109 年度衛生福利部食品藥物管理署委託科技計畫
「精進新興生醫產品 GTP 符合性管理制度之研析」

新興生醫產品 GTP 研習會

林書仲 GMP 顧問 ／ 社團法人中華無菌製劑協會

吳皇昇 總經理 ／ 美商 UPS 集團
麥肯國際物流有限公司

楊逸萍 研究員 ／ 臺北榮民總醫院
醫學研究部

楊利君 技術長 ／ 尚博生物科技有限公司

主辦單位： 衛生福利部食品藥物管理署

承辦單位： 社團法人台灣生醫品質保證協會

109 年 7 月 10 日(五)

目　　錄

109 年度「新興生醫產品 GTP 研習會」

議　程

〔**直播場次**〕109 年 7 月 10 日（五）09:30 – 17:00

時　間	講　題	講　師
09:00 –09:30	報到以及課前測驗	
09:30 – 09:40	長官致詞	
09:40 – 10:30	新興生醫產品的無菌保證： 潔淨室/潔淨空氣設備 的設計與無菌操作的考量要點	社團法人 中華無菌製劑協會 林書仲 顧問
10:40 – 10:50	休息	
10:50 – 12:00	細胞組織物溫控運輸	麥肯國際物流 吳皇昇 總經理
12:00 – 13:00	午餐	
13:00 – 13:50	新興生物醫學科技發展新知	臺北榮民總醫院 楊逸萍 博士
14:00 – 14:10	休息	
14:10 – 15:20	流式細胞儀 儀器驗證、品質管制	尚博生物科技有限公司 楊利君 技術長
15:20 – 16:00	課後測驗	

注意事項：為維護您的權益，報名前請務必詳閱下列注意事項：

1. 本次活動全程免費，請學員預先測試及確認使用之設備及網路能正常運作及觀看 youtube 直播，可於課程開始前 20 分鐘內連線查看。
2. 此次會議為單向直播無互動說明會，請於"意見調查表"問卷中，提出問題或寄信至協會 tsqa.gtp@gmail.com 信箱，會將問題整理好給講師後，會後約一

個月回覆。

3. **有報名課程並確實完成課前、後測驗之學員才會授予課程時數證明**，公務員另有公務人員時數認證（共計 6 小時，僅限全程參予者）。

4. 本次活動若適逢天災（地震、颱風等）不可抗拒因素，將延期舉辦，時間另行通知。若有任何問題，請電洽承辦單位。

5.承辦單位保留報名資格審核、變更研討會議程及講者權利；若有任何未盡事宜承辦單位得隨時補充、說明並修改之。

6. 部分上課內容因涉及產權或公司機密，講義和上課播放之簡報可能會有些微不同，但不會影響學員們進行測驗之權益。

109 年度「新興生醫產品 GTP 研習會」
直播場次

注意事項：報名課程並**確實完成課前、後測驗之學員**才會授予課程時數證明，公務員另有公務人員時數認證（共計 6 小時，僅限全程參予者）。

課前測驗: 開放時間:7/10 09:00-10:10

https://www.surveycake.com/s/9x3Ar

課後測驗: 開放時間:7/10 15:00-18:00

https://www.surveycake.com/s/QGBQo

意見調查表:

https://www.surveycake.com/s/Rq2A8

講師簡歷

林書仲　顧問

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經　歷	

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- 葛蘭素威康股份有限公司製造部經理/品保部經理/技術部經理
- 普強股份有限公司品保部經理/製造部經理/製造部主任/微生物師
- 信東化學股份有限公司研究課課長/品管課股長/研究員

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經　歷	
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專 長	
溫控物流、國際快遞業經營管理、供應鏈管理、危險品空運運輸實務	

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經　歷	
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楊利君　技術長

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請參閱後兩頁	

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ACADEMIC QUALIFICATIONS

2000- 2002:

National Yang Ming Medical University
Master's degree of Anatomy and cell biology

Thesis Title:Tanshinone IIA isolated from Salvia miltiorrhiza elicits the cell death of human endothelial cells

Supervisor: Dr. Yat-Pang Chau

1997- 2000:

***Chinese Culture University* , Bachelor's degree of Biology**

EMPLOYMENT HISTORY

Cell-bio Biotechnology Co.,Ltd

- 2016~ Chief of Technology
- 2008~2016 Product manager
- 2006~2008 Project Supervisor
- 2004~2006 Product specialist

EXPERIENCE & CERTIFICATION

I am working with life science product promotion and company stretagy planning over 15 years , during first decade , I'm travalling frequently between Asia , Europe and North America to bring latest novel technology back to Taiwan . I'm fully focus on cell base analysis platform especially in the field of Flow Cytometry and Image Cytometry as a **F**ield **A**pplication **S**pecialist and also **F**ield **S**ervice **E**ngineer . I'm also fully participate company decision and marketing strategy for 10 years and responsible for organizing company structure. Please see following major skill and experience I collect currently :

(Order by the date from latest)

- CELLINK Life Scoence Authorize Cell Imager FAS & FSE
- CELLINK Life Scoence Authorize single cell printer FAS & FSE
- SONY MBU Authorize Flow Cytometry FAS & FSE for Spectrum Cell Analyzer
- SONY MBU Authorize Flow Cytometry FAS & FSE for Automatic Cell Sorter
- ChemoMetech A/S Authorize Image Cytometry FAS & FSE
- Crestoptics S.p.A Authorize Spinning Disk Confocal Technology FAS & FSE
- TissueGnostics Authorize TissueFAXS Tissue Cytometry FAS & FSE.
- Beckton Dickinson Authorize High Content Screennin Technology FAS & FSE
- Beckton Dickinson Authorize Spinning Disk Confocal bioimager FAS & FSE
- Cellular Technology LTD Authorize ImmunoSpot Technology FAS & FSE
- Beckton Dickinson Authorize Flow cytometry FACS101 and FACS200 trainer
- Experience in public speaking over 20 years
- Proficient computer skills for daily use documentation

新興生醫產品的無菌保證：潔淨室/潔淨空氣設備的設計與無菌操作的考量要點

林書仲　GMP 顧問

社團法人中華無菌製劑協會

新興生醫產品的無菌保證：潔淨室/潔淨空氣設備的設計與無菌操作的考量要點

林書仲
GMP 顧問
社團法人中華無菌製劑協會
2020-07-10

大綱

1. 高度法規管制的製藥業
   1. 淺談GXP
   2. 注射劑產品的關鍵品質屬性(CQA)與無菌保證程度(SAL)
   3. 選擇適當的滅菌方法
2. 潔淨室/潔淨空氣設備設計的考量要點
   1. 潔淨室與潔淨空氣設備
   2. 潔淨室的分級與驗證
   3. 環境監測
3. 人工無菌作業的考量要點
   1. 人是最大的汙染源
   2. 避免人為介入A級區
   3. 人工無菌操作考量要點

1. 高度法規管制的製藥業

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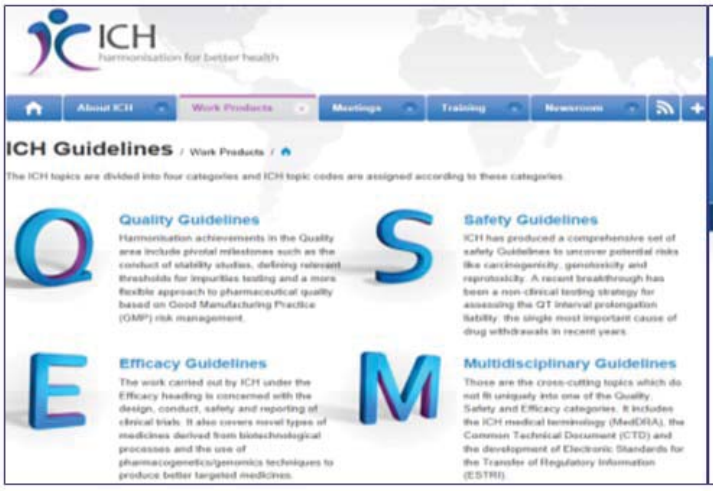
高度法規管制的製藥業－全球化

藥品銷售許可證

Marketing Authorization

藥品製造許可證

Manufacturing Authorization



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1.1 淺談GXP

GXP：GCP、GDP、 GLP、 GMP、GTP…

Output：Products，Services

X：Process

Good Practice vs. Best Practice：Best Practice → Current GMP

TFDA's GMP & GTP： FDA → PIC/S

ATMP：EMA vs. PIC/S

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藥廠GMP查核的六大系統

FDA查核的GMP六大系統

1. 品質系統
2. 製造系統
   1. 廠房設施設備系統
   2. 物料系統
   3. 生產系統
   4. 包裝貼標系統
   5. 實驗室管制系統

參考資料：FDA Quality Systems Approach to Pharmaceutical CGMP Regulations " 2006 Section III G. Six-system Inspection Model

PIC/S GMP Guide

第一章 製藥品質系統

第二章 人事

第三章 廠房設施與設備

第四章 文件

第五章 生產

第六章 品質管制

第七章 委外活動

第八章 申訴與產品回收

第九章 自我查核

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21世紀的GMP要求

FDA Initiatives

Pharmaceutical cGMPs for the 21st Century - A Risk-Based Approach
September 2004 (Final Report)

Guiding Principles:

- Risk-based orientation ICH Q9
- Science-based policies and standards ICH Q8
- Integrated quality systems orientation ICH Q10
- International cooperation
- Strong public health protection

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1.2 注射劑產品的關鍵品質屬性(CQA)與無菌保證程度(SAL)

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USP General Chapters <1>
Injections and Implanted Drug Products – Product Quality Tests

1. Universal Tests
    1. *Description/Appearance* *(USP Monograph 已不收載)*
    2. Identification
    3. Assay
    4. Impurities
    5. Foreign and Particulate Matters
    6. Sterility Test
    7. Bacterial Endotoxins
    8. Container Contents
    9. Packaging Systems (Container, Closure, Extractables and Leachables)
    10. Container closure integrity
    11. Labeling
2. Specific Tests
    1. …

USP General Chapters <1046>
CELLULAR AND TISSUE-BASED PRODUCTS

Final Product Release Specifications

1. Sterility Test
2. Mycoplasma
3. Endotoxins
4. Identity
5. Purity
6. Potency
7. Dose
8. Others

無菌產品風險最高的CQA：無菌性

- 藥品消費者(病患)是最弱勢的客戶(人都可能患病需要醫療)
- 許多醫療傷亡悲劇造成新法規的要求(例如，滅菌確效)
  - 美國NECC：黴菌污染爆發腦膜炎
  - 台灣某藥廠：細菌汙染(R. pickettii)，全面回收

64 Killed, >750 Sick

無菌操作→最終滅菌

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無菌試驗的SAL

4.2 An end-product test for sterility is limited in its ability to detect contamination as it utilises only a small number of samples in relation to the overall batch size, and secondly, culture media may only stimulate growth of some, but not all, microorganisms. Therefore, an end-product testing for sterility only provides an opportunity to detect major failures in the sterility assurance system.

-- PE 009-14 Annex 17 Real Time Release Testing and Parametric Release

(破壞性試驗，取樣量少，培養基差異，0.1%汙染率被偵測機率：2%)

The probability of failing a sterility test given a contamination rate of 0.1% (an unacceptably high level of contamination) is 2% (where $n = 20$).

-- USP 41<1222>Terminally Sterilized Pharmaceutical Products- Parametric Release

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無菌操作的SAL
培養基充填合格標準的演變

早期標準：0.1%(算數的→統計學的)

現行標準 (PE 009-14 Annex 1)

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：

1)充填少於5000單元者，不得有任何污染單元。

2)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。

3)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

最新標準：The target should be zero growth. -- Annex 1 draft, 2020 條文9.48
取消前3項規定，新增較嚴規定：產品隔離，找出污染根本原因，改善後再確效(三次)，成功後才可恢復生產。

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最終滅菌的SAL

For terminally sterilized products, sterility assurance is defined in terms of the probability of nonsterility (PNS), or the probability of the terminal sterilization process generating a nonsterile unit (PNSU). Terminal sterilization processes must achieve a consistent validated performance of a PNSU of $\leq 10^{-6}$ (a probability of NMT 1 nonsterile unit in 1 million units produced)

-- USP 41 <1211> Sterility Assurance

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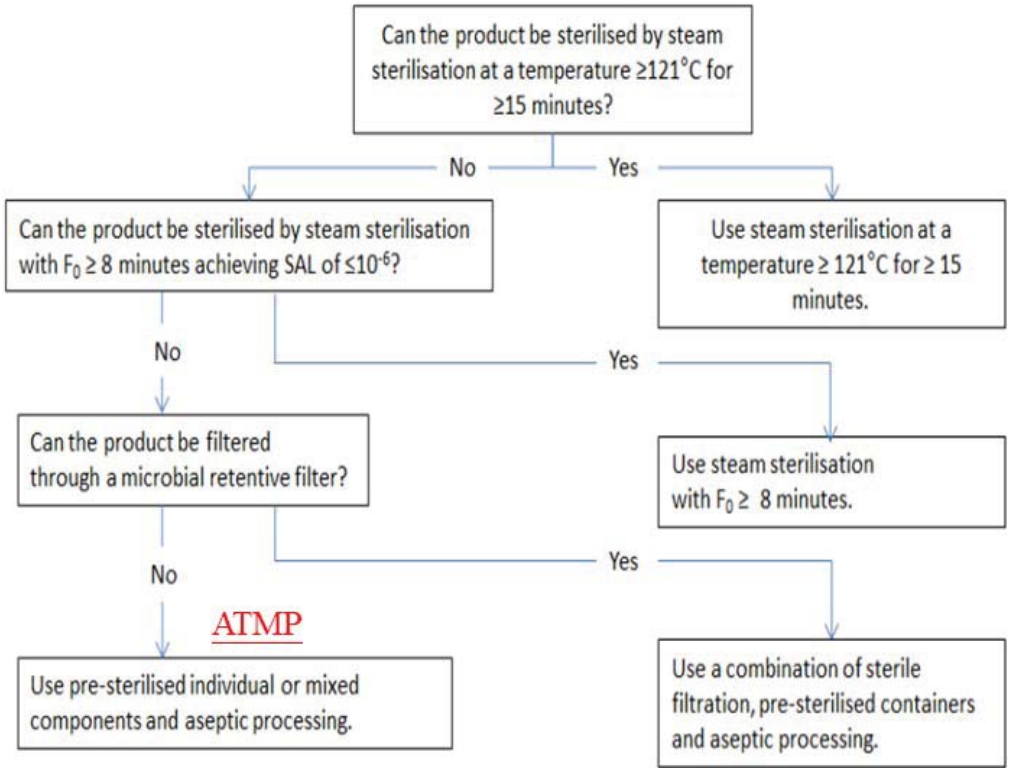
1.3 選擇適當的滅菌方法

EMA：Guideline on Sterilisation of the Medicinal Product, Active Substance, Excipient and Primary Container, 2019

1 Decision tree for sterilisation choices for aqueous products



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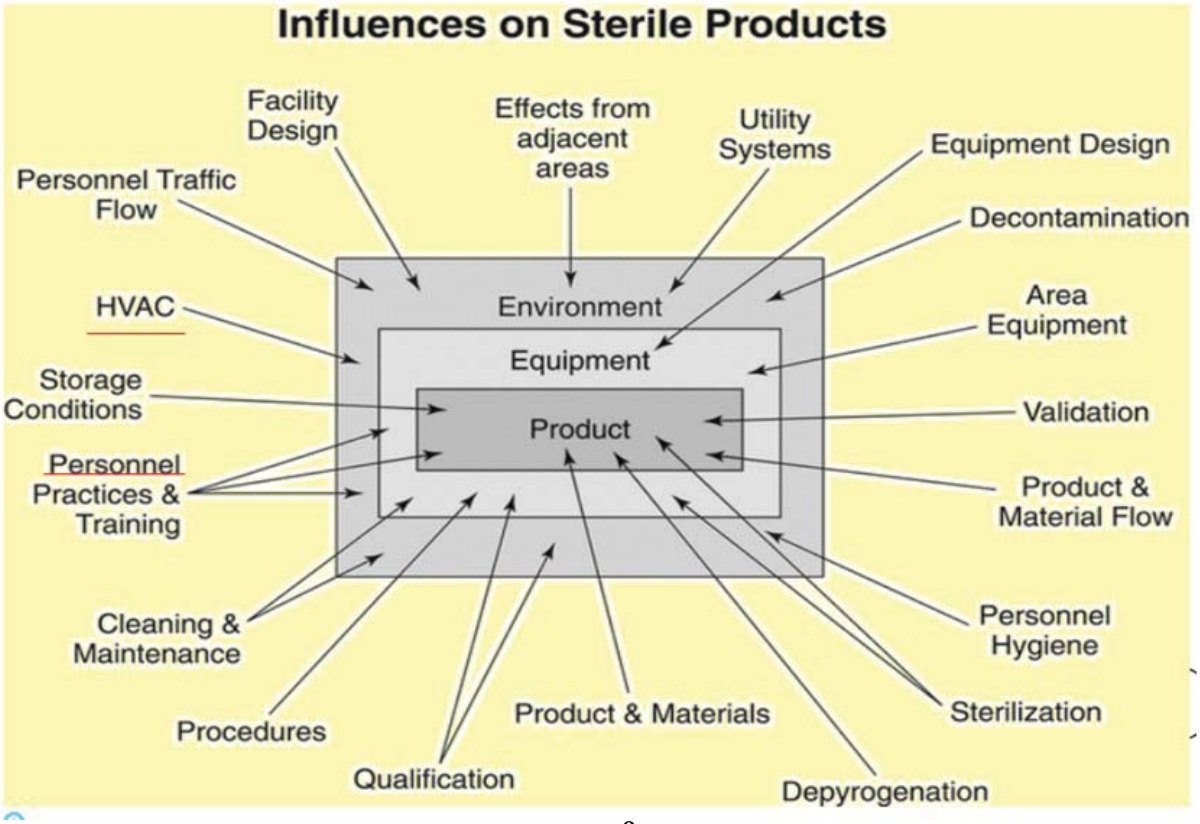
影響無菌產品品質的 因素 - USP 41 <1211>

製藥廠的 污染管制策略Contamination Control Strategy(CCS)



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2. 潔淨室/潔淨空氣設備設計的考量要點

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2.1 潔淨室與潔淨空氣設備

潔淨室 (Cleanroom)

A room designed, maintained, and controlled to prevent particulate and microbial contamination of drug products. Such a room is assigned and reproducibly meets an appropriate air cleanliness level. Grade A will be referred to as Grade A zone.

-- Annex 1 Draft, 2020

潔淨空氣設備(Clean Air Equipment)

Unidirectional Airflow Units (UDAFs)：Vertical, Horizontal

Restricted Access Barrier Systems (RABS) ：Active, Passive, Open, Closed

Isolators：Open, Closed

Biosafety Cabinet (BSC)：Class I, II (Type A1, A2, B1, B2) , III

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RABS或Isolator(潔淨空氣設備)的背景環境

4.21 For RABS used for aseptic processing, the background environment should meet at least Grade B. The background environment for open isolators should meet Grade C or D, based on a risk assessment. Airflow studies should be performed to demonstrate the absence of air ingress during interventions, such as door openings.

(RABS 背景：B級；Isolator：C或D)

4.22 The background environment of a closed isolator should correspond to a minimum of Grade D. The disinfection/decontamination programme should be included as a key consideration when performing the risk assessment for the CCS of an isolator. Where additional process risks are identified, a higher grade of background should be considered. The decision as to the supporting background environment should be documented in the CCS.

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2.2 潔淨室分級與驗證 - 分級

4.28 Cleanroom classification is part of a cleanroom qualification and is a method of assessing the level of air cleanliness against a specification for a cleanroom or clean air equipment by measuring the non-viable airborne particulate concentration. Reference for the classification of the cleanrooms and clean air equipment can be found in the ISO 14644 series of standards. -- Annex 1, 2020 draft

(分級：量測總微粒數，完全根據ISO14644的要求)

4.29 For cleanroom classification, the airborne particulates equal to or greater than 0.5 and 5 µm should be measured. For Grade A zone and Grade B at rest, classification should include measurement of particles equal to or greater than 0.5 µm; however, measurement using a second, larger particle size, e.g. 1 µm in accordance with ISO 14644 may be considered. This measurement should be performed both at rest and in operation. The maximum permitted airborne particulate concentration for each grade is given in Table 1.

(ISO5(A級動靜態與B級靜態)無5 µm的限量標準，可能要考量1 µm)

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潔淨室驗證 - 驗證項目

4.27 Cleanroom Qualification is the overall process of assessing the level of compliance of a classified cleanroom or clean air equipment with its intended use. As part of the qualification requirements of Annex 15, the qualification of cleanrooms and clean air equipment should include (where relevant to the design/operation of the installation):

i. Installed filter leakage and integrity testing.
ii. Airflow measurement - Volume and velocity.
iii. Air pressure difference measurement.
iv. Airflow direction and visualisation.
v. Microbial airborne and surface contamination.
vi. Temperature measurement.
vii. Relative humidity measurement.
viii. Recovery testing.
ix. Containment leak testing.

- *Annex 15：URS, DQ, IQ, OQ, PQ*
- *驗證項目：與ISO14644大致相同但增加微生物管制*

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潔淨室分級與驗證–微粒子限量表

Table 1: Maximum permitted airborne particulate concentration during classification

Grade	Maximum limits for particulates ≥ 0.5 µm/m³		Maximum limits for particulates ≥ 5 µm/m³	
動態	at rest	in operation	at rest	in operation
A ISO 5 Class 100	3 520	3 520	Not applicable	Not applicable
B ISO 7 Class 10,000	3 520	352 000	Not applicable	2 900
C ISO 8 Class 100,000	352 000	3 520 000	2 900	29 000
D	3 520 000	Not defined[a]	29 000	Not defined[a]

(a) For Grade D, in operation limits are not defined. The company should establish in operation limits based on a risk assessment and historical data where applicable.

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微生物限量表

Table 2: Limits for microbial contamination during qualification

Grade	Air sample cfu/m^3	Settle plates (diameter 90 mm) cfu/4 hours [a]	Contact plates (diameter 55 mm) cfu/plate
A[b]	No growth[b]		
B	10	5	5
C	100	50	25
D	200	100	50

(a) Settle plates should be exposed for the duration of operations and changed as required after 4 hours. Exposure time should be based on recovery studies and should not allow desiccation of the media used.

(b) It should be noted that for Grade A, the expected result should be no growth.

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再驗證項目

4.34 The requalification of cleanrooms and clean air equipment should be carried out periodically following defined procedures. The requirement for requalification of cleanroom areas is as follows:

Table 3: Minimum test requirements for the requalification of cleanrooms

Grade	Determination of the concentration of airborne viable and non-viable particles	Integrity Test of Terminal Filters	Airflow volume measurement	Verification of air pressure difference between rooms	Air Velocity test
A	Yes	Yes	Yes	Yes	Yes
B	Yes	Yes	Yes	Yes	*
C	Yes	Yes	Yes	Yes	*
D	Yes	Yes	Yes	Yes	*

* performed according to a risk assessment documented as part of the CCS. However, required for filling zones (e.g. when filling terminally sterilised products) and background to Grade A RABS.

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再驗證頻率

- For Grade A & B areas, the maximum time interval for requalification is 6 months. For Grade C & D areas, the maximum time interval for requalification is 12 months.

(再驗證最大時間間隔：A、B區(六個月) C、D區(12個月))

- Appropriate requalification consisting of at least the above tests should also be carried out following completion of remedial action implemented to rectify an out-of-compliance equipment or facility condition or after changes to equipment, facility or processes.

(異常維修或廠房、設施、設備、製程變更後應再驗證)

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2.3 環境監測 – 作業中監測

9.5 Routine monitoring of cleanrooms, clean air equipment and personnel should be performed in operation throughout all critical stages, including equipment set-up.

(關鍵作業全程監測，由裝機開始)

9.6 The monitoring of Grade A zones should demonstrate the maintenance of aseptic processing conditions during critical operations. Monitoring should be performed at locations posing the highest risk of contamination to the sterile equipment surfaces, container, closures and product. The selection of monitoring locations and the orientation and positioning of sampling devices should be justified and appropriate to obtain reliable data from the critical zones.

(監測最高風險的位置、考量取樣器角度、方位)

26

微粒子監測限量表

9.15 The limits for environmental monitoring of airborne particulate concentrations for each graded area are given in Table 6.

Table 6: Limits for airborne particulate concentration for the monitoring of non-viable contamination.

Grade	Maximum limits for particulates ≥ 0.5 µm/m³		Maximum limits for particulates ≥ 5 µm/m³	
	at rest	in operation	at rest	in operation
A	3 520	3 520	29	29
B	3 520	352 000	29	2 900
C	352 000	3 520 000	2 900	29 000
D	3 520 000	Not defined[(a)]	29 000	Not defined[(a)]

與表一的差異

[(a)] For Grade D, in operation limits are not defined. The company should establish in operation limits based on a risk assessment and on historical data, where applicable.

27

微生物監測限量表

Table 7: Maximum action limits for viable particle **contamination**

Grade	Air sample cfu/m³	Settle plates (diam. 90 mm) cfu/4 hours [(a)]	Contact plates (diam. 55mm), cfu/ plate [(c)]	Glove print, Including 5 fingers on both hands cfu/ glove
A	No growth[(b)]			
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

與表二的差異

[(a)] Settle plates should be exposed for the duration of operations and changed as required after 4 hours (exposure time should be based on validation including recovery studies and it should not have any negative effect on the suitability of the media used). Individual settle plates may be exposed for less than 4 hours.

[(b)] It should be noted that for Grade A, any growth should result in an investigation.

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

A級區

9.16 For the Grade A zone, particulate monitoring should be undertaken for the full duration of critical processing, including equipment assembly.

(A級區須全程監測，從設備組裝開始)

9.17 The Grade A zone should be monitored continuously (for particulates ≥0.5 and ≥5 μm) and with a suitable sample flow rate (at least 28 litres (1ft3) per minute) so that all interventions, transient events and any system deterioration is captured. The system should frequently correlate each individual sample result with the limits in Table 6 at such a frequency that any potential excursion can be identified and responded to in a timely manner. Alarms should be triggered if alert levels are exceeded. Procedures should define the actions to be taken in response to alarms including the consideration of additional microbial monitoring.

(微粒計數器取樣量，即時回饋，啟動警報，採取行動)

29

有害物質

9.19 The selection of the monitoring system should take into account any risk presented by the materials used in the manufacturing operation (for example, those involving live organisms, powdery products or radiopharmaceuticals) that may give rise to biological or chemical hazards

(有害物質：活菌、粉末、放射物質)

9.20 In the case where contaminants are present due to the processes involved and would potentially damage the particle counter or present a hazard (e.g. live organisms, powdery products and radiation hazards), the frequency and strategy employed should be such as to assure the environmental classification both prior to and post exposure to the risk. An increase in viable particle monitoring should be considered to ensure comprehensive monitoring of the process. Additionally, monitoring should be performed during simulated operations. Such operations should be performed at appropriate intervals. The approach should be defined in the CCS.

(暴露於有害物質的前、後時間監測；增加微生物監測；APS)

30

人員微生物監測

9.32 Personnel gloves (and any part of the gown that may potentially have direct impact on the product sterility (e.g. the sleeves if these enter a critical zone) should be monitored for viable contamination after critical operations and on exit from the cleanroom. Other surfaces should be monitored at the end of an operation

(手套、袖子監測：介入關鍵區或離開潔淨室；　額頭、前胸：作業結束)

9.33 Microbial monitoring of personnel in the Grade A zone and Grade B area should be performed to assess their aseptic behaviour. Where filling operations are manual in nature e.g. hand filling, the process in its entirety may be considered as one critical intervention. In these cases, the frequency of microbial monitoring of gowning should be based on scientific principles and justified as part of the CCS. Where monitoring is routinely performed by manufacturing personnel, consideration should be given to periodic monitoring under the supervision of the quality unit.

(人工無菌操作屬於全程介入，如何監測？ 授權生產人員執行監測時QA需定期監督)

31

建立趨勢：設定警界水平與行動限量

9.8 Appropriate alert levels and action limits should be set for the results of viable and non-viable particle monitoring. Alert levels should be established based on results of cleanroom qualification tests or trend data and should be subject to periodic review.

(設定警界水平與行動限量：根據驗證與日常控數據，定期檢討)

9.9 Alert levels for Grade A (non-viable particles only) Grade B, Grade C and Grade D should be set such that adverse trends (e.g. a numbers of events or individual events that indicate a deterioration of cleanliness) are detected and addressed.

(設定警界水平：發現異常趨勢(OOT))

32

3. 人工無菌作業的考量要點

3.1 人是最大的 汙染源

33

潔淨服 - A、B級區

7.14 The description of clothing required for each grade is given below:

Grade A / B: Dedicated garments to be worn under a sterilized suit. Sterile headgear should enclose all hair (including facial hair) and where separate from the rest of the gown, it should be tucked into the neck of the sterile suit.

(內襯衣，分離頭罩塞入連身無菌服)

A sterile face mask and sterile eye coverings (e.g. goggles) should be worn to cover and enclose all facial skin and prevent the shedding of droplets and particulates. *(無菌口罩、護目鏡罩住臉部所有皮膚)*

Appropriate sterilized, non-powdered, rubber or plastic gloves and sterilized footwear (such as overboots) should be worn. Trouser-legs should be tucked inside the footwear and garment sleeves into the gloves.

(無菌無粉手套、褲管塞入長靴，衣袖塞入手套)

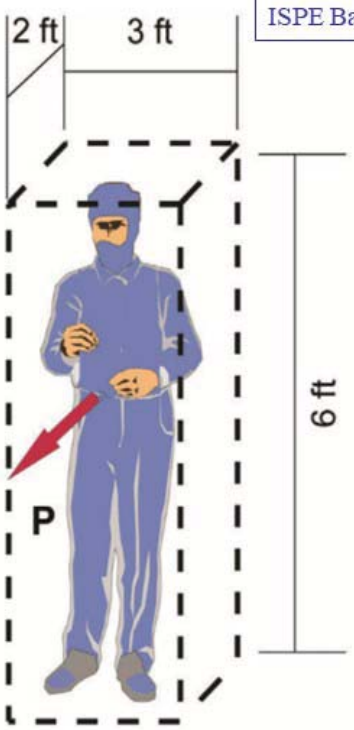
The protective clothing should minimize shedding of fibres or particulate matter and retain particulates shed by the body. Garments should be packed and folded in such a way as to allow operators to gown without contacting the outer surface of the garment.

(無菌服不釋放微粒並能阻止身體微粒逸散)

34

無菌衣的保護效果

Figure 11.2: Human Particle Generation



ISPE Baseline Vol. 03 Sterile Product Manufacturing Facilities 3rd ed. 2018

- The gross volume of the occupied space = 36 ft³.
- From this we deduct the volume of the occupant leaving net occupied volume = 33 ft³.
- Assume that the at-rest condition in the zone is ISO 5 at ≥ 0.5 µm. This would be equivalent to 100 particles/ft³ at the class limit, yielding a total of 3,300 particles ≥ 0.5 µm in the net occupied volume.
- From available data, the source strength of particle generation (**P**) in a cleanroom from an operator can be taken as 10,000 particles/sec, or 600,000 particles/min at ≥ 0.5 µm.
- For a unidirectional airflow system, the airflow volume to the zone is 90 ft/min × 6 sq ft = 540 ft³/min.
- If we consider the distribution of particles in this air from the human source, the average particle count in the zone is 600,000/540 particles/ft³ = 1111 particles/ft³. This assumes particles do not migrate outside the 2 ft × 3 ft space. This exceeds 100 particles/ft³ or ISO 5.
- From this we can conclude that it is essential to keep operators out of ISO 5/Grade A areas.
- It is important to realize that this simple model assumes that correctly fitting cleanroom garments are being worn. When a human body is enclosed in a garment the air boundary layer against the skin is heated, causing air to move upwards at a rate of 30 cm/sec, carrying skin particles and bacteria towards the openings in the suit. To minimize dissemination of contamination, suits must be well fitting, be made of small pore fabric, and be closed at the neck, hood, and cuffs.

Note for Figure 11.2: Consider the space around an operator as the worst case within a cleanroom.

實驗艙體積：36ft³
淨體積：33ft³
A級標準：100 個/ft³
淨體積含：3,300個
人產生：600,000個/分
氣流量：540 ft³ /分
殘留量：1111 個/ft³
殘留量> A級標準
結論：人需在A級區外

人的污染風險：
皮膚周圍之上升熱氣流(30cm/sec)可穿透無菌衣帶出微粒子與微生物

無菌衣的保護性：
尺寸合身，小孔徑纖維布料，穿著時緊閉頸部、頭罩、袖口

35

無菌操作人員訓練

7.5 The personnel working in a Grade A zone and Grade B areas should be trained for aseptic gowning and aseptic practices. Compliance with aseptic gowning procedures should be assessed and confirmed, periodically reassessed at least annually and should involve both visual and microbial assessment (using monitoring locations such as hands, arms, chest and forehead. Refer to paragraph 9.30 for the expected limits).

(更衣驗證：A、B級區工作人員，至少每年一次)

(驗證內容：觀察更衣過程與微生物評估)

The unsupervised access to Grade A zone and Grade B areas where aseptic operations are or will be conducted should be restricted to appropriately qualified personnel, who have passed the gowning assessment and have participated in a successful aseptic process simulation (APS).

(只有通過更衣驗證，參與APS合格的人員才可進入A、B級區)

36

不合格人員淘汰機制與再驗證

7.7 There should be systems in place for disqualification of personnel from entry into cleanrooms based on aspects including ongoing assessment and/or identification of an adverse trend from the personnel monitoring program and/or after participation in a failed APS.

(淘汰機制：根據持續評估的結果，監測結果不良趨勢，APS 失敗)

Once disqualified, retraining and requalification should be completed before permitting the operator to have any further involvement in aseptic practices. For operators entering Grade B cleanrooms or performing intervention into Grade A zone, this requalification should include consideration of participation in a successful APS.

(補救：再訓練、再驗證，APS 成功才可再進入A、B級區作業)

37

3. 人工無菌作業的考量要點

3.2 避免人為介入

38

採用先進的無菌技術

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

(採用 RABS, Isolator；機械手臂，自動化)

39

降低無菌操作的汙染風險

8.16 Aseptic manipulations (including non-intrinsic aseptic connections) should be minimized through the use of engineering design solutions such as preassembled and sterilized equipment. Whenever feasible, product contact piping and equipment should be pre-assembled, and sterilized in place.

(事先組裝，原位滅菌)

8.117 The use of closed systems can reduce the risk of extraneous contamination such as microbial, particulate and chemical from the adjacent environment. Closed systems should always be designed to reduce the need for, and complexity of manual interventions.

(使用密閉系統可降低汙染風險，減少複雜的人工介入)

40

採用無菌的密閉系統

8.120 The background in which closed systems are located should be based on their design and the processes undertaken. For aseptic processing and where there are any risks that system integrity may be compromised, the system should be located in a Grade A zone. If the system can be shown to remain integral at every usage (e.g. via pressure testing and/or monitoring) then a lower classified area may be used.

If the closed system is opened (e.g. for maintenance of a bulk manufacturing line) then this should be performed in a classified area appropriate to the materials (e.g. Grade C for terminally sterilization processes, or Grade A for aseptic processing) or be subject to further cleaning and disinfection (and sterilization in case of aseptic processes).

(密閉系統(SUS)作業背景：A，或C如果完整性無虞)

(SUS包括：bags, filters, tubing, connectors, valves, storage bottles and sensors)

(密閉系統被打開後的作業背景：C(最終滅菌，或A(無菌操作))

41

3. 人工無菌作業的考量要點

3.3人工無菌操作考量要點

Ref. : PDA TR62 Recommended Practices for Manual Aseptic Processes, 2013

42

在單向氣流櫃的人工無菌操作設計原則

- 操作環境： UAFH (或BSC)
  - 適當的工作空間 *(物料，緩衝，操作空間)*
  - 所有暴露的原物料持續維持在HEPA過濾的潔淨空氣下(first air)
  - 無菌操作必須在潔淨空氣下，中間不被其他物件或手套阻隔

43

設備

- 有汙染風險的電器設備應盡可能放置於作業環境外，如果有困難時，須由副操作員來調整必要的設定。
- 特別注意會產生排氣的設備(例如攪拌器)，避免汙染環境。
- 液體的傳送應使用位於操作環境外的蠕動馬達(Peristaltic Pump) ，不要使用自動定量吸管(Automatic Pipettes) ，因有排氣汙染風險。

- 為減少設備移動時造成汙染，可於容器事先做記號，標示所須加入的量。*(q.s. by volume)*
- 須準備額外的已滅菌的零組件或器皿，提供可立即更換的需求

44

操作人員安排

- 操作者應以團隊方式工作：主操作員於ISO 5環境操作，副操作員幫忙移進或移出ISO 5的物件，或其他於ISO 5內比較不是關鍵的操作 。其他支援人員只能於周遭環境工作
- 主操作人員應戴上無菌手套與袖套，不得接觸未消毒或未滅菌的物品
- 主操作者於ISO 5環境下操作，雙手不得離開ISO 5的環境，必要離開時，當重新進入前須更換無菌手套與袖套(適當時)，或再消毒手套。
- 副操作員於ISO 5作業時，或與主操作員相互傳遞物件時也須戴上無菌手套/袖套。

45

無菌物品傳送

- 不須無菌操作的步驟應由其他操作員於ISO 5外圍操作
- 產品接觸的表面必須滅菌，且多層保護，移入更乾淨的環境時可逐層脫去。(D →C →B)
- 已滅菌物品移入ISO 5環境時必須使用無菌方式移除最後一層包裝
- 使用的物件應事先組裝再滅菌，以避免過多的人工無菌組裝
- 操作中不要移入大型物件。

46

無菌操作技巧

- 操作者須經常消毒或更換無菌手套
- 操作無菌物料時須使用無菌的工具或器具，不可直接以手套接觸，無菌工具須置於無菌放置架或吊架上，避免直接接觸工作台面。
- 製程中使用無菌原料時，盡可能將原料事先秤重，裝於密封的容器，滅菌，再無菌添加。

47

無菌取樣

- 設計取樣方法(一次或定時取樣)，以降低汙染。
- 於無菌桶取樣時，一次取樣，再依需求分裝。或
- 以生產後的殘留量做為樣品。
- 利用無菌隔膜(septum)或無菌聯結器(connectors)的技術來降低取樣的汙染風險

48

製程設計與演練

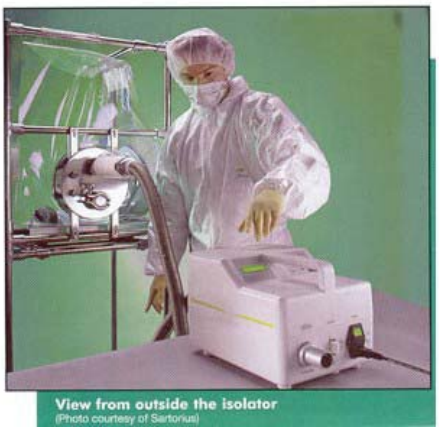
- 製程設計完成後，應練習多次，記錄演練時的空氣流向，將操作步驟，物件的放置位置更細緻化。
- 強烈建議使工程批(engineering run)來開發製程
- 製造標準書須有足夠的細節，讓操作者能了解並遵守要求的操作。
- 由副操作員或其他操作員完成批次記錄。

49

環境監控

- 環境監控應不具侵入性，避免污染ISO 5的環境。
- 製程中的空氣取樣，包括落下菌培養皿可藉由特殊設計的設備，使不會汙染環境。
- 表面的監測於作業結束後使用接觸平板或擦拭方法監測。


Gelatin membrane filter sampling inside isolator


View from outside the isolator
(Photo courtesy of Sartorius)

50

謝謝聆聽！

Q & A

51

細胞組織物溫控運輸

吳皇昇　總經理

美商 UPS 集團麥肯國際物流有限公司

AGENDA

- 生物材料的流通
- 生物物質之國際運輸規範輸規範
- 國際郵寄之包裝運送
- 國際空運之包裝運送
- IATA-DGR寄送規格
- 感染性生物物質之基本三層包裝系統
- 常見溫控運輸溫層
- 包裝運輸載具
- 單一溫層配置包材
- 溫控監測設備及軌跡追蹤系統
- Q & A

生物材料的流通

運送方式：郵寄、空運、區域運送

包裝、標示、文件規定

目的

- 減少包裝受損與洩漏之可能性
- 減少可能造成傳染之暴露
- 提高運輸效率

生物物質之國際運輸規範輸規範

UNITED NATIONS(聯合國):《RECOMMENDATIONS ON THE TRANSPORT OF DANGEROUS GOODS, 危險性貨物運輸建議》

UNIVERSAL POSTAL UNION (UPU,全球郵政聯盟):《UNIVERSAL POSTAL CONVENTION, 全球郵政公約》

INTERNATIONAL CIVIL AVIATION ORGANIZATION (ICAO, 國際民用航空組織):《TECHNICAL INSTRUCTIONS FOR THE SAFE TRANSPORT OF DANGEROUS GOODS BY AIR》-依據UN的RECOMMENDATIONS為基礎

生物物質之國際運輸規範輸規範

INTERNATIONAL AIR TRANSPORT ASSOCIATION (IATA, 國際空運協會):《DANGEROUS GOODS REGULATIONS, 危險性貨品規章》-此規範最完善

WORLD HEALTH ORGANIZATION (WHO, 世界衛生組織): 《 GUIDELINE FOR THE SAFE TRANSPORT OF INFECTIOUS SUBSTANCES AND DIAGNOSTIC SPECIMENS》

國際郵寄之包裝運送

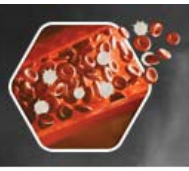
UNIVERSAL POSTAL UNION

優點：便宜、快速、手續簡便

缺點：

- 無法寄冷凍品
- 大部分的國家不接受RG2以上的生物材料寄送

國際郵寄之包裝運送



人體感染性生物材料危險等級範例 (Risk Group, RG)

◆基因重組實驗手則，中華民國九十二年五月增修。

等級	範例
RG-1	醋酸菌、乳酸菌、釀酒酵母、食用菇 、部分疫苗株等
RG-2	大腸桿菌, 肉毒桿菌, 破傷風, 白喉, 傷寒, 登革熱, 腸病毒等
RG-3	炭疽桿菌, 肺結核菌, 非典型肺炎, HIV1, 2型, H7N9, 日本腦炎, 漢他病毒等
RG-4	伊波拉病毒, 剛果出血熱病, 拉沙熱病, 綠猴病(Marburg)等

國際郵寄之包裝運送

UPU分類方式

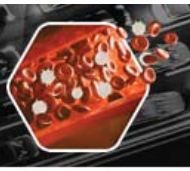
- 非感染性活生物物質(NON-INFECTIOUS PERISHABLE BIOLOGICAL SUBSTANCE, NPBS) ：危險等級第一級
- 感染性活生物物質：危險等級第二、三、四級 (INFECTIOUS PERISHABLE BIOLOGICAL SUBSTANCES, IPBS)

國際空運之包裝運送

IATA分類方式

- 感染性物質(INFECTIOUS SUBSTANCES)
- 基因改造微生物(GENETICALLY MODIFIED MICROORGANISMS)：以基因工程技術有目的的改造微生物的基因，且其在自然界中並不會出現

IATA-DGR寄送規格



IATA DANGEROUS GOODS REGULATIONS (DGR, 危險品規章)

- 危險物品的定義包含危險等級第二、三、四級的生物材料：CLASS 6.2
  - CATEGORY A：UN 2814 OR UN 2900；PI 620
  - CATEGORY B：UN 3373-；-PI 650
  - 僅為動物病原微生物（非人畜共通之微生物）：UN2900
- 基因改造的生物材料：
  - 感染性物質：：UN 2814 OR UN 2900
  - 非感染性物質：CLASS 9 UN 3245 ；PI 913
- 生物材料之冷凍保存管：UN 1845；PI904

IATA-DGR寄送規格

包裝上需清楚記載寄收件人姓名地址及連絡電話

記載微生物學名

包裝材料需通過IATA包裝規範（PACKAGING INSTRUCTION ）

- 認證核可公司：AIR SEA ATLANTA, ALL-PAK, INC. 等

隨包裹需具備三種文件

- 運送者之危險物品申報單(SHIPPER'S DECLARATION FOR DANGEROUS GOODS)
- 出貨單或帳單
- 輸出/入許可

感染性生物物質之基本三層包裝系統

內層容器

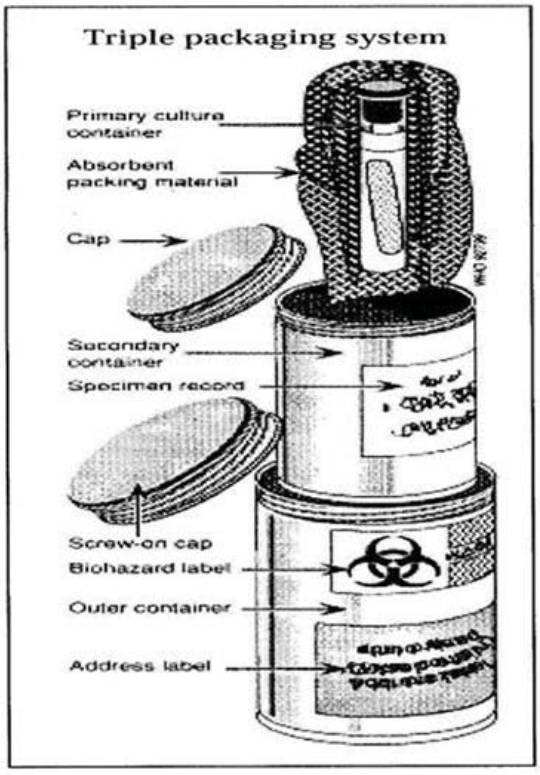
- 裝載標本,防水、防漏並貼上指示內容物之適當標示
- 內層容器外面要包裹足量之吸收性材料以吸收溢出之液體

第二層包裝

- 防水,防漏並保護內層容器

外層包裝

- 保護第二層包裝在運輸過程中免受物理性破壞



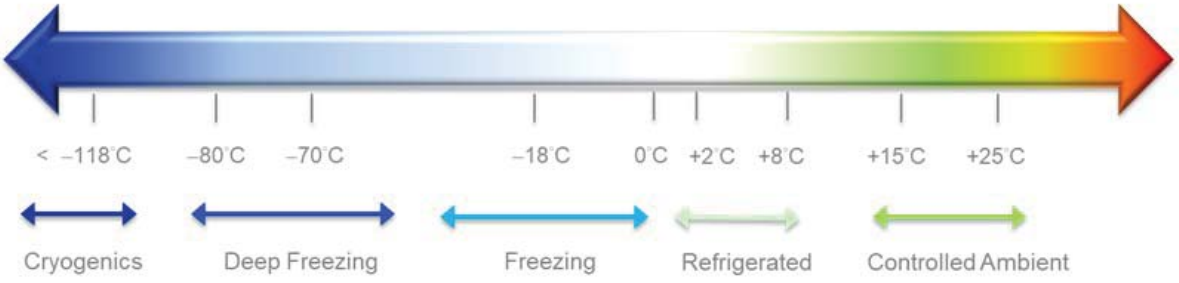
感染性生物物質之基本三層包裝系統

WHERE YOU WANT TO GO.

MARKEN
a UPS Company

常見溫控運輸溫層

5 common temperature controlled ranges that Marken handles:



WHERE YOU WANT TO GO.

MARKEN
a UPS Company

包裝運輸載具

Active Units

- ✓ Use fans, thermostats, batteries and internal refrigeration components
- ✓ For bulk investigational drug shipments
- ✓ Long transit times
- ✓ Require constant monitoring & specific temperature parameters

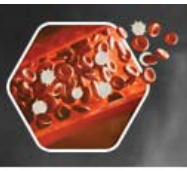
Single-Use

- ✓ Combines frozen and/or refrigerated 'gel-packs'
- ✓ Usually with polystyrene or polyurethane insulation (foam)
- ✓ Economically priced. Used for 'single-use' applications
- ✓ Short transit time

Passive

- ✓ High-quality insulation (Credo) materials with advanced PCMs
- ✓ PCMs conditioned and packed at same temperature as cargo
- ✓ Excellent performance with little monitoring

包裝運輸載具

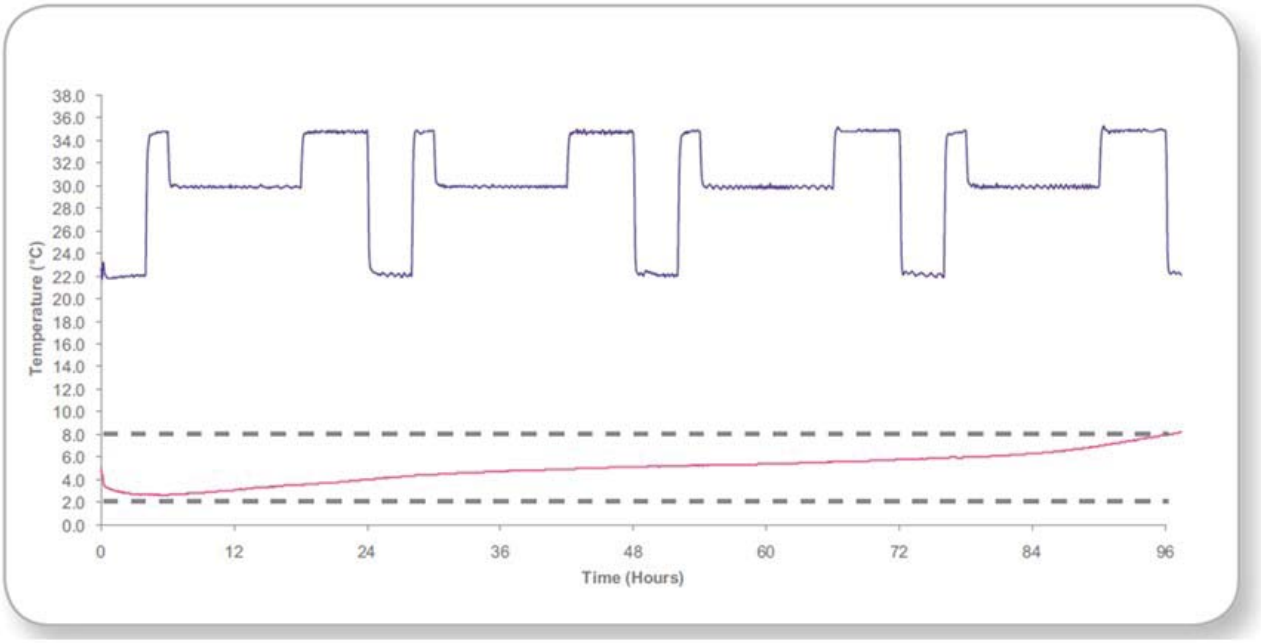


KryoTrans

INTELSIUS

包裝運輸載具

Credo® 12 Litre – Series 4 12 96 ISTA 7D **Summer Profile**



WHERE YOU WANT TO GO.

MARKEN
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單一溫層配置包材

Credo System

- ✓Global Credo re-usable program
- ✓From 4L to full-pallet loads
- ✓Marken manages reverse logistics
- ✓Inner cardboard box to protect material
- ✓Cleaning, inspection and replacement managed by Marken

WHERE YOU WANT TO GO.

MARKEN
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溫控監測設備及軌跡追蹤系統

- ✓ Lane Mapping
- ✓ Temperature recorder alternatives
- ✓ Monitoring the Environment
  - ✓ Air pressure
  - ✓ Vibration
  - ✓ UV lights
- ✓ GPS Tracking/Recording
  - ✓ Device used to geo-fence and monitor designated vehicle route to delivery.
  - ✓ Live-time notifications are sent if route is exited or entered by vehicle
  - ✓ Allows for quick intervention if vehicle exits the designated route

ELPRO

SENSITECH

american thermal instruments

Marken sentry

ONASSET INTELLIGENCE

Available Sensors

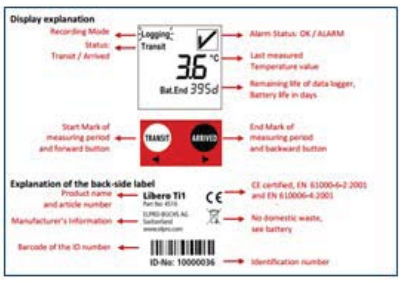
- GPS
- Temperature
- Light
- Pressure
- Shock
- Vibration
- Motion
- Humidity (option)

WHERE YOU WANT TO GO.

MARKEN a UPS Company

溫控監測設備及軌跡追蹤系統

- ✓ Global coverage
  - ✓ 7500 units deployed across our global network
- ✓ High Visibility
  - ✓ Sentry enables stakeholder overview and updates
- ✓ Real Time Tracking/Monitoring
  - ✓ Pre Alerts to CMO of incoming apheresis material
  - ✓ Pre Alerts to clinics to prepare patient and clinicians
  - ✓ Automatic milestone reporting in Maestro
  - ✓ GeoFence lanes and handovers
- ✓ Accepted on 95 % of Commercial Airlines
  - ✓ Technical acceptance by Civil Aviation Authority in all regions
- ✓ Elpro Libero
  - ✓ Te1-PY Multi-use one-year logger with LCD display
  - ✓ Preconfigured per SOP at start of shipment
  - ✓ Download and report at end of shipment



WHERE YOU WANT TO GO.

MARKEN a UPS Company


QUESTIONS?
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新興生物醫學科技發展新知

(此部分講師不便提供講義)

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臺北榮民總醫院 醫學研究部

流式細胞儀儀器驗證與品質管制

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楊利君 技術長

尚博生物科技有限公司