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）

PE009-12 (1 October 2015)

衛生福利部

中華民國 105 年 10 月

序

藥品品質攸關國民健康，為維護國民用藥安全，並建構西藥製造業持續的競爭優勢，復配合行政院「加強生物技術產業推動方案」，衛生福利部將「提升我國GMP管理層次及國產製藥品質」列為施政首要目標之一。

我國自民國71年5月公布實施「優良藥品製造標準（GMP）」以來，國內西藥廠製藥水準已有大幅度的提升。隨後，於民國84年推動無菌製劑確效作業，復於民國88年10月21日公告「藥品確效作業實施表」，全面推動藥品實施確效作業。隨著製藥產業國際化之潮流，衛生福利部近年來積極參與國際事務，尋求國際合作，並於102年1月起正式成為國際醫藥品稽查協約組織（The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme, PIC/S）之會員，目前該組織已有46個會員，其所公布之「Guide to GMP for Medicinal Products」與歐盟GMP同步，為國際GMP標準。

配合推動藥品GMP標準國際化，本署於96年8月30日公布國際醫藥品稽查協約組織（PIC/S）藥品優良製造規範指導手冊（總則與附則），101年6月27日藥事法修正第57條及依其授權衛生福利部於102年7月30日公告修正之「藥物優良製造準則」第三條之規定，藥物製造含外銷專用產品，其製造、加工、分裝、包裝、儲存及運銷，應符合中央衛生主管機關參照國際醫藥品稽查協約組織（PIC/S）其規範所訂定之西藥藥品優良製造規範。

PIC/S組織所公布之藥品GMP指引主要分為二部（Part I及Part II）及附則（Annexes），第一部（Part I）涵蓋藥品製造之GMP作業原則，第二部（Part II）則涵蓋原料藥之GMP作業原則，而附則提供特殊領域之詳細作業規範，不同之附則可運用於特定產品或作業之操作。本次公告修正「西藥藥品優良製造規範(第一部、附則)」係依據PIC/S組織公布之PE009-11及PE009-12版本，修正附則2、14及15三個部分；對於生物藥品及血液製劑有更加詳盡的規範，關於驗證及確效亦有許多新增及修訂，以符合國際之趨勢。未來，PIC/S 組織若更新其GMP條文時，衛生福利部將配合更新並公告週知，以使我國製藥業能及時與國際接軌，提升製藥品質以立足於國際。

衛生福利部食品藥物管理署

中華民國 105 年 10 月

第一部（Part I）

目　錄

附 則（Annexes）

目　錄

第一章　品質管理（QUALITY MANAGEMENT）

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，符合上市許可的要求，且不會由於安全性、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。	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 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 the distributors.
為可靠達成該品質目標，應有全面設計並正確實施的品質保證系統。該系統涵蓋優良製造規範、品質管制及品質風險管理，應充分文件化，並監測其效果。品質保證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員另有其他法律責任。	To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented system of Quality Assurance incorporating Good Manufacturing Practice, and thus Quality Control and Quality Risk Management. It should be fully documented and its effectiveness monitored. All parts of the Quality Assurance systems 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).
品質保證、優良製造規範、品質管制及品質風險管理的基本概念是相互關聯的。在本章中將予以描述，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 Assurance, Good Manufacturing Practice, Quality Control 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.
品質保證（QUALITY ASSURANCE）	

1.1. 品質保證是一個廣泛的概念。該概念涵蓋單獨或共同影響產品品質的所有事項。品質保證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，品質保證係結合優良製造規範加上本指引範圍外之其他因素。該適合於藥品製造的品質保證系統應確保下列事項：	1.1 Quality Assurance 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 Assurance therefore incorporates Good Manufacturing Practice plus other factors outside the scope of this Guide. The system of Quality Assurance appropriate for the manufacture of medicinal products should ensure that:
i. 藥品之設計與開發方式應考慮優良製造規範的要求；	i. medicinal products are designed and developed in a way that takes account of the requirements of Good Manufacturing Practice ;
ii. 生產和管制作業應予清楚界定，並採用優良製造規範；	ii. production and control operations are clearly specified and Good Manufacturing Practice adopted;
iii. 管理責任應予清楚界定；	iii. managerial responsibilities are clearly specified;
iv. 為正確之原料及包裝材料的製造、供應與使用做出安排；	iv. arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;
v. 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；	v. all necessary controls on intermediate products, and any other in-process controls and validations are carried out;
vi. 最終產品依界定的程序，正確地操作及核對；	vi. the finished product is correctly processed and checked, according to the defined procedures;

vii. 未經被授權人員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；	vii. 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;
viii. 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；	viii. 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;
ix. 有自我查核及/或品質稽查的程序，以定期評估品質保證系統之有效性及適用性。	ix. there is a procedure for self-inspection and/or quality audit which regularly appraises the effectiveness and applicability of the quality assurance system.
藥品優良製造規範（GMP） **GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS (GMP)**	
1.2. 優良製造規範係品質保證的一部分，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或產品規格所要求之品質標準。GMP 的基本要求為：	1.2 Good Manufacturing Practice is that part of Quality Assurance which ensures that Medicinal products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorisation or product specification. 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:
a. 經適當資格檢定與訓練的人員；	a. appropriately qualified and trained personnel;
b. 足夠的廠房與作業空間；	b. adequate premises and space;
c. 適當的設備及支援服務；	c. suitable equipment and services;
d. 正確的原物料、容器及標籤；	d. correct materials, containers and labels;
e. 經核定之程序及指令；	e. approved procedures and instructions;
f. 適當之儲存及運送；	f. 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. 訓練操作者正確地執行程序；	v. operators are trained to carry out procedures correctly;
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。任何重大的偏差均已完整記錄並經調查；	vi. records are made, manually an(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. Any significant deviations are fully recorded and investigated;
vii. 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；	vii. records of manufacture including distribution which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;
viii. 產品的運銷(批發)應使其對於產品品質的任何風險降到最低；	viii. the distribution (wholesaling) of the products minimises any risk to their quality;
ix. 應有一套自銷售或供應點回收任何批次產品之系統；	ix. a system is available to recall any batch of product, from sale or supply;
x. 審查關於上市產品的申訴，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。	x. complaints about marketed products are examined, the causes of quality defects investigated and appropriate measures taken in respect of the defective products and to prevent re-occurrence.

品質管制（QUALITY CONTROL）	
1.3. 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：	1.3 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、檢查和檢驗原料、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, inspecting 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品質管制部門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 personnel and by methods approved by Quality Control;
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, 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，非經被授權人員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. 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。除非該產品以特別的大包裝生產，否則應保留在其最終包裝中。	viii. sufficient reference samples of starting materials and products are r etained to permit future examination of the product if necessary and that the product is retained in its final pack unless exceptionally large packs are produced.
產品品質檢討（PRODUCT QUALITY REVIEW）	
1.4. 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。	1.4 Regular periodic or rolling quality reviews of all licensed 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.
考量先前之檢討，通常應每年執行一次並加以文件化，且至少包含下列項目：	Such reviews should normally be conducted and documented annually, taking into account previous reviews, and should include at least:
i. 用於產品之起始原料及包裝材料，特別是那些來自新來源者之檢討。	i. A review of starting materials including packaging materials used in the product, especially those from new sources.
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 preventative 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/ 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.

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。該矯正措施之理由應予文件化。雙方同意之矯正預防措施應以適時且有效的方式完成。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。	The manufacturer and marketing authorisation holder should evaluate the results of this review, where different, and an assessment made of whether corrective and preventative action or any revalidation should be undertaken. Reasons for such corrective actions should be documented. Agreed corrective and preventative actions should be completed in a timely and effective manner. 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員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 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）	
1.5. 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。	1.5 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.
1.6 品質風險管理系統應確保下列項目：	1.6 The quality risk management system should ensure that:

- 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；	- 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;
- 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。	- 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。	Examples of the processes and applications of quality risk management can be found inter alia in Annex 20.

第二章　組織與人事（PERSONNEL）

原則（PRINCIPLE）	
一套令人滿意之品質保證系統的建立和維持，以及藥品的正確製造，均仰賴人員。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 establishment and maintenance of a satisfactory system of quality assurance and 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。賦予每一個人的責任不應過廣，以致呈現對於品質的風險。	2.1 The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. 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。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。	2.2 The manufacturer must have an organisation chart. 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.
關鍵人員（KEY PERSONNEL）	

2.3 關鍵人員包括生產主管、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員。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 2.5、2.6 及 2.7 中所列之部分職務。	2.3 Key Personnel includes 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 2.5., 2.6. and 2.7.
2.4 …	2.4 …
2.5 生產部門的主管通常有下列職責：	2.5 The head of the Production Department 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. 確保生產紀錄送到品質管制部門前，已由被授權人員評估與簽章；	iii. to ensure that the production records are evaluated and signed by an authorised person before they are sent to the Quality Control Department;
iv. 檢查/核對其部門、廠房設施及設備的維護保養；	iv. to check the 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.
2.6 品質管制部門的主管通常有下列職責：	2.6 The head of the Quality Control Department 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 sees fit, starting materials, packaging materials, and intermediate, bulk and finished products;
ii. 評估批次紀錄；	ii. to evaluate batch records;
iii. 確保已執行所有必要的試驗；	iii. to ensure that all necessary testing is carried out;
iv. 核准規格、抽樣指令、檢驗方法及其他品質管制程序；	iv. to approve specifications, sampling instructions, test methods and other Quality Control procedures;
v. 受託檢驗者之核准及監督；	v. to approve and monitor any contract analysts;
vi. 檢查/核對其部門、廠房設施與設備的維護保養；	vi. to check the maintenance of his department, premises and equipment;
vii. 確保已完成適當的確效；	vii. to ensure that the appropriate validations are done;
viii. 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。品質管制部門的其他職責概述於第六章。	viii. to ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need. Other duties of the Quality Control Department are summarised in Chapter 6.
2.7 生產和品質管制的主管通常有一些分擔或共同負擔之關於品質的職責。這些職責應受國家法規的規範，包括：	2.7 The heads of Production and Quality Control generally have some shared, or jointly exercised, responsibilities relating to quality. These may include, subject to any national regulations:
➢ 書面的程序和其他文件的認可，包括修訂在內；	➢ the authorisation of written procedures and other documents, including amendments;
➢ 製造環境的監測與管制；	➢ the monitoring and control of the manufacturing environment;
➢ 工廠衛生；	➢ plant hygiene;
➢ 製程確效；	➢ process validation;
➢ 訓練；	➢ training;
➢ 原物料供應商的認可及監督；	➢ the approval and monitoring of suppliers of materials;
➢ 受託製造廠的認可及監督；	➢ the approval and monitoring of contract manufacturers;

➢ 原物料及產品之儲存條件的指示與監測；	➢ the designation and monitoring of storage conditions for materials and products;
➢ 紀錄的保存；	➢ the retention of records;
➢ 符合 GMP 要求之監督；	➢ the monitoring of compliance with the requirements of GMP;
➢ 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。	➢ the inspection, investigation, and taking of samples, in order to monitor factors which may affect product quality.
訓練（TRAINING）	
2.8 藥廠對於因其職責會進入生產區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。	2.8 The manufacturer should provide training for all the personnel whose duties take them into production 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.
2.9 除了有關優良製造規範的理論與實務的基本訓練之外，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。	2.9 Beside the basic training on the theory and practice of 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.
2.10 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。	2.10 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.
2.11 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。	2.11 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.
2.12 訓練期間，應充分討論品質保證的概念及所有能增進其理解與執行的措施。	2.12 The concept of Quality Assurance and all the measures capable of improving its understanding and implementation should be fully discussed during the training sessions.
個人衛生（PERSONAL HYGIENE）	
2.13 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。	2.13 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.
2.14 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。	2.14 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.
2.15 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。	2.15 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.

2.16 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。	2.16 Every person entering the manufacturing areas should wear protective garments appropriate to the operations to be carried out.
2.17 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。	2.17 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.
2.18 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。	2.18 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.
2.19 應指導工作人員使用洗手設施。	2.19 Personnel should be instructed to use the hand-washing facilities.
2.20 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，收載於相關補充指引中。	2.20 Any specific requirements for the manufacture of special groups of products, for example sterile preparations, are covered in the Supplementary Guidelines.

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 Area）		
3.6	為使因交叉污染所引起之嚴重醫療傷害的風險降到最低，對於一些特殊藥品的生產，例如高致敏性物質（例如：青黴素類）或生物性製劑（例如：來自活的微生物），應有專用且自足圍堵的設施；尚有一些產品，例如某些抗生素、某些荷爾蒙、某些細胞毒類、某些高活性藥物及非藥品的生產不得在同一設施中為之。如採取特別的預防措施，並執行必要的確效時，在例外的情形下，可以接受在同一設施中的時段切換生產原則。工業毒物諸如殺蟲劑及除草劑，不得於藥品之廠房設施中製造。	3.6	In order to minimise the risk of a serious medical hazard due to cross contamination, dedicated and self-contained facilities must be available for the production of particular medicinal products, such as highly sensitising materials (e.g. penicillins) or biological preparations (e.g. from live micro-organisms). The production of certain additional products, such as certain antibiotics, certain hormones, certain cytotoxics, certain highly active drugs and non-medicinal products should not be conducted in the same facilities. For those products, in exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations are made. The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of medicinal products.
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 管路工程、照明裝置、通氣口以及其他設施之設計與定位應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 Pipe work, 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	3.13 Weighing of starting materials usually

計之一間隔離的秤量室內為之。	should be carried out in a separate weighing room designed for that 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 Productions 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 for the 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. Receptions 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 products 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 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.
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, deionized 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[1]，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[1] together with the evaluation for compliance to a stated specification.
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.
[1] 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。	[1] 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.

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，並以規定的資料標示。	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 data.
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，皆應防止產品及原物料受微生物及其他污染。	5.10 At every stage of processing, products and materials 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。特別適用於高活性或高致敏性物質的處理。	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 active or 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、清潔…等)，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 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 occur, 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.
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。	5.17 Normally, the production of non-medicinal products should be avoided in areas and with the equipment destined for the production of medicinal products.
生產中交叉污染的防止 （PREVENTION OF CROSS-CONTAMINATION IN PRODUCTION）	
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物料及產品所產生的粉塵、氣體、蒸氣、噴霧或微生物、設備上的殘留物及因作業人員的服裝等。該風險的嚴重性隨污染物的種類及被污染的產品而異，其中最具危害的污染物是高致敏性物質、含有活體的生物製劑、某些荷爾蒙類、細胞毒類及其他高活性的物質。污染尤對以注射、大劑量及/或長期投用的產品之使用最具風險。	5.18 Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, vapours, sprays or organisms from materials and products in process, from residues on equipment, and from operators' clothing. The significance of this risk varies with the type of contaminant and of product being contaminated. Amongst the most hazardous contaminants are highly sensitising materials, biological preparations containing living organisms, certain hormones, cytotoxics, and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection, those given in large doses and/or over a long time.

5.19 交叉污染應以適當的技術或有組織的措施避免之，例如：	5.19 Cross-contamination should be avoided by appropriate technical or organisational measures, for example:
a) 在隔離的區域(對諸如青黴素類、活疫苗、活細菌製劑及一些其他生物性製劑的產品所要求)，或採分隔時段切換生產，其後應緊接著適當的清潔處理；	a) production in segregated areas (required for products such as penicillins, live vaccines, live bacterial preparations and some other biologicals), or by campaign (separation in time) followed by appropriate cleaning;
b) 備有適當的氣鎖室及空氣抽除設備；	b) providing appropriate air-locks and air extraction;
c) 將未經處理或未經充分處理的空氣之再循環或再進入所引起的污染風險降到最低；	c) minimising the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;
d) 製造具交叉污染特別風險之產品的區域內應保持穿著防護裝；	d) keeping protective clothing inside areas where products with special risk of cross-contamination are processed;
e) 設備的無效清潔是交叉污染的普遍來源，故應使用已知有效的清潔及去污染程序；	e) using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross contamination;
f) 使用密閉的生產系統；	f) using "closed systems" of production;
g) 檢驗設備上的殘留物並使用清潔狀態標籤。	g) testing for residues and use of cleaning status labels on equipment.
5.20 應依規定程序定期檢查防止交叉污染的措施及其有效性。	5.20 Measures to prevent cross-contamination and their effectiveness should be checked periodically according to set procedures.
確效（Validation ）	
5.21 確效試驗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。	5.21 Validation studies should reinforce Good Manufacturing Practice and be conducted in accordance with defined procedures. Results and conclusions should be recorded.

5.22 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。	5.22 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.
5.23 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。	5.23 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.
5.24 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。	5.24 Processes and procedures should undergo periodic critical revalidation to ensure that they remain capable of achieving the intended results.
原料（STARTING MATERIALS）	
5.25 原料的採購是一項重要的作業，應有對供應商具特別且充分瞭解的人員參與。	5.25 The purchase of starting materials is an important operation which should involve staff who have a particular and thorough knowledge of the suppliers.
5.26 原料僅可向在相關規格上列名之經認可的供應商購買；可能時，應直接向生產者購買。建議藥廠建立原料規格時應與供應商討論。涉及原料之生產與管制的所有層面，包括其處理、標示、分/包裝的要求，以及申訴和拒用的程序等，與製造廠及供應商討論是有助益的。	5.26 Starting materials should only be purchased from approved suppliers named in the relevant specification and, where possible, directly from the producer. It is recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers. It is of benefit that all aspects of the production and control of the starting material in question, including handling, labelling and packaging requirements, as well as complaints and rejection procedures are discussed with the manufacturer and the supplier.

5.27 每一次交貨，應檢查/核對容器的包裝、封條的完整性及送貨單與供應商標示之一致性。	5.27 For each delivery, the containers should be checked for integrity of package and seal and for correspondence between the delivery note and the supplier's labels.
5.28 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。	5.28 If one material delivery is made up of different batches, each batch must be considered as separate for sampling, testing and release.
5.29 儲存區的原料應適當地標示 (請參見第五章，第十三條)。標籤上應至少記載下列資料：	5.29 Starting materials in the storage area should be appropriately labelled (see Chapter 5, Item 13). Labels should bear at least the following information:
➢ 產品的指定名稱及其內部參考代碼(可行時)；	➢ the designated name of the product and the internal code reference where applicable;
➢ 接收時所給予的批號；	➢ a batch number given at receipt;
➢ 合適時，內容物的狀態(例如：待驗中、檢驗中、放行、拒用)；	➢ where appropriate, the status of the contents (e.g. in quarantine, on test, released, rejected);
➢ 合適時，末效日期或再檢驗的日期。	➢ 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，上述所有資料不必以易讀的方式印在標籤上。	When fully computerised storage systems are used, all the above information should not necessarily be in a legible form on the label.
5.30 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，第十三條)。	5.30 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, Item 13).
5.31 僅有經品質管制部門放行，且還在架儲期間內的原料始可使用。	5.31 Only starting materials which have been released by the Quality Control Department and which are within their shelf-life should be used.

5.32 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稱入或量入潔淨且適切標示的容器中。	5.32 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.
5.33 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。	5.33 Each dispensed material and its weight or volume should be independently checked and the check recorded.
5.34 每一批次調配的原料應保存在一起，並明顯地標示。	5.34 Materials dispensed for each batch should be kept together and conspicuously labelled as such.
半製品/中間產品及待分/包裝產品的操作作業（PROCESSING OPERATIONS INTERMEDIATE AND BULK PRODUCTS）	
5.35 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。	5.35 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.
5.36 半製品/中間產品或待分/包裝產品應保存在適當的條件下。	5.36 Intermediate and bulk products should be kept under appropriate conditions.
5.37 關鍵製程應經確效(參見本章之「確效」)。	5.37 Critical processes should be validated (see "VALIDATION" in this Chapter).
5.38 任何必要的製程中管制及環境管制均應執行並予記錄。	5.38 Any necessary in-process controls and environmental controls should be carried out and recorded.
5.39 與預期產率的任何顯著偏差均應予記錄並加以調查。	5.39 Any significant deviation from the expected yield should be recorded and investigated.
包裝材料（PACKAGING MATERIALS）	
5.40 直接包裝材料及經印刷的包裝材料之採購、處理及管制應比照原料給予同等注意。	5.40 The purchase, handling and control of primary and printed packaging materials should be accorded attention similar to that given to starting materials.

5.41 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。	5.41 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.
5.42 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。	5.42 Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.
5.43 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。	5.43 Outdated or obsolete primary packaging material or printed packaging material should be destroyed and this disposal recorded.
分/包裝作業（PACKAGING OPERATIONS）	
5.44 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。	5.44 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.
5.45 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。	5.45 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.
5.46 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。	5.46 The name and batch number of the product being handled should be displayed at each packaging station or line.

5.47 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。	5.47 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.
5.48 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。	5.48 Containers for filling should be clean before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.
5.49 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。	5.49 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.
5.50 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。	5.50 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.
5.51 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。	5.51 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.
5.52 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。	5.52 Checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.
5.53 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。	5.53 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.
5.54 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：	5.54 On-line control of the product during packaging should include at least checking the following:
a) 包裝的一般外觀；	a) general appearance of the packages;
b) 包裝是否完整；	b) whether the packages are complete;
c) 是否使用正確的產品與包裝材料;	c) whether the correct products and

	packaging materials are used;
d) 任何套印是否正確；	d) whether any over-printing is correct;
e) 分/包裝線上監視器的正確運轉。	e) 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.
5.55 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。	5.55 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.
5.56 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。	5.56 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.
5.57 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。	5.57 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 uncoded printed materials are returned to stock.
最終產品（FINISHED PRODUCTS）	
5.58 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。	5.58 Finished products should be held in quarantine until their final release under conditions established by the manufacturer.
5.59 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)。	5.59 The evaluation of finished products and documentation which is necessary before release of product for sale are described in Chapter 6 (Quality Control).
5.60 放行後，最終產品應依藥廠既訂條件作為可用庫存品儲存。	5.60 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）	

5.61 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。	5.61 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.
5.62 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。	5.62 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.
5.63 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。	5.63 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.
5.64 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。	5.64 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.

5.65 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。	5.65 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 with 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.

第六章 品質管制（QUALITY CONTROL）

原則（PRINCIPLE）	
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(詳見第一章)。	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 (see also Chapter 1).
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，保存原物料與產品的對照樣品，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, keep the reference samples of materials and products, 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 PRACTICE）	
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。	6.5 Control Laboratory premises and equipment should meet the general and specific requirements for Quality Control areas given in Chapter 3.

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/受託檢驗所詳述的原則下，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, Contract Analysis, 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:
➢ 規格；	➢ specifications;
➢ 抽樣程序；	➢ sampling procedures;
➢ 檢驗程序和紀錄(包括分析工作單及/或實驗室筆記本)；	➢ testing procedures and records (including analytical worksheets and/or laboratory notebooks);
➢ 分析報告及/或檢驗證明書；	➢ analytical reports and/or certificates;
➢ 環境監測數據/資料（要求時）；	➢ data from environmental monitoring, where required;
➢ 檢驗方法的確效紀錄（可行時）；	➢ validation records of test methods, where applicable;
➢ 儀器校正與設備維護保養的程序及紀錄。	➢ procedures for and records of the calibration of instruments and maintenance of equipment.
6.8 與批次紀錄有關的任何品質管制文件，應保存至該批次產品的末效日期後一年。	6.8 Any Quality Control documentation relating to a batch record should be retained for one year after the expiry date of the batch.
6.9 某些類型的數據 (如：分析檢驗結果、產率、環境的管制…等)建議應以允許趨勢評估的方式保存其紀錄。	6.9 For some kinds of data (e.g. analytical tests results, yields, environmental controls, ...) it is recommended that records in a manner permitting trend evaluation be kept.

6.10 除批次紀錄之部分資訊外，其他原始資料，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 record, other original data such as laboratory notebooks and/or records should be retained and readily available.
抽樣（SAMPLING）	
6.11 抽樣應依經認可之書面程序執行。該程序描述下列項目：	6.11 The sample taking should be done in accordance with approved written procedures that describe:
➢ 抽樣的方法；	➢ the method of sampling;
➢ 使用的設備；	➢ the equipment to be used;
➢ 抽取的樣品量；	➢ the amount of the sample to be taken;
➢ 任何要求將樣品再細分的指令；	➢ instructions for any required sub-division of the sample;
➢ 使用之樣品容器的類型及條件；	➢ the type and condition of the sample container to be used;
➢ 經抽取樣品之容器的識別；	➢ the identification of containers sampled;
➢ 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；	➢ any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials;
➢ 儲存條件；	➢ the storage conditions;
➢ 抽樣設備之清潔與儲存的指令。	➢ instructions for the cleaning and storage of sampling equipment.
6.12 對照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。	6.12 Reference 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).
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。	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.
6.14 來自每批最終產品的對照樣品應儲存至該批產品之末效日期後一年。最終產品通常應保存在其最終包裝中，並儲存在建議的條件下。在原料的安定性容許	6.14 Reference samples from each batch of finished products should be retained till one year after the expiry date. Finished products should usually be kept in their

下，其樣品(不包括溶劑、氣體及水)應保存至該產品放行後至少兩年。相關規格中提到其安定性較短者，該兩年的保存期限得縮短之。原物料及產品之對照樣品的數量應至少足以允許執行一次完整的再驗。	final packaging and stored under the recommended conditions. Samples of starting materials (other than solvents, gases and water) should be retained for at least two years after the release of the product if their stability allows. This period may be shortened if their stability, as mentioned in the relevant specification, is shorter. Reference samples of materials and products should be of a size sufficient to permit at least a full re-examination.
檢驗（TESTING）	
6.15 分析方法應予確效。上市許可中所描述的所有檢驗作業皆應依認可的方法執行之。	6.15 Analytical methods should be validated. All testing operations described in the marketing authorisation should be carried out according to the approved methods.
6.16 獲得的結果應予記錄並檢查/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 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:
a) 原物料或產品名稱，及其劑型(可行時)；	a) name of the material or product and, where applicable, dosage form;
b) 批號，及其製造廠及/或供應商(合適時)；	b) batch number and, where appropriate, the manufacturer and/or supplier;
c) 相關規格與檢驗程序的參考資料；	c) references to the relevant specifications and testing procedures;
d) 檢驗的結果，包括觀察、計算及任何檢驗證明書的參考資料；	d) test results, including observations and calculations, and reference to any certificates of analysis;
e) 檢驗日期；	e) dates of testing;
f) 執行該檢驗之人員的簽名；	f) initials of the persons who performed the testing;
g) 合適時，確認檢驗及計算結果之人員的簽名；	g) initials of the persons who verified the testing and the calculations, where appropriate;
h) 放行或拒用(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	h) a clear statement of release or rejection (or other status decision) and the dated

章。	signature of the designated responsible person.
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、容量玻璃器皿、溶液、對照標準品及培養基等之品質，並應依書面的程序製備。	6.19 Special attention should be given to the quality of laboratory reagents, volumetric glassware and solutions, reference standards and culture media. They should be prepared in accordance with written procedures.
6.20 預定供長期使用的實驗室試劑，應標記其配製日期及配製人員的簽章。不穩定的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。	6.20 Laboratory reagents intended for prolonged use should be marked with the preparation date and the signature of the person who prepared them. The expiry date of unstable 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.
6.21 必要時，應將用於檢驗作業之任何物質(例如：試劑及對照標準品)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。	6.21 Where necessary, the date of receipt of any substance used for testing operations (e.g. reagents 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.
6.22 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。	6.22 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）	
6.23 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）。	6.23 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.
6.24 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。	6.24 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.

6.25 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。	6.25 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.
6.26 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。	6.26 The on-going 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 on-going stability programme (stability chambers among others) should be qualified and maintained following the general rules of Chapter 3 and annex 15.
6.27 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：	6.27 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:
•每種含量與不同批量之批次數目（合適時）	• number of batch(es) per strength and different batch sizes, if applicable
•相關的物理、化學、微生物學及生物學的檢驗方法	• relevant physical, chemical, microbiological and biological test methods
•允收標準	• acceptance criteria
•檢驗方法的參考資料	• reference to test methods
•容器封蓋系統的描述	• description of the container closure

	system(s)
•測試間隔（時間點）	• testing intervals (time points)
•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)	• description of the conditions of storage (standardised ICH conditions for long term testing, consistent with the product labelling, should be used)
•其他特別適用於該藥品的參數。	• other applicable parameters specific to the medicinal product.
6.28 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）。	6.28 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 recommendations).
6.29 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。	6.29 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.

6.30 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。	6.30 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.
6.31 持續進行之安定性試驗的結果，應使關鍵人員，特別是被授權人員能夠取得。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。	6.31 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.
6.32 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，應向主管機關報告，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，考慮對於已上市產品之批次可能造成的衝擊。	6.32 Out of specification or significant atypical trends should be investigated. Any confirmed out of specification result, or significant negative trend, 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.
6.33 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。	6.33 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.

第七章 委受託製造與檢驗（CONTRACT MANUFACTURE AND ANALYSIS）

原則（PRINCIPLE）	
委受託製造與檢驗應正確地予以界定、協議及管制，以避免因誤解而可能導致不滿意品質的產品或作業。委託者與受託者間應有清楚訂定雙方職責的書面契約。該契約應清楚約定，負責放行每批供銷售之產品的被授權人員執行其完整職責的方式。	Contract manufacture and analysis must be correctly defined, agreed and controlled in order to avoid misunderstandings which could result in a product or work of unsatisfactory quality. There must be a written contract between the Contract Giver and the Contract Acceptor which clearly establishes the duties of each party. The contract must clearly state the way in which the authorised person releasing each batch of product for sale exercises his full responsibility.
註：本章規定藥廠對於授予銷售與製造許可之主管機關應負的責任。本章無意以任何方式影響委託者與受託者對於消費者之個別義務。	Note: This Chapter deals with the responsibilities of manufacturers towards the Component Authorities of the Participating authorities with respect to the granting of marketing and manufacturing authorisations. It is not intended in any way to affect the respective liability of contract acceptors and contract givers to consumers.
一般規定（GENERAL）	
7.1 該委託契約，應有涵蓋製造及/或委/受託檢驗之書面契約及其有關的技術安排。	7.1 There should be a written contract covering the manufacture and/or analysis arranged under contract and any technical arrangements made in connection with it.
7.2 為委受託製造與檢驗之所有安排，包括技術或其他安排中所建議之任何改變，均應符合相關產品之上市許可。	7.2 All arrangements for contract manufacture and analysis including any proposed changes in technical or other arrangements should be in accordance with the marketing authorisation for the product concerned.

委託者（THE CONTRACT GIVER）	
7.3 委託者應負責評估受託者成功履行要求之工作的能力，並負責藉由該契約，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。	7.3 The Contract Giver is responsible for assessing the competence of the Contract Acceptor to carry out successfully the work required and for ensuring by means of the contract that the principles and Guidelines of GMP as interpreted in this Guide are followed.
7.4 委託者應提供受託者所有必需的資訊，以使其依上市許可及任何其他法律要求，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 The Contract Giver should provide the Contract Acceptor with all the information necessary to carry out the contracted operations correctly in accordance with the marketing authorisation and any other legal requirements. 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 premises, equipment, personnel, other materials or other products.
7.5 委託者應確保受託者所交付之所有處理過的產品及原物料均符合其規格，或這些產品係經由被授權人員放行。	7.5 The Contract Giver should ensure that all processed products and materials delivered to him by the Contract Acceptor comply with their specifications or that the products have been released by an authorised person.
受託者（THE CONTRACT ACCEPTOR）	
7.6 受託者應有適當的廠房設施與設備、知識與經驗及能勝任的人員，滿意地執行委託者所託付的工作。接受委託製造僅得由取得製造許可者為之。	7.6 The Contract Acceptor must have adequate premises and equipment, knowledge and experience, and competent personnel to carry out satisfactorily the work ordered by the Contract Giver. Contract manufacture may be undertaken only by a manufacturer who is the holder of a manufacturing authorisation.
7.7 受託者應確認所交付的所有產品或原物料皆符合其預定之目的。	7.7 The Contract Acceptor should ensure that all products or materials delivered to him are suitable for their intended purpose.
7.8 受託者未經委託者之事先評估及同	7.8 The Contract Acceptor should not pass to a

意，不得將契約所委託的任何工作轉託給第三方。受託者與任何第三方間所做的任何安排，應確保其製造及檢驗資訊以原委託者與受託者間約定的相同方式提供之。	third party any of the work entrusted to him 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 the manufacturing and analytical information is made available in the same way as between the original Contract Giver and Contract Acceptor.
7.9 受託者應避免對委託者委託製造及/或檢驗之產品品質可能會造成不良影響的任何活動。	7.9 The Contract Acceptor should refrain from any activity which may adversely affect the quality of the product manufactured and/or analysed for the Contract Giver.
合約（THE CONTRACT）	
7.10 委託者與受託者間應簽訂契約。該契約明定雙方關於產品製造與管制的個別責任。契約中的技術層面應由具有製藥技術、檢驗及優良製造規範之適當知識的勝任人員擬定。製造及檢驗的所有安排均應依上市許可的規定，並為雙方所同意。	7.10 A contract should be drawn up between the Contract Giver and the Contract Acceptor which specifies their respective responsibilities relating to the manufacture and control of the product. Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in pharmaceutical technology, analysis and Good Manufacturing Practice. All arrangements for manufacture and analysis must be in accordance with the marketing authorisation and agreed by both parties
7.11 契約應明定被授權人員放行供銷售之批次的方式，以確保每一批次皆已符合上市許可的要求而製造與檢查/核對。	7.11 The contract should specify the way in which the authorised person releasing the batch for sale ensures that each batch has been manufactured and checked for compliance with the requirements of Marketing Authorisation.
7.12 契約中應清楚載明何方負責採購、測試及放行原物料、承擔生產及品質管制，含製程中管制，以及何方負責抽樣及檢驗。委託檢驗契約中應載明受託者是否應於製造者之廠房中抽樣。	7.12 The contract should describe clearly who is responsible for purchasing materials, testing and releasing materials, undertaking production and quality controls, including in-process controls, and who has responsibility for sampling and analysis. In

	the case of contract analysis, the contract should state whether or not the Contract Acceptor should take samples at the premises of the manufacturer.
7.13 製造、檢驗及運銷之紀錄及對照樣品應由委託者保存，或可為委託者取得。當有申訴或懷疑有瑕疵時，應能取得與產品品質評估有關的任何紀錄。這應明定於委託者之不良品/回收程序中。	7.13 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 must be accessible and specified in the defect/recall procedures of the Contract Giver.
7.14 契約應明定容許委託者訪視受託者的廠房設施及設備。	7.14 The contract should permit the Contract Giver to visit the facilities of the Contract Acceptor.
7.15 委/受託檢驗時，受託者應了解其應受主管機關的查核。	7.15 In case of contract analysis, the Contract Acceptor should understand that he is subject to inspection by the competent Authorities.

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

原則（PRINCIPLE）	
所有申訴及其他可能之瑕疵產品有關的資訊，均應遵循書面的程序詳實審核。為對所有意外事件作準備，應設計一套系統，以便必要時，能立即且有效地自市場回收已知或懷疑其有瑕疵的產品。	All complaints and other information concerning potentially defective products must be carefully reviewed according to written procedures. In order to provide for all contingencies, a system should be designed to recall, if necessary, promptly and effectively products known or suspected to be defective from the market.
申訴（COMPLAINTS）	
8.1 應指定人員，並配以足夠的支援人員給予協助，以負責處理申訴及決定要採取的措施。該指定人員若非被授權人員，應使被授權人員知悉任何申訴、調查或回收事宜。	8.1 A person should be designated responsible for handling the complaints and deciding the measures to be taken together with sufficient supporting staff to assist him. If this person is not the authorised person, the latter should be made aware of any complaint, investigation or recall.
8.2 若涉及可能之產品瑕疵的申訴，應有書面的程序描述要採取的行動，包括考慮回收的需要。	8.2 There should be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.
8.3 關於產品瑕疵的任何申訴，應記錄其全部原始細節並徹底調查。負責品質管制的人員通常應參與這些問題的研究。	8.3 Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. The person responsible for Quality Control should normally be involved in the study of such problems.
8.4 任一批次中發現或懷疑有產品瑕疵時，應考慮檢查/核對其他批次的產品，以確定其是否也受到影響。特別是可能含有該瑕疵批次之再加工的其他批次應予調查。	8.4 If a product defect is discovered or suspected in a batch, consideration should be given to checking other batches should be checked in order to determine whether they are also affected. In particular, other batches

	which may contain reworks of the defective batch should be investigated.
8.5 因申訴而做之所有決定與採取之措施應予記錄，並對照其對應的批次紀錄。	8.5 All the decisions and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.
8.6 申訴紀錄應定期檢討，以發現需注意及可能造成已上市產品回收之特定或重發性問題的任何跡象。	8.6 Complaints records should be reviewed regularly for any indication of specific or recurring problems requiring attention and possibly the recall of marketed products.
8.7 應特別注意確立申訴是否因仿冒所引起。	8.7 Special attention should be given to establishing whether a complaint was caused because of counterfeiting.
8.8 藥廠若由於可能有製造瑕疵、產品變質、發現仿冒品或任何其他嚴重的產品品質問題，而考慮採取行動時，應通知主管機關。	8.8 The Competent Authorities should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, detection of counterfeiting or any other serious quality problems with a product.
回收（RECALLS）	
8.9 應指定人員負責回收之執行與協調，並應給予足夠的支援人力，以適切迅速的程度處理所有回收事宜。該負責人員通常應與銷售部門相互獨立且該人員並非被授權人員者，應使被授權人員知悉任何回收作業。	8.9 A person should be designated as responsible for execution and co-ordination of recalls and should be supported by sufficient staff to handle all the aspects of the recalls with the appropriate degree of urgency. This responsible person should normally be independent of the sales and marketing organisation. If this person is not the authorised person, the latter should be made aware of any recall operation.
8.10 為有效的組織任何回收作業，應建立書面的程序、定期檢查/核對，且於必要時予以更新。	8.10 There should be established written procedures, regularly checked and updated when necessary, in order to organise any recall activity.
8.11 回收作業應能立即且在任何時候啟動。	8.11 Recall operations should be capable of

	being initiated promptly and at any time.
8.12 因產品有瑕疵或懷疑其有瑕疵，而要將其回收時，應立即通知可能已經對其運銷該產品之所有國家的主管機關。	8.12 All Competent Authorities of all countries to which products may have been distributed should be informed promptly if products are intended to be recalled because they are, or are suspected of, being defective.
8.13 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和直銷客戶的充分資訊（連同地址、上、下班時間的電話/傳真號碼、送交的批次和數量），包含輸出的產品和醫療用樣品在內。	8.13 The distribution records should be readily available to the person(s) 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.
8.14 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安全區域。	8.14 Recalled products should be identified and stored separately in a secure area while awaiting a decision on their fate.
8.15 回收過程之進度應予記錄並提出最終報告。該報告應包含送交產品與收回產品的數量調和。	8.15 The progress of the recall process should be recorded and a final report issued, including a reconciliation between the delivered and recovered quantities of the products.
8.16 回收作業之安排的有效性應予定期評估。	8.16 The effectiveness of the arrangements for recalls should be evaluated regularly.

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)

* 本附則中關於小瓶之上蓋規定條款於 2010 年 3 月 1 日生效。	*Provisions on capping of vials in this Annex will enter into force on 1 March 2010 only.
原則（PRINCIPLE）	
為使微生物學上之污染，與微粒及熱原污染之風險降到最低，無菌產品之製造應受制於特別之要求。大部分的要求取決於參與人員之技巧、訓練及態度。品質保證特別重要，且這種類型之製造應嚴格遵循，謹慎建立經確效的製備方法及程序。無菌性或其他品質層面之信賴度不得僅仰賴於最終製程或最終產品的檢驗。	The manufacture of sterile products is subject to special requirements in order to minimise risks of microbiological contamination, and of particulate and pyrogen contamination. Much depends on the skill, training and attitudes of the personnel involved. Quality Assurance is particularly important, and this type of manufacture must strictly follow carefully established and validated methods of preparation and procedure. Sole reliance for sterility or other quality aspects must not be placed on any terminal process or finished product test.
註：本附則並未規定關於測定空氣、表面等之微生物及微粒的潔淨度之詳細方法。請參考其他的規範，例如 EN/ISO 標準。	Note: This guidance does not lay down detailed methods for determining the microbiological and particulate cleanliness of air, surfaces, etc. Reference should be made to other documents such as the EN/ISO Standards.
概述（GENERAL）	
1. 無菌產品的製造應在潔淨區中執行，人員及/或設備與原物料進入該潔淨區，應分別經由各氣鎖室。潔淨區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。	1. The manufacture of sterile products should be carried out in clean areas, entry to which should be through airlocks for personnel and/or for equipment and materials. Clean areas should be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency.
2. 組件的準備、產品的製備及充填之不同作業應在潔淨區內之個別的區域中為之。製造作業劃分成兩類；第一類，其產品係經最終滅菌，及第二類，其產品在製程中的某些階段或全部階段係以無菌技術執行。	2. The various operations of component preparation, product preparation and filling should be carried out in separate areas within the clean area. Manufacturing operations are divided into two categories; firstly those where the product is terminally sterilised, and secondly those which are conducted aseptically at some or all stages.

3. 無菌產品之製造，其潔淨區是依要求的環境特徵分級。為使處理中之產品或原物料的微粒或微生物污染之風險降到最低，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。	3. Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate environmental cleanliness level in the operational state in order to minimise the risks of particulate or microbial contamination of the product or materials being handled.
為符合「動態」的條件，這些區域應經設計，使其在靜態時達到特定之空氣潔淨度標準。「靜態」，指該生產設施已完成生產設備之安裝並在運轉中，但無操作人員在場的狀態。「動態」，指設備已於操作狀態中運轉，且有特定人數執行操作。	In order to meet “in operation” conditions these areas should be designed to reach certain specified air-cleanliness levels in the “at rest” occupancy state. The “at rest” state is the condition where the installation is installed and operating, complete with production equipment but with no operating personnel present. The “in operation” state is the condition where the installation is functioning in the defined operating mode with the specified number of personnel working.
對於每間潔淨室或每套潔淨室，皆應界定其「動態」及「靜態」 的狀態。	The “in operation” and “at rest” states should be defined for each clean room or suite of clean rooms.
無菌藥品的製造區分成四個等級。	For the manufacture of sterile medicinal products 4 grades can be distinguished.
A 級： 高風險作業的局部區域，例如，充填區、橡皮塞貯盆、開口安瓿、小瓶及執行無菌連接等區域。通常，此種環境由層流工作站提供。在開放潔淨室應用（open clean room application）的作業位置，層流空氣系統應提供每秒 0.36 至 0.54 公尺（指引值）的均勻空氣流速。 層流性（laminarity）的維持應予以證明並確效。單向氣流（uni-directional air flow）及較低速率可使用於密閉的隔離裝置及手套箱（glove boxes）。	Grade A: The local zone for high risk operations, e.g. filling zone, stopper bowls, open ampoules and vials, making aseptic connections. Normally such conditions are provided by a laminar air flow work station. Laminar air flow systems should provide a homogeneous air speed in a range of 0.36 – 0.54 m/s(guidance value) at the working position in open clean room applications. The maintenance of laminarity should be demonstrated and validated. A uni-directional air flow and lower velocities may be used in closed isolators and glove boxes.
B 級： 對於無菌操作之製備及充填，B 級區為 A 級區的背景環境。	Grade B: For aseptic preparation and filling, this is the background environment for the grade A zone.

C 級與 D 級： 無菌產品的製造中，C 級與 D 級區係執行較非關鍵性階段的潔淨區。	Grade C and D: Clean areas for carrying out less critical stages in the manufacture of sterile products.

潔淨室及潔淨空氣裝置分級
（CLEAN ROOM AND CLEAN AIR DEVICE CLASSIFICATION）

4. 潔淨室及潔淨空氣裝置應依 EN ISO 14644-1 予以分級。分級應與操作過程之環境監測清楚區分。下表提供每一個等級所容許的最大浮游微粒濃度：	4. Clean rooms and clean air devices should be classified in accordance with ENISO 14644-1. Classification should be clearly differentiated from operational process environmental monitoring. The maximum permitted airborne particle concentration for each grade is given in the following table:

等 級	每立方公尺等於或大於下述粒徑之微粒的最大容許量			
	靜態		動態	
	0.5 μm	5.0 μm	0.5 μm	5.0 μm
A	3,520	20	3,520	20
B	3,520	29	352,000	2,900
C	352,000	2,900	3,520 000	29,000
D	3,520,000	29,000	未界定	未界定

Grade	Maximum permitted number of particles/m^3 equal to or greater than the tabulated size			
	At rest		In operation	
	0.5 μm	5.0 μm	0.5 μm	5.0 μm
A	3,520	20	3,520	20
B	3,520	29	352,000	2,900
C	352,000	2,900	3,520 000	29,000
D	3,520,000	29,000	Not defined	Not defined

5. 針對 A 級區分級之驗證，每一個取樣位置應採取最少樣品容量 1m3。A 級之浮游微粒分級為 ISO 4.8，依≥ 5.0 μm 微粒限量決定。B 級 (靜態)之浮游微粒分級為 ISO 5，係考慮兩種微粒大小。對於 C 級 (靜態及動態)，浮游微粒分級分別為 ISO 7 及 ISO 8。對於 D 級 (靜態)，浮游微粒分級為 ISO 8。針對分級，EN/ISO 14644-1 界定最低取樣點數及樣品量，考量最大的微粒大小及所收集的數據之估算方式，作為	5. For classification purposes in Grade A zones, a minimum sample volume of 1m3 should be taken per sample location. For Grade A the airborne particle classification is ISO 4.8 dictated by the limit for particles ≥5.0 μm. For Grade B (at rest) the airborne particle classification is ISO 5 for both considered particle sizes. For Grade C (at rest & in operation) the airborne particle classification is ISO 7 and ISO 8

各分級限量之基礎。	respectively. For Grade D (at rest) the airborne particle classification is ISO 8. For classification purposes EN/ISO 14644-1 methodology defines both the minimum number of sample locations and the sample size based on the class limit of the largest considered particle size and the method of evaluation of the data collected.
6. 為分級之目的，應使用具短取樣管的手提式微粒計數器，因具長管線的遙控取樣系統 ≧5 μm 之微粒的沉降速率相對較高。單向氣流系統中，應使用等速採樣頭（isokinetic sample heads）。	6. Portable particle counters with a short length of sample tubing should be used for classification purposes because of the relatively higher rate of precipitation of particles ≥5.0μm in remote sampling systems with long lengths of tubing. Isokinetic sample heads should be used in unidirectional airflow systems.
7. 「動態」之等級可在正常操作或模擬操作中確認。當需要模擬最差狀況時，則於培養基充填期間予以確認。對於確認持續遵循指定的潔淨度分級，EN ISO 14644-2 提供關於其測試的資訊。	7. "In operation" classification may be demonstrated during normal operations, simulated operations or during media fills as worst-case simulation is required for this. EN ISO 14644-2 provides information on testing to demonstrate continued compliance with the assigned cleanliness classifications.
潔淨室及潔淨空氣裝置的監測（CLEAN ROOM AND CLEAN AIR DEVICE MONITORING）	
8. 潔淨室及潔淨空氣裝置應在動態中例行監測，且監測位置應依正式的風險分析研究，及在潔淨室及/或潔淨空氣裝置之分級期間所得結果為基礎。	8. Clean rooms and clean air devices should be routinely monitored in operation and the monitoring locations based on a formal risk analysis study and the results obtained during the classification of rooms and/or clean air devices.

9. 對於A級區，應在關鍵操作的全程中監測微粒，包括設備組裝在內，除非證明製程中之污染物會損壞微粒計數器或呈現危害，例如活微生物及放射性的危害；在此種情況下，設備之例行安裝操作期間的監測，應在暴露於該風險之前為之。模擬操作期間之監測亦應執行。A級區應以適當的頻率及採樣量加以監測，使所有介入、短暫突發事件及任何系統劣化皆會被偵測到，且如果超出警戒限量將會啟動警報器。當進行充填時，在充填點，因產品本身產生之微粒或小液滴，充填點可能無法一直維持≥5.0 μm 之微粒的限量是可接受的。	9. For Grade A zones, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly, except where justified by contaminants in the process that would damage the particle counter or present a hazard, e.g. live organisms and radiological hazards. In such cases monitoring during routine equipment set up operations should be undertaken prior to exposure to the risk. Monitoring during simulated operations should also be performed. The Grade A zone should be monitored at such a frequency and with suitable sample size that all interventions, transient events and any system deterioration would be captured and alarms triggered if alert limits are exceeded. It is accepted that it may not always be possible to demonstrate low levels of ≥5.0 μm particles at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself.
10. 針對 B 級區，雖取樣頻率可能會減少，但仍建議使用類似的系統。微粒監測系統之重要性應由相鄰之 A 級區及 B 級區間的隔離效果確定。B 級區應依此頻率及適當的採樣量加以監測，使得污染程度之變化，及系統之任何劣化將會被偵測到，且若超出警戒限量將啟動警報器。	10. It is recommended that a similar system be used for Grade B zones although the sample frequency may be decreased. The importance of the particle monitoring system should be determined by the effectiveness of the segregation between the adjacent Grade A and B zones. The Grade B zone should be monitored at such a frequency and with suitable sample size that changes in levels of contamination and any system deterioration would be captured and alarms triggered if alert limits are exceeded.

11. 浮游微粒監測系統可能包括獨立的微粒計數器，以歧管相繼連接取樣點到個別微粒計數器之網狀系統，或該二者之組合。所選擇之系統必須適合所考量的微粒大小。使用遙控取樣系統時，必須考慮在管線中微粒之減失（例如：沈降附著），以決定取樣管線之長度及管線中之任何彎曲的半徑。監測系統之選擇應考量使用於製造作業之原料所呈現之任何風險，例如涉及活微生物或放射性藥品者。	11. Airborne particle monitoring systems may consist of independent particle counters; a network of sequentially accessed sampling points connected by manifold to a single particle counter; or a combination of the two. The system selected must be appropriate for the particle size considered. Where remote sampling systems are used, the length of tubing and the radii of any bends in the tubing must be considered in the context of particle losses in the tubing. The selection of the monitoring system should take account of any risk presented by the materials used in the manufacturing operation, for example those involving live organisms or radiopharmaceuticals.
12. 為監測目的，使用自動化系統之採樣量，通常與該系統之採樣速率有關（具函數關係）。其樣品容量與使用於潔淨室及潔淨空氣裝置之正式分級的採樣量不需要相同。	12. The sample sizes taken for monitoring purposes 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 clean rooms and clean air devices.
13. 在 A 級區及 B 級區中，≥ 5.0 μm 微粒濃度計數的監測具有特別的重要性，因為它對於失敗之早期檢測是一重要診斷工具。≥ 5.0 μm 微粒計數之偶爾顯示，可能係由於電子雜訊、迷光（stray light）、偶合等所致之非真實計數（false counts）。然而，連貫性或規則性的低計數，可能是一污染事件的指標，且應加以調查。該等事件可能指出 HVAC 系統之早期異常、充填設備異常，或者，亦可能係在機器安裝及例行操作期間不良操作實務的徵兆。	13. In Grade A and B zones, the monitoring of the ≥5.0 μm particle concentration count takes on a particular significance as it is an important diagnostic tool for early detection of failure. The occasional indication of ≥5.0 μm particle counts may be false counts due to electronic noise, stray light, coincidence, etc. However consecutive or regular counting of low levels is an indicator of a possible contamination event and should be investigated. Such events may indicate early failure of the HVAC system, filling equipment failure or may also be diagnostic of poor practices during machine set-up and routine operation.

14. 在「靜態」表中所示之微粒限量應在作業完成後的無人狀態中，於 15-20 分鐘(指引值)之短暫「清除」期間（“clean up” period）中達成。	14. The particle limits given in the table for the “at rest” state should be achieved after a short “clean up” period of 15-20 minutes (guidance value) in an unmanned state after completion of operations.
15. C 級與 D 級區之動態監測應依品質風險管理的原則執行。其要求及警戒/行動值將取決於所執行操作作業之本質，但應於「清除期間」內達到建議之靜態潔淨區要求。	15. The monitoring of Grade C and D areas in operation should be performed in accordance with the principles of quality risk management. The requirements and alert/action limits will depend on the nature of the operations carried out, but the recommended “clean up period” should be attained.
16. 其他特徵，例如溫度及相對濕度，取決於產品及執行之作業的性質。這些參數不應影響已定義之潔淨度標準。	16. Other characteristics such as temperature and relative humidity depend on the product and nature of the operations carried out. These parameters should not interfere with the defined cleanliness standard.

17. 在各種不同等級從事之作業的實例，如下表所示（亦請參見第 28 及 35 節段）：

等級	最終滅菌產品的作業實例（請參見第 28-30 節）
A	當產品的充填處於異常風險時。
C	當溶液的調製處於異常風險時、產品的充填。
D	供後續充填溶液的製備及組件之準備。

等級	無菌製備作業的實例（請參見第 31-35 節）
A	無菌製備與充填。
C	要過濾之溶液的調製。
	待過濾溶液之製備。
D	洗滌後之組件的處理。

17. Examples of operations to be carried out in the various grades are given in the table below (see also paragraphs 28 to 35):

Grade	Examples of operations for terminally sterilised products (see para. 28-30)
A	**Filling of products, when unusually at risk**
C	**Preparation of solutions, when unusually at risk. Filling of products**
D	**Preparation of solutions and components for subsequent filling**

Grade	Examples of operations for aseptic preparations (see para. 31-35)
A	**Aseptic preparation and filling**
C	**Preparation of solutions to be filtered**
D	**Handling of components after washing**

18. 從事無菌作業時，作業區應時常使用諸如落菌培養皿、容量測定空氣取樣及表面取樣(例如擦拭法與培養皿接觸法)等方法監測。使用於動態中的取樣方法不得影響區域的保護措施。當審查最終產品放行的批次文件時，監測結果應列入考慮。關鍵操作後應監測表面及人員。	18. Where aseptic operations are performed monitoring should be frequent using methods such as settle plates, volumetric air and surface sampling (e.g. swabs and contact plates). Sampling methods used in operation should not interfere with zone protection. Results from monitoring should be considered when reviewing batch documentation for finished product release. Surfaces and personnel should be monitored after critical operations.
生產作業外之作業，例如在系統確效、清潔及滅菌處理後，亦需執行微生物學監測。	Additional microbiological monitoring is also required outside production operations, e.g. after validation of systems, cleaning and sanitation.

19. 動態潔淨區之微生物監測的建議限量

	微生物污染的建議限量[(a)]			
等級	空氣樣品 cfu/m^3	落菌培養皿 (直徑 90 mm)，cfu/4 時[(b)]	接觸培養皿 (直徑 55 mm)，cfu/培養皿	手套指印 印 5 根手指/手套 cfu/手套
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

註： (a) 這些都是平均值.
(b) 個別的落菌培養皿暴露時間得少於 4 小時.

19. Recommended limits for microbiological monitoring of clean areas in operation:

	Recommended limits for microbial contamination[(a)]			
Grade	Air sample cfu/m^3	Settle plates (diam. 90 mm) cfu/4hours[(b)]	Contact plates (diam. 55 mm), cfu/plate	Glove print 5 fingers cfu/glove
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

Notes: **(a) These are average values.**
(b) Individual settle plates may be exposed for less than 4 hours.

20. 微粒及微生物監測的結果，應設定適當的警戒與行動限量。作業程序應規定超出這些限量時之矯正措施。	20. Appropriate alert and action limits should be set for the results of particulate and microbiological monitoring. If these limits are exceeded, operating procedures should prescribe corrective action.

隔離裝置技術（ISOLATOR TECHNOLOGY）	
21. 隔離裝置技術之使用，將製造區域之人為的介入降到最低，可顯著降低無菌製造產品受來自環境之微生物污染的風險。隔離及轉送裝置有多種設計。隔離裝置及其背景環境應經設計以使其達到個別區域要求之空氣品質。隔離裝置由不同材料所建造，該等材料多少會有穿孔及漏裂之傾向。轉送裝置會有單門、雙門，到與滅菌機制結合之完全密閉系統等不同設計。	21. The utilisation of isolator technology to minimise human interventions in processing areas may result in a significant decrease in the risk of microbiological contamination of aseptically manufactured products from the environment. There are many possible designs of isolators and transfer devices. The isolator and the background environment should be designed so that the required air quality for the respective zones can be realised. Isolators are constructed of various materials more or less prone to puncture and leakage. Transfer devices may vary from a single door to double door designs to fully sealed systems incorporating sterilisation mechanisms.
22. 原物料轉入及轉出隔離裝置是污染的最大潛在來源之一。即使層流空氣可能不會存在於所有此種裝置的作業區中是被認可的，但一般而言，隔離裝置的內部區域通常是高風險作業的局部區域。	22. The transfer of materials into and out of the unit is one of the greatest potential sources of contamination. In general the area inside the isolator is the local zone for high risk manipulations, although it is recognised that laminar air flow may not exist in the working zone of all such devices.
23. 背景環境所需之空氣等級取決於隔離裝置的設計及其應用。該背景環境應加以管制，且應至少在 D 級背景環境下執行該無菌操作。	23. The air classification required for the background environment depends on the design of the isolator and its application. It should be controlled and for aseptic processing be at least grade D.
24. 隔離裝置應僅在適當確效後始得採用。確效應考慮隔離裝置技術之全部關鍵性因素，例如，隔離裝置內部與外部（背景環境）的空氣品質、隔離裝置的滅菌處理、轉送過程及隔離裝置的完整性等。	24. Isolators should be introduced only after appropriate validation. Validation should take into account all critical factors of isolator technology, for example the quality of the air inside and outside (background) the isolator, sanitation of the isolator, the transfer process and isolator integrity.
25. 監測應例行執行，且應包含隔離裝置及手套/袖套系統頻繁之洩漏試驗。	25. Monitoring should be carried out routinely and include frequent leak testing of the isolator and glove/sleeve system.
成型/充填/密封技術（BLOW/FILL/SEAL TECHNOLOGY）	

26. 成型/充填/密封設備係為一定目的建造之機器。容器從熱塑性塑膠粒成型、充填並密封之連續作業，完全由此自動化機器完成。若作業人員使用 A/B 級衣著時，則配備有效 A 級氣浴裝置而使用於無菌操作生產的成型/充填/密封設備，得安裝在至少 C 級的環境中。該背景環境在靜態時，應符合微生物及浮游微粒的限量；在動態時，只要符合微生物的限量。使用於生產最終滅菌產品之成型/充填/密封設備，應安裝在至少為 D 級的環境中。	26. Blow/fill/seal units are purpose built machines in which, in one continuous operation, containers are formed from a thermoplastic granulate, filled and then sealed, all by the one automatic machine. Blow/fill/seal equipment used for aseptic production which is fitted with an effective grade A air shower may be installed in at least a grade C environment, provided that grade A/B clothing is used. The environment should comply with the viable and non viable limits at rest and the viable limit only when in operation. Blow/fill/seal equipment used for the production of products which are terminally sterilised should be installed in at least a grade D environment.
27. 因這是特殊的技術，故至少要特別注意下列事項： - 設備之設計及驗證 - 原位清潔(cleaning-in-place)及原位滅菌(sterilisation-in-place)的確效及再現性 - 設備座落之背景潔淨室環境 - 操作者之訓練及著衣 - 設備之關鍵區域的介入，包括在充填開始前之任何無菌組裝在內。	27. Because of this special technology particular attention should be paid to, at least the following: - equipment design and qualification - validation and reproducibility of cleaning-in-place and sterilisation-inplace - background clean room environment in which the equipment is located - operator training and clothing - interventions in the critical zone of the equipment including any aseptic assembly prior to the commencement of filling.
最終滅菌的產品（TERMINALLY STERILISED PRODUCTS）	
28. 為提供微生物與微粒污染的低風險環境，以適合於過濾與滅菌，組件之準備及大多數產品之製備應至少在 D 級中為之。當該產品有微生物污染之高風險或異常風險時（例如，因該產品滋養微生物生長，或滅菌前必需長期間保存，或主要需在密閉設備中加工但無法達成者），則其準備/製備應在 C 級環境中執行。	28. Preparation of components and most products should be done in at least a grade D environment in order to give low risk of microbial and particulate contamination, suitable for filtration and sterilisation. Where the product is at a high or unusual risk of microbial contamination, (for example, because the product actively supports microbial growth or must be held for a long period before sterilisation or is necessarily processed not mainly in closed vessels), then preparation should be carried out in a grade C environment.

29. 最終滅菌產品的充填，應至少在 C 級環境中為之。	29. Filling of products for terminal sterilisation should be done in at least a grade C environment.
30. 產品處於來自環境的污染之異常風險者，例如，因充填作業緩慢，或容器為廣口，或在密封前必需暴露數秒鐘以上的時間，其充填應在具有至少 C 級背景環境之 A 級區中為之。軟膏劑、乳膏劑、懸液劑及乳劑於最終滅菌前，其製備與充填，通常應在 C 級環境中為之。	30. Where the product is at unusual risk of contamination from the environment, for example because the filling operation is slow or the containers are wide-necked or are necessarily exposed for more than a few seconds before sealing, the filling should be done in a grade A zone with at least a grade C background. Preparation and filling of ointments, creams, suspensions and emulsions should generally be carried out in a grade C environment before terminal sterilisation.
無菌製備（ASEPTIC PREPARATION）	
31. 洗滌後的組件，應在至少 D 級環境中處理。無菌原料與組件的處理應在具有 B 級背景的 A 級環境中執行，除非須經滅菌，或在製程中的後段經由微生物滯留濾器過濾。	31. Components after washing should be handled in at least a grade D environment. Handling of sterile starting materials and components, unless subjected to sterilisation or filtration through a micro-organism-retaining filter later in the process, should be done in a grade A environment with grade B background.
32. 製程中待無菌過濾之溶液的製備，應在 C 級環境中為之；不經無菌過濾者，其原物料的準備與產品的製備，應在具有 B 級背景的 A 級環境中為之。	32. Preparation of solutions which are to be sterile filtered during the process should be done in a grade C environment; if not filtered, the preparation of materials and products should be done in a grade A environment with a grade B background.
33. 無菌製備之產品的處理及充填應在具有 B 級背景的 A 級環境中為之。	33. Handling and filling of aseptically prepared products should be done in a grade A environment with a grade B background.
34. 完成封塞前，部分封閉之容器的轉送，如使用在冷凍乾燥中，應在具有 B 級背景的 A 級環境中，或應在 B 級環境中以密閉的轉送盤為之。	34. Prior to the completion of stoppering, transfer of partially closed containers, as used in freeze drying, should be done either in a grade A environment with grade B background or in sealed transfer trays in a grade B environment.
35. 製程中暴露之無菌軟膏劑、乳膏劑、懸液劑及乳劑不經後續過濾者，其製備與充填應在具有 B 級背景的 A 級環境中執行。	35. Preparation and filling of sterile ointments, creams, suspensions and emulsions should be done in a grade A environment, with a grade B background, when the product is exposed and is not subsequently filtered.

組織與人事（PERSONNEL）	
36. 應僅有所需之最少人員可在潔淨區的現場，在無菌作業期間這是特別重要。檢查與管制應盡可能在潔淨區外執行。	36. Only the minimum number of personnel required should be present in clean areas; this is particularly important during aseptic processing. Inspections and controls should be conducted outside the clean areas as far as possible.
37. 潔淨區中工作的所有人員（包含從事清潔及維修保養之人員），應接受有關正確製造無菌產品之規範的定期訓練。該訓練應包含衛生及微生物學的基本原理。有必要將未接受過此種訓練的外部人員（例如，建築或維修保養的承包商）帶進無菌區時，應特別注意對其指導及監督。	37. All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive regular training in disciplines relevant to the correct manufacture of sterile products. This training should include reference to hygiene and to the basic elements of microbiology. When outside staff who have not received such training (e.g. building or maintenance contractors) need to be brought in, particular care should be taken over their instruction and supervision.
38. 已從事於非目前製造過程使用的動物組織材料或微生物培養物之工作人員，不得進入無菌產品區，除非已遵守嚴格且清楚界定的進入程序。	38. Staff who have been engaged in the processing of animal tissue materials or of cultures of micro-organisms other than those used in the current manufacturing process should not enter sterile-product areas unless rigorous and clearly defined entry procedures have been followed.
39. 高標準的個人衛生及潔淨度是必要的。對參與無菌製劑製造的人員，應指導其提報任何可能引起異常數目或類型之污染物脫落的狀況；對該等狀況，定期健康檢查是有其必要的。對可能引起不適當之微生物危險的人員採取之行動，應由指派之權責人員決定。	39. High standards of personal hygiene and cleanliness are essential. Personnel involved in the manufacture of sterile preparations should be instructed to report any condition which may cause the shedding of abnormal numbers or types of contaminants; periodic health checks for such conditions are desirable. Actions to be taken about personnel who could be introducing undue microbiological hazard should be decided by a designated competent person.
40. 潔淨區中不得配戴手錶、珠寶及使用化妝品。	40. Wristwatches, make-up and jewellery should not be worn in clean areas.
41. 衣服之更換與洗滌應遵循指定之書面程序，以將潔淨區衣著的污染或帶入潔淨區之污染物降至最低。	41. Changing and washing should follow a written procedure designed to minimise contamination of clean area clothing or carry-through of contaminants to the clean areas.

42. 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。	42. 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 contamination.
43. 每一等級的區域要求之衣著，其說明如下：	43. The description of clothing required for each grade is given below:
D級： 人員的頭髮及蓄留之鬍鬚，應予覆蓋。應穿著一般的保護套裝及適當的鞋子或鞋套。為避免任何來自潔淨區外的污染，應採取適當的措施。	Grade D: Hair and, where relevant, beard should be covered. A general protective suit and appropriate shoes or overshoes should be worn. appropriate measures should be taken to avoid any contamination coming from outside the clean area.
C 級： 人員的頭髮、蓄留之鬍鬚及八字鬍，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，及適當的鞋子或鞋套。此衣著應無纖維或微粒異物釋出。	Grade C: Hair and where relevant beard and moustache should be covered. A single or two-piece trouser suit, gathered at the wrists and with high neck and appropriate shoes or overshoes should be worn. They should shed virtually no fibres or particulate matter.
A/B 級： 頭罩應完全包覆頭髮，及如有蓄留鬍鬚及八字鬍；頭罩末端應塞入套裝的領子內；應戴面罩，以防止液滴之散逸。應穿戴經適當滅菌、未沾粉末的橡皮或塑膠手套及滅菌過或消毒過的鞋子；褲管底端應塞入鞋內，衣袖應塞入手套內。防護衣實際上應幾無纖維或微粒物釋出，並阻擋由身體脫落的微粒。	Grade A/B: Headgear should totally enclose hair and, where relevant, beard and moustache; it should be tucked into the neck of the suit; a face mask should be worn to prevent the shedding of droplets. Appropriate sterilised, non-powdered rubber or plastic gloves and sterilised or disinfected footwear should be worn. Trouser-legs should be tucked inside the footwear and garment sleeves into the gloves. The protective clothing should shed virtually no fibres or particulate matter and retain particles shed by the body.
44. 廠外衣服不得帶入通往B級及C級區之更衣室中。應對每位在 A/B 級區之工作人員，在每一工作時段提供潔淨無菌(經滅菌或經適當滅菌)的防護裝。作業期間，應定期消毒手套。面罩及手套至少應在每一工作時段更換之。	44. Outdoor clothing should not be brought into changing rooms leading to grade B and C rooms. For every worker in a grade A/B area, clean sterile (sterilised or adequately sanitised) protective garments should be provided at each work session. Gloves should be regularly disinfected during operations. Masks and gloves should be changed at least for every working session.

45. 潔淨區的衣服應以不致積聚可能會在後來脫落之額外污染物的方式清潔及處理。這些作業應遵循書面程序。對於此類衣服，最好有其單獨的洗衣設備。衣服之不適當的處理會損傷其纖維，從而可能增加微粒脫落的風險。	45. Clean area clothing should be cleaned and handled in such a way that it does not gather additional contaminants which can later be shed. These operations should follow written procedures. Separate laundry facilities for such clothing are desirable. Inappropriate treatment of clothing will damage fibres and may increase the risk of shedding of particles.
廠房（PREMISES）	
46. 潔淨區內，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，且所有暴露的表面可容許重覆使用清洗劑，及消毒劑(如有使用時)。	46. In clean areas, all exposed surfaces should be smooth, impervious and unbroken in order to minimise the shedding or accumulation of particles or micro-organisms and to permit the repeated application of cleaning agents, and disinfectants where used.
47. 為減少灰塵的積聚及利於清潔，不應有無法清潔的凹處，且應盡量避免突出的壁架、儲架、杯架/櫃及設備。門之設計應避免無法清潔的凹處；因此，滑動門可能不合適。	47. To reduce accumulation of dust and to facilitate cleaning there should be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment. Doors should be designed to avoid those uncleanable recesses; sliding doors may be undesirable for this reason.
48. 夾層天花板應予密封，以防止來自其上方空間的污染。	48. False ceilings should be sealed to prevent contamination from the space above them.
49. 管線、管道及其他公用設施之安裝，應使其不產生凹處、未密封的開口及難以清潔的表面。	49. Pipes and ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces which are difficult to clean.
50. A/B 級區之無菌製造場所，應禁用水槽與排水設施。其他區域，應在機器、水槽及排水設施間裝配空氣阻斷裝置。潔淨度等級較低的潔淨室內，其地板的排水設施應裝配捕集器或水封，以防止逆流。	50. Sinks and drains should be prohibited in grade A/B areas used for aseptic manufacture. In other areas air breaks should be fitted between the machine or sink and the drains. Floor drains in lower grade clean rooms should be fitted with traps or water seals to prevent backflow.
51. 更衣室應設計成氣鎖室，用來提供不同更衣階段之實體的隔離，以將防護裝之微生物及微粒污染減到最低。更衣室應以過濾的空氣有效地沖洗。在靜態時，更衣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。進入與離開潔淨區，使用各自的更衣室有時是必要的。通常，洗手設備應只在更衣室的第一個階段提供。	51. Changing rooms should be designed as airlocks and used to provide physical separation of the different stages of changing and so minimise microbial and particulate contamination of protective clothing. They should be flushed effectively with filtered air. The final stage of the changing room should, in the at-rest state, be the same grade as the area into

	which it leads. The use of separate changing rooms for entering and leaving clean areas is sometimes desirable. In general hand washing facilities should be provided only in the first stage of the changing rooms.
52. 氣鎖室兩邊的門不得同時開啟，應啟動互鎖系統或視覺及/或聽覺的警報系統，以防止在同一時間有一個以上的門同時開啟。	52. Both airlock doors should not be opened simultaneously. An interlocking system or a visual and/or audible warning system should be operated to prevent the opening of more than one door at a time.
53. 全部的作業條件下，相對於較低潔淨度等級的周圍區域，過濾過的空氣應維持其正壓及空氣的流動，且應有效地沖洗該潔淨區。不同等級之毗鄰潔淨室應有 10-15 pa (1.0-1.5 mm 水柱)的壓差（指引值）。最大風險區域的保護措施應予特別注意。該區域為產品及接觸產品之潔淨組件所暴露之直接環境。需要圍堵某些物質，例如，致病性、高毒性、放射性或活病毒或活細菌的原料或產品的情況時，其空氣供應及壓差的各種建議可能需要修改。對於某些作業，設施的去污染與離開潔淨室之空氣的處理可能是必須的。	53. A filtered air supply should maintain a positive pressure and an air flow relative to surrounding areas of a lower grade under all operational conditions and should flush the area effectively. Adjacent rooms of different grades should have a pressure differential of 10-15 pascals (guidance values). Particular attention should be paid to the protection of the zone of greatest risk, that is, the immediate environment to which a product and cleaned components which contact the product are exposed. The various recommendations regarding air supplies and pressure differentials may need to be modified where it becomes necessary to contain some materials, e.g. pathogenic, highly toxic, radioactive or live viral or bacterial materials or products. Decontamination of facilities and treatment of air leaving a clean area may be necessary for some operations.
54. 應證明空氣流動的型態不會造成污染風險，例如，應小心確保空氣流動不會將人員、作業或機器產生之微粒散佈到較高產品風險的區域。	54. It should be demonstrated that air-flow patterns do not present a contamination risk, e.g. care should be taken to ensure that air flows do not distribute particles from a particlegenerating person, operation or machine to a zone of higher product risk.
55. 應提供警報系統，以顯示空氣供應上的失靈。在壓差重要的區域間，應安裝壓差計。這些壓差應定期記錄，或用其他的方法予以文件化。	55. A warning system should be provided to indicate failure in the air supply. Indicators of pressure differences should be fitted between areas where these

	differences are important. These pressure differences should be recorded regularly or otherwise documented.
設備（EQUIPMENT）	
56. 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：在一個滅菌的隧道中）。	56. 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).
57. 設備、配件及支援服務之設計與安裝，應盡可能使其作業(註：非生產作業)、維護保養及修理能在潔淨區外執行。需要滅菌者，應盡可能在完成組裝後為之。	57. As far as practicable equipment, fittings and services should be designed and installed so that operations, maintenance and repairs can be carried out outside the clean area. If sterilisation is required, it should be carried out, wherever possible, after complete reassembly.
58. 倘若設備之維護保養已在潔淨區內執行，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，於製造作業再開始前，該區域應予清潔、消毒及/或滅菌(合適時)。	58. When equipment maintenance has been carried out within the clean area, the area should be cleaned, disinfected and/or sterilised where appropriate, before processing recommences if the required standards of cleanliness and/or asepsis have not been maintained during the work.
59. 水處理設施及輸送系統，應經設計、建造及維護保養，以確保適當品質之可靠水源。該系統之運轉不得超出其設計能量（capacity）。注射用水應以阻止微生物生長的方式生產、儲存及輸送，例如在 70 ℃以上恆定循環。	59. Water treatment plants and distribution systems should be designed, constructed and maintained so as to ensure a reliable source of water of an appropriate quality. They should not be operated beyond their designed capacity. Water for injections should be produced, stored and distributed in a manner which prevents microbial growth, for example by constant circulation at a temperature above 70 °C.
60. 所有設備，例如：滅菌器、空氣處理及過濾系統、空氣通氣口及氣體過濾器、水處理、水製造、儲存與輸送系統，均應確效及有計畫的維護保養；其再使用應經核可。	60. All equipment such as sterilisers, air handling and filtration systems, air vent and gas filters, water treatment, generation, storage and distribution systems should be subject to validation and planned maintenance; their return to use should be approved.
衛生處理（SANITATION）	

61. 潔淨區的衛生處理特別重要，應依書面程序徹底清潔。使用消毒劑者，應採用一種以上的消毒劑。為了檢測抗藥性菌株的產生，應進行定期監測。	61. The sanitation of clean areas is particularly important. They should be cleaned thoroughly in accordance with a written programme. Where disinfectants are used, more than one type should be employed. Monitoring should be undertaken regularly in order to detect the development of resistant strains.
62. 消毒劑與清潔劑應監測其微生物的污染；稀釋液應保存在預先洗淨的容器中，且除非經過滅菌，應只在界定的期間內儲存。使用於 A 級及 B 級區的消毒劑與清潔劑，使用前應是無菌的。	62. Disinfectants and detergents should be monitored for microbial contamination; dilutions should be kept in previously cleaned containers and should only be stored for defined periods unless sterilised. Disinfectants and detergents used in Grades A and B areas should be sterile prior to use.
63. 潔淨區的燻蒸對於降低不易接近/進入之處所的微生物污染，可能是有用的。	63. Fumigation of clean areas may be useful for reducing microbiological contamination in inaccessible places.
製程作業（PROCESSING）	
64. 所有製程階段中，包含滅菌前的階段，應採取預防措施，以將污染降到最低。	64. Precautions to minimise contamination should be taken during all processing stages including the stages before sterilisation.
65. 源自於微生物的製劑，不得於其他藥品之製造區域中製備或充填；然而，在去活化後之死微生物體的疫苗或細菌萃取物疫苗，可在其他無菌藥品之相同的廠房設施中充填。	65. Preparations of microbiological origin should not be made or filled in areas used for the processing of other medicinal products; however, vaccines of dead organisms or of bacterial extracts may be filled, after inactivation, in the same premises as other sterile medicinal products.
66. 無菌作業的確效，應包含使用營養培養基之製程模擬試驗（培養基充填）。營養培養基的選擇應基於產品的劑型及營養培養基之選擇性、澄明度、濃度及滅菌的適合性。	66. Validation of aseptic processing should include a process simulation test using a nutrient medium (media fill). Selection of the nutrient medium should be made based on dosage form of the product and selectivity, clarity, concentration and suitability for sterilisation of the nutrient medium.
67. 製程模擬試驗應盡可能模擬例行的無菌製造過程，並包含所有關鍵的後續製造步驟，並應考量已知在正常生產中，及在最差狀況發生的各種介入。	67. The process simulation test should imitate as closely as possible the routine aseptic manufacturing process and include all the critical subsequent manufacturing steps. It

	should also take into account various interventions known to occur during normal production as well as worst-case situations.
68. 製程模擬試驗應對每個作業輪班，執行三次連續滿意的模擬試驗作為初始確效，並在界定的時間間隔及對 HVAC 系統、設備、製程與輪班次數有任何重大變更後，重複執行。通常，製程模擬試驗應對每一輪班與製程每年重複兩次。	68. Process simulation tests should be performed as initial validation with three consecutive satisfactory simulation tests per shift and repeated at defined intervals and after any significant modification to the HVAC system, equipment, process and number of shifts. Normally process simulation tests should be repeated twice a year per shift and process.
69. 使用於培養基充填的容器數目應足使其能夠有效評估。對於小批量的生產，其培養基充填的容器數目應至少等於該產品批次的批量。目標值應為無生長並適用下列規定：	69. The number of containers used for media fills should be sufficient to enable a valid evaluation. For small batches, the number of containers for media fills should at least equal the size of the product batch. The target should be zero growth and the following should apply:
● 充填少於 5000 單元者，不得有任何污染單元。	● When filling fewer than 5000 units, no contaminated units should be detected.
● 充填 5000 至 10,000 單元者： a) 有一個受污染單元時，應予以調查，包含重複執行培養基充填的考量在內； b) 有二個受污染單元時，應於調查後，就其原因進行再確效。	● When filling 5,000 to 10,000 units: a) One (1) contaminated unit should result in an investigation, including consideration of a repeat media fill; b) Two (2) contaminated units are considered cause for revalidation, following investigation.
● 充填多於 10,000 單元者， a) 有一個受污染單元時，應予以調查； b) 有二個受污染單元時，應於調查後，就其原因進行再確效[1]。	● When filling more than 10,000 units: a) One (1) contaminated unit should result in an investigation; b) Two (2) contaminated units are considered cause for revalidation, following investigation[1].
[1] *關於無菌操作之確效的進一步細節，請參考 PIC/S 關於無菌操作之確效的建議 (PI 007)* 。	[1] *For further details on the validation of aseptic processing, please refer to the PIC/S Recommendation on the Validation of Aseptic Processing (PI 007)*
70. 對於任何測試之單元數，其微生物污染之間歇性事件，可能是低度污染的徵象應予調查。對於重大失敗之調查，應包括對前次成功的培養基充填後，所製造批次之無菌性保證的可能影響。	70. For any run size, intermittent incidents of microbial contamination may be indicative of low-level contamination that should be investigated. Investigation of gross failures should include the potential impact on the sterility assurance of batches manufactured since the last successful media fill.

71. 應注意任何確效不得損及製程。	71. Care should be taken that any validation does not compromise the processes.
72. 水源、水處理設備及經過處理的水均應定期監測其化學及生物學的污染，及內毒素(當合適時)，該監測的結果及採取的任何行動之紀錄均應予以保存。	72. Water sources, water treatment equipment and treated water should be monitored regularly for chemical and biological contamination and, as appropriate, for endotoxins. Records should be maintained of the results of the monitoring and of any action taken.
73. 潔淨區中，尤其是當無菌作業正進行時，應保持最小的作業活動，且人員的移動應加以管制並使其井然有序，以避免由於過度激烈的活動引起微粒及微生物的過度散落。由於作業人員穿戴衣著的特質，周遭的溫度與濕度不應高到令其不舒適。	73. Activities in clean areas and especially when aseptic operations are in progress should be kept to a minimum and movement of personnel should be controlled and methodical, to avoid excessive shedding of particles and organisms due to over-vigorous activity. The ambient temperature and humidity should not be uncomfortably high because of the nature of the garments worn.
74. 原料之微生物學上的污染應為最低。經由監測顯示需要微生物學上之品質要求者，其規格應包含該要求。	74. Microbiological contamination of starting materials should be minimal. Specifications should include requirements for microbiological quality when the need for this has been indicated by monitoring.
75. 潔淨區中，容易產生纖維的容器與原物料，應降至最低。	75. Containers and materials liable to generate fibres should be minimised in clean areas.
76. 合適時，應採取措施，將最終產品的微粒污染降至最低。	76. Where appropriate, measures should be taken to minimise the particulate contamination of the end product.
77. 組件、容器及設備在最終清潔過程後，應以使其不再被污染的方式處理。	77. Components, containers and equipment should be handled after the final cleaning process in such a way that they are not recontaminated.
78. 組件、容器及設備之洗滌及乾燥與滅菌的間隔期間，以及其滅菌與使用之間隔期間，應縮至最短，且應受適合其儲存條件的時間限制。	78. The interval between the washing and drying and the sterilisation of components, containers and equipment as well as between their sterilization and use should be minimised and subject to a time-limit appropriate to the storage conditions.
79. 從溶液製備開始至其滅菌之時間，或從溶液製備開始至其經微生物滯留濾器過濾之時間，應縮至最短。每一產品考量其組成及規定之儲存方法，應有設定之最長容	79. The time between the start of the preparation of a solution and its sterilisation or filtration through a micro-organism-retaining filter should be

許時間。	minimised. There should be a set maximum permissible time for each product that takes into account its composition and the prescribed method of storage.
80. 滅菌前應監測其負荷菌。緊接滅菌前之污染應有作業限量，該限量與要採用之滅菌方法的效能有關。對於無菌充填的產品及最終滅菌的產品之每一批次皆應執行負荷菌分析。對於最終滅菌產品設定為過度滅菌參數者，負荷菌得僅在適當排定之時間間隔監測。對參數放行系統，負荷菌分析應對每一批次執行，並作為製程中測試。合適時，應監測內毒素含量。所有溶液，尤其是大型輸注液，應通過微生物滯留濾器過濾。如果可能，該過濾器位置應緊接於充填之前。	80. The bioburden should be monitored before sterilisation. There should be working limits on contamination immediately before sterilisation, which are related to the efficiency of the method to be used. Bioburden assay should be performed on each batch for both aseptically filled product and terminally sterilised products. Where overkill sterilisation parameters are set for terminally sterilised products, bioburden might be monitored only at suitable scheduled intervals. For parametric release systems, bioburden assay should be performed on each batch and considered as an in-process test. Where appropriate the level of endotoxins should be monitored. All solutions, in particular large volume infusion fluids, should be passed through a microorganism-retaining filter, if possible sited immediately before filling.
81. 潔淨區進行無菌作業所需要之組件、容器、設備及任何其他物品，應予滅菌，並通過密封在牆壁中的雙門滅菌器進入該潔淨區，或經由可達到不會導入污染的相同目的之程序進入。非可燃性氣體應通過微生物滯留濾器。	81. Components, containers, equipment and any other article required in a clean area where aseptic work takes place should be sterilised and passed into the area through double-ended sterilisers sealed into the wall, or by a procedure which achieves the same objective of not introducing contamination. Noncombustible gases should be passed through micro-organism retentive filters.
82. 任何新程序的效能都應予以確效，且該確效應依其性能表現歷史為基礎，在排定時間間隔進行確認，或在製程或設備做出任何重大變更時，亦應進行確認。	82. The efficacy of any new procedure should be validated, and the validation verified at scheduled intervals based on performance history or when any significant change is made in the process or equipment.
滅菌（STERILISATION）	

83. 所有滅菌過程應予以確效。當採用的滅菌方法為非現行版本之相關藥典所述的方法，或當該藥典方法使用於非單純水性或油性溶液的產品時，應予特別注意。可行時，加熱滅菌是首選的方法。在任何情況中，滅菌過程應符合上市與製造許可。	83. All sterilisation processes should be validated. Particular attention should be given when the adopted sterilisation method is not described in the current edition of the European Pharmacopoeia, or when it is used for a product which is not a simple aqueous or oily solution. Where possible, heat sterilisation is the method of choice. In any case, the sterilisation process must be in accordance with the marketing and manufacturing authorisations.
84. 任何滅菌過程在被採用前，對產品及其在每一種要滅菌處理之裝載型式的所有部位，達成所期望滅菌條件效能的適當性，應以物理量測及生物指示劑(合適時)加以證明。該滅菌過程的有效性應在排定的時間間隔，至少每年一次，及每當對設備做出重大修改時，加以確認。這些結果的紀錄應予以保存。	84. Before any sterilisation process is adopted its suitability for the product and its efficacy in achieving the desired sterilising conditions in all parts of each type of load to be processed should be demonstrated by physical measurements and by biological indicators where appropriate. The validity of the process should be verified at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment. Records should be kept of the results.
85. 為有效滅菌，物料的全部皆應接受所需之處理，且該過程應經設計以確保其已達成有效滅菌。	85. For effective sterilisation the whole of the material must be subjected to the required treatment and the process should be designed to ensure that this is achieved.
86. 所有滅菌過程，應建立經確效的裝載型式。	86. Validated loading patterns should be established for all sterilisation processes.
87. 生物指示劑應視為監測滅菌之附加方法。生物指示劑應依製造者的指示儲存及使用，並應以陽性對照品核對其品質。如果使用生物指示劑，應採取嚴格的防範措施，以避免由其移轉微生物污染。	87. Biological indicators should be considered as an additional method for monitoring the sterilisation. They should be stored and used according to the manufacturer’s instructions, and their quality checked by positive controls. If biological indicators are used, strict precautions should be taken to avoid transferring microbial contamination from them.

88. 應有清楚區分未滅菌及已滅菌產品的方法。每一個盛裝產品或組件的籃子、盤子或其他搬運架，皆應清楚標示其名稱、批號及是否經滅菌。合適時，可使用指示劑，例如高壓蒸氣滅菌指示帶，標示一個批次（或次批次）是否已完成滅菌過程，惟其結果無法實際作為該批次為無菌的可靠指標。	88. There should be a clear means of differentiating products which have not been sterilised from those which have. Each basket, tray or other carrier of products or components should be clearly labelled with the material name, its batch number and an indication of whether or not it has been sterilised. Indicators such as autoclave tape may be used, where appropriate, to indicate whether or not a batch (or sub-batch) has passed through a sterilisation process, but they do not give a reliable indication that the lot is, in fact, sterile.
89. 每一個滅菌操作應有其滅菌紀錄，且應當作批次放行程序的一部份予以核准。	89. Sterilisation records should be available for each sterilisation run. They should be approved as part of the batch release procedure.
加熱滅菌法（STERILISATION BY HEAT）	
90. 每一個加熱滅菌週期應記錄在具足夠大刻度的時間/溫度圖表上，或以具有適當準確度與精密度之其他適當設備記錄。使用於控制及/或記錄之溫度探針的位置，應在確效時即已決定；可行時，亦應以置放在相同位置之第二個獨立溫度探針核對。	90. Each heat sterilisation cycle should be recorded on a time/temperature chart with a sufficiently large scale or by other appropriate equipment with suitable accuracy and precision. The position of the temperature probes used for controlling and/or recording should have been determined during the validation, and where applicable also checked against a second independent temperature probe located at the same position.
91. 化學或生物指示劑雖亦可使用，但不得取代物理量測。	91. Chemical or biological indicators may also be used, but should not take the place of physical measurements.
92. 滅菌時間之期間的量測於開始前，應有足夠的時間容許裝載物的全部達到所要求的溫度。該時間應針對要處理之每一種裝載型式訂定。	92. Sufficient time must be allowed for the whole of the load to reach the required temperature before measurement of the sterilising time-period is commenced. This time must be determined for each type of load to be processed.

93. 在加熱滅菌週期的高溫階段後，應採取防範措施，防止經滅菌的裝載物在冷卻中受到污染。與產品接觸之任何冷卻流體或氣體應已滅菌，除非能顯示任何洩漏的容器不會被核准使用。	93. After the high temperature phase of a heat sterilisation cycle, precautions should be taken against contamination of a sterilised load during cooling. Any cooling fluid or gas in contact with the product should be sterilised, unless it can be shown that any leaking container would not be approved for use.
濕熱滅菌法（MOIST HEAT）	
94. 溫度與壓力均應用來監測濕熱滅菌過程。通常，控制儀器裝置與監測儀器裝置及其記錄圖表應各自獨立。對這些使用之自動控制與監測系統應加以確效，以確保其符合關鍵過程的要求。系統及滅菌週期之錯誤，應由系統所記錄並為操作者觀察到。滅菌期間，獨立溫度指示器的讀數，應與圖表記錄器例行核對。滅菌艙底部裝有排水口的滅菌器，可能亦須在滅菌期間全程記錄該位置的溫度。真空階段為該滅菌週期之一部分者，對該艙應執行頻繁的洩漏試驗。	94. Both temperature and pressure should be used to monitor the process. Control instrumentation should normally be independent of monitoring instrumentation and recording charts. Where automated control and monitoring systems are used for these applications they should be validated to ensure that critical process requirements are met. System and cycle faults should be registered by the system and observed by the operator. The reading of the independent temperature indicator should be routinely checked against the chart recorder during the sterilisation period. For sterilisers fitted with a drain at the bottom of the chamber, it may also be necessary to record the temperature at this position, throughout the sterilisation period. There should be frequent leak tests on the chamber when a vacuum phase is part of the cycle.
95. 非置於密封容器中而要滅菌之產品，應以容許空氣之移除及蒸氣之穿透，而在滅菌後能防止再污染的材料包覆之。裝載物的所有部位在要求的溫度及期間應與滅菌劑保持接觸。	95. The items to be sterilised, other than products in sealed containers, should be wrapped in a material which allows removal of air and penetration of steam but which prevents recontamination after sterilisation. All parts of the load should be in contact with the sterilising agent at the required temperature for the required time.
96. 應注意確保用於滅菌的蒸氣具有適當的品質，且其所含之添加物濃度不致引起產品或設備污染。	96. Care should be taken to ensure that steam used for sterilisation is of suitable quality and does not contain additives at a level which could cause contamination of product or equipment.

乾熱滅菌法（DRY HEAT）	
97. 乾熱滅菌採用的製程，應包含艙內空氣的循環及正壓的維持，以防止非無菌空氣的進入。任何容許進入的空氣，應通過 HEPA 過濾器。製程亦需移除熱原時，使用內毒素的挑戰試驗應列為確效的一部分。	97. The process used should include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. Any air admitted should be passed through a HEPA filter. Where this process is also intended to remove pyrogens, challenge tests using endotoxins should be used as part of the validation.
輻射滅菌法（STERILISATION BY RADIATION）	
98. 輻射滅菌主要用於對熱敏感的原物料與產品的滅菌。許多藥品及一些包裝材料是對輻射線敏感的，因此，本方法僅在經由實驗確認其對於產品不具有害效應時，始可使用。紫外線照射通常不是一個可接受的滅菌方法。	98. Radiation sterilisation is used mainly for the sterilisation of heat sensitive materials and products. Many medicinal products and some packaging materials are radiation-sensitive, so this method is permissible only when the absence of deleterious effects on the product has been confirmed experimentally. Ultraviolet irradiation is not normally an acceptable method of sterilisation.
99. 輻射滅菌程序中，輻射劑量應予以量測。為達此目的，應使用與劑量率無關的劑量指示劑，以提供產品本身接受之劑量的定量性量測。在裝載物中應插入足夠數目與分布的劑量計，以確保在輻射照射器中一直都有一個劑量計。使用塑膠劑量計者，應在其校正的時間限度內使用。劑量計的吸光度應在暴露於輻射後的短時間內讀取。	99. During the sterilisation procedure the radiation dose should be measured. For this purpose, dosimetry indicators which are independent of dose rate should be used, giving a quantitative measurement of the dose received by the product itself. Dosimeters should be inserted in the load in sufficient number and close enough together to ensure that there is always a dosimeter in the irradiator. Where plastic dosimeters are used they should be used within the time-limit of their calibration. Dosimeter absorbances should be read within a short period after exposure to radiation.
100. 生物指示劑可作為附加的管制使用。	100. Biological indicators may be used as an additional control.
101. 確效程序應確保考量到包裝密度上之差異所造成的效應。	101. Validation procedures should ensure that the effects of variations in density of the packages are considered.

102. 原物料之處理程序，應防止已輻射滅菌與未經輻射滅菌之原物料間的混雜。輻射敏感性的變色圓片，亦應使用在每件包裝上，以區分已輻射滅菌及未經輻射滅菌的包裝。	102. Materials handling procedures should prevent mix-up between irradiated and nonirradiated materials. Radiation sensitive colour disks should also be used on each package to differentiate between packages which have been subjected to irradiation and those which have not.
103. 總輻射劑量應在預定的照射時間內達到。	103. The total radiation dose should be administered within a predetermined time span.
環氧乙烯滅菌（STERILISATION WITH ETHYLENE OXIDE）	
104. 本方法應只用在沒有其他方法可用的情形。在滅菌製程確效期間，應顯示對產品無損害的效應，及其除氣所容許的條件與時間，可將任何殘留氣體及反應產物減低至該類型產品或原物料界定之允許限量。	104. 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 are such as to reduce any residual gas and reaction products to defined acceptable limits for the type of product or material.
105. 氣體與微生物細胞間的直接接觸是必需的。為避免可能會包在像結晶或乾燥蛋白質這類物質之微生物的存在，應採取預防措施。包裝材料的特質與數量會顯著影響該滅菌過程。	105. 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 and quantity of packaging materials can significantly affect the process.
106. 暴露於氣體之前，應使原物料達到該過程所要求之濕度與溫度的平衡狀態。達到該狀態所需的時間，應針對在滅菌前應縮減至最短的相對需求加以均衡。	106. Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process. The time required for this should be balanced against the opposing need to minimise the time before sterilisation.
107. 每一個滅菌週期皆應以適當的生物指示劑試驗片監測，並將適當數量之試驗片分佈在整個裝載。取得的資訊應涵蓋於批次紀錄中。	107. Each sterilisation cycle should be monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load. The information so obtained should form part of the batch record.

108. 每一滅菌週期，應將完成該週期所用的時間、滅菌期間艙內的壓力、溫度、濕度、所使用之氣體濃度及氣體總量做成紀錄。滅菌週期的全程，應將壓力與溫度記錄在一張圖表上。該等紀錄應納入該批次紀錄中。	108. For each sterilisation cycle, records should be made of the time taken to complete the cycle, of the pressure, temperature and humidity within the chamber during the process and of the gas concentration and of the total amount of gas used. The pressure and temperature should be recorded throughout the cycle on a chart. The record(s) should form part of the batch record.
109. 滅菌後，裝載物應以管制的方式，在通風的條件下儲存，以容許將殘留氣體及反應產物降低到界定的水準，此製程應予以確效。	109. After sterilisation, the load should be stored in a controlled manner under ventilated conditions to allow residual gas and reaction products to reduce to the defined level. This process should be validated.
不能在其最終容器中滅菌之藥品的過濾（FILTRATION OF MEDICINAL PRODUCTS WHICH CANNOT BE STERILISED IN THEIR FINAL CONTAINER）	
110. 可在最終容器中滅菌者，只使用過濾除菌不被認為是足夠的。目前可用的方法中，蒸氣滅菌是較好的。產品不能在最終容器中滅菌者，溶液或液體可通過0.22 μm（或更小）之孔徑，或至少具有同等微生物滯留性質之濾器，濾入預先已滅菌的容器中。此種濾器能移除大多數的細菌及黴菌，但不能移除全部的病毒或黴漿菌，應考慮以某種程度的熱處理補充該過濾過程。	110. Filtration alone is not considered sufficient when sterilisation in the final container is possible. With regard to methods currently available, steam sterilisation is to be preferred. If the product cannot be sterilised in the final container, solutions or liquids can be filtered through a sterile filter of nominal pore size of 0.22 micron (or less), or with at least equivalent micro-organism retaining properties, into a previously sterilised container. Such filters can remove most bacteria and moulds, but not all viruses or mycoplasmas. Consideration should be given to complementing the filtration process with some degree of heat treatment.
111. 與其他滅菌製程相較，由於過濾方法有潛在之附加風險，所以，在緊接於充填前，進一步透過一個滅菌過之微生物滯留濾器作為第二道過濾是可取的。最終的無菌過濾應盡可能接近於充填點為之。	111. Due to the potential additional risks of the filtration method as compared with other sterilisation processes, a second filtration via a further sterilised microorganism retaining filter, immediately prior to filling, may be advisable. The final sterile filtration should be carried out as close as possible to the filling point.
112. 濾器之纖維脫落應為最少。	112. Fibre-shedding characteristics of filters should be minimal.

113. 使用前應證明滅菌過之濾器的完整性，且應在使用後，立即以適當的方法，例如起泡點、擴散流或持壓試驗確認。過濾已知容量的大量溶液所需之時間及通過濾器要使用之壓差，應在確效期間予以決定。例行製造中，與之任何顯著之差異，應予以註記及調查。這些檢查的結果應包含在該批次的紀錄中。關鍵之氣體及空氣通氣過濾器應在使用後確認其完整性。其他濾器亦應在適當的時間間隔確認其完整性。	113. The integrity of the sterilised filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test. The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter should be determined during validation and any significant differences from this during routine manufacturing should be noted and investigated. Results of these checks should be included in the batch record. The integrity of critical gas and air vent filters should be confirmed after use. The integrity of other filters should be confirmed at appropriate intervals.
114. 同一濾器不得使用超過一個工作天，除非已經過確效。	114. The same filter should not be used for more than one working day unless such use has been validated.
115. 濾器不得因移除產品之成分或將其組成物釋入產品，而影響到產品。	115. The filter should not affect the product by removal of ingredients from it or by release of substances into it.
無菌產品的完成（FINISHING OF STERILE PRODUCTS）	
以下為 PE009-8 GMP Guide 新增：	
116. 經部分封塞之冷凍乾燥小瓶應一直維持在 A 級條件下，直到橡皮塞完全塞入為止。	116. Partially stoppered freeze drying vials should be maintained under Grade A conditions at all times until the stopper is fully inserted.
117. 容器應以經過適當確效的方法封閉。以熔封法封閉的容器，例如玻璃或塑膠的安瓿應接受百分之百之完整性試驗。其他容器樣品，應依適當的程序檢查其完整性。	117. Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. glass or plastic ampoules should be subject to 100% integrity testing. Samples of other containers should be checked for integrity according to appropriate procedures.
118. 鋁蓋捲縮定位在經封塞之小瓶前，該無菌充填小瓶之容器封塞系統並不完整。因此，鋁蓋捲縮應在膠塞塞入後盡快執行。	118. The container closure system for aseptically filled vials is not fully integral until the aluminium cap has been crimped into place on the stoppered vial. Crimping of the cap should therefore be performed as soon as possible after stopper insertion.

119. 因鋁蓋捲縮設備會產生大量非微生物性微粒，該設備應裝設於配有適當抽氣裝置之隔離站中。	119. As the equipment used to crimp vial caps can generate large quantities of nonviable particulates, the equipment should be located at a separate station equipped with adequate air extraction.
120. 小瓶之捲縮封蓋，可作為無菌操作過程執行，或在無菌核心外，作為潔淨過程執行，惟前者應使用經滅菌的蓋子。採用後者時，小瓶應以 A 級條件保護，直到離開無菌操作區的作業點。之後，經封塞的小瓶應以 A 級空氣保護，直到鋁蓋已經捲縮為止。	120. Vial capping can be undertaken as an aseptic process using sterilised caps or as a clean process outside the aseptic core. Where this 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.
121. 小瓶之膠塞有漏塞或位置偏移者，應在捲縮封蓋前移除。封蓋作業站需要人員介入時，應使用適當的技術，防止直接接觸小瓶，並使微生物污染減到最低。	121. Vials with missing or displaced stoppers should be rejected prior to capping. Where human intervention is required at the capping station, appropriate technology should be used to prevent direct contact with the vials and to minimise microbial contamination.
122. 限制性進入屏障(RABS)及隔離裝置可能有助於確保所需之條件，並將人員直接介入捲縮封蓋作業中之情形減到最低。	122. Restricted access barriers and isolators may be beneficial in assuring the required conditions and minimising direct human interventions into the capping operation.
123. 真空下密封的容器，應在適當及預先設定的期間後，測試該真空度的維持。	123. Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period.
124. 已充填的容器應個別檢查其外來污染或其他瑕疵。以目視檢查者，應在適當且經控制的照明與背景條件下執行。執行該檢查的作業人員，應通過定期的視力健檢，戴眼鏡者，應戴上眼鏡接受健檢，並在產品檢查中給予定時的休息。使用其他檢查方法者，其過程應予以確效，並在一定時間間隔檢查該設備的性能。其結果應予以記錄。	124. Filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. When inspection is done visually, it should be done under suitable and controlled conditions of illumination and background. Operators doing the inspection should pass regular eye-sight checks, with spectacles if worn, and be allowed frequent breaks from inspection. Where other methods of inspection are used, the process should be validated and the performance of the equipment checked at intervals. Results should be recorded.
品質管制（QUALITY CONTROL）	

125. 最終產品的無菌試驗，應僅被認為是一系列確保無菌性之控制下的最後措施。該測試應就所涉產品加以確效。	125. The sterility test applied to the finished product should only be regarded as the last in a series of control measures by which sterility is assured. The test should be validated for the product(s) concerned.
126. 在允許以參數放行的情形下，應特別注意全部製造過程的確效與監測。	126. In those cases where parametric release has been authorised, special attention should be paid to the validation and the monitoring of the entire manufacturing process.
127. 無菌試驗所抽取之樣品，須為整個批次中的代表性樣品，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：	127. 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, e.g.:
a) 對於經無菌充填的產品，其樣品應包含在該批次之開始與結束時，及在任何重大介入後充填的容器；	a) for products which have been filled aseptically, samples should include containers filled at the beginning and end of the batch and after any significant intervention;
b) 對於以最終容器形式加熱滅菌的產品，應考慮取自該滅菌裝載中可能最冷位置的樣品。	b) for products which have been heat sterilised in their final containers, consideration should be given to taking samples from the potentially coolest part of the load.

附則 2　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）	
製造生物原料藥及產品所使用之方法，是在擬訂適當法規管制上的一個關鍵因素。	The methods employed in the manufacture of biological medicinal substances and products are a critical factor in shaping the appropriate regulatory control.
因此，生物原料藥及產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之全部範圍的原料藥及產品之指導原則。	Biological medicinal substances and products can be defined therefore largely by reference to their method of manufacture. This annex provides guidance on the full range of medicinal substances and products defined as biological.
本附則分成兩個主要部分：	This annex is divided into two main parts:
a) A 部分包含從製造生物原料藥及產品之管制種批與細胞庫或原料到最終作業與測試的補充指導原則。	a) Part A contains supplementary guidance on the manufacture of biological medicinal substances and products, from control over seed lots and cell banks or starting material through to finishing activities and testing.
b) B 部分包含特定之生物原料藥及產品類別的進一步指導原則。	b) Part B contains further guidance on selected types of biological medicinal substances and 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導原則。本附則的範圍有兩個方面：	This annex, along with several other annexes of the 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，主要指導原則為 GMP 第二部。對於生物產品之隨後製造步驟的指導原則則為 GMP 第一部。對於某些類別之產品（例如，細胞來源之新興生醫產品）的所有製造步驟都需要以無菌技術執行。	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. For some types of product (e.g. Advanced Therapy Medicinal Products (ATMP) cell-based products) all manufacturing steps need to be conducted aseptically.
b) 產品類別－本附則提供經界定為生物藥品之全部範圍的原料藥及產品之指導原則。	b) Type of product - this annex provides guidance on the full range of medicinal substances and products defined as biological.

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。抗生素並非被界定或納為生物產品，惟，在進行生物性的製造階段，可以使用本附則中的指導原則。對於由分離人類血液或血漿衍生之藥品的指導原則涵蓋於附則 14。非基因轉殖植物產品的指導原則涵蓋於附則 7（未涵蓋於西藥藥品優良製造規範之範圍）。	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 substances but GMP principles should always be adhered to. The inclusion of some early steps of manufacture within the scope of the annex does not imply that those steps will be routinely subject to inspection by the authorities. Antibiotics are not defined or included as biological products, however where biological stages of manufacture occur, guidance in this Annex may be used. 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：	In certain cases, other legislation may be applicable to the starting materials for biologicals:
(a) 對於工業製造之產品（例如，藥品）所使用的組織與細胞，其捐贈、採集與檢驗可能由國家法規所涵蓋。	(a) For tissue and cells used for industrially manufactured products (such as pharmaceuticals), the donation, procurement and testing of tissue and cells may be covered by national legislation.
(b) 在使用血液或成分血作為新興生醫產品的起始原料時，國家法規可能對捐血者之篩選與血液及成分血的收集與檢驗加以技術要求。	(b) Where blood or blood components are 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[1].

(c) 經基因改造之有機體的製造與管制需要遵從當地與國家的要求。在處理任何基因改造之微生物的設施，應建立適當的圍堵並維持之。為了建立並維持包括防止交叉污染之措施在內的適當生物安全等級，應參照國家法規規定且仍應遵守 GMP 要求。	(c) 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 including measures to prevent cross contamination. There should be no conflicts with GMP requirements.

表 1. 對於在附則 2 範圍內之製造活動的說明性指引

原料類別與來源	產品舉例	適用於本指引之製造步驟以灰色表示			
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，ATMPs 免疫血清	植物、器官、組織或體液的收集	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；酵素酶、蛋白質	MCB、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	基因重組產品、單株抗體、過敏原、疫苗、基因治療（病毒與非病毒載體、質體）	MCB 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，ATMPs	主基因轉殖庫，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，工作基因轉殖庫	栽種、收成	起始萃取、分離、純化、修飾	配方調製、充填
6. 人類來源	尿衍生酵素酶、荷爾蒙	液體的收集	混合及/或起始處理	分離與純化	配方調製、充填
7. 人類及/或動物來源	基因治療：基因改造細胞	起始組織/細胞的捐贈、採集與檢驗	製造載體與細胞純化及處理	細胞的活體外基因改造，建立 MCB、WCB 或初代細胞批	配方調製、充填
	體細胞治療	起始組織/細胞的捐贈、採集與檢驗	建立 MCB、WCB 或初代細胞批或細胞庫	細胞分離，培養物純化，與非細胞成分組合	配方調製、充填
	組織工程產品	起始組織/細胞的捐贈、採集與檢驗	起始處理，分離與純化，建立 MCB、WCB、初代細胞批或細胞庫	細胞分離，培養物純化，與非細胞成分組合	配方調製、充填
GMP 要求遞增→					
縮寫的解釋，參見術語彙編					

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

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, ATMPs immunosera	Collection of plant, organ, tissue 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 Gene Therapy (viral and non-viral vectors, plasmids)	Establishment & maintenance of MCB and WCB, MSL, WSL	Cell culture and /or fermentation	Isolation, purification, modification	Formulation, filling
4. Animal sources: transgenic	Recombinant proteins, ATMPs[4]	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, allergen	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 and/or animal sources[7]	Gene therapy: genetically modified cells[6]	Donation, procurement and testing of starting tissue/cells[8]	Manufacture vector[7] and cell purification and processing,	Ex-vivo genetic modification of cells, Establish MCB, WCB or primary cell lot	Formulation, filling
	Somatic cell Therapy	Donation, procurement and testing of starting tissue/cells[8]	Establish MCB, WCB or primary cell lot or cell pool	Cell isolation, culture purification, combination with non-cellular components	Formulation, filling
	Tissue engineered Products	Donation, procurement and testing of starting tissue/cells[8]	Initial processing, isolation and purification, establish MCB, WCB, primary cell lot or cell pool	Cell isolation, culture, purification, combination with non-cellular components	Formulation, filling
Increasing GMP requirements→					

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.

[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.

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

[7] Where these are viral vectors, the main controls are as for virus manufacture (row 2).

[8] In the EEA, human tissues and cells must comply with Directive 2004/23/EC and implementing Directives at these stages

原則（PRINCIPLE）	
製造生物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 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.
與使用化學與物理技術製造的傳統藥品具高度一致性不同，生物原料藥及產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 medicinal substances and products involves biological processes and materials, such as cultivation of cells or extraction of material 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 their 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，這提供外來微生物污染物增長的機會。此外，許多產品承受寬廣範圍之純化技術的能力是有限的，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, many products are 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、上市許可與臨床試驗許可的規格），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。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。應使用環境管制與監測，以及可行時，使用連同密閉系統之原位清潔及滅菌系統，可以顯著地減少意外污染與交叉污染的風險。	Specifications related to products (such as those in Pharmacopoeial monographs, Marketing Authorisation (MA), and Clinical Trial Authorisation (CTA)) will dictate whether and to what stage substances and materials can have a defined level of bioburden or need to be sterile. For biological materials that cannot be sterilized (e.g. by filtration), processing must be conducted aseptically to minimise the introduction of contaminants. The application of appropriate environmental controls and monitoring and, wherever feasible, in-situ cleaning and sterilization 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。納入人體組織或細胞的生物藥品，例如，某些 ATMPs 必須遵從對其捐贈、採集與檢驗階段的國家要求。這種原料的採集與檢驗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（仍顧全捐贈者保密性）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。	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 medicinal substances and products. Biological medicinal products which incorporate human tissues or cells, such as certain ATMPs must comply with national requirements for the donation, procurement and testing stages[9]. Collection and testing of this material must be done in accordance with an appropriate quality system and in accordance with applicable national requirements[10]. Furthermore, national requirements[11]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.
生物原料藥及產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狀腦病病原體的風險最小化。	Biological medicinal substances and 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 部分.一般指引（PART A. GENERAL GUIDANCE）	
人員（PERSONNEL）	

1.	在生物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）應接受與製造產品及其工作（包括保護產品、人員與環境的任何特定措施在內）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 medicinal products are manufactured and tested should receive training, and periodic retraining, specific to the products manufactured and to their work, including any specific 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、基因改造生物、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 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（PREMISE AND EQUIPMENT）	
5. 作為管制策略之一部分，切記原料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。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（例如，宿主有機體，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 product and the production step, bearing in mind the level of contamination of the starting materials and the risks to the product. The environmental monitoring programme in addition to Annex 1 should be supplemented by the inclusion of methods to detect the presence of specific microorganisms (e.g. host organism, 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。事實上，環境監測與原料負荷菌檢驗計畫是用於確認管制的狀態。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，在 ATMPs 之製造期間的處理)，應已具備相關措施，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 之適當部分的原則與要求納入考慮。	6.	Manufacturing and storage facilities, processes and environmental classifications should be designed to prevent the extraneous contamination of products. Although contamination is likely to become evident during processes such as fermentation and cell culture, prevention of contamination is more appropriate than detection and removal. In fact, the environmental monitoring and material bioburden testing programs are intended to verify a state of control. 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, manipulations during the manufacture of ATMPs) 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 requirements from the appropriate sections of Annex 1[12] when selecting environmental classification cascades and associated controls.
7.	對於處理直到去活化之前，在製造環境中能持久存在之活細胞，應使用專用生產區。對於能引起嚴重人類疾病之病原微生物的製造，應使用專用生產區。	7.	Dedicated production areas should be used for the handling of live cells, capable of persistence in the manufacturing environment, until inactivation. Dedicated production area should be used for the manufacture of pathogenic organisms capable of causing severe human disease[13]

8. 使用品質風險管理原則，當下列或等同的（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 using QRM principles:
(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徵之知識（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) 當生產的性質為由來自多個小批次之不同起始原料時（例如，細胞來源的產品），在開發管制策略的期間欲考慮併行性作業的可接受性時，應將例如捐贈者的健康狀況與來自特定患者之產品及/或該些產品對特定患者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 (e.g. cell-based products), factors such as the health status of donors and the risk of total loss of product from and/or for specific patients should be taken into account when considering the acceptance of concurrent working during development of the control strategy.
(c) 為防止活有機體與孢子（有關時）進入非相關的區域或設備，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 HVAC 系統納入考慮。對於有機體與孢子之移除的清潔與去污染應經確效。	(c) Live organisms and spores (where relevant) are prevented from entering non-related areas or equipment. Control measures to remove the organisms and spores before the subsequent manufacture of other products, these control measures should also take the HVAC system into account. Cleaning and decontamination for the removal of the organisms and spores should be validated.

(d) 針對所製造之微生物，在相鄰的區域中，環境監測也應在製造期間與清潔去污染完成之後執行。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。	(d) Environmental monitoring, specific for the micro-organism being manufactured, is also 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.
(e) 在區域內移動或移除產品、設備、附屬設備（例如，用於校正與確效）與拋棄式物品時，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類毒素製品與未去活化產品的污染）的方式執行。	(e) 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).
(f) 以時段切換的製造，應緊接著執行經確效的清潔與去污染程序。	(f) Campaign-based manufacturing followed by validated cleaning and decontamination procedures.

9. 對於最終操作[註]，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：生物產品之特定需求，且取決於在同一設施中其他產品的特徵，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 operations[14], the need for dedicated facilities will depend on consideration of the above together with additional considerations such as the specific needs of the biological 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.
註：調製、充填及分包裝	[14] 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）不得與產品安全性相衝突。	10. The measures and procedures necessary for containment (i.e. for environment and operator safety) should not conflict with those for product safety.
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小，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（不循環）的空調系統。	11. Air handling units should be designed, constructed and maintained to minimize 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，並以適當的警報裝置連續監測。	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被活有機體或細胞的任何污染。	13.	Equipment used during handling of live organisms and cells, including those for sampling, should be designed to prevent any contamination of the live organism or cell during processing.
14.	一級圍堵應經設計並定期測試，以確保防止生物劑（biological agents）逸入直接的工作環境。	14.	Primary containment[15] should be designed and periodically tested to ensure the prevention of escape of biological agents into the immediate working environment.
15.	可能時，應使用「原位清潔」與「原位蒸氣」(「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.	基於適當的品質風險管理原則，空氣通氣口濾器應為疏水性，對其預定使用壽命應在適當的間隔以完整性測試予以確效。	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小。遵守當地的法規是必要的，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. Compliance with local regulations is required to minimize 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/關鍵的添加物或成分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，這些物質可依所界定的時間保存在生產區中，原料必須適當地儲存。	18. Due to the variability of biological products or processes, relevant/critical additives or ingredients may have to be measured or weighed during the production process. In these cases, stocks of these substances 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. Materials must be stored appropriately.
動物（ANIMALS）	
19. 廣泛的動物物種被用來製造許多生物藥品或起始原料。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 or starting materials. These can be divided into 2 broad types of sources:
(a) 活的動物組，牛群與羊群：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) 在屍體剖檢後及來自機構：例如，屠宰場衍生的動物組織與細胞，例如來自動物組織之異種異體的細胞與支持一些 ATMPs 之生長的細胞、餵養細胞，對於酵素、抗凝血劑與激素的屠宰場來源（羊與豬）。此外，動物也可以在品質管制中使用於一般的含量測定，例如，熱原性，或特定的效價含量測定法，例如，百日咳疫苗（小鼠）、熱原性（兔子）、卡介苗（豚鼠）。	(b) Animal tissues and cells derived post- mortem and from establishments such as abattoirs: examples include xenogeneic cells from animal tissues and cells, feeder cells to support the growth of some ATMPs, abattoir sources for enzymes, anticoagulants and hormones (sheep and pigs). 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源（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物料之藥物或產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者（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 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 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 medicinal substance(s) or product(s) in which the 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 (where applicable) to establish the last negative donation. The withdrawal period of therapeutic agents used to treat source 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/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，健康的鳥群或獸群）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，自來源動物建立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.	對於動物收容、照護與隔離的國家要求，應當加以注意。生物產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 for animal quarters, care and quarantine[16]. Housing for animals used in production and control of biological 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、生物劑與所執行的檢驗，應當加以適當地識別，以防止任何混雜的風險，並且管制所有已經識別的危害。	25.	Animals, biological agents, and tests carried out should be appropriately identified to prevent any risk of mix up and to control all identified hazards.
文件製作（DOCUMENTATION）			
26.	生物起始原料之規格，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.	Specifications for biological starting 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.	構成一個批次所需的材料，在有些產品類型可能需要特別界定，特別是用在 ATMPs 的體細胞。對於自體使用與已捐贈配對的情況，所製造的產品應當視為一個批次。	27.	Some product types may require specific definition of what materials constitutes a batch, particularly somatic cells in the context of ATMPs. For autologous and donor- matched situations, the manufactured product should be viewed as a batch.
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產品的末效日期後 30 年。應特別注意對於特殊使用案例維持產品的可追溯性，例如，已捐贈配對之細胞。當血液成分在藥品製造過程作為支持材料或原料使用時，則適用國家要求。對於 ATMPs，關於包括造血細胞在內之人體細胞的可追溯性要求，必須遵從國家法規中所規定的原則。對於達成可追溯性與保存期間所需要的安排，應納入各負責方之間的技術協議中。	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[17]. Traceability records[18]must be retained for 30 years after the expiry date of the product. Particular care should be taken to maintain the traceability of products for special use cases, such as donor-matched cells. National requirements apply to blood components when they are used as supportive or raw material in the manufacturing process of medicinal products[19]. For ATMPs, traceability requirement regarding human cells including haematopoietic cells must comply with the principles laid down in national legislation[20]. The arrangements necessary to achieve the traceability and retention period should be incorporated into technical agreements between the responsible parties.
生產（PRODUCTION）			

29.	由於許多生物原料與產品的固有變異性，對於在產品生命週期的不同階段，例如，製程設計，增加製程穩健性，因而減低製程變異性與提高再現性的步驟，應當在產品品質檢討的期間加以再評估。	29.	Given the variability inherent in many biological substances and 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細胞來源的 ATMPs，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 cell based ATMPs 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.
起始原料（STARTING 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，使用可能失敗的原物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 substances in Part II.
32.	起始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 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。對於起始原料的品質與關於無菌製造過程所需要的管制，特別是對於細胞來源的產品（其最終滅菌通常是不可能而且對於移除微生物副產物之能力是有限的）承擔了較大的重要性。當上市許可或臨床試驗許可規定可允許之負荷菌的類型與量時，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 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 materials and on the aseptic manufacturing process, particularly for cell-based products, where final sterilisation is generally not possible and the ability to remove microbial by-products is limited, assume greater importance. Where an MA or CTA 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.	當起始原料應予滅菌時，可能時應使用熱處理法。當需要時，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 sterilization of starting 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. 採集活組織及活細胞相關負荷菌的減低，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、謹慎管制，且應在上市許可或在臨床試驗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 and carefully controlled, they should be removed from the manufacturing process at the stage specified in the MA or CTA.[21]
36. 對於使用人體組織與細胞作為起始原料的生物藥品：	36. For human tissues and cells used as starting materials for biological medicinal products:
(a) 其採集、捐贈與檢驗，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相關核准，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[22].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進口時，必須符合相等之品質與安全性的國家標準。追溯性與嚴重不良反應及嚴重不良事件通知之規定，可明訂於國家法規中。	(b) Where such human cells or tissues are imported they must meet equivalent national standards of quality and safety[23]. The traceability and serious adverse reaction and serious adverse event notification requirements may be set out in national legislation[24].
(c) 可能有一些情況，作為生物藥品之起始原料使用的細胞與組織之處理，將會在組織機構（庫）中執行，例如，在建立主細胞庫之前，取得早期細胞株或細胞庫。	(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, e.g. to derive early cell lines or banks prior to establishing a Master Cell Bank, MCB [25].

(d) 組織與細胞在裝運到藥品製造廠之前，是由組織機構（庫）中的權責人員放行，自此以後，適用正常的藥品起始原料管制。由組織機構（庫）所供給之所有組織/細胞的檢驗結果，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。倘若具備防止組織及細胞的交叉污染管制時，在從組織機構（庫）取得檢驗結果之前須先行製造，則已由組織機構（庫）中的權責人員放行的組織與細胞，可以裝運到藥品製造廠。	(d) Tissue and cells are released by the Responsible Person 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廠，必須由負責的各方之間的書面協議加以管制。製造廠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) 從組織機構（庫）直到接收者之連續追溯性要求，包括與細胞或組織接觸的材料在內應加以維持，反之亦然。	(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（庫）、發起者、上市許可持有者）之間應具備一份技術協議，其中界定包括權責人員在內之各方的責任。	(g) A technical agreement should be in place between the responsible parties (e.g. manufacturers, tissue establishment, Sponsors, MA Holder) which defines responsibilities of each party, including the RP.
37. 關於基因治療：	37. With regard to gene therapy[26]:
(a) 對於由病毒載體組成的產品，其起始原料是獲得病毒載體的組成物，亦即，供轉染包裝細胞的主病毒種庫或質體及包裝細胞株之 MCB。	(a) For products consisting of viral vectors, the starting materials are the components from which the viral vector is obtained, i.e. the master virus seed or the plasmids to transfect the packaging cells and the MCB of the packaging cell line.
(b) 對於由質體、非病毒載體與基因改造而非病毒或病毒載體組成之微生物的產品，其起始原料是用於產生生產細胞的組成物，亦即，質體、宿主細菌與重組微生物細胞之 MCB。	(b) For products consisting of plasmids, non-viral vectors and genetically modified micro-organisms other than viruses or viral vectors, the starting materials are the components used to generate the producing cell, i.e. the plasmid, the host bacteria and the MCB of the recombinant microbial cells.
(c) 對於基因改造的細胞，其起始原料是用於獲得基因改造細胞的組成物，亦即，製造載體與人體或動物細胞製備物的起始原料。	(c) For genetically modified cells, the starting materials are the components used to obtain the genetically modified cells, i.e. the starting materials to manufacture the vector and the human or animal cell preparations.

(d) 自製造基因轉殖所使用的載體或質體之細胞庫系統起，適用 GMP 的原則。	(d) The principles of GMP apply from the bank system used to manufacture the vector or plasmid used for gene transfer.
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，包含符合國家對人體細胞之要求在內。	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[27], including 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。此系統可能不適用於所有類型的 ATMPs。	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. Such a system may not be applicable to all types of ATMPs.
40. 種批或細胞庫、原料藥與最終產品之間的世代數目（倍增、代數），應與上市許可或臨床試驗許可上的規格一致。	40. The number of generations (doublings, passages) between the seed lot or cell bank, the drug substance and finished product should be consistent with specifications in the MA or CTA.

41.	作為產品生命週期管理的一部分，種批與細胞庫的建立，包括主世代與工作世代在內，應在經證明適當的情況下執行。這應包括經適當管制的環境，以保護種批與細胞庫以及處理它的人員。在建立種批與細胞庫的期間，不同活的或傳染性的物質（例如病毒、細胞株或細胞品系）不得同時在相同區域中處理或不得同時由同一組人處理。對於僅可適用 GMP 原則之種批或細胞庫產生之前的階段，應具備能支持可追溯性之文件，包括對產品安全性具潛在影響相關問題之開發期間所使用的組成物（例如，生物來源的試劑），適用時應涵蓋從最初來源尋求與基因開發階段。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 circumstances which are demonstrably appropriate. 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 stages prior to the master seed or cell bank generation, where only the principles of GMP may be applied, documentation should be available to support traceability including issues related to components used during development with potential impact on product safety (e.g. reagents of biological origin) from initial sourcing and genetic development if applicable. For vaccines the requirements of pharmacopoeial monographs will apply[28].

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檢驗。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甦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少的方式予以儲存與使用（例如，儲存在密封容器中之液態氮的氣相中）。對於在相同區域或設備中不同病毒種及/或細胞之儲存，其管制措施應可防止混雜，並且應考慮其傳染性，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 or alteration (e.g. stored in the vapour phase of liquid nitrogen in sealed containers). 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.
44.	細胞來源的藥品通常是從有限的繼代數目所得到的細胞庫存品所產生。異於主細胞庫及工作細胞庫的兩層系統，從細胞庫存品所生產操作的數目是受到擴增後所得到可分裝數目所限制，並且不涵蓋該產品的整個生命週期。細胞庫存品的變更應涵蓋於確效計畫書中。	44.	Cell based medicinal products 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 covered by a validation protocol.

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。超過設定值的偏差及所採取的矯正與預防措施，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.	最好將庫存品分散並存放在不同的地點，以減少總損失的風險。在該等地點的管制應能提供前述的保證。	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，應依照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 of the final 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，以使污染的風險減到最少。無菌製備時，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 to minimise the risk of contamination. 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、酸或鹼溶液及消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，對於確保正確連接該等桶槽應加以注意。	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降到最低是必要的。	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，應有經確效的去污染措施。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代表性品系進行確效。	55.	Accidental spillages, especially of live organisms, must be dealt with quickly and safely. Validated 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 potentially hazardous organism is involved, production and control materials, including paperwork, must be adequately disinfected, or the information transferred out by other means.
57.	對於滅菌、消毒、病毒移除或去活化所使用的方法，應進行確效。	57.	The methods used for sterilisation, disinfection, virus removal or inactivation should be validated[29]

58.	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。	58.	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.
59.	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，移轉到第二個容器中。	59.	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.
60.	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。	60.	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 sterilization methods of columns should be defined.
61.	游離輻射使用於藥品的製造時，其進一步的指引應參考附則 12。	61.	Where ionising radiation is used in the manufacture of medicinal products, Annex 12 should be consulted for further guidance.

62.	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範圍之內，例如，時間及/或溫度。	62.	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.
63.	處理具有活生物體之容器的作業，必須以防止其他產品之污染或活生物體流入工作環境或外部環境的方式予以執行之。此風險評估應將該等有機體的存活力及其生物學上的分類列入考慮。	63.	Activities in handling containers, which have 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. This risk assessment should take into consideration the viability of such organisms and their biological classification.
64.	在標籤的製作、印刷、儲存與應用上應當注意，包括對患者專一性之特定產品的任何特定內文，或在直接容器與間接包裝上標明內容物使用基因工程。在產品使用於自體用途的情況，獨特的病人識別用語與「僅供自體使用」的陳述，應標示在直接容器標籤上。	64.	Care should be taken in the preparation, printing, storage and application of labels, including any specific text for patient-specific products or signifying the use of genetic engineering of the contents on the primary container and secondary packaging. In the case of products used for autologous use, the unique patient identifier and the statement “for autologous use only” should be indicated on the immediate label.
65.	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。	65.	The compatibility of labels with ultra-low storage temperatures, where such temperatures are used, should be verified.

66.	在採集之後，獲知捐贈者及/或動物的健康資訊對產品品質有影響時，應考慮採取回收程序。	66.	Where donor and/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）			
67.	確保生物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。	67.	In-process controls have a greater importance in ensuring the consistency of the quality of biological 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.
68.	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，將使用最長製程中儲存期間之中間產品所製成之最終產品批次納入考量。	68.	Where intermediates can be stored for extended periods of time (days, weeks or longer), consideration should be given to the inclusion of final product batches made from materials held for their maximum in-process periods in the on-going stability programme.
69.	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，且上市許可或臨床試驗許可允許時，可開發經修改的檢驗與樣品留存策略，並且加以文件化。	69.	Certain types of cells (e.g. autologous cells used in ATMPs) may be available in limited quantities and, where allowed in the MA or CTA, a modified testing and sample retention strategy may be developed and documented.
70.	對於細胞來源的 ATMPs，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）。	70.	For cell-based ATMPs, 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.

71.	對於短架儲期的產品，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，並且考慮添料之管制與屬性。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。當最終產品由於其短架儲期而不可能完成檢驗時，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－在可獲得完整最終製程分析結果之前與之後：	71.	For products with a short shelf life, 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 input 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 possible 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 - before and after full end process analytical test results are available:

a) 批次操作紀錄與從環境監測的結果（可取得時）經由指定人員的評估，其中應包括生產條件、異於正常程序的所有偏差及可以獲得的分析結果，以供權責人員審查與有條件的核定。	a) Assessment by designated person(s) of batch processing records and results from environmental monitoring (where available) which should cover production conditions, all deviations from normal procedures and the available analytical results for review and conditional certification by the Responsible Person.
b) 在最終產品出貨之前，由權責人員評估最後檢驗與其他可獲得的資訊，以供最終產品之核定。	b) Assessment of the final analytical tests and other information available before end product dispatch for final product certification by the Responsible Person.
c) 在產品出貨後，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，並且採取相關的矯正與預防行動，以防止重複發生。	c) 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 after product dispatch. Such events should be fully investigated and the relevant corrective and preventative actions taken to prevent recurrence documented.
如果在出貨後得到不滿意的檢驗結果時，程序應描述權責人員將採取的措施。	A procedure should describe those measures which will be taken by the Responsible Person if unsatisfactory test results are obtained after dispatch.
B 部分：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）	

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檢驗在內。應具備證明供應鏈可追溯性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[30] and clear roles of participants in the supply chain, typically including a sufficiently detailed and current process map, should be in place.
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與管制措施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。	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 and control measures when compiling their assessment of risk and mitigation factors. Such organizations include the World Organisation for Animal Health (OIE, Office International des Epizooties [31]). 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、品質與動植物衛生法規。	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 organizations [32] which verify compliance with the requirements of food, safety, quality and veterinary and plant health legislation.
3.	在如屠宰場之機構，製藥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 PIC/S GMP 以外的來源，但應顯示提供同等的管制水準。	3.	Control measures for the pharmaceutical raw materials at establishments such as abattoirs should include appropriate elements of 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 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 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.
6.	預定用於異種異體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。	6.	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.
7.	對於異種異體細胞治療產品，應遵循與動物細胞之採集與檢驗有關的適當指引。	7.	For xenogeneic cell therapy products appropriate guidance in relation to procurement and testing of animal cells should be followed [33].
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 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應依照文件化的程序儲存。	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 product and the hold times must be validated.
3.	含有經去活化之產品的桶槽，不得在含有活生物體的區域中開啟或抽樣。	3.	Vessels containing inactivated product 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，必須遵循製造指令或批次紀錄。	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 the manufacturing instructions or the batch record.
5.	在製造或測試中，當要使用較高生物安全等級的有機體時（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，以確保雜質在經界定之範圍內的一致產品，該範圍為製程能力能將雜質減低至可接受的水準。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 harvests, 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（包含餵養細胞在內，如使用時）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，可能可接受源自相同製造技術平台所產生之產品的數據，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 cycle 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-fragments (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上市許可或臨床試驗許可條件。動物可從生產移出之收集時程表與條件，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 MA or CTA 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 部分所給予的措施），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源所污染。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，以使暴露於微生物體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「Guideline on Good Agricultural and Collection Practice for Starting Materials of Herbal origin」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'[34] should be taken into account when drawing up such criteria.
B9.	**基因治療產品（GENE THERAPY PRODUCTS[35]）**		
	基因治療產品可能有 2 種類型（載體與基因改造細胞），而且，在本條項中，兩者都在該指引的範圍之內。對於細胞來源的基因治療產品，在第 B10 條項中之一些指引層面，可適用。		There are potentially 2 types of GT products (vectors and genetically modified cells) and both are within the scope of the guidance in this section. For cell based GT products, some aspects of guidance in section B10 may be applicable.

1.	由於在基因治療產品之製造上所使用的細胞自人類（自體或異體）或動物（異種）取得，所以，有被外來病源污染的潛在風險。對於自感染之捐贈者取得的自體物質之隔離，必須施予特別的考慮。對於起始原料、冷凍保護劑、培養基、細胞與載體之管制與測試措施的穩健性，應基於品質風險管理原則，並且與上市許可或臨床試驗許可一致。對於病毒載體生產所使用之既定細胞株及其管制與測試措施，也應同樣基於品質風險管理原則；合適時，應使用病毒種批與細胞庫系統。	1.	Since the cells used in the manufacture of gene therapy products are obtained either from humans (autologous or allogeneic) or animals (xenogeneic), there is a potential risk of contamination by adventitious agents. Special considerations must be applied to the segregation of autologous materials obtained from infected donors. The robustness of the control and test measures for such starting materials, cryoprotectants, culture media, cells and vectors should be based on QRM principles and in line with the MA or CTA. Established cell lines used for viral vector production and their control and test measures should similarly be based on QRM principles. Virus seed lots and cell banking systems should be used where relevant.
2.	諸如基因物質的本質、載體的類型（病毒或非病毒）與細胞的類型等因素，皆與潛在雜質、外來病源物與交叉污染的範圍有關，應該作為整體開發策略的一部分納入考慮，以使風險減到最少。這個策略應作為製程、製造與儲存設施及設備、清潔與去污染程序、包裝、標示以及運銷之設計的基礎使用。	2.	Factors such as the nature of the genetic material, type of (viral or non-viral) vector and type of cells have a bearing on the range of potential impurities, adventitious agents and cross-contaminations that should be taken into account as part of the development of an overall strategy to minimise risk. This strategy should be used as a basis for the design of the process, the manufacturing and storage facilities and equipment, cleaning and decontamination procedures, packaging, labelling and distribution.

3.	基因治療藥品之製造與檢驗引起關於最終產品的安全性與品質之特定問題，以及對於接收者與工作人員的安全性問題。對於操作者、環境與患者的安全，應適用以風險為依據的方法，並適用生物危害分級制度執行管制。由當地及如果可適用時，由國際所制定的法規，其安全性措施應加以應用。	3.	The manufacture and testing of gene therapy medicinal products 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. Legislated local and, if applicable, international safety measures should be applied.
4.	人流（包括品質管制與維護保養人員在內）與物流，包括儲存與檢驗（例如，起始原料、製程中與最終產品樣品及環境監測樣品）的動線在內，應基於品質風險管理原則加以管制之，可能時，應使用單向動線。這應將在含有不同基因改造有機體之區域與不含有基因改造有機體之區域間的移動納入考慮。	4.	Personnel (including QC and maintenance staff) and material flows, including those for storage and testing (e.g. starting materials, in-process and final product samples and environmental monitoring samples), should be controlled on the basis of QRM principles, where possible utilising unidirectional flows. This should take into account movement between areas containing different genetically modified organisms and areas containing non-genetically-modified organisms.
5.	對於處理之有機體的種類所需要之任何特殊的清潔與去污染方法，應在設施與設備之設計上加以考慮。可能時，環境監測計畫應納入包含可培養該等特定有機體之方法，以供檢測其存在。	5.	Any special cleaning and decontamination methods required for the range of organisms being handled should be considered in the design of facilities and equipment. Where possible, the environmental monitoring programme should be supplemented by the inclusion of methods to detect the presence of the specific organisms being cultivated.

6.	當使用複製受限載體時，應具備措施，以防止野生型病毒的導入，該等病毒可能導致複製型重組載體之形成。	6.	Where replication limited vectors are used, measures should be in place to prevent the introduction of wild-type viruses, which may lead to the formation of replication competent recombinant vectors.
7.	應具備對於處理活有機體之意外釋放的緊急計畫。這個計畫應針對圍堵、操作員保護、清潔、去污染與安全恢復供使用等提出方法與程序。對於在受影響之區域中，當下產品與任何其他事項之影響，也應進行評估。	7.	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. An assessment of impact on the immediate products and any others in the affected area should also be made.
8.	對於病毒載體製造的廠房設施，應經由特定措施與其他區域予以隔離。對於隔離的安排應證明是有效的。可能時，應使用密閉系統，樣品收集、添加與移轉應防止病毒物質的釋放。	8.	Facilities for the manufacture of viral vectors should be separated from other areas by specific measures. The arrangements for separation should be demonstrated to be effective. Closed systems should be used wherever possible, sample collection additions and transfers should prevent the release of viral material.
9.	不同病毒基因治療載體在相同區域中同時製造，是不能接受的。非病毒載體在相同區域中同時生產，應基於品質風險管理原則加以管制之。在時段切換生產間的轉換程序，應證明是有效的。	9.	Concurrent manufacture of different viral gene therapy vectors in the same area is not acceptable. Concurrent production of non-viral vectors in the same area should be controlled on the basis of QRM principles. Changeover procedures between campaigns should be demonstrated to be effective

10. 載體與基因改造細胞之生產應提供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品）到最終產品的可追溯性。	10. A description of the production of vectors 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.
11. 含有及/或由基因改造有機體所組成之產品的運送，應遵照適當的法規。	11. Shipment of products containing and/or consisting of GMO should conform to appropriate legislation.
(a) 運送應在具適當圍堵安排之專用於該等活動的設施中進行。	(a) These should take place in facilities dedicated to such activities where appropriate containment arrangements exist.
(b) 使來自不同患者之細胞間，其交叉污染與混雜之可能性減到最低的措施是必需的（包括在 A 部分第 10 條所概述的考慮事項在內）。這應包括使用經確效的清潔程序，同時使用不同的病毒載體應受到基於品質風險管理原則的管制。有些病毒載體（例如，Retro- or Lenti- viruses）在基因改造細胞之製造過程中不能使用，直到其已顯示沒有複製型污染載體為止。	(b) Measures (including considerations outlined under paragraph 10 in Part A) to minimise the potential for cross- contamination and mix-up between cells from different patients are required. This should include the use of validated cleaning procedures. The concurrent use of different viral vectors should be subject to controls based on QRM principles. Some viral vectors (e.g. Retro- or Lenti-viruses) cannot be used in the manufacturing process of genetically modified cells until they have been shown to be devoid of replication-competent contaminating vector.
(c) 必須維持可追溯性要求。一個批次，從細胞來源到最終產品容器，應有清楚的定義。	(c) Traceability requirements must be maintained. There should be a clear definition of a batch, from cell source to final product container(s).

(d) 對於利用非生物學方法遞送基因的產品，其物理化學性質應加以文件化，並且進行測試。	(d) For products that utilise non-biological means to deliver the gene, their physico-chemical properties should be documented and tested.
B10. 體細胞與異體細胞治療產品及組織工程產品（SOMATIC AND XENOGENEIC CELL THERAPY PRODUCTS AND TISSUE ENGINEERED PRODUCTS[36]）	
對於基因改造細胞來源之產品，未分類為基因治療產品者，在第 B9 條項中之一些指引層面，可適用。	For genetically modified cell based products that are not classified as GT products, some aspects of guidance in section B9 may be applicable.
1. 當它們可以獲得時，其添加的物質（例如，細胞產品、生物分子、生物材料、支架材料、基質）應使用經授權的來源（亦即，通過符合評估程序，並經發給證書的藥品或醫療器材）。	1. Use should be made, where they are available, of authorised sources (i.e. licensed medicinal products or medical devices which have gone through a conformity assessment procedure [37]) of additional substances (such as cellular products, bio-molecules, bio-materials, scaffolds, matrices).
2. 當醫療器材（包含客製化器材在內）為產品的一部分時：	2. Where devices, including custom-made devices, are incorporated as part of the products:
(a) 在藥品製造廠與醫療器材製造廠之間應有書面協議，該協議應對該醫療器材提供足夠的資訊，避免其性質在 ATMP 之製造期間中的改變，這應包括對該醫療器材所提出之管制變更的要求。	(a) There should be written agreement between the manufacturer of the medicinal product and the manufacturer of the medical device, which should provide enough information on the medical device to avoid alteration of its properties during manufacturing of the ATMP. This should include the requirement to control changes proposed for the medical device.
(b) 這份技術協議也應要求在該醫療器材製造中相關偏差的資訊交換。	(b) The technical agreement should also require the exchange of information on deviations in the manufacture of the medical device.

3.	由於體細胞是自人類（自體或異體）或動物（異種）取得，所以，有被外來病源污染的潛在風險。對於自受感染之捐贈者或涉及細胞混合取得之自體物質的隔離，必須施予特別的考慮。對於這些來源物質，應確保已具備穩健的管制與檢驗措施。從其收集組織與細胞的動物，應依照在相關指引中所界定的原則進行飼養與處理。	3.	Since somatic cells are obtained either from humans (autologous or allogeneic) or animals (xenogeneic), there is a potential risk of contamination by adventitious agents. Special considerations must be applied to the segregation of autologous materials obtained from infected donors or related to cell pooling. The robustness of the control and test measures put in place for these source materials should be ensured. Animals from which tissues and cells are collected should be reared and processed according to the principles defined in the relevant guidelines[38].
4.	在任何低溫階段之特定要求，例如，在冷凍或解凍期間溫度改變的速度，應謹慎關注。儲存艙的類型、擺置與存取過程，應使交叉污染的風險減到最低，並保持產品的品質與便利其準確的存取。具陽性反應血清標記之產品，其安全的處理與儲存，應具備文件化的程序。	4.	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.	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，並且考慮苛養性有機體的檢測。	5.	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 consider the detection of fastidious organism.

6. 合適時，應具備安定性監測計畫與足量的對照及留存樣品，以允許進一步的檢查。	6. Where relevant, a stability-monitoring programme should be in place together with reference and retain samples in sufficient quantity to permit further examination.
附則 2 的術語彙編（GLOSSARY TO ANNEX 2）	
這些條項只包括在附則 2 中使用並且需要進一步解釋的術語。在法規中已經存在的定義僅予交互參照。	Entries are only included where the terms are used in Annex 2 and require further explanation. Defintions which already exist in legislation are cross-referenced only.
佐劑 可增強對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.
新興生醫產品 意指任何下列人用藥品：基因治療產品、體細胞治療產品與組織工程產品。	**Advance Therapeutic Medicinal Products (ATMP)** ATMP means any of the following medicinal products for human use: gene therapy medicinal products, somatic cell therapy medicinal products and tissue engineered medicinal products[39].
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.
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 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 衍生自範圍內的淋巴細胞殖株，是產自人類與動物反應大多數「非自體」分子上之抗原決定位。	**Polyclonal antibodies** derived from a range of lymphocyte clones, produced in human and animals in response to the epitopes on most 'non-self' molecules.
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作業室組，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.
負荷菌 在原料、培養基、生物物質、中間產品或產品中所存在之微生物的量與類型（亦即，不宜存在與否）。當其超出規格的量及/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，而且對其特徵描述以及品質的判定，需要結合物理－化學－生物學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[40]
生物安全等級 對於範圍從 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）之不同危害有機體的安全處理所需要之圍堵條件。	**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。	**Campaigned 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作業室環境之系統。	**Closed system** Where a drug substance or product is not exposed to the immediate room environment during manufacture.
圍堵的使用 培養、儲存、使用、運送、銷毀或處置基因改造有機體的操作，並且使用屏障（物理/化學/生物）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.
審慎的釋出 將基因改造有機體審慎的釋出到環境中。	**Deliberate release** The deliberate release into the environment of genetically modified organisms.
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 轉殖基因至細胞之過程，涉及遞送系統中（稱為載體）所含的表現系統，該載體可以是病毒也可以是非病毒來源。在基因轉殖後，基因改造細胞也稱為轉導細胞。	**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*.
基因改造有機體 意指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。	**Genetically modified organism (GMO)** means 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.
半抗原 低分子量的分子，其本身不具抗原性，除非與一個「攜帶者」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 在活的生物體內所執行的程序。	**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顯而易見時，為追溯生物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 biological medicinal substances or products which may be adversely affected by the use or incorporation of animal or human materials when either such materials fail release tests due to the presence of contaminating agent(s) or when conditions of concern become apparent in the source animal or human.

主細胞庫 為可分裝之單一細胞株，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 MCB。	**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.
主病毒種庫 同上，但與病毒有關；	**Master virus seed (MVS)** as above, but in relation to viruses;
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.
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 organism.
多產品設施 同時或以時段切換模式製造範圍內之不同的生物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, either concurrently or in campaign mode, a range of different biological medicinal substances and products and within which equipment train(s) 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改造、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 為有限數量的使用，經最少的增殖至足夠數量的初代細胞。	**Primary cell lot** a pool of primary cells minimally expanded to attain a sufficient number for a limited number of applications.

權責人員 是負責確保每一批次的（生物）原料藥或藥品已經遵守現行有效法規，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"[41].
血液或組織機構權責人員 這一術語是等同於歐盟 「權責人員」術語。	**Responsible Person (RP) for blood or tissue establishment** This term is equivalent to the EU term "Responsible Person"[42].
支架 為一支柱物、遞送載體或基質。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 provided 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改變，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 effects.
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 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改造之載體；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.
工作細胞庫 衍生自主細胞庫的微生物或細胞之均質混合物，均勻分裝於若干容器中，並以確保安定性的方式儲存及供生產使用。	**Working cell bank (WCB)** a homogeneous pool of micro-organisms or cells, that are distributed uniformly into a number of containers derived from a MCB that are stored in such a way to ensure stability and for use in production.
工作病毒種庫 同上，但與病毒有關，	**Working virus seed (WVS)** as above but in relation to viruses,
工作基因轉殖庫 同上，但用於基因轉殖植物或動物。	**working transgenic bank** as above but for transgenic plants or animals.
人畜共通傳染病 會傳染給人類的動物疾病。	**Zoonosis** Animal diseases that can be transmitted to humans.

[1] In the EEA, this is Directive 2002/98/EC and its Commission Directives.

[2] In the EEA, this is Directive 1998/81/EC on contained use of genetically modified micro-organisms.

[9] In the EEA, these are Directive 2004/23/EC and Directive 2006/17/EC.

[10] In the EEA, this is the Commission Directive 2006/86/EC.

[11] In the EEA, this is Directive 2006/86/EC.

[12] PICS Guide to GMP

[13] In the EEA, this would correspond to pathogenic organisms of i.e. Biosafety level 3 or 4 according to Council Directive 90/679/EEC.

[14] Formulation, filling and packaging

[15] See main GMP Glossary on 'Containment'.

[16] In the EEA, Directive 201/63/EC took effect on 1St January 2013.

[17] In the EEA see Article 15 of Regulation 1394/ 2007.

[18] In the EEA, see ENTR/F/2/SF/dn D(2009) 35810, 'Detailed guidelines on good clinical practice specific to advanced therapy medicinal Products' for further information on traceability.

[19] In the EEA, these are Directives 2002/98/EC and 2005/61/EC.

[20] In the EEA, these are Directives 2004/23/EC and 2006/86/EC.

[21] Some situations in which antibiotic use may be justified include maintenance of plasmids in expressionsystems and in fermentation. Generally, antibiotics used in humans should be avoided because of the potential development of antibiotic resistant strains. Additionally, the use of antibiotics is not an effective mechanism to control microbial contamination.

[22] In the EEA, this is Directive 2004/23/EC and its Commission directivees.

[23] In the EEA, they must be equivalent to those laid down in Directive 2004/23/EC.

[24] In the EEA, this is Directive 2006/86/EC.

[25] In the EEA, such processing steps, are under the scope of 2004/23/EC and the Responsible Person(RP)

[26] In the EEA, see details in section 3.2 of Directive 2009/120/EC.

[27] In the EEA, this includes compliance with Directive 2004/23 EC for human cells.

[28] In the EEA, this is Ph Eur monograph 2005;153 "Vaccines for human use".

[29] In the EEA, see CHMP guidance.

[30] See PIC/S GMP Chapter 5.

[31] http://www.oie.int/eng/en_index.htm

[32] In the EEA, this is the Food and Veterinary Office http://ec.europa.eu/food/fvo/index_en.htm.

[33] In the EEA, reference is made to the EMA Guideline document on xenogeneic cell-based medicinal products (EMEA/CHMP/CPWP/83508/2009)

[34] EMA, WHO or equivalent

[35] In the EEA, Part IV (1) of Directive 2001/83/EC as revised in 2009 contains a definition of gene therapy(GT) medicinal products.

[36] In the EEA, Annex I, Part IV (2) of Directive 2001/83/EC as amended in 2009 contains a definition of somatic cell therapy (SCT) medicinal products and the definition of a tissue engineered medicinal product is given in Article 2 of Regulation 1394/2007/EC.

[37] In the EU/EEA, these devices are marked "CE".

[38] In the EEA, see CHMP guidance.

[39] In the EEA, see Article 2(1) of Regulation EC 1394/2007.

[40] In the EEA, see Annex 1 to 2001/83/EC – 3.2.1.1(b).

[41] In the EEA, see Article 48 of Directive 2001/83/EC and Article 52 of Directive 2001/82/EC.

[42] In the EEA, see Article 17 of Directive 2004/23/EC.

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 °C、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 ^{o}C 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 ^{o}C.

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 °C 時液化的氣體。	**Cryogenic gas** Gas which liquefies at 1.013 bar at temperatures below –150 °C.
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 °C 是完全氣態，或在 50 °C 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 °C or has a vapour pressure exceeding 3 bar at + 50 °C.
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 °C 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 –50°C.
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以設定。	21. The minimum observed dose, as measured by the routine dosimeters, necessary to ensure that all irradiation containers receive the 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）

原則（PRINCIPLE）	
研究用藥品應依藥品優良製造規範的原則與詳細的指引生產。其他相關指引並適合於產品之開發階段者，亦應列入考慮。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。	Investigational medicinal products should be produced in accordance with the principles and the detailed guidelines of Good Manufacturing Practice for Medicinal Products. Other guidelines should be taken into account where relevant and as appropriate to the stage of development of the product. Procedures need to be flexible to provide for changes as knowledge of the process increases, and appropriate to the stage of development of the product.
臨床試驗上，相較於使用已上市藥品治療的病人，受試者可能會有較多的風險。將GMP應用於研究用藥品的製造上，係要確保受試者不會處於風險中，及臨床試驗結果不會受到源自不滿意之製造的不適當安全性、品質或療效所影響。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，並證明其正當性。	In clinical trials there may be added risk to participating subjects compared to patients treated with marketed products. The application of GMP to the manufacture of investigational medicinal products is intended to ensure that trial subjects are not placed at risk, and that the results of clinical trials are unaffected by inadequate safety, quality or efficacy arising from unsatisfactory manufacture. 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.

與上市的藥品相較，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、後續的包裝設計、常有隨機與盲性試驗的需要及藥品交互污染與混雜之風險的增加，而且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，或可能將上市產品已經重新包裝或經以某種方式修改過，因此會涉及附加的複雜性。	The production of investigational medicinal products involves added complexity in comparison to marketed products by virtue of the lack of fixed routines, variety of clinical trial designs, consequent packaging designs, the need, often, for randomisation and blinding and 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, or, marketed products may be used which have been re-packaged or modified in some way.
這些挑戰需要對GMP應用於研究用藥品有充分瞭解並受過訓練的人員。與試驗委託者的合作是必需的。試驗委託者對包含研究用藥品的品質在內之臨床試驗的一切層面，需負最終責任。	These challenges require personnel with a thorough understanding of, and training in, the application of GMP to investigational medicinal products. Co-operation is required with trial sponsors who undertake the ultimate responsibility for all aspects of the clinical trial including the quality of investigational medicinal products.
因製造作業複雜性的增加，需有高度有效的品質系統。	The increased complexity in manufacturing operations requires a highly effective quality system.
本附則另包含關於下訂單、裝運及退回研究用藥品的指引。這些指引是連結並補充藥品優良臨床試驗準則。	The annex also includes guidance on ordering, shipping, and returning clinical supplies, which are at the interface with, and complementary to, guidelines on Good Clinical Practice.
註（Notes）	
非研究用藥品（Non-investigational medicinal product）	

除研究用藥品外，安慰劑或比對產品可能提供給參與試驗的受試者。這些藥品可能為預防、診斷或治療的理由，而當做支持或免除給藥使用，及（或）可能為確保對受試者提供適當的醫療照護之所需。該等藥品亦可能依計畫書使用於誘發生理學上的反應。這些藥品不在研究用藥品的定義內，而且可能由試驗委託者或試驗主持人所提供。試驗委託者應確保該等藥品與執行該試驗許可申請書一致，且不論其是否為已上市藥品或已重新分/包裝，皆應考慮到其來源，確保該等藥品具有為本試驗目的之適當品質。本項工作宜有一位被授權人員的意見及參與。	Products other than the test product, placebo or comparator may be supplied to subjects participating in a trial. Such products may be used as support or escape medication for preventative, diagnostic or therapeutic reasons and/or needed to ensure that adequate medical care is provided for the subject. They may also be used in accordance with the protocol to induce a physiological response. These products do not fall within the definition of investigational medicinal products and may be supplied by the sponsor, or the investigator. The sponsor should ensure that they are in accordance with the notification/request for authorisation to conduct the trial and that they are of appropriate quality for the purposes of the trial taking into account the source of the materials, whether or not they are the subject of a marketing authorisation and whether they have been repackaged. The advice and involvement of an Authorised Person is recommended in this task.
製造許可與重組（Manufacturing authorisation and reconstitution）	
研究用藥品之全部與部分製造，以及各種分裝、包裝或展現樣式的各種過程，須持有製造許可。但對於重組，這種許可將不需要。為此目的，重組應被理解為一個簡單的過程：	Both the total and partial manufacture of investigational medicinal products, as well as the various processes of dividing up, packaging or presentation, is subject to a manufacturing authorisation. This authorisation, however, shall not be required for reconstitution. For the purpose of this provision, reconstitution shall be understood as a simple process of:
• 將研究用藥品進行溶解或分散，以投用於受試者，或，	• dissolving or dispersing the investigational medicinal product for administration of the product to a trial subject, or,
• 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。	• diluting or mixing the investigational medicinal product(s) with some other substance(s) used as a vehicle for the purposes of administering it.

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。	Reconstitution is not mixing several ingredients, including the active substance, together to produce the investigational medicinal product.
在一過程可被界定為重組之前，研究用藥品就必須存在。	An investigational medicinal product must exist before a process can be defined as reconstitution.
重組的過程必須要在給藥前儘快進行。	The process of reconstitution has to be undertaken as soon as practicable before administration.
這個過程必須要界定於臨床試驗申請/研究用藥品文件檔案與臨床試驗計畫書或相關文件中，該等文件可在現場取得。	This process has to be defined in the clinical trial application / IMP dossier and clinical trial protocol, or related document, available at the site.
術語彙編（GLOSSARY）	
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 means the deliberate disguising of the identity of the product in accordance with the instructions of the sponsor. Unblinding means the disclosure of the identity of blinded products.
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或已上市藥品（亦即，活性對照品），或安慰劑。	**Comparator product** An investigational or marketed product (i.e. active control), or placebo, used as a reference in clinical trial.
研究用藥品 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。	**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者，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.
訂單 製造、分/包裝及/或裝運一定單位數之研究用藥品的指令。	**Order** Instruction to process, package and/or ship a certain number of units of investigational product(s).
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.
裝運 指依訂單分/包裝及寄送臨床試驗研究用藥品的作業。	**Shipping** The operation of packaging for shipment, 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 organization which takes responsibility for the initiation, management and/or financing of a clinical trial.
品質管理（QUALITY MANAGEMENT）	
1. 製造廠或輸入商應考量應用GMP原則與指引於研究用藥品，其設計、建立及確認的品質系統，應以書面程序描述，並可為試驗委託者取得。	1. The Quality System, designed, set up and verified by the manufacturer or importer, should be described in written procedures available to the sponsor, taking into account the GMP principles and guidelines applicable to investigational medicinal products.
2. 開發期間，研究用藥品之規格及製造指令得以變更。該變更的完整管制及可追溯性應予以保存。	2. The product specifications and manufacturing instructions may be changed during development but full control and traceability of the changes should be maintained.
組織與人事（PERSONNEL）	
3. 所有參與研究用藥品的人員，應經這類藥品特定要求之適當訓練。	3. All personnel involved with investigational medicinal products should be appropriately trained in the requirements specific to these types of product.
即使參與之人數不多，對於每個批次仍應有各別的人員分別負責生產與品質管制。	Even in cases where the number of staff involved is small, there should be, for each batch, separate people responsible for production and quality control.

4. 被授權人員應確保備有符合GMP要求的系統，且應具有藥品開發及臨床試驗過程的廣博知識。認證研究用藥品之被授權人員之相關指引，規定於本附則的第38至41條。	4. The Authorised Person should ensure that there are systems in place that meet the requirements of GMP and have a broad knowledge of pharmaceutical development and clinical trial processes. Guidance for the Authorised Person in connection with the certification of investigational medicinal products is given in paragraphs 38 to 41.
廠房設施與設備（PREMISES AND EQUIPMENT）	
5. 由於可能無法充分瞭解研究用藥品之毒性、效價與潛在致敏性，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/檢驗方法及允收限值，應反應這些風險的本質。合適時，應考慮時段切換作業。在清潔溶劑的選定上，應考量藥品的溶解度。	5. The toxicity, potency and sensitising potential 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. Consideration should be given to campaign working where appropriate. Account should be taken of the solubility of the product in decisions about the choice of cleaning solvent.
文件（DOCUMENTATION）	
規格與指令（Specifications and instructions）	
6. 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，應依知識的現況而盡可能廣泛之。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、法規與藥典的要求，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等性等任何對產品品質的連帶影響。	6. Specifications (for starting materials, primary packaging materials, intermediate, bulk products and finished products), manufacturing formulae and processing and packaging instructions should be as comprehensive as possible given the current state of knowledge. They should be periodically re-assessed during development and updated as necessary. Each new version should take into account the latest data, current technology used, regulatory and pharmacopoeial requirements, 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 bio equivalence.

7. 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，應予以調查並文件化。	7. 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 documented.
研究用藥品訂單（Order）	
8. 研究用藥品訂單應要求一定單位數之製造、及/或分/包裝、及/或其裝運，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。這應經過正式的授權，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。	8. The order should request the processing and/or packaging of a certain number of units and/or their shipping and be given by or on behalf of the sponsor to the manufacturer. It should be in writing (though it may be transmitted by electronic means), and precise enough to avoid any ambiguity. It should be formally authorised and refer to the Product Specification File and the relevant clinical trial protocol as appropriate.
產品規格檔案（Product specification file）	
9. 產品規格檔案（參見術語彙編）應隨產品開發持續更新，並確保可適當追溯至先前版本。該檔案應包含或引述下列文件：	9. The Product Specification File (see glossary) should be continually updated as development of the product proceeds, ensuring appropriate traceability to the previous versions. It should include, or refer to, the following documents:
• 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；	• Specifications and analytical methods for starting materials, packaging materials, intermediate, bulk and finished product;
• 製造方法；	• Manufacturing methods;
• 製程中檢驗及方法；	• In-process testing and methods;
• 核准的標籤複印本；	• Approved label copy;
• 相關臨床試驗計畫書及隨機化編碼（合適時）；	• Relevant clinical trial protocols and randomisation codes, as appropriate;
• 與合約提供者（委託者）之相關技術協議書（合適時）；	• Relevant technical agreements with contract givers, as appropriate;
• 安定性數據；	• Stability data;
• 儲存及裝運條件。	• Storage and shipment conditions.

上述項目並不意謂其為完全的或無遺漏的，其內容會依產品及開發階段而改變。該資訊應構成被授權人員認證與放行一特定批次之適當性的評估基礎，且應可被其取得。不同的製造步驟在不同場所進行時，於不同被授權人員的權責下，以各別檔案保存限於各該場所之相關活動的資訊，是可以接受的。	The above listing is not intended to be exclusive or exhaustive. The contents will vary depending on the product and stage of development. The information 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/her. 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.
製造配方及操作指令（Manufacturing formulae and Processing instructions）	
10. 每一製造作業或供應，應有清楚且適當之書面指令及紀錄。當作業不具反覆性時，可能不必制定主配方與操作指令。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。	10. For every manufacturing operation or supply there should be clear and adequate written instructions and written records. Where an operation is not repetitive it may not be necessary to produce Master Formulae and Processing Instructions. 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.
11. 產品規格檔案的資訊應使用於制訂有關製造、分/包裝、品質管制檢驗、儲存條件及裝運的詳細書面指令。	11. The information in the Product Specification File should be used to produce the detailed written instructions on processing, packaging, quality control testing, storage conditions and shipping.
分/包裝指令（Packaging instructions）	

12. 研究用藥品通常是爲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，包含爲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。爲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。	12. 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 any retention samples to be kept. Sufficient reconciliations should take place to ensure the correct quantity of each product required has been accounted for at each stage of processing.
製造、測試及分/包裝批次紀錄（Processing, testing and packaging batch records）	
13. 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，以及開發其製造作業。	13. 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 the procedures used and any changes made, enhance knowledge of the product and develop the manufacturing operations.
14. 批次製造紀錄應至少保存至相關法規明定的期間。	14. Batch manufacturing records should be retained at least for the periods specified in relevant regulations.
生產（PRODUCTION）	
分/包裝材料（Packaging materials）	
15. 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。	15. Specifications and quality control checks should include measures to guard against unintentional unblinding due to changes in appearance between different batches of packaging materials.
製造操作（Manufacturing operations）	

16. 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正當性。	16. 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.
17. 研究用藥品的生產過程雖不被期望確效到例行生產所需要的程度。但廠房設施與設備的驗證是被期望的。對於無菌產品，滅菌過程的確效應與許可上市之產品達到相同的標準。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。	17. Production processes for investigational medicinal products are not expected to be validated to the extent necessary for routine production but premises and equipment are expected to be qualified. For sterile products, the validation of sterilising processes should be of the same standard as for products authorised for marketing. Likewise, when required, virus inactivation/removal and that of other impurities of biological origin should be demonstrated, to assure the safety of biotechnologically derived products, by following the scientific principles and techniques defined in the available guidance in this area.

18. 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。	18. Validation of aseptic processes presents special problems when 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.
可適用於比對用產品的原則（Principles applicable to comparator product）	
19. 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。	19. If a product is modified, data should be available (e.g. stability, comparative dissolution, bioavailability) to demonstrate that these changes do not significantly alter the original quality characteristics of the product.
20. 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用畢日期。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。	20. The expiry date stated for the comparator product in its original packaging might not be applicable to the product where it has been repackaged in a different container that may not offer equivalent protection, or be compatible with the product. A suitable use-by date, taking into account the nature of the product, the characteristics of the container and the storage conditions to which the article 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.
盲性作業（Blinding operations）	

21. 產品經盲性，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。	21. 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 the batch numbers of the products before the blinding operation. Rapid identification of product should also be possible in an emergency.
隨機化編碼（Randomization code）	
22. 應說明使用於分/包裝研究用藥品之任何隨機化編碼的產生、保全、分配、處理和保存之作業程序，以及其解碼機制。適當的紀錄應予以保存。	22. Procedures should describe the generation, security, distribution, handling and retention of any randomisation code used for packaging investigational products, and code-break mechanisms. Appropriate records should be maintained.
分/包裝（Packaging）	
23. 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，將產品混雜的風險減到最低。	23. 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 mix up must be minimised by using appropriate procedures and/or, specialised equipment as appropriate and relevant staff training.
24. 研究用藥品的包裝與標示比已上市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。	24. 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 marketed products, particularly when "blinded" products with similar appearance are used. Precautions against mis-labelling such as label reconciliation, line clearance, in-process control checks by appropriately trained staff should accordingly be intensified.
25. 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。	25. 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.
標示作業（Labelling）	

26. 表1摘述下列26至30條的內容。下列的資訊應包含在標籤上，除非可證明其不包含之正當理由，例如，中央電子隨機系統的使用：	26. Table 1 summarises the contents of articles 26-30 that follow. The following information should be included on labels, unless its absence can be justified, e.g. use of a centralised electronic randomisation system:
a) 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）；	a) 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);
b) 藥品劑型、給藥途徑、劑型單元數，以及如為開放性試驗[1]，其名稱/識別符號及強度/效價；	b) pharmaceutical dosage form, route of administration, quantity of dosage units, and in the case of open trials[1], the name/identifier and strength/potency;
c) 用以識別內容物與分/包裝作業之批號及/或代碼；	c) the batch and/or code number to identify the contents and packaging operation;
d) 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；	d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;
e) 試驗受試者之識別號碼、試驗/治療號碼及訪視號碼（合適時）；	e) the trial subject identification number/treatment number and where relevant, the visit number;
f) 試驗主持人之姓名（如果未包含在(a)或(d)中）；	f) the name of the investigator (if not included in (a) or (d));
g) 使用說明(可參考供受試者或投用該產品者所製作之說明書或其他解釋文件)；	g) directions for use (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product);
h) 「僅供臨床試驗使用」或相似措辭；	h) “For clinical trial use only” or similar wording;
i) 儲存條件；	i) the storage conditions;
j) 使用期間【用畢日期、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；	j) 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;
k) 「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。	k) “keep out of reach of children” except when the product is for use in trials where the product is not taken home by subjects.

27. 已給予受試者載有藥品、臨床試驗及緊急解盲所需資料之主要接洽對象的地址與電話號碼之說明書或卡片，且已指示其隨身攜帶時，則該地址與電話號碼不需出現於標籤上。	27. The address and telephone number of the main contact for information on the product, clinical trial and for emergency unblinding need not appear on the label where the subject has been given a leaflet or card which provides these details and has been instructed to keep this in their possession at all times.
28. 細節應以研究用藥品要使用之所在國家的官方語言標示。除在29至30條中所述情況之直接容器外，第26條所列之細節應標示於直接包裝及間接包裝上。關於在直接包裝與間接包裝上之標籤內容的要求摘述於表1，可包括其他語言。	28. Particulars should appear in the official language(s) of the country in which the investigational medicinal product is to be used. The particulars listed in Article 26 should appear on the primary packaging and on the secondary packaging (except for the cases described in Articles 29 and 30). The requirements with respect to the contents of the label on the primary and secondary packaging are summarised in table 1. Other languages may be included.
29. 提供受試者或投用該藥品者之產品係置於連同間接包裝之直接包裝內，且該間接包裝帶有第26條所列舉的特定項目時，直接包裝（或包含直接包裝之任何密封的給藥裝置）之標籤上應包含下列資訊：	29. When the product is to be provided to the trial subject or the person administering the medication within a primary packaging together with secondary packaging that is intended to remain together, and the secondary packaging carries the particulars listed in paragraph 26, the following information should be included on the label of the primary package (or any sealed dosing device that contains the primary packaging):
a) 試驗委託者、受託研究機構或試驗主持人的名稱/姓名；	a) name of sponsor, contract research organisation or investigator;
b) 藥品劑型、給藥途徑（得限於口服固體劑型）、劑型單元數及在如為開放性試驗時，名稱或姓名/識別符號以及強度/效價；	b) pharmaceutical dosage form, route of administration (may be excluded for oral solid dose forms), quantity of dosage units and in the case of open label trials, the name/identifier and strength/potency;
c) 批號及/或代碼，以識別內容物及分/包裝作業；	c) batch and/or code number to identify the contents and packaging operation;
d) 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；	d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;

e) 試驗受試者之識別號碼/治療（或處理）號碼及訪視號碼（合適時）。	e) the trial subject identification number/treatment number and where relevant, the visit number.
30. 直接包裝採泡殼包裝或其上之小單元，諸如安瓿不能標示第26條要求之特定項目時，該項目應標示於外包裝。其直接容器仍應包含下列項目：	30. If the primary packaging takes the form of blister packs or small units such as ampoules on which the particulars required in paragraph 26 cannot be displayed, outer packaging should be provided bearing a label with those particulars. The immediate container should nevertheless contain the following:
a) 試驗委託者、受託研究機構或試驗主持人之名稱/姓名；	a) name of sponsor, contract research organisation or investigator;
b) 給藥途徑（得限於口服固體劑型）及在如為開放性試驗時，名稱或姓名/識別符號以及強度/效價；	b) route of administration (may be excluded for oral solid dose forms) and in the case of open label trials, the name/identifier and strength/potency;
c) 批號及/或代碼，以識別內容物及分/包裝作業；	c) batch and/or code number to identify the contents and packaging operation;
d) 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；	d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;
e) 試驗受試者之識別號碼/治療（或處理）號碼及訪視號碼（合適時）。	e) the trial subject identification number/treatment number and where relevant, the visit number.
31. 標示作業可包含符號或統計圖表，以釐清上述某些資料。可標示附加的資料、警告及/或處理指示[2]。	31. Symbols or pictograms may be included to clarify certain information mentioned above. Additional information, warnings and/or handling instructions may be displayed[2].
32. 具有某些特徵的臨床試驗，下列的特定項目應加到原始容器上，但不得遮蔽原始的標示資料：	32. For clinical trials with certain characteristics the following particulars should be added to the original container but should not obscure the original labelling:
i) 試驗委託者、受託研究機構或試驗主持人的名稱或姓名；	i) name of sponsor, contract research organisation or investigator;
ii) 能夠辨識該試驗之場所、試驗主持人及受試者之試驗對照代碼。	ii) trial reference code allowing identification of the trial site, investigator and trial subject.

33. 有變更用畢日期之必要者，應對研究用藥品貼上附加的標籤。該附加標籤應載明新的用畢日期，並重複該批號。這可覆蓋貼在原用畢日期上。為品管的理由，不可貼在原批號上。該作業應在適當的製造場所為之，但有正當理由時，得於試驗場所由該臨床試驗場所之藥師或符合國家法規之其他健康照護專業人員執行，或在其監督下為之。該做法不可能時，得由受過適當訓練之臨床試驗監督人員為之。其作業應依GMP原則、特定及標準之作業程序以及視情形依契約為之，並應由第二者核對。該附加的標示，應在試驗文件及在批次紀錄上適當記載。	33. If it becomes necessary to change the use-by date, an additional label should be affixed to the investigational medicinal product. This additional label should state the new use-by date and repeat the batch number. It may be superimposed on the old use-by date, but for quality control reasons, not on the original batch number. This operation should be performed at an appropriately authorised manufacturing site. However, when justified, it may be performed at the investigational site by or under the supervision of the clinical trial site pharmacist, or other health care professional in accordance with national regulations. Where this is not possible, it may be performed by the clinical trial monitor(s) who should be appropriately trained. The operation should be performed in accordance with GMP principles, specific and standard operating procedures and under contract, if applicable, and should be checked by a second person. This additional labelling should be properly documented in both the trial documentation and in the batch records.
品質管制（QUALITY CONTROL）	
34. 由於製程可能無法標準化或完全確效，於確保每批產品皆符合其規格上，檢驗作業擔負重責。	34. As processes may not be standardised or fully validated, testing takes on more importance in ensuring that each batch meets its specification.
35. 品質管制之執行應依該產品規格檔案及要求之資訊。盲性之確認應執行並記錄。	35. Quality control should be performed in accordance with the Product Specification File and in accordance with the required information. Verification of the effectiveness of blinding should be performed and recorded.
36. 樣品的留存是為了達成兩個目的：第一，為提供分析測試的樣品，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：	36. Samples are retained to fulfil two purposes; firstly to provide a sample for analytical testing and secondly to provide a specimen of the finished product. 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、包裝在直接包裝的產品或最終產品的樣品。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, product contained in its primary packaging 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包裝單元之樣品。這是為識別目的而儲存。例如，倘若發生需要時，用以辨識其外觀、包裝、標示、說明書、批號、末效日期等。	*Retention sample*: a sample of a packaged unit from a batch of finished product for each packaging run/trial period. It is stored for identification purposes. For example, presentation, packaging, labelling, leaflet, batch number, expiry date should the need arise.
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。	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.
研究用藥品的對照與留存樣品，包含盲性產品在內，應在使用批次的最終臨床試驗完成後，或正式終止後保存至少兩年，取兩者中期間較長者。	Reference and retention samples of investigational medicinal product, including blinded product should be kept for at least two years after completion or formal discontinuation of the last clinical trial in which the batch was used, whichever period is the longer.
直到臨床報告完成製作前，應對留存樣品的保存列入考量，以便在調查不一致試驗結果時，使產品同一性能確認，並成為調查之一部分。	Consideration should be given to keeping retention samples until the clinical report has been prepared to enable confirmation of product identity in the event of, and as part of an investigation into inconsistent trial results.
37. 對照與留存樣品的儲存場所，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。	37. The storage location of Reference and Retention samples should be defined in a Technical Agreement between the sponsor and manufacturer(s) and should allow timely access by the competent authorities.

對照樣品應有足夠數量，以允許至少在兩個時機，依照所提交之臨床試驗研究用藥品文件檔案，對該批次從事全項分析對照。	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 IMP dossier submitted for authorisation to conduct the clinical trial.
如為留存樣品，若其紀錄提供足夠資訊時，可接受以書面或電子紀錄儲存有關最終包裝的資訊。若為後者，該系統應符合附則11的要求。	In the case of retention samples, it is acceptable to store information related to the final packaging as written or electronic records if such records provide sufficient information. In the case of the latter, the system should comply with the requirements of Annex 11.
批次放行（RELEASE OF BATCHES）	
38. 於被授權人員確認相關的要求已符合前，不得放行研究用藥品（詳見第43條）。適合時，被授權人員應考量第40條所列之要項。	38. Release of investigational medicinal products (see paragraph 43) 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 in paragraph 40 as appropriate.
39. [...]PIC/S不採用	39. [...]*
40. 於放行前，每一批次之認證評估，合適時，可包括：	40. Assessment of each batch for certification prior to release may include as appropriate:
• 批次紀錄，包含品管報告、製程中檢驗報告及放行報告，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或檢驗，且應由依品質系統授權之人員完成與背書；	• 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 or tests, and should be completed and endorsed by the staff authorised to do so according to the quality system;
• 生產條件；	• production conditions;
• 廠房設施、製程及方法的確效狀態；	• the validation status of facilities, processes and methods;
• 最終包裝品的檢查；	• examination of finished packs;
• 合適時，在輸入後所執行之所有分析或檢驗的結果；	• where relevant, the results of any analyses or tests performed after importation;

• 安定性報告；	• stability reports;
• 來源及儲存與裝運條件之確認；	• the source and verification of conditions of storage and shipment;
• 關於製造廠品質系統之稽查報告；	• audit reports concerning the quality system of the manufacturer;
• 輸出國家的主管機關證明該製藥廠係經授權，以製造供輸出之研究用藥品或比對用產品的文件；	• Documents certifying that the manufacturer is authorised to manufacture investigational medicinal products or comparators for export by the appropriate authorities in the country of export;
• 合適時，上市許可的法規要求、適用的GMP標準及任何遵循GMP之官方證明；	• where relevant, regulatory requirements for marketing authorisation, GMP standards applicable and any official verification of GMP compliance;
• 負責產品放行者所知悉與該批次品質有關的所有其他因素。	• all other factors of which the QP is aware that are relevant to the quality of the batch.
上述因素的關聯性受該產品的原產地、製造廠、該製品之上市狀態（在美、日、歐盟或在第三國具有或不具有上市許可）及其開發階段的影響。	The relevance of the above elements is affected by the country of origin of the product, the manufacturer, and the marketed status of the product (with or without a marketing authorisation, in the EU or in a third country) and its phase of development.
試驗委託者應確保被授權人員，在證明該批次時，所考慮的要項與要求的資料一致。詳見第44條。	The sponsor should ensure that the elements taken into account by the Authorised Person when certifying the batch are consistent with the required information. See also 44.
41. 如研究用藥品於不同的場所製造與分/包裝時，在不同的被授權人員監督下，合適時，應遵循相關建議。	41. Where investigational medicinal products are manufactured and packaged at different sites under the supervision of different Authorised Persons, recommendations should be followed as applicable.

42. 當地法規容許時，分/包裝或標示得在試驗主持人的場所，由臨床試驗藥師或該等法規允許的其他健康照護專業人員執行，或在其監督下為之。該情形，被授權人員不需認證該作業。然試驗委託者仍應負責確保該作業經適當的文件化並依GMP原則執行，及應尋求被授權人員在這方面的意見。	42. Where, permitted in accordance with local regulations, packaging or labelling is carried out at the investigator site by, or under the supervision of a clinical trials pharmacist, or other health care professional as allowed in those regulations, the Authorised Person is not required to certify the activity in question. The sponsor is nevertheless responsible for ensuring that the activity is adequately documented and carried out in accordance with the principles of GMP and should seek the advice of the Authorised Person in this regard.
裝運（SHIPPING）	
43. 直到二階段程序經被授權人員的認證及滿足相關要求之放行完成前，研究用藥品應維持於試驗委託者的管制下。試驗委託者應確保明訂於臨床試驗申請並被被授權人認可的細節與被主管機關最終接受者一致。符合本要求之適當的安排應予建立。實際上，這最好可經由產品規格檔案的變更管制過程達成，並將其界定於被授權人與試驗委託人之間的技術協議中。該二階段程序均應予以記錄，並保存於試驗委託者或其代表保管之相關檔案中。	43. Investigational medicinal products should remain under the control of the Sponsor until after completion of a two-step procedure: certification by the Authorised Person; and release following fulfilment of the relevant requirements. The Sponsor should ensure that the details set out in the clinical trial application and considered by the Authorised Person are consistent with what is finally accepted by the Competent Authorities. Suitable arrangements to meet this requirement should be established. In practical terms, this can best be achieved through a change control process for the Product Specification File and defined in a Technical Agreement between the Authorised Person and the Sponsor. Both steps should be recorded and retained in the relevant trial files held by or on behalf of the sponsor.
44. 研究用藥品的裝運，應依試驗委託者或其代表在裝運單中之指示為之。	44. Shipping of investigational products should be conducted according to instructions given by or on behalf of the sponsor in the shipping order.
45. 研究用藥品裝運至試驗主持人之場所前，適當的負責人員應可取得解碼方法。	45. De-coding arrangements should be available to the appropriate responsible personnel before investigational medicinal products are shipped to the investigator site.

46. 製造或輸入者所製作之裝運藥品的詳細清單應予以保存。該清單應特別提示收件者的身分識別。	46. A detailed inventory of the shipments made by the manufacturer or importer should be maintained. It should particularly mention the addressees' identification.
47. 從一試驗場所到另一試驗場所轉送研究用藥品，應屬例外。該轉送應為標準作業程序所涵蓋。離開製造廠的管制外之產品歷史，涵蓋例如在原始試驗場所的試驗監測報告及儲存條件紀錄應予以審查，並當作該產品轉送適當性評估的一部分，另應尋求被授權人員的意見。如有必要，該產品應退回製造廠或其他被授權之製造廠重貼標籤，並由被授權人員認證/證明。紀錄應予以保存並確保可完全追溯。	47. Transfers of investigational medicinal products from one trial site to another should remain the exception. Such transfers should be covered by standard operating procedures. The product history while outside of the control of the manufacturer, through for example, trial monitoring reports and records of storage conditions at the original trial site should be reviewed as part of the assessment of the product’s suitability for transfer and the advice of the Authorised Person should be sought. The product should be returned to the manufacturer, or another authorised manufacturer for re-labelling, if necessary, and certification by a Authorised Person. Records should be retained and full traceability ensured.
申訴（COMPLAINTS）	
48. 由產品品質所引起的相關申訴，其完成調查後之結論，應在製造或輸入者與試驗委託者間（若兩者不同時）討論。這應有被授權人員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。	48. The conclusions of any investigation carried out in relation to a complaint which could arise from the quality of the product should be discussed between the manufacturer or importer and the sponsor (if different). 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.
回收品和退回品（RECALLS AND RETURNS）	
回收品（Recalls）	
49. 取回研究用藥品之程序及其文件化應經試驗委託者與製造或輸入者（若兩者不同時）同意。試驗主持人及監測人員需瞭解於該取回程序中之義務。	49. Procedures for retrieving investigational medicinal products and documenting this retrieval should be agreed by the sponsor, in collaboration with the manufacturer or importer where different. The investigator and monitor need to understand their obligations under the retrieval procedure.

50. 試驗委託者應確保將使用於臨床試驗之任何比對用藥品或其它藥品的供應者有一套系統，以聯繫試驗委託者回收其供應之任何產品的需要。	50. The Sponsor should ensure that the supplier of any comparator or other medication to be used in a clinical trial has a system for communicating to the Sponsor the need to recall any product supplied.
退回品（Returns）	
51. 研究用藥品應依同意的條件退回。該條件由試驗委託者界定，並在核可之書載程序中明定。	51. Investigational medicinal products should be returned on agreed conditions defined by the sponsor, specified in approved written procedures.
52. 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。	52. Returned investigational medicinal products should be clearly identified and stored in an appropriately controlled, dedicated area. Inventory records of the returned medicinal products should be kept.
銷毀（Destruction）	
53. 試驗委託者應負責，將未使用的及/或退回之研究用藥品銷毀。因此，研究用藥品非有試驗委託者之事先書面授權，不得銷毀。	53. The Sponsor is responsible for the destruction of unused and/or returned investigational medicinal products. Investigational medicinal products should therefore not be destroyed without prior written authorization by the Sponsor.
54. 送交、使用及收回的藥品數量應由試驗委託者或其代表就每一試驗場所及每一試驗期間予以記錄、數量調和及確認。每一試驗場所及每一試驗期間未使用之研究用藥品的銷毀，應僅於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。銷毀作業的紀錄應以所有作業皆可獲得說明的方式執行。這些紀錄應由試驗委託者保存。	54. The delivered, used and recovered quantities of product should be recorded, reconciled and verified by or on behalf of the sponsor for each trial site and each trial period. Destruction of unused investigational medicinal products should be carried out for a given trial site or a given trial period only after any discrepancies have been investigated and satisfactorily explained and the reconciliation has been accepted. Recording of destruction operations should be carried out in such a manner that all operations may be accounted for. The records should be kept by the Sponsor.

55. 當研究用藥品的銷毀時，應將載明日期之銷毀證明書或收據提供給試驗委託者。這些文件應清楚地識別或可追溯到所涉批次及/或病人代碼及銷毀之實際數量。	55. When destruction of investigational medicinal products takes place a dated certificate of, or receipt for destruction, should be provided to the sponsor. These documents should clearly identify, or allow traceability to, the batches and/or patient numbers involved and the actual quantities destroyed.
表1. 標示細節摘要 **Table1. SUMMARY OF LABELLING DETAILS (§26 to 30)**	
a) 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）；	a) 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);
b) 藥品劑型、給藥途徑、劑型單元數，以及如為開放性試驗[3]，其名稱/識別符號及強度/效價；	b) pharmaceutical dosage form, route of administration, quantity of dosage units, and in the case of open trials[3], the name/identifier and strength/potency;
c) 用以識別內容物與分/包裝作業之批號及/或代碼；	c) the batch and/or code number to identify the contents and packaging operation;
d) 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；	d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;
e) 試驗受試者之識別號碼、試驗/治療號碼及訪視號碼（合適時）；	e) the trial subject identification number / treatment number and where relevant, the visit number;
f) 試驗主持人之姓名（如果未包含在(a)或(d)中）；	f) the name of the investigator (if not included in (a) or (d));
g) 使用說明（可參考供受試者或投用該產品者所製作之說明書或其他解釋文件）；	g) directions for use (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product;
h) 「僅供臨床試驗使用」或相似措辭；	h) “for clinical trial use only” or similar wording;
i) 儲存條件；	i) the storage conditions;
j) 使用期間【用畢日期、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；	j) 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;
k) 「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。	k) “keep out of reach of children” except when the product is for use in trials where the product is not taken home by subjects.

一般情況 對直接包裝與間接包裝（第26條） 特別事項 a[4]至k	**GENERAL CASE** For both the primary and secondary packaging (§26) Particulars a[4] to k
直接包裝 在整個期間中在直接包裝與間接包裝保持在一時（第29條）[5] a[6] b[7] c d e	**PRIMARY PACKAGE** Where primary and secondary packaging remain together throughout (§29)[5] a[6] b[7] c d e
直接包裝 泡型包裝或小包裝單元（第30條）[5] a[6] b[7,8] c d e	**PRIMARY PACKAGE** Blisters or small packaging units (§30)[5] a[6] b[7,8] c d e
[1] 對於封閉式盲性試驗，其標示應包括指示「安慰劑或[名稱/識別符號]及[強度/效價]」的陳述。	[1] For closed blinded trials, the labelling should include a statement indicating "placebo or [name/identifier] + [strength/potency]".
[2] 例如，細胞毒類產品或需要特殊儲存條件之產品的標籤。	[2] E.g. labels for cytotoxic products or for products requiring special storage conditions
[3] 對於封閉性盲性試驗，其標示應包括指示「安慰劑或[名稱/標識符]及[強度/效價]」的陳述。	[3] For closed blinded trials, the labelling should include a statement indicating "placebo or [name/identifier] + [strength/potency]".
[4] 已給予受試者載有藥品、臨床試驗及緊急解盲所需資料之主要接洽對象的地址與電話號碼之說明書或卡片，且已指示其隨身攜帶時，則該地址與電話號碼不需出現於標籤上（第 27 條）。	[4] The address and telephone number of the main contact for information on the product, clinical trial and for emergency unblinding need not appear on the label where the subject has been given a leaflet or card which provides these details and has been instructed to keep this in their possession at all times (§ 27).
[5] 當間接包裝/外包裝帶有第 26 條中所列舉的特別事項時。	[5] When the outer packaging carries the particulars listed in Article 26.
[6] 不需要包括藥品、臨床試驗及緊急解盲所需資料之主要接洽對象的地址與電話號碼。	[6] The address and telephone number of the main contact for information on the product, clinical trial and for emergency unblinding need not be included.

[7] 口服固體劑型投用途徑可以排除。	[7] Route of administration may be excluded for oral solid dose forms.
[8] 藥物劑型與劑量單元數量可以省略。	[8] The pharmaceutical dosage form and quantity of dosage units may be omitted.

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）

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].
註：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 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，為提供分析測試的樣品，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。	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.
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）

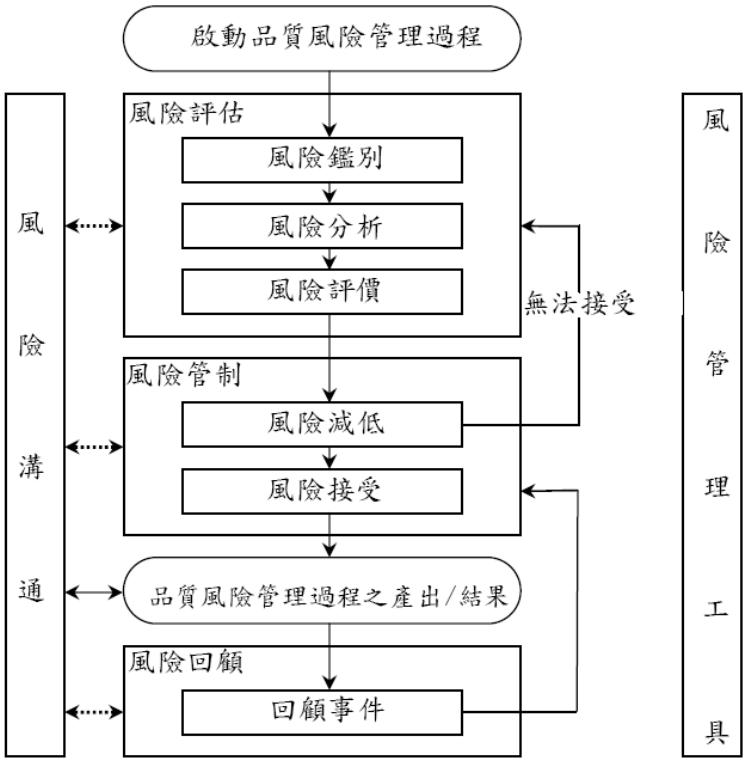
*本附則為自願性的/非強制性的。	* This Annex is voluntary.
序文和適用範圍 （FOREWORD AND SCOPE OF APPLICATION）	
1. 新的 GMP 附則 20 相當於 ICH Q9 關於品質風險管理的指引。它對於品質風險管理提供系統性方法之指引，以利遵守從 GMP 及其他品質之要求。當應用正式的品質風險管理方法時，它包括要使用之原理及可能使用之過程、方法和工具的選項。	1. The new GMP Annex 20 corresponds to ICH Q9 guideline on Quality Risk Management. It provides 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	5. While the GMP guide is primarily

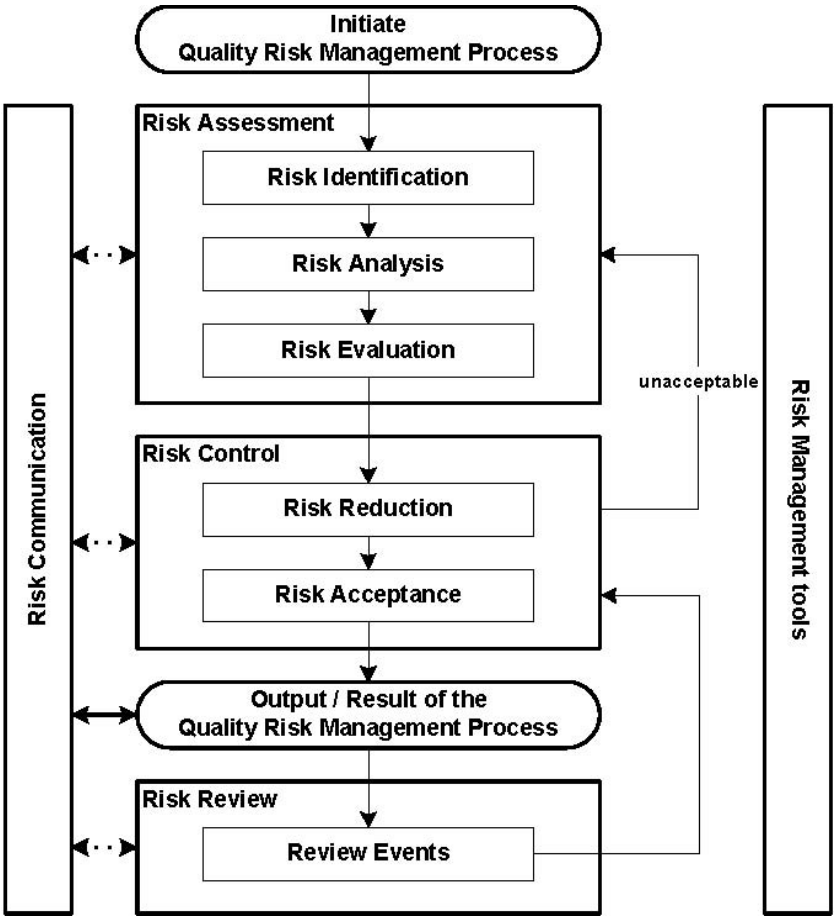
指引則與其他品質指引具有關聯，並包括對主管機關之特定部門。	addressed to manufacturers, the ICH Q9 guideline, has relevance for other quality guidelines and includes specific sections for regulatory agencies.
6. 然而，為了連貫性及完整性，已將 ICH Q9 指引完全轉為 GMP 附則 20。	6. However, for reasons of coherence and completeness, the ICH Q9 guideline has 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	9. The manufacturing and use of a drug

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。	(medicinal) product, including its components, necessarily entail some degree of risk. The risk to its quality is just one 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）亦得認定為可接受。	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 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，其詳細程度是與其特定風險相稱。	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 (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.


啟動品質風險管理過程
風險評估
風險鑑別
風險分析
風險評價
無法接受
風險管制
風險減低
風險接受
品質風險管理過程之產出/結果
風險回顧
回顧事件
風險溝通
風險管理工具


Initiate
Quality Risk Management Process
Risk Assessment
Risk Identification
Risk Analysis
Risk Evaluation
unacceptable
Risk Control
Risk Reduction
Risk Acceptance
Output / Result of the
Quality Risk Management Process
Risk Review
Review Events
Risk Communication
Risk Management tools

16. 因為決策可能發生在過程中的任何一點，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。	16. Decision nodes are not shown in the diagram 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、損害或對人體健康之衝擊的背景資訊及/或數據；	• Assemble background information and/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	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

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。	best quality risk management practices might not entirely eliminate risk. In these 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	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

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)。	to be utilized for events that might impact the original quality risk management decision, 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。	40. Quality risk management should be integrated into existing operations and 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	Decision maker(s) – Person(s) with the competence and authority to make

質風險管理決策的人。	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 指出一個變數之改變方向或比率的統計學術語。	Trend –a statistical term referring to the direction or rate of change of a variable(s)

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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善。	To facilitate continual improvement in 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).