、賦形劑、包裝及標示材料的使用在內）的開發、製造、運銷，以及檢查和申請/審查程序之整個生命週期。	13. This guideline provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality. These aspects include development, manufacturing, distribution, and the inspection and submission/review processes throughout the lifecycle of drug substances, drug (medicinal) products, biological and biotechnological products (including the use of raw materials, solvents, excipients, packaging and labeling materials in drug (medicinal) products, biological and biotechnological products).
品質風險管理的原則 （PRINCIPLES OF QUALITY RISK MANAGEMENT）	
14. 品質風險管理之二個主要原則是：	14. Two primary principles of quality risk management are:
• 品質風險之評估應以科學知識為基礎且最終連結到對病人的保護；以及	• The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and
• 品質風險管理過程之努力、正式性及文件制作的程度應與風險之層級相稱。	• The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.
一般品質風險管理過程 (GENERAL QUALITY RISK MANAGEMENT PROCESS)	
15. 品質風險管理是對藥物產品整個生命週期之品質風險的評價、管制、溝通及檢討之系統性的過程。品質風險管理的模式概述於圖 1。其他模式也可使用。該架構之每一構成部分的重點可能因個案而異，但健全的過程會將所有要素納入考慮，其詳細	15. Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle. A model for quality risk management is outlined in the diagram

程度是與其特定風險相稱。	(Figure 1). Other models could be used. The emphasis on each component of the framework might differ from case to case but a robust process will incorporate consideration of all the elements at a level of detail that is commensurate with the specific risk.





16. 因為決策可能發生在過程中的任何一點，	16. Decision nodes are not shown in the diagram

所以決策結節(decision nodes)未顯示在上圖中。基於支持如此決策之資訊，這些決策可能會因而回到先前的步驟並尋求進一步的資訊，調整風險模式或甚至終止風險管理程序。**註：**流程圖中之「無法接受」並非只指法令、立法或行政管制的要求，而且亦指回顧風險評價過程的必要性。	above because decisions can occur at any point in the process. These decisions might be to return to the previous step and seek further information, to adjust the risk models or even to terminate the risk management process based upon information that supports such a decision. Note: "unacceptable" in the flowchart does not only refer to statutory, legislative or regulatory requirements, but also to the need to revisit the risk assessment process.
責任（Responsibilities）	
17. 品質風險管理活動，通常，但不是一直都由跨學科的團隊所從事。當組成團隊時，除了具有關於品質風險管理過程之知識的人員外，還應包含來自適當領域（例如，品質部門、業務開發、工程、法規事務、生產操作、銷售及行銷、法律、統計及臨床）的專家。	17. Quality risk management activities are usually, but not always, undertaken by interdisciplinary teams. When teams are formed, they should include experts from the appropriate areas (e.g. quality unit, business development, engineering, regulatory affairs, production operations, sales and marketing, legal, statistics and clinical) in addition to individuals who are knowledgeable about the quality risk management process.
18. *決策者*應該：	18. Decision *makers* should:
• 在其組織之不同職能與部門間負起協調品質風險管理的責任；而且	• take responsibility for coordinating quality risk management across various functions and departments of their organization; and
• 確保品質風險管理程序是經過界定、佈署及審查，並可獲得適當的資源。	• assure that a quality risk management process is defined, deployed and reviewed and that adequate resources are available.
引進品質風險管理程序（Initiating a Quality Risk Management Process）	
19. 品質風險管理過程應包含系統性決策程序，該過程經設計並可用於協調、幫助及改善基於科學所作風險之決策。使用於啟動及規劃一個品質風險管理過程之可能步驟包含如下：	19. Quality risk management should include systematic processes designed to coordinate, facilitate and improve science-based decision making with respect to risk. Possible steps used to initiate and plan a quality risk management process might include the following:
• 界定問題及/或風險疑問，包含確認風險之潛在性的相關假設在內；	• Define the problem and/or risk question, including pertinent assumptions identifying the potential for risk
• 組合有關風險評價之潛在危害、損害	• Assemble background information and/

或對人體健康之衝擊的背景資訊及/或數據；	or data on the potential hazard, harm or human health impact relevant to the risk assessment
• 確認一位領導者及必要的資源；	• Identify a leader and necessary resources
對風險管理過程規定其決策制定的時間表、可傳送的資訊及適當的層級。	Specify a timeline, deliverables and appropriate level of decision making for the risk management process
風險評價（Risk Assessment）	
20. 風險評價包含危害 之辨識及暴露於那些危害（如下面所界定）所相關之風險的分析與評估。品質風險評價始於完善界定問題的描述或風險問題。當完善界定風險問題時，則解決該風險問題所需要的適當風險管理工具(參見在第 5 節的範例)及資訊類型將更易辨識。為風險評價之目的，有三個基本問題，常有助於清楚界定風險：	20. Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards (as defined below). Quality risk assessments begin with a well-defined problem description or risk question. When the risk in question is well defined, an appropriate risk management tool (see examples in section 5) and the types of information needed to address the risk question will be more readily identifiable. As an aid to clearly defining the risk(s) for risk assessment purposes, three fundamental questions are often helpful:
1. 什麼可能出錯？	1. What might go wrong?
2. 出錯的可能性(機率)為何？	2. What is the likelihood (probability) it will go wrong?
3. 後果(嚴重性)為何？	3. What are the consequences (severity)?
21. ***風險辨識***為系統性的使用資訊，以辨識有關風險問題的危害或問題描述。資訊可能包含歷史數據、理論分析、根據情報的意見，以及利害關係人的關切事項。風險辨識提示「什麼可能出錯？」的問題，包含辨識其可能的後果。這提供品質風險管理程序之後續步驟的基礎。	21. ***Risk identification*** is a systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders. Risk identification addresses the “What might go wrong?” question, including identifying the possible consequences. This provides the basis for further steps in the quality risk management process.
22. ***風險分析***是與經辨識之危害所關聯的風險進行估計。它是連結於事件發生之可能性及損害之嚴重度的定性與定量過程。在有些風險管理工具中，檢測損害的能力（可檢測性）亦是風險估計中的因素。	22. ***Risk analysis*** is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. In some risk management

	tools, the ability to detect the harm (detectability) also factors in the estimation of risk.
23. ***風險評估***是將經辨識及分析的風險與已知的風險標準進行比對。風險評估是就所有三個基本問題考量其證據的強度。	23. ***Risk evaluation*** compares the identified and analyzed risk against given risk criteria. Risk evaluations consider the strength of evidence for all three of the fundamental questions.
24. 在執行有效之風險評價時，數據套組的健全性/耐用性是重要的，因為這決定產出（output）的品質。揭露不確定性（uncertainty）之假設及合理來源，將提高該產出之信心及/或幫助確認其限制。不確定性是由於過程的不完整知識及其預期或非預期之變異性的組合。不確定性之典型來源包括知識上的差距、製藥科學與製程瞭解上的差距、傷害的來源(例如過程的失敗模式、變異性的來源)，以及問題檢測的機率。	24. In doing an effective risk assessment, the robustness of the data set is important because it determines the quality of the output. Revealing assumptions and reasonable sources of uncertainty will enhance confidence in this output and/or help identify its limitations. Uncertainty is due to combination of incomplete knowledge about a process and its expected or unexpected variability. Typical sources of uncertainty include gaps in knowledge gaps in pharmaceutical science and process understanding, sources of harm (e.g., failure modes of a process, sources of variability), and probability of detection of problems.
25. 風險評價之產出是風險之定量估計或風險範圍之定性***描述***。當風險以定量表達時，使用數字表達其機率，或風險可以定性描述(例如「高」、「中」或「低」)表達。惟描述應盡可能界定其細節。有時可使用「風險分數」（risk score），以再進一步界定風險分級上的描述。在定量風險評價上，風險估計值指在假定之一套產生風險的情況下，提供一個特定後果的可能性。因此，逐一定量風險估計對於特別的結果是有用的。或者，有些風險管理工具使用一個相對風險計量（relative risk measure），以將不同層級嚴重度及機率組合成相對風險之一個整體估計值。在評分過程的中間步驟有時可以使用定量風險估計。	25. The output of a risk assessment is either a quantitative estimate of risk or a qualitative ***description*** of a range of risk. When risk is expressed quantitatively, a numerical probability is used. Alternatively, risk can be expressed using qualitative descriptors, such as “high”, “medium”, or “low”, which should be defined in as much detail as possible. Sometimes a "risk score" is used to further define descriptors in risk ranking. In quantitative risk assessments, a risk estimate provides the likelihood of a specific consequence, given a set of risk-generating circumstances. Thus, quantitative risk estimation is useful for one particular consequence at a time. Alternatively, some risk management tools use a relative risk measure to combine multiple levels of severity and probability into an overall estimate of relative risk. The intermediate

	steps within a scoring process can sometimes employ quantitative risk estimation.
風險管制 （Risk Control）	
26. ***風險管制***包括為***降低***及/或接受風險之決策制定。風險管制之目的是要將風險減到一個可以接受的程度。使用於風險管制之努力程度應與風險的重要性成正比。為瞭解/確認風險管制之最適化等級，決策者可使用不同的過程，包含成本效益分析在內。	26. ***Risk control*** includes decision making to ***reduce*** and/or accept risks. The purpose of risk control is to reduce the risk to an acceptable level. The amount of effort used for risk control should be proportional to the significance of the risk. Decision makers might use different processes, including benefit-cost analysis, for understanding the optimal level of risk control.
27. 風險管制可以聚焦於下列問題：	27. Risk control might focus on the following questions:
• 風險是否高於可接受的程度？	• Is the risk above an acceptable level?
• 可做什麼以減低或消除風險？	• What can be done to reduce or eliminate risks?
• 效益、風險及資源三者之適當的平衡是什麼？	• What is the appropriate balance among benefits, risks and resources?
• 是否由於管制經辨識之風險的結果，而導入新的風險？	• Are new risks introduced as a result of the identified risks being controlled?
28. 當品質風險超過規定的（可接受的）水準時，***風險減低***將焦點放在減輕或避免品質風險的過程上（參見流程圖 1）。「風險減低」可能包括為減輕損害之嚴重度及機率所採取的行動。提高危害及品質風險之可檢測性的過程，亦可做為風險管制策略的一部分。風險減低措施之實施可能將新的風險導入系統中，或增加其他既有風險的嚴重性。因此，在實施風險減低過程後，應重新檢視風險評價，以確認及評估風險之任何可能的變更。	28. ***Risk reduction*** focuses on processes for mitigation or avoidance of quality risk when it exceeds a specified (acceptable) level (see Fig. 1). Risk reduction might include actions taken to mitigate the severity and probability of harm. Processes that improve the detectability of hazards and quality risks might also be used as part of a risk control strategy. The implementation of risk reduction measures can introduce new risks into the system or increase the significance of other existing risks. Hence, it might be appropriate to revisit the risk assessment to identify and evaluate any possible change in risk after implementing a risk reduction process.
29. ***風險接受***是對接受風險的一個決定。風險的接受可能是正式決定接受殘留風險，或可能是被動接受非特定殘留風險之決定。對於某些類型的損害，即使施行最好的品質風險管理，也不能完全消除風險。在這些情況中，可能同意其已經應用一個適當品質風險管理策略，且將品質風險降低至	29. ***Risk acceptance*** is a decision to accept risk. Risk acceptance can be a formal decision to accept the residual risk or it can be a passive decision in which residual risks are not specified. For some types of harms, even the best quality risk management practices might not entirely eliminate risk. In these

一個規定的（可接受的）水準。這個（規定的）可接受的水準受到多個參數影響，且應由不同個案之基礎決定之。	circumstances, it might be agreed that an appropriate quality risk management strategy has been applied and that quality risk is reduced to a specified (acceptable) level. This (specified) acceptable level will depend on many parameters and should be decided on a case-by-case basis.
風險溝通（Risk Communication）	
30. ***風險溝通***是在決策者與其他人員間關於風險及風險管理資訊的分享。各方都可以在風險管理過程的任何階段進行溝通（參見流程圖1：虛線箭頭）。品質風險管理過程之產出/結果應適當地溝通並且加以文件化（參見流程圖1：實線箭頭）。溝通可能包括那些有利害關係之各方間的溝通，例如主管機關與業者、業者與病人、在公司內、業界或主管機關內部等。所包含之資訊可能關於品質之風險的存在、性質、型式、機率、嚴重性、接受性、管制、處理、可檢測性或其它層面。不必就每一個風險的接受進行溝通。在業者與主管機關間，關於品質風險管理決策的溝通，可以透過法規及指引規範之既有管道進行。	30. ***Risk communication*** is the sharing of information about risk and risk management between the decision makers and others. Parties can communicate at any stage of the risk management process (see Fig. 1: dashed arrows). The output/result of the quality risk management process should be appropriately communicated and documented (see Fig. 1: solid arrows). Communications might include those among interested parties; e.g., regulators and industry, industry and the patient, within a company, industry or regulatory authority, etc. The included information might relate to the existence, nature, form, probability, severity, acceptability, control, treatment, detectability or other aspects of risks to quality. Communication need not be carried out for each and every risk acceptance. Between the industry and regulatory authorities, communication concerning quality risk management decisions might be effected through existing channels as specified in regulations and guidances.
風險檢討（Risk Review）	
31. 風險管理應是品質管理過程中持續進行的部分。檢討或監測事件的機制應予實施。	31. Risk management should be an ongoing part of the quality management process. A mechanism to review or monitor events should be implemented.
32. 風險管理過程的產出/結果應檢討並考慮採用新的知識及經驗。一旦啟動一個品質風險管理過程，則該過程應持續應用於可能衝擊原來品質風險管理決策之事件，不論是計畫性的(例如產品檢討、檢查、稽核、變更管制等之結果)或非計畫性的(例如調查失敗的根本原因、回收)，皆應繼續	32. The output/results of the risk management process should be reviewed to take into account new knowledge and experience. Once a quality risk management process has been initiated, that process should continue to be utilized for events that might impact the original quality risk management decision,

利用該過程。任何檢討的頻率應以風險之水準/程度為基礎。風險的檢討可能包含風險之接受決策的重新考慮(第 4.4 節)。	whether these events are planned (e.g. results of product review, inspections, audits, change control) or unplanned (e.g. root cause from failure investigations, recall). The frequency of any review should be based upon the level of risk. Risk review might include reconsideration of risk acceptance decisions (section 4.4).
風險管理方法 （RISK MANAGEMENT METHODOLOGY）	
33. 品質風險管理係支持以科學的及實用的方法制定決策。藉由現行關於評價風險之機率、嚴重性及有時是檢測性之知識，提供文件化、透明且可再現的方法，以完成品質風險管理過程的步驟。	33. Quality risk management supports a scientific and practical approach to decision-making. It provides documented, transparent and reproducible methods to accomplish steps of the quality risk management process based on current knowledge about assessing the probability, severity and sometimes detectability of the risk.
34. 傳統上，對品質之風險，會以各種非正式的方式（經驗的及/或內部的程序），譬如觀察、趨勢及其他資訊的彙集為基礎加以評價及管理。該等方法可持續提供有用的資訊，而這些資訊可支持諸如申訴、品質缺陷、偏離及資源配置之處理的主題。	34. Traditionally, risks to quality have been assessed and managed in a variety of informal ways (empirical and/ or internal procedures) based on, for example, compilation of observations, trends and other information. Such approaches continue to provide useful information that might support topics such as handling of complaints, quality defects, deviations and allocation of resources.
35. 此外，製藥產業及主管機關可使用經公認之風險管理工具及/或內部程序（例如，標準作業程序）評價及管理風險。下述內容為這些工具當中的一些非詳細周全的清單（附則 1 與第 8 章提供進一步的細節）。	35. Additionally, the pharmaceutical industry and regulators can assess and manage risk using recognized risk management tools and/ or internal procedures (e.g., standard operating procedures). Below is a non-exhaustive list of some of these tools (further details in Annex 1 and chapter 8):
• 基本風險管理簡易方法（流程表、檢查單等）；	• Basic risk management facilitation methods (flowcharts, check sheets etc.)
• 失敗模式效應分析(FMEA)；	• Failure Mode Effects Analysis (FMEA)
• 失敗模式效應及關鍵性分析(FMECA)；	• Failure Mode, Effects and Criticality Analysis (FMECA)
• 缺失之樹狀分析(FTA)；	• Fault Tree Analysis (FTA)
• 危害分析及關鍵管制點(HACCP)；	• Hazard Analysis and Critical Control Points (HACCP)
• 危害操作性分析(HAZOP)；	• Hazard Operability Analysis (HAZOP)

• 事先危害分析(PHA)；	• Preliminary Hazard Analysis (PHA)
• 風險分級及篩選；	• Risk ranking and filtering
• 輔助性統計工具。	• Supporting statistical tools
36. 在原料藥及醫藥品品質相關之特定領域運用這些工具可能是適當的。品質風險管理方法及輔助性統計工具可合併使用(例如機率性的風險評價)。合併使用提供可促進靈活的應用品質風險管理原則。	36. It might be appropriate to adapt these tools for use in specific areas pertaining to drug substance and drug (medicinal) product quality. Quality risk management methods and the supporting statistical tools can be used in combination (e.g. Probabilistic Risk Assessment). Combined use provides flexibility that can facilitate the application of quality risk management principles.
37. 品質風險管理之嚴格性及正式性的程度應反映可利用的知識，並應與所要論述之問題的複雜性，及/或關鍵性相當。	37. The degree of rigor and formality of quality risk management should reflect available knowledge and be commensurate with the complexity and/ or criticality of the issue to be addressed.
品質風險管理整合於產業及管制運作中 （INTEGRATION OF QUALITY RISK MANAGEMENT INTO INDUSTRY AND REGULATORY OPERATIONS）	
38. 當品質風險管理整合入品質系統中時，品質風險管理是一個支持基於科學及實用之決策的過程(參見附件 II)。如同在前言中所概述，品質風險管理的適當使用並不免除業者需遵從主管機關要求的義務。然而，有效的品質風險管理可以促成更好及更明智的決策，可以就一個公司處理潛在風險之能力對主管機關提供更大的保證，以及可能影響直接管制監督的範圍及程度。此外，品質風險管理還可促使各方更好的使用資源。	38. Quality risk management is a process that supports science-based and practical decisions when integrated into quality systems (see Annex II). As outlined in the introduction, appropriate use of quality risk management does not obviate industry's obligation to comply with regulatory requirements. However, effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks, and might affect the extent and level of direct regulatory oversight. In addition, quality risk management can facilitate better use of resources by all parties.
39. 業者及法規人員在品質風險管理過程上之訓練，提供對制定決策過程更多的瞭解，並建立對品質風險管理結果的信心。	39. Training of both industry and regulatory personnel in quality risk management processes provides for greater understanding of decision-making processes and builds confidence in quality risk management outcomes.
40. 品質風險管理應整合入既有操作中，並適當地文件化。附件 II 提供情況範例。在其	40. Quality risk management should be integrated into existing operations and

中，品質風險管理過程之使用可能提供以後在各種製藥操作，用得上的資訊。 這些範例只是為說明之目的而提供，不得將之視為一個最終的或詳細周全的清單。這些實例無意在現行法規明訂之要求外，創造任何新的期待。	documented appropriately. Annex II provides examples of situations in which the use of the quality risk management process might provide information that could then be used in a variety of pharmaceutical operations. These examples are provided for illustrative purposes only and should not be considered a definitive or exhaustive list. These examples are not intended to create any new expectations beyond the requirements laid out in the current regulations.
41. 業界及法規作業之範例（參見附件 II）：	41.Examples for industry and regulatory operations (see Annex II):
• 品質管理	• Quality management
42. 產業作業及活動範例（參見附件 II）：	42.Examples for industry operations and activities (see Annex II):
• 開發；	• Development
• 設施、設備及公用設施；	• Facility, equipment and utilities
• 物料管理；	• Materials management
• 生產；	• Production
• 實驗室管制及安定性試驗；	• Laboratory control and stability testing
• 包裝及標示。	• Packaging and labeling
43. 法規作業的範例（參見附件 II）：	43.Examples for regulatory operations (see Annex II):
• 檢查及評價活動	• Inspection and assessment activities
44. 雖然法規決策將持續在一個區域性的基礎上為之，但品質風險管理原則之普遍瞭解及應用可增進相互的信心，並在相同資訊的基礎上提升管制者間更為一致的決策。該協力合作，在整合及支持品質風險管理實務之政策及準則的發展上可能是重要的。	44. While regulatory decisions will continue to be taken on a regional basis, a common understanding and application of quality risk management principles could facilitate mutual confidence and promote more consistent decisions among regulators on the basis of the same information. This collaboration could be important in the development of policies and guidelines that integrate and support quality risk management practices.
定義（DEFINITIONS）	
決策者 具有資格及權能去做出適當且適時之品質風險管理決策的人。	Decision maker(s) – Person(s) with the competence and authority to make appropriate and timely quality risk management decisions

可檢測性 發現或確定一個危害之存在、出現或事實的能力。	Detectability -the ability to discover or determine the existence, presence, or fact of a hazard
傷害 對健康的損害，包含因產品品質或有效性之減失而導致的損害在內。	Harm –damage to health, including the damage that can occur from loss of product quality or availability
危害 傷害的潛在來源 (ISO/IEC Guide 51)。	Hazard - the potential source of harm (ISO/IEC Guide 51)
產品生命週期 產品從初始開發，經過上市直到產品終止之生命的全部階段。	Product Lifecycle –all phases in the life of the product from the initial development through marketing until the product's discontinuation
品質 一個產品、系統或製程之一組固有性質符合要求的程度（參見 ICH Q6A 針對藥物原料和藥物產品之 “品質” 的定義）。	Quality –the degree to which a set of inherent properties of a product, system or process fulfills requirements (see ICH Q6a definition specifically for "quality" of drug substance and drug (medicinal) products.)
品質風險管理 對藥品跨越產品生命週期之品質的風險為評價、管制、溝通及檢討之一個系統性的過程。	Quality risk management –a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle
品質系統 一個系統之全部層面的總和，用以實施品質政策並確保符合品質目標。	Quality system –the sum of all aspects of a system that implements quality policy and ensures that quality objectives are met
要求 病人或其代理人【例如，健康照護專業人員、主管機關及立法者】之明示或暗示的需求或期待。在本文件中，“要求” 不但指稱法律、立法或管制的要求，而且亦指稱該等需求及期望。	Requirements –the explicit or implicit needs or expectations of the patients or their surrogates (e.g. health care professionals, regulators and legislators). In this document, “requirements” refers not only to statutory, legislative, or regulatory requirements, but also to such needs and expectations.
風險 傷害之發生的機率及該傷害之嚴重度的組合(ISO/IEC Guide 51)。	Risk –the combination of the probability of occurrence of harm and the severity of that harm (ISO/IEC Guide 51)
風險接受 接受風險的決策(ISO Guide 73)。	Risk acceptance –the decision to accept risk (ISO Guide 73)
風險分析 與業經確認之危害所關聯的風險之估計。	Risk analysis –the estimation of the risk associated with the identified hazards

風險評價 一個組織資訊之系統性過程，用以支持在風險管理過程中做出的風險決策。這包含危害之確認及與暴露於該等危害有關之風險的分析及評估。	Risk assessment –a systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.
風險溝通 在決策者與其他利害關係人間，關於風險及風險管理之資訊的分享。	Risk communication –the sharing of information about risk and risk management between the decision maker and other stakeholders
風險管制 執行風險管理決策的行動(ISO Guide 73)。	Risk control –actions implementing risk management decisions (ISO Guide 73)
風險評估 使用定量或定性尺度，比較估計之風險與已知之風險基準，以決定風險的重要性。	Risk evaluation –the comparison of the estimated risk to given risk criteria using a quantitative or qualitative scale to determine the significance of the risk
風險確認 資訊之系統性使用，以藉由風險疑問或問題描述能確認傷害(危害)之潛在來源。	Risk identification –the systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description
風險管理 將品質管理政策、程序和實務系統性的應用於評價、管制、溝通及檢討風險的工作。	Risk management –the systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating and reviewing risk
風險減低 為減少傷害之發生機率及該傷害之嚴重度所採取的行動。	Risk reduction –actions taken to lessen the probability of occurrence of harm and the severity of that harm
風險檢討 考慮（如合適時）關於風險之新知識及經驗，以檢討或監測風險管理過程的產出/結果。	Risk review –review or monitoring of output/results of the risk management process considering (if appropriate) new knowledge and experience about the risk
嚴重度 衡量危害之可能後果。	Severity –a measure of the possible consequences of a hazard
利害關係人 可能影響或受風險影響，或感受其本身受風險影響之任何個人、團體或組織。決策者可能也是利害關係人。為本準則之目的，主要利害關係人是病人、健康照護專業人員、主管機關及業界。	Stakeholder –any individual, group or organization that can affect, be affected by, or perceive itself to be affected by a risk. Decision makers might also be stakeholders. For the purposes of this guideline, the primary stakeholders are the patient, healthcare professional, regulatory authority, and industry
趨勢	Trend –a statistical term referring to the

指出一個變數之改變方向或比率的統計學術語。	direction or rate of change of a variable(s)

8. 參考文獻 （References）

ICH Q8 Pharmaceutical Development. ISO/IEC Guide 73:2002 - Risk Management - Vocabulary - Guidelines for use in Standards.
ISO/IEC Guide 51:1999 - Safety Aspects - Guideline for their inclusion in standards.
Process Mapping by the American Productivity & Quality Center, 2002, ISBN 1928593739.
IEC 61025 - Fault Tree Analysis (FTA).
IEC 60812 Analysis Techniques for system reliability—Procedures for failure mode and effects analysis (FMEA).
Failure Mode and Effect Analysis, FMEA from Theory to Execution, 2nd Edition 2003, D. H. Stamatis, ISBN 0873895983.
Guidelines for Failure Modes and Effects Analysis (FMEA) for Medical Devices, 2003 Dyadem Press, ISBN 0849319102.
The Basics of FMEA, Robin McDermott, Raymond J. Mikulak, Michael R. Beauregard 1996, ISBN 0527763209.
WHO Technical Report Series No 908, 2003, Annex 7 Application of Hazard Analysis and Critical Control Point (HACCP) methodology to pharmaceuticals.
IEC 61882 - Hazard Operability Analysis (HAZOP).
ISO 14971:2000 - Application of Risk Management to Medical Devices.
ISO 7870:1993 - Control Charts.
ISO 7871:1997 - Cumulative Sum Charts.
ISO 7966:1993 - Acceptance Control Charts.
ISO 8258:1991 - Shewhart Control Charts.
What is Total Quality Control?; The Japanese Way, Kaoru Ishikawa (Translated by David J. Liu), 1985, ISBN 0139524339.

附件I：風險管理方法和工具 （Appendix I: Risk Management Methods and Tools）

本附件之目的在於就可能被業界及主管機關使用於品質風險管理之一些主要工具，提供其一般的概觀及參考資料。這些參考資料是為幫助取得關於特定工具之更多知識及細節而納入。這不是一個詳細周全的清單。重點是沒有任何一件或一套工具可適用於品質風險管理程序之每一種情況。	The purpose of this appendix is to provide a general overview of and references for some of the primary tools that might be used in quality risk management by industry and regulators. The references are included as an aid to gain more knowledge and detail about the particular tool. This is not an exhaustive list. It is important to note that no one tool or set of tools is applicable to every situation in which a quality risk management procedure is used.

I.1 基本風險管理之簡易方法 （Basic Risk Management Facilitation Methods）

一些藉由組織數據及促進決策之制定，以普遍用來建構風險管理之簡單技術是：	Some of the simple techniques that are commonly used to structure risk management by organizing data and facilitating

	decision-making are:
• 流程圖；	• Flowcharts
• 檢查單；	• Check Sheets
• 過程圖示；	• Process Mapping
• 原因和效應圖表（亦稱為石川圖或魚骨圖）。	• Cause and Effect Diagrams (also called an Ishikawa diagram or fish bone diagram)
I.2 失敗模式效應分析 （Failure Mode Effects Analysis (FMEA)）	
FMEA (參見 IEC 60812) 係就程序及其對結果及/或產品性能之可能的效應，提供潛在失敗模式的評估。失敗模式一旦建立，風險減低便可用以排除、圍堵、減少或控制該潛在失敗。FMEA 倚賴對產品及製程的瞭解。FMEA 在方法上將複雜程序的分析分解成可管理的步驟。對於總結失敗之重要模式、引起這些失敗的因素及這些失敗之可能效應，這是一個強而有力的工具。	FMEA (see IEC 60812) provides for an evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance. Once failure modes are established, risk reduction can be used to eliminate, contain, reduce or control the potential failures. FMEA relies on product and process understanding. FMEA methodically breaks down the analysis of complex processes into manageable steps. It is a powerful tool for summarizing the important modes of failure, factors causing these failures and the likely effects of these failures.
潛在的使用領域 （Potential **Areas of Use(s)**）	
FMEA 可用於安排風險優先順序及監測風險管制活動的效果。	FMEA can be used to prioritize risks and monitor the effectiveness of risk control activities.
FMEA 可應用於設備及設施，及可用於分析製造作業及其對產品或製程的影響。這可辨識使系統脆弱之因素/操作。FMEA 之產出/結果可用為設計或進一步分析或指引資源配置的基礎。	FMEA can be applied to equipment and facilities and might be used to analyze a manufacturing operation and its effect on product or process. It identifies elements/operations within the system that render it vulnerable. The output/ results of FMEA can be used as a basis for design or further analysis or to guide resource deployment.
I.3失敗模式，效應及關鍵性分析（Failure Mode Effects and Criticality Analysis，FMECA）	

FMEA 可加以延伸，納入結果之嚴重程度的調查、其個別之發生機率，以及其檢測性，轉變為失敗模式，效應及關鍵性分析（FMECA；參見 IEC 60812）。為執行這樣的分析，應建立產品或製程規格。	FMEA might be extended to incorporate an investigation of the degree of severity of the consequences, their respective probabilities of occurrence, and their detectability, thereby becoming a Failure Mode Effect and Criticality Analysis (FMECA; see IEC 60812). In order for such an analysis to be performed, the product or process specifications should be established.
FMECA 能確認在何處追加預防措施，可能將風險減至最低。	FMECA can identify places where additional preventive actions might be appropriate to minimize risks.
潛在的使用領域（Potential **Areas of Use(s)**）	
FMECA 在製藥產業之應用，應主要用於與製造過程有關之失敗及風險；然而，並不侷限於該應用。FMECA 之結果是每一失敗模式之相對風險"分數"。該分數在相對風險的基礎上，將這些模式分級。	FMECA application in the pharmaceutical industry should mostly be utilized for failures and risks associated with manufacturing processes; however, it is not limited to this application. The output of an FMECA is a relative risk “score” for each failure mode, which is used to rank the modes on a relative risk basis.
I.4 缺失之樹狀分析 （Fault Tree Analysis，FTA）	
FTA 工具(參見 IEC 61025)是假定一個產品或製程有功能性失效之方法。這個工具每次只評估造成系統(或子系統)失效的一個原因，但可將失效之數個原因以確認其為原因鏈的方式組合在一起。該結果以缺失模式樹的形式圖示之。在該模式樹中的每一層級，其缺失模式間的關連以邏輯運算符號（"及"、"或"等）描述之。FTA 有賴於專家對製程的瞭解，以確認原因的因素。	The FTA tool (see IEC 61025) is an approach that assumes failure of the functionality of a product or process. This tool evaluates system (or subsystem) failures one at a time but can combine multiple causes of failure by identifying causal chains. The results are represented pictorially in the form of a tree of fault modes. At each level in the tree, combinations of fault modes are described with logical operators (AND, OR, etc.). FTA relies on the experts’ process understanding to identify causal factors.
潛在的使用領域 （Potential Areas of Use(s)）	

FTA 得用於建立導致失敗之根本原因的路徑。FTA 得用來調查申訴或偏離，以完全瞭解其根本原因，並確保其預定的改善將會完全解決該問題，而不會引起其他問題（亦即，解決了一個問題卻又引起另一個不同的問題）。缺失之樹狀分析是評估多重因素對於一個已知問題影響的有效工具。FTA 之產出包含可見的失敗模式描述。這對於風險評價及監測計畫的開發都有助益。	FTA can be used to establish the pathway to the root cause of the failure. FTA can be used to investigate complaints or deviations in order to fully understand their root cause and to ensure that intended improvements will fully resolve the issue and not lead to other issues (i.e. solve one problem yet cause a different problem). Fault Tree Analysis is an effective tool for evaluating how multiple factors affect a given issue. The output of an FTA includes a visual representation of failure modes. It is useful both for risk assessment and in developing monitoring programs.
I.5 危害分析及關鍵管制點 （Hazard Analysis and Critical Control Points，HACCP）	
HACCP 是為確保產品品質、可靠性及安全性之系統性、積極性及預防性的工具(參見 WHO Technical Report Series No 908, 2003 Annex 7)。這是一個結構化的方法。該方法應用技術和科學的原理，分析、評估、預防及管制由產品之設計、開發、生產及使用的危害所產生之風險或不良後果。	HACCP is a systematic, proactive, and preventive tool for assuring product quality, reliability, and safety (see WHO Technical Report Series No 908, 2003 Annex 7). It is a structured approach that applies technical and scientific principles to analyze, evaluate, prevent, and control the risk or adverse consequence(s) of hazard(s) due to the design, development, production, and use of products.
HACCP 包含下列 7 個步驟：	HACCP consists of the following seven steps:
(1) 對製程的每一個步驟執行危害分析，並確認其預防措施；	(1) conduct a hazard analysis and identify preventive measures for each step of the process;
(2) 決定關鍵管制點；	(2) determine the critical control points;
(3) 建立關鍵限量；	(3) establish critical limits;
(4) 建立一個監測關鍵管制點的系統；	(4) establish a system to monitor the critical control points;
(5) 建立當監測出關鍵管制點不在管制狀態時，應採取的矯正措施；	(5) establish the corrective action to be taken when monitoring indicates that the critical control points are not in a state of control;
(6) 建立系統，證實 HACCP 系統在有效運作中；	(6) establish system to verify that the HACCP system is working effectively;
(7) 建立一個保存紀錄之系統。	(7) establish a record-keeping system.
潛在的使用領域（Potential Areas of Use(s)）	

HACCP 可能用於確認和管理與物理學、化學及生物學上之危害(包括微生物學上的污染) 相關聯的風險。當對產品及製程之瞭解足夠廣泛，以支持關鍵管制點的確認時，則 HACCP 最為有用。HACCP 分析的產出是風險管理資訊。不僅在製造過程上，且亦在其他生命週期的階段中，該資訊皆有助於關鍵管制點的監測。	HACCP might be used to identify and manage risks associated with physical, chemical and biological hazards (including microbiological contamination). HACCP is most useful when product and process understanding is sufficiently comprehensive to support identification of critical control points. The output of a HACCP analysis is risk management information that facilitates monitoring of critical points not only in the manufacturing process but also in other life cycle phases.
I.6 危害操作性分析 （Hazard Operability Analysis，HAZOP）	
HAZOP（參見 IEC 61882）係以假定風險事件是由於偏離設計或作業目的而引起之理論為基礎。這是一個系統性腦力激盪技術。該技術利用所謂"指引字語"來確認危害。"指引字語"（例如，"無"、"更多"、"異於"、"部分"等）應用於相關的參數（例如，污染、溫度）上，以幫助確認離開正常使用或設計目的之潛在偏離。這常常使用一組人員組成之團隊。這些人員具有涵蓋該製程或產品之設計及其應用的專門知識。	HAZOP (see IEC 61882) is based on a theory that assumes that risk events are caused by deviations from the design or operating intentions. It is a systematic brainstorming technique for identifying hazards using so-called “guide-words”. “Guide-words” (e.g., No, More, Other Than, Part of, etc.) are applied to relevant parameters (e.g., contamination, temperature) to help identify potential deviations from normal use or design intentions. It often uses a team of people with expertise covering the design of the process or product and its application.
潛在的使用領域（Potential Areas of Use(s)）	
HAZOP 可適用於原料及藥品之製造過程，包括委外生產與配方及上游供應商、設備和設施。這亦已使用於製藥工業，主要以評估製程安全性的危害。類似於 HACCP 之情況，HAZOP 分析之產出是一個對風險管理之關鍵作業的清單。這有助於製造過程中之關鍵點的定期監測。	HAZOP can be applied to manufacturing processes, including outsourced production and formulation as well as the upstream suppliers, equipment and facilities for drug substances and drug (medicinal) products. It has also been used primarily in the pharmaceutical industry for evaluating process safety hazards. As is the case with HACCP, the output of a HAZOP analysis is a list of critical operations for risk management. This facilitates regular monitoring of critical points in the manufacturing process.
I.7 事先危害分析 （Preliminary Hazard Analysis，PHA）	

PHA 是一個分析工具，該工具應用先前關於一個危害或失效之經驗或知識為基礎，以確認將來可能引起損害之危害、危害狀況及事件，並預測其在一定的活動、設施、產品或系統之發生機率。其工具包含：	PHA is a tool of analysis based on applying prior experience or knowledge of a hazard or failure to identify future hazards, hazardous situations and events that might cause harm, as well as to estimate their probability of occurrence for a given activity, facility, product or system. The tool consists of:
1) 確認風險事件發生的可能性，	1) the identification of the possibilities that the risk event happens,
2) 對健康可能造成之傷害或損害程度的定性評估，	2) the qualitative evaluation of the extent of possible injury or damage to health that could result and
3) 利用綜合事件之嚴重性及可能性將危害相對分級，以及	3) a relative ranking of the hazard using a combination of severity and likelihood of occurrence, and
4) 確認可能之改善措施。	4) the identification of possible remedial measures
潛在的使用領域（Potential Areas of Use(s)）	
當情況不允許使用一個更廣泛技術，則在分析既有系統或危害之優先順序時， PHA 可能是很有用的。這可用於產品、製程及設施之設計，亦可評估一般產品類型、次為產品分類及後為特殊產品之危害。PHA 是最普遍使用於一個計畫之開發的初期。那時候關於細部設計或作業程序都只有很少的資訊。因此，這常常會是進一步研究的一個前導。典型地，在 PHA 中確認之危害，將與像在本節中規定之其他風險管理工具一起，進一步加以評價。	PHA might be useful when analyzing existing systems or prioritizing hazards where circumstances prevent a more extensive technique from being used. It can be used for product, process and facility design as well as to evaluate the types of hazards for the general product type, then the product class, and finally the specific product. PHA is most commonly used early in the development of a project when there is little information on design details or operating procedures; thus, it will often be a precursor to further studies. Typically, hazards identified in the PHA are further assessed with other risk management tools such as those in this section.
I.8 風險分級及篩選（Risk Ranking and Filtering）	
風險分級及篩選是將風險比較與分級的工具。複雜系統之風險分級典型地需要對每一風險之多樣的定量和定性因素加以評估。這個工具包含視需要，將一個基本風險問題分解成許多構成要素，以捕捉在此風險中所涉及之因素。這些因素結合成一個單一的相對風險分數，而後可用以將風險分級。“篩選器”是以對風險分數進行加權或減去的形式存在，可用為將風險分級改變尺度或使風險分級合適於管理或政策	Risk ranking and filtering is a tool for comparing and ranking risks. Risk ranking of complex systems typically requires evaluation of multiple diverse quantitative and qualitative factors for each risk. The tool involves breaking down a basic risk question into as many components as needed to capture factors involved in the risk. These factors are combined into a single relative risk score that can then be used for ranking risks.

目標。	"Filters," in the form of weighting factors or cut-offs for risk scores, can be used to scale or fit the risk ranking to management or policy objectives.
潛在的使用領域（Potential Areas of Use(s)）	
風險分級及過濾可用於將製造場所排定優先順序，以供主管機關或工業界檢查/稽核。於風險組合與其需被管理的潛在後果之多樣化，且難以使用單一工具進行比較的情況時，風險分級方法尤其有效。當管理上需要在相同組織架構內，評估定量及定性評價之風險時，風險分級是有用的。	Risk ranking and filtering can be used to prioritize manufacturing sites for inspection/audit by regulators or industry. Risk ranking methods are particularly helpful in situations in which the portfolio of risks and the underlying consequences to be managed are diverse and difficult to compare using a single tool. Risk ranking is useful when management needs to evaluate both quantitatively-assessed and qualitatively-assessed risks within the same organizational framework.
I.9 輔助性統計工具 （Supporting Statistical Tools）	
統計工具可支持及促進品質風險管理。它們可進行有效的數據評價，幫助決定數據套組的重要性，並促成更可靠的決策。下面提供在製藥工業普遍使用之一些主要的統計工具清單：	Statistical tools can support and facilitate quality risk management. They can enable effective data assessment, aid in determining the significance of the data set(s), and facilitate more reliable decision making. A listing of some of the principal statistical tools commonly used in the pharmaceutical industry is provided:
(i) 管制圖，例如：	(i) Control Charts, for example:
- 允收管制圖 (參見 ISO 7966)；	-Acceptance Control Charts (see ISO 7966)
- 具有算術平均值和警告限量的管制圖 (參見 ISO 7873)；	-Control Charts with Arithmetic Average and Warning Limits (see ISO 7873)
- 累積總和圖 (ISO 7871);	-Cumulative Sum Charts (see ISO 7871)
- Shewhart 管制圖(參見 ISO 8258)；	-Shewhart Control Charts (see ISO 8258)
- 加權移動平均。	-Weighted Moving Average
(ii) 實驗設計（DOE）；	(ii) Design of Experiments (DOE)
(iii)直方圖；	(iii) Histograms
(iv) Pareto 圖；	(iv) Pareto Charts
(v) 製程能力分析。	(v) Process Capability Analysis

附件II：品質風險管理的可能應用 （Appendix II: Potential Applications for Quality Risk Management）	
本附件意在確認產業界及主管機構可能運用之品質風險管理的原則及工具。然而，特定風險管理工具之選擇完全取決於特定事實及情況。這些案例係為說明之目的而提供，並且只是建議可能運用之品質風險管理。本附件無意在超過現行法規之要求，創設任何新的期待。	This Appendix is intended to identify potential uses of quality risk management principles and tools by industry and regulators. However, the selection of particular risk management tools is completely dependent upon specific facts and circumstances. These examples are provided for illustrative purposes and only suggest potential uses of quality risk management. This Annex is not intended to create any new expectations beyond the current regulatory requirements.
II.1品質風險管理當作完整品質管理的一部分 （Quality Risk Management as Part of Integrated Quality Management）	
文件（Documentation）	
檢討對現行法規所期望的解釋與應用。	To review current interpretations and application of regulatory expectations
決定標準作業程序、準則等之需要性及/或開發其內容。	To determine the desirability of and/or develop the content for SOPs, guidelines, etc.
訓練與教育 （Training and education）	
以人員之教育、經驗及工作習慣，以及以先前訓練之定期評價(例如，其成效)為基礎，決定職前及/或持續訓練的適當性。	To determine the appropriateness of initial and/or ongoing training sessions based on education, experience and working habits of staff, as well as on a periodic assessment of previous training (e.g., its effectiveness)
確認使人員可靠地執行作業且對產品品質無不良衝擊所需的訓練、經驗、資格檢定及體能。	To identify the training, experience, qualifications and physical abilities that allow personnel to perform an operation reliably and with no adverse impact on the quality of the product
品質缺陷 （Quality defects）	
提供基礎，以辨識、評估及溝通可疑的品質缺陷、申訴、趨勢、偏離、調查、偏離規格結果等之潛在的品質影響。	To provide the basis for identifying, evaluating, and communicating the potential quality impact of a suspected quality defect, complaint, trend, deviation, investigation, out of specification result, etc.
促進風險之溝通及決定適當的行動，並會同主管機關處理重大的產品缺陷(例如，回收)。	To facilitate risk communications and determine appropriate action to address significant product defects, in conjunction with regulatory authorities (e.g., recall)
稽核/檢查 （Auditing/Inspection）	

界定內部與外部稽核的頻率及範圍，考慮諸如以下的因素：	To define the frequency and scope of audits, both internal and external, taking into account factors such as:
• 既有之法定要求；	• Existing legal requirements
• 公司或設施之整體狀態和歷史；	• Overall compliance status and history of the company or facility
• 公司之品質風險管理措施的健全性；	• Robustness of a company's quality risk management activities
• 場所之複雜性；	• Complexity of the site
• 製造過程之複雜性；	• Complexity of the manufacturing process
• 產品之複雜性及其治療上的重要性；	• Complexity of the product and its therapeutic significance
• 品質缺陷之次數及重要性(例如，回收)；	• Number and significance of quality defects (e.g, recall)
• 先前稽核/檢查之結果；	• Results of previous audits/inspections
• 建築物、設備、製程、關鍵人員之重大變更；	• Major changes of building, equipment, processes, key personnel
• 製造產品之經驗(例如頻率、數量、批數)；	• Experience with manufacturing of a product (e.g. frequency, volume, number of batches)
• 官方管制實驗室之檢驗結果。	• Test results of official control laboratories
定期檢討 （Periodic review）	
在產品品質檢討之內，選擇、評估及解釋數據之趨勢結果；	To select, evaluate and interpret trend results of data within the product quality review
解釋監測數據（例如支持再確效或變更抽樣之適當性的評價）。	To interpret monitoring data (e.g., to support an assessment of the appropriateness of revalidation or changes in sampling)
變更管理/變更管制 （Change management / change control）	
變更之管理是基於在藥劑開發上及製造期間所累積之知識及資訊；	To manage changes based on knowledge and information accumulated in pharmaceutical development and during manufacturing
評估變更對最終產品之可用性/可得性的影響；	To evaluate the impact of the changes on the availability of the final product
評估設施、設備、原物料、製程之變更或技術移轉對產品品質之影響；	To evaluate the impact on product quality of changes to the facility, equipment, material, manufacturing process or technical transfers
決定在變更實施前之適當行動，例如追加之測試、（再）驗證、（再）確效或與管理機構之溝通。	To determine appropriate actions preceding the implementation of a change, e.g., additional testing, (re)qualification, (re)validation or communication with regulators
持續改善 （Continual improvement）	
促進製程在產品生命週期全程之持續改	To facilitate continual improvement in

善。	processes throughout the product lifecycle.
II.2品質風險管理作為受管理作業的一部分（Quality Risk Management as Part of Regulatory Operations）	
檢查及評價措施 （Inspection and assessment activities）	
協助資源配置，包含，例如檢查計畫及頻率，以及檢查和評價強度在內(參見"附件 II.1 的“稽核”段)；	To assist with resource allocation including, for example, inspection planning and frequency, and inspection and assessment intensity (see "Auditing" section in Annex II.1)
評估例如，品質缺陷、潛在回收及檢查結果之重要性；	To evaluate the significance of, for example, quality defects, potential recalls and inspectional findings
決定檢查後之後續措施的適當性及類型；	To determine the appropriateness and type of post-inspection regulatory follow-up
評估由業界提出之資訊，包含藥劑開發的資訊在內；	To evaluate information submitted by industry including pharmaceutical development information
評估所提出之變異或變更的影響；	To evaluate impact of proposed variations or changes
確認應在檢查者與評估者間溝通之風險，以幫助更佳瞭解風險將如何管制或已受管制【例如，參數放行、製程分析技術(PAT)】。	To identify risks which should be communicated between inspectors and assessors to facilitate better understanding of how risks can be or are controlled (e.g., parametric release, Process Analytical Technology (PAT)).
II.3品質風險管理作為開發的一部分 （Quality Risk Management as Part of Development）	
設計一個高品質產品及其製造過程，以一致地交付預定性能的產品（參見 ICH Q8）；	To design a quality product and its manufacturing process to consistently deliver the intended performance of the product (see ICH Q8)
提高涵蓋寬廣範圍之物料屬性(例如，粒子大小分佈、含水量、流動性質)之產品性能的知識、作業選項及製程參數；	To enhance knowledge of product performance over a wide range of material attributes (e.g. particle size distribution, moisture content, flow properties), processing options and process parameters
評估原料、溶劑、原料藥（API）起始物、原料藥（APIs）、賦形劑或包裝材料的關鍵屬性；	To assess the critical attributes of raw materials, solvents, Active Pharmaceutical Ingredient (API) starting materials, APIs, excipients, or packaging materials

建立適當的規格、確認關鍵製程參數，及建立製造管制(例如，使用得自藥劑開發研究的資料。該資料與品質屬性之臨床重要性及在操作期間管制其能力有關)；	To establish appropriate specifications, identify critical process parameters and establish manufacturing controls (e.g., using information from pharmaceutical development studies regarding the clinical significance of quality attributes and the ability to control them during processing)
減少品質屬性的變異性： • 降低產品及原物料的缺陷； • 降低製造的缺陷。	To decrease variability of quality attributes: • reduce product and material defects • reduce manufacturing defects
評估關於放大批量及技術移轉之進一步研究（例如，生體相等性、安定性）的需求：	To assess the need for additional studies (e.g., bioequivalence, stability) relating to scale up and technology transfer
使用“設計空間”的概念(參見 ICH Q8)。	To make use of the “design space” concept (see ICH Q8)
II.4 設施、設備和公用設施的品質風險管理 （Quality Risk Management for Facilities, Equipment and Utilities）	
設施/設備的設計 （Design of facility / equipment）	
當設計建築物及設施時，決定其適當的區域，例如：	To determine appropriate zones when designing buildings and facilities, e.g.,
• 物料及人員的動線；	• flow of material and personnel
• 使污染減至最低；	• minimize contamination
• 防蟲鼠措施；	• pest control measures
• 混雜的防止；	• prevention of mix-ups
• 開放設備相對於密閉設備；	• open versus closed equipment
• 潔淨室相對於隔離裝置技術；	• clean rooms versus isolator technologies
• 專用或隔離的設施/設備。	• dedicated or segregated facilities / equipment
對設備及容器，決定其適當接觸產品之材料(例如不銹鋼等級、墊圈、潤滑劑的選擇)；	To determine appropriate product contact materials for equipment and containers (e.g., selection of stainless steel grade, gaskets, lubricants)
決定適當之公用設施(例如，蒸汽、氣體、電源、壓縮空氣、加熱、通風及空調(HVAC)、水)；	To determine appropriate utilities (e.g., steam, gases, power source, compressed air, heating, ventilation and air conditioning (HVAC), water)
相關之設備，決定適當之預防性維護保養(例如必要之備用零件的清單)。	To determine appropriate preventive maintenance for associated equipment (e.g., inventory of necessary spare parts)
設施的衛生狀況 （Hygiene aspects in facilities）	

使產品免於受到環境之危害，包含化學、微生物學、物理學上的危害(例如，決定適當的服裝及更衣、衛生相關事項)；	To protect the product from environmental hazards, including chemical, microbiological, and physical hazards (e.g., determining appropriate clothing and gowning, hygiene concerns)
保護環境（例如人員及潛在的交叉污染）的免於受到與所製造之產品造成相關的危害。	To protect the environment (e.g., personnel, potential for cross-contamination) from hazards related to the product being manufactured
設施/設備/公用設施的驗證 （Qualification of facility/ equipment/utilities）	
決定設施、建築物、生產設備及/或實驗室儀器之驗證範圍及程度（包含適當的校正方法）。	To determine the scope and extent of qualification of facilities, buildings, and production equipment and/or laboratory instruments (including proper calibration methods)
設備的清潔及環境管制 （Cleaning of equipment and environmental control）	
以預定用途為基礎，區分影響及決策 (例如多重目的相對於單一目的，批次生產相對於連續生產)；	To differentiate efforts and decisions based on the intended use (e.g., multi- versus single-purpose, batch versus continuous production)
決定可接受的（規定的）清潔確效限量。	To determine acceptable (specified) cleaning validation limits
校正/預防性維護保養（Calibration/preventive maintenance）	
設定適當的校正及維護保養時程表。	To set appropriate calibration and maintenance schedules
電腦系統及電腦管制設備 （Computer systems and computer controlled equipment）	
選擇電腦硬體及軟體的設計(例如，模組的、故障耐受性)；	To select the design of computer hardware and software (e.g., modular, structured, fault tolerance)
決定確效的程度，例如，	To determine the extent of validation, e.g.,
• 關鍵性能參數的確認；	• identification of critical performance parameters
• 需求及設計的選擇；	• selection of the requirements and design
• 程式碼的回顧；	• code review
• 測試的程度及測試方法；	• the extent of testing and test methods
• 電子紀錄及簽章的可靠性。	• reliability of electronic records and signatures
II.5 品質風險管理作為原/物料管理的一部分（Quality Risk Management as Part of Materials Management）	
供應商及合約製造商（受委託製造者）的評價及評估 （Assessment and evaluation of suppliers and contract manufacturers）	

提供供應商及合約製造商（受委託製造者）一個廣泛的評估(例如稽核、供應商品質協議)。	To provide a comprehensive evaluation of suppliers and contract manufacturers (e.g., auditing, supplier quality agreements)
原料 （Starting material）	
評估與原料上之變異有關聯的差異及可能的品質風險（例如年齡、合成路徑）。	To assess differences and possible quality risks associated with variability in starting materials (e.g., age, route of synthesis).
原物料的使用 （Use of materials）	
決定使用待驗中的原物料是否適當(例如，為後續之廠內處理)；	To determine whether it is appropriate to use material under quarantine (e.g., for further internal processing)
決定退回物品之重製、再加工、使用的適當性。	To determine appropriateness of reprocessing, reworking, use of returned goods
儲存、物流和運銷條件 （Storage, logistics and distribution condition s）	
評估裝置之適當性，以確保適當儲存及輸送條件的維持(例如溫度、濕度、容器之設計)；	To assess the adequacy of arrangements to ensure maintenance of appropriate storage and transport conditions (e.g., temperature, humidity, container design)
結合其他 ICH 指引，決定在儲存或運輸條件上之差異對產品品質的影響【例如，冷鏈管理 (cold chain management)】；	To determine the effect on product quality of discrepancies in storage or transport conditions (e.g. cold chain management) in conjunction with other ICH guidelines
維護基礎設施（例如，確保正確裝運條件、暫時儲存、危害性原物料及受管制原物料之處理、海關報關/海關結關的能力）；	To maintain infrastructure (e.g. capacity to ensure proper shipping conditions, interim storage, handling of hazardous materials and controlled substances, customs clearance)
提供確保藥品之可得性的資訊（例如，供應鏈之風險分級）。	To provide information for ensuring the availability of pharmaceuticals (e.g., ranking risks to the supply chain).
II.6 品質風險管理作為生產的一部分 （Quality Risk Management as Part of Production）	
確效 （Validation）	
確認查證、驗證及確效措施之範圍及程度(例如分析方法、製程、設備及清潔方法)；	To identify the scope and extent of verification, qualification and validation activities (e.g., analytical methods, processes, equipment and cleaning methods
決定後續管理措施的程度(例如抽樣、監測及再確效)；	To determine the extent for follow-up activities (e.g., sampling, monitoring and re-validation)
區分關鍵性與非關鍵性製程步驟，以便於確效研究之設計。	To distinguish between critical and non-critical process steps to facilitate design of a validation study
製程中抽樣及測試 （In-process sampling & testing）	

評估製程中之管制測試的頻率及程度(例如證明在核准之管制條件下縮減測試的正當性)；	To evaluate the frequency and extent of in-process control testing (e.g., to justify reduced testing under conditions of proven control)
評估並證明結合參數放行及即時放行之製程分析技術（PAT）的使用之合理性。	To evaluate and justify the use of process analytical technologies (PAT) in conjunction with parametric and real time release
生產計畫 （Production planning）	
決定適當之生產計畫（例如，專用的、時段切換的及併行性的生產順序）。	To determine appropriate production planning (e.g., dedicated, campaign and concurrent production process sequences).
II.7 品質風險管理當作實驗室管制及安定性研究的一部分 （Quality Risk Management as Part of Laboratory Control and Stability Studies）	
偏離規格結果 （Out of specification results）	
在調查偏離規格結果期間中，用於確認可能的根本原因及矯正措施。	To identify potential root causes and corrective actions during the investigation of out of specification results
再驗期間/末效日期 （Retest period / expiration date）	
評估半製品/中間產物、賦形劑及原料之儲存與檢驗的適當性。	To evaluate adequacy of storage and testing of intermediates, excipients and starting materials
II.8 品質風險管理做為包裝與標示的一部分（Quality Risk Management as Part of Packaging and Labelling）	
包裝設計 （Design of packages）	
設計外包裝以保護經直接包材包裝的產品(例如確保產品之真實性、標示之易讀性)。	To design the secondary package for the protection of primary packaged product (e.g., to ensure product authenticity, label legibility)
容器封蓋系統的選擇 （Selection of container closure system）	
決定容器封蓋系統之關鍵性參數。	To determine the critical parameters of the container closure system
標籤管制 （Label controls）	
基於不同產品標籤可能產生混雜，包含相同標籤之不同版本在內，設計標籤之管制程序。	To design label control procedures based on the potential for mix-ups involving different product labels, including different versions of the same label

術語彙編（GLOSSARY）

下面所提供的定義適用於本準則所使用的語詞。在其他文件內容中，這些語詞可能會有不同的意義。	Definitions given below apply to the words as used in this Guide. They may have different meanings in other contexts.
行動限量 如果超過時，需要有立即的後續追蹤與矯正行動所建立的基準。	**Action limit** Established criteria, requiring immediate follow-up and corrective action if exceeded.
氣鎖室 具兩個或兩個以上之門的密閉空間，且是介於兩個或兩個以上不同潔淨度等級作業室之間，其目的是在需要進入這些作業室時，管制彼此間的氣流。此係為人員或貨物所設計的，並由人員或貨物所使用。	**Air lock** An enclosed space with two or more doors, and which is interposed between two or more rooms, e.g. of differing class of cleanliness, for the purpose of controlling the air-flow between those rooms when they need to be entered. An air-lock is designed for and used by either people or goods.
警戒限量 提供可能偏離正常條件之早期警告所建立的基準，其未必是決定性的矯正行動基礎，但需要有後續的追蹤調查。	**Alert limit** Established criteria giving early warning of potential drift from normal conditions which are not necessarily grounds for definitive corrective action but which require follow-up investigation.
被授權人 為被管理者所承認具有必需的基礎科學與技術背景以及經驗的人。	**Authorised person** Person recognised by the authority as having the necessary basic scientific and technical background and experience.
批/批次 經一個或一系列過程所處理過之界定數量的原料、包裝材料或產品，使其可被預期為均質的。	**Batch (or lot)** A defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous.

註：要完成製造的某些階段，可能需要把一批次分成幾個次批次，再將其合併在一起，以形成一個最終的均質批次。如為連續製造時，則該批次必須是具有表現其預期之均質性特徵所界定時間的生產量·	Note： To complete certain stages of manufacture, it may be necessary to divide a batch into a number of subbatches, which are later brought together to form a final homogeneous batch. In the case of continuous manufacture, the batch must correspond to a defined fraction of the production, characterised by its intended homogeneity.
對於最終產品的管制，一批藥品是包含由相同的原料之初始質量所製成的劑型之全部單元，且已經經歷一個單一系列的製造操作或一個單一的滅菌操作，如在連續生產操作時，則是在一定期間所製造的全部單元。	For the control of the finished product, a batch of a medicinal products comprises all the units of a pharmaceutical form which are made from the same initial mass of material and have undergone a single series of manufacturing operations or a single sterilisation operation or, in the case of a continuous production process, all the units manufactured in a given period of time.
批號 具有可區別的數字及/或文字之組合，可明確地辨識一個批次。	**Batch number (or lot number)** A distinctive combination of numbers and/or letters which specifically identifies a batch.
生物發生器 一種圍堵系統，例如醱酵槽，生物媒劑是隨其它物質導入其內，以便經由與其它物質反應引起它們的增殖或它們的其它物質之生產。通常，生物發生器是與調節、管制、連接、物料添加與物料收回的裝置套合。	**Biogenerator** A contained system, such as a fermenter, into which biological agents are introduced along with other materials so as to effect their multiplication or their production of other substances by reaction with the other materials. Biogenerators are generally fitted with devices for regulation, control, connection, material addition and material withdrawal.
生物媒介物 微生物（包括基因工程的微生物在內）、細胞培養以及胞內寄生物，不管是致病性的或是非致病性的。	**Biological agents** Microorganisms, including genetically engineered microorganisms, cell cultures and endoparasites, whether pathogenic or not.
待分/包裝產品 已完成所有製造階段，但不包含最終包裝之任何產品。	**Bulk product** Any product which has completed all processing stages up to, but not including, final packaging.

校正 在規定條件下，建立量測儀器或量測系統所指示數值，或物質量度器所代表數值，與其所對應對照標準的已知數值間之關係的一套操作·	**Calibration** The set of operations which establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by a material measure, and the corresponding known values of a reference standard.
細胞庫 ***細胞庫系統***：是指一個產品的連續批次所藉以製造的系統，其是經由在衍生自相同種細胞庫（充分鑑定特性且沒有污染存在）的細胞中培養所製造。使用來自種細胞庫的細胞，以製備工作細胞庫。這種細胞庫系統，應對超過其繼代數或例行生產期間所達成的細胞加倍之次數確效之。 ***主細胞庫***：經單次操作分裝到多個容器中的細胞（經充分鑑定特性），以確保其均質性的方式操作，並以確保其安定性的方式予以儲存。通常，種細胞庫是儲存在零下 70℃或更低。 ***工作細胞庫***：從種細胞庫所衍生的細胞，擬供生產用細胞的製備之用。通常，工作細胞庫是儲存在零下 70℃或更低。	**Cell bank** ***Cell bank system*:** A cell bank system is a system whereby successive batches of a product are manufactured by culture in cells derived from the same master cell bank (fully characterised for identity and absence of contamination). A number of containers from the master cell bank are used to prepare a working cell bank. The cell bank system is validated for a passage level or number of population doublings beyond that achieved during routine production ***Master cell bank*:** A culture of (fully characterised) cells distributed into containers in a single operation, processed together in such a manner as to ensure uniformity and stored in such a manner as to ensure stability. A master cell bank is usually stored at -70°C or lower. ***Working cell bank*:** A culture of cells derived from the master cell bank and intended for use in the preparation of production cell cultures. The working cell bank is usually stored at -70°C or lower.
細胞培養 自多細胞生物體所分離的細胞，於體外增殖的結果。	**Cell culture** The result from the in-vitro growth of cells isolated from multicellular organisms.

潔淨區 一個具有所界定的微粒與微生物污染管制之環境的區域，其是以減低這個區域之內污染物的導入、產生以及滯留的方式所建造與使用。	**Clean area** An area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area.
註：不同的環境管制的程度，是界定於附則 1 之無菌藥品的製造。	Note: The different degrees of environmental control are defined in the Supplementary Guidelines for the Manufacture of sterile medicinal products.
潔淨區/圍堵區 會同時達成潔淨區及圍堵區雙重目標所建造與運轉的區域。	**Clean/contained area** An area constructed and operated in such a manner that will achieve the aims of both a clean area and a contained area at the same time.
圍堵 把生物媒介物或其他實體侷限在所界定的空間之行動。 ***一級圍堵***：一種阻止生物媒介物散逸到緊鄰之作業區的圍堵系統。包括用密閉容器或生物安全櫃，連同其確保安全的作業程序。 ***次級圍堵***：一種阻止生物媒介物散逸到外界環境或其他作業區的圍堵系統。包括具有特殊設計空氣處理之作業室的使用、供物質的退出之氣鎖室及/或滅菌器，以及確保安全的作業程序。在許多情況中，可以增加一級圍堵的有效性。	**Containment** The action of confining a biological agent or other entity within a defined space. ***Primary containment*:** A system of containment which prevents the escape of a biological agent into the immediate working environment. It involves the use of closed containers or safety biological cabinets along with secure operating procedures. ***Secondary containment*:** A system of containment which prevents the escape of a biological agent into the external environment or into other working areas. It involves the use of rooms with specially designed air handling, the existence of airlocks and/or sterilises for the exit of materials and secure operating procedures. In many cases it may add to the effectiveness of primary containment.

圍堵區 為避免外界環境受到來自此區域之內的生物媒介物污染為目的所設計與運轉的區域（並配置適當的空氣處理及過濾裝置）。	**Contained area** An area constructed and operated in such a manner (and equipped with appropriate air handling and filtration) so as to prevent contamination of the external environment by biological agents from within the area.
管制區 為管制潛在污染之導入（趨近 D 級的空氣供應可能是適當的）以及活的有機體之意外釋放的後果所建造與運轉的一個區域。所執行的管制之水準應反映此製程中所使用之有機體的本質。此區域對緊鄰的外界環境至少應維持負壓，並能提供小量浮游污染物的有效移除。	**Controlled area** An area constructed and operated in such a manner that some attempt is made to control the introduction of potential contamination (an air supply approximating to grade D may be appropriate), and the consequences of accidental release of living organisms. The level of control exercised should reflect the nature of the organism employed in the process. At a minimum, the area should be maintained at a pressure negative to the immediate external environment and allow for the efficient removal of small quantities of airborne contaminants.
電腦化系統 包含數據之輸入、電子處理以及所要使用於提報或自動管制的資料之輸出的系統。	**Computerised system** A system including the input of data, electronic processing and the output of information to be used either for reporting or automatic control.
交叉污染 一種原料或產品被他種原料或產品所污染。	**Cross contamination** Contamination of a starting material or of a product with another material or product.
天然植物（植物藥品） 新鮮的或乾燥的藥用植物或其藥用的部份。	**Crude plant (vegetable drug)** Fresh or dried medicinal plant or parts thereof.
低溫容器 為盛裝極低溫之液化氣體所設計的一種容器。	**Cryogenic vessel** A container designed to contain liquefied gas at extremely low temperature.
鋼瓶 為盛裝高壓氣體所設計的一種容器。	**Cylinder** A container designed to contain gas at a high pressure.

異域生物體 一種生物媒介物，其對應的疾病不存在於一個特定的國家或地理區域，或者是其疾病是在一個特定的國家或地理區域所進行的預防措施或根除計畫的主題。	**Exotic organism** A biological agent where either the corresponding disease does not exist in a given country or geographical area, or where the disease is the subject of prophylactic measures or an eradication programme undertaken in the given country or geographical area.
最終產品 已經經歷生產之全部階段，包含分/包裝於最終容器的藥品·	**Finished product** A medicinal products which has undergone all stages of production, including packaging in its final container.
草本藥品 只含有植物性材料及/或植物藥製劑當作有效成分的藥品。	**Herbal medicinal products** Medicinal products containing, as active ingredients, exclusively plant material and/or vegetable drug preparations.
受感染的 受到外在生物媒介物所污染，且因此具有散佈感染的能力。	**Infected** Contaminated with extraneous biological agents and therefore capable of spreading infection.
製程中管制 在生產期間所執行的檢查，以便監視及調整(必要時)此製程，以確保此產品符合其規格。環境或設備的管制，也可被視為是製程中管制的一部份。	**In-process control** Checks performed during production in order to monitor and if necessary to adjust the process to ensure that the product conforms to its specification. The control of the environment or equipment may also be regarded as a part of in-process control.
半製品/中間產品 為經過部份處理的原料，其在變成待分/包裝產品之前，必須要經歷進一步的製造步驟。	**Intermediate product** Partly processed material which must undergo further manufacturing steps before it becomes a bulk product.
可液化的氣體 在正常灌充溫度與壓力下，在鋼瓶中保持液態的氣體。	**Liquifiable gases** Those which, at the normal filling temperature and pressure, remain as a liquid in the cylinder.
歧管 經設計能使一個或多個氣體容器在同一時間從同一來源灌充的設備或裝置。	**Manifold** Equipment or apparatus designed to enable one or more gas containers to be filled simultaneously from the same source.

製造 為藥品的原物料與物品的採購、生產、品質管制、放行、儲存、運銷以及相關管制的所有作業。	**Manufacture** All operations of purchase of materials and products, Production, Quality Control, release, storage, distribution of medicinal products and the related controls.
藥廠/製造廠 製造許可的持有者。	**Manufacturer** Holder of a manufacturing authorisation.
培養基充填 使用一種微生物生長培養基評估無菌製程的方法。（培養基充填是模擬產品的充填、液體培養基試驗、液體培養基充填等的同義詞）。	**Media fill** Method of evaluating an aseptic process using a microbial growth medium. (Media fills are synonymous to simulated product fills, broth trials, broth fills etc.).
藥用植物 其全株或其部份供藥用目的使用的植物。	**Medicinal plant** Plant the whole or part of which is used for pharmaceutical purpose.
藥品 擬供人用的任何藥品或相似的產品，其須受到製造國或進口國的衛生法規所管制。	**Medicinal products** Any medicine or similar product intended for human use, which is subject to control under health legislation in the manufacturing or importing State.
分/包裝 為了使一個待分/包裝產品變成一個最終產品所必須經歷的所有操作作業，包含其充填與標示在內。	**Packaging** All operations, including filling and labelling, which a bulk product has to undergo in order to become a finished product.
註：通常，無菌充填不被視為是分/包裝的一部份，亦即待分/包裝產品是已充填於直接容器但尚未經最終包裝的產品。	Note: Sterile filling would not normally be regarded as part of packaging, the bulk product being the filled, but not finally packaged, primary containers.
包裝材料 在藥品分/包裝上所使用的任何材料，但為輸送或裝運所使用的外包裝除外。包裝材料被稱為直接或間接包裝材料，是依其是否會直接與產品接觸而定。	**Packaging material** Any material employed in the packaging of a medicinal products, excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

程序 直接或間接與一種藥品之製造所要執行的操作、所要採取的注意措施以及所要應用的方法之相關說明。	**Procedures** Description of the operations to be carried out, the precautions to be taken and measures to be applied directly or indirectly related to the manufacture of a medicinal products.
生產 在藥品的調製上，從原物料的接收經製造與分/包裝到最終產品之完成所牽涉到的所有作業。	**Production** All operations involved in the preparation of a medicinal products, from receipt of materials, through processing and packaging, to its completion as a finished product.
驗證 證明任何設備能正確運轉並真正導致所預期的結果之行動。確效一詞有時候是擴及結合驗證觀念。	**Qualification** Action of proving that any equipment works correctly and actually leads to the expected results. The word validation is sometimes widened to incorporate the concept of qualification.
品質管制 參見第一章。	**Quality control** See Chapter **1.**
隔離/待驗 原料或包裝材料、半製品/中間產品、待分/包裝產品或最終產品，在等候放行或拒用的決定時，以實體或經由其他有效方法隔離的狀態。	**Quarantine** The status of starting or packaging materials, intermediate, bulk or finished products isolated physically or by other effective means whilst awaiting a decision on their release or refusal.
放射性藥品 「放射性藥品」意指當準備使用之時，為藥用目的而含有一種或多種放射性核種（放射性同位素）的任何一種藥品。	**Radiopharmaceutical** "Radiopharmaceutical" means any medicinal products which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a pharmaceutical purpose.
數量調和 在考慮正常變異適當容許量下，對產品或物料的產出或使用，其理論量與實際量間的一個比較。	**Reconciliation** A comparison, making due allowance for normal variation, between the amount of product or materials theoretically and actually produced or used.
紀錄/記錄 參見第四章。	**Record** See Chapter 4.

回收再利用 在製造的一個界定階段中，將合乎所需品質之先前批次的全部或一部份導入另外一個批次之中。	**Recovery** The introduction of all or part of previous batches of the required quality into another batch at a defined stage of manufacture.
重製/重處理 從一個界定階段所生產出無法符合品質的一批產品，將其全部或一部份經由一個或一個以上的附加操作，使其變成可以接受之品質的再加工作業。	**Reprocessing** The reworking of all or part of a batch of product of an unacceptable quality from a defined stage of production so that its quality may be rendered acceptable by one or more additional operations.
退回 把可能有或沒有品質瑕疵的藥品，送回藥廠或經銷商。	**Return** Sending back to the manufacturer or distributor of a medicinal products which may or may not present a quality defect.

種批 ***種批系統***：是指從已知繼代數的相同種批衍生一個製品的連續批次所憑藉的一個系統。對於例行生產，一個工作種批是從主種批所製備出。最終產品是從工作種批所衍生，且所歷經的繼代數不得超過經臨床研究上顯示為安全與有效疫苗的繼代。要記錄主種批與工作種批的起源與繼代歷史。 ***主種批***：在確保均勻性、並防止污染及確保安定性的方式下，將一種增殖的微生物，以單次操作，從單一的培養液分裝到多個容器中。液態型式的主種批，通常是儲存在零下70℃或更低的溫度。冷凍乾燥型式的主種批，則儲存在一已知能確保其安定性的溫度下。 ***工作種批***：從主種批所衍生且擬供生產使用的一種增殖的微生物。工作種批是分裝到多個容器中，並依照主種批所述方法儲存。	**Seed lot** ***Seed lot system*:** A seed lot system is a system according to which successive batches of a product are derived from the same master seed lot at a given passage level. For routine production, a working seed lot is prepared from the master seed lot. The final product is derived from the working seed lot and has not undergone more passages from the master seed lot than the vaccine shown in clinical studies to be satisfactory with respect to safety and efficacy. The origin and the passage history of the master seed lot and the working seed lot are recorded. ***Master seed lot*:** A culture of a micro-organism distributed from a single bulk into containers in a single operation in such a manner as to ensure uniformity, to prevent contamination and to ensure stability. A master seed lot in liquid form is usually stored at or below -70°C. A freeze-dried master seed lot is stored at a temperature known to ensure stability. ***Working seed lot*:** A culture of a micro-organism derived from the master seed lot and intended for use in production. Working seed lots are distributed into containers and stored as described above for master seed lots.
規格 參見第四章。	**Specification** See Chapter 4.
原料 用於生產一種藥品所使用的任何物質，但包裝材料除外。	**Starting material** Any substance used in the production of a medicinal products, but excluding packaging materials.
無菌性 無菌性是指沒有活的有機體存在。無菌試驗的條件收載於歐洲藥典或其他相關的藥典中。	**Sterility** Sterility is the absence of living organisms. The conditions of the sterility tests are given in the European (or other relevant) Pharmacopoeia.*

所採用的程序與預防措施，應使最終產品每一百萬（10^6）個單元中含不超過 1 個活微生物的理論水準。	＊The procedures and precautions employed should be such as to give a theoretical level of not more than one living micro-organism in 10^6 units in the final product.
確效 依照優良製造準則的原則，證明任何程序、製程、設備、原物料、活動或系統能確實導致所預期的結果之行動（亦請參見驗證項目）。	**Validation** Action of proving, in accordance with the principles of Good Manufacturing Practice, that any procedure, process, equipment, material, activity or system actually leads to the expected results (see also qualification).