109年「斷層掃描用正子放射同位素調製機構品質查核及管理」主題論壇

無菌作業

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GMP 顧問
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2020-06-06

大綱

1. 無菌作業 I (14:10 ~ 15:00)
   1. 高度法規管制的製藥業
   2. 注射劑產品的關鍵品質屬性(CQA)與無菌保證程度(SAL)
   3. 潔淨室的分級、驗證與環境監測
2. 無菌作業 II & III (15:20 ~ 17:00)
   1. 無菌作業的考量要點(避免人工介入的污染)
   2. 無菌過濾與濾膜完整性試驗
   3. 無菌充填與封蓋

無菌作業 I

1.1 高度法規管制的製藥業

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

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

PET產品(與今天主題)相關的法規與技術指導手冊

TFDA：斷層掃描用正子放射同位素優良調製作業指引 , 2019
FDA： CFR Title 21 Part 212
Guidance for PET Drugs — CGMP, 2011
USP：<823> Positron Emission Tomography Drugs for Compounding, Investigational, and Research Uses
<1823> Positron Emission Tomography Drugs - Information

PIC/S：GMP Guides Part 1, Part 2,
Annex 3 放射性藥品的製造 *(核能研究所核醫製藥中心)*
Annex 1 無菌藥品的製造(draft 2020)
ISO： ISO 14644 Cleanrooms and associated controlled environments
Part 1: Classification of air cleanliness by particle concentration, 2015
PDA：TR26 Sterilizing Filtration of Liquid, 2008
TR62 Recommended Practices for Manual Aseptic Processes, 2013

PI/S GMP Annex 3 放射性藥品的製造

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（新增）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			

1.2 注射劑產品的關鍵品質屬性(CQA)與無菌保證程度(SAL)

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 *(PET 免除？)*
   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

USP <1823>
7. PET Product Quality Attributes

7.1 Appearance
7.2 pH
7.3 Total Radioactivity and Strength
7.4 Radionuclidic Identity
7.5 Radionuclidic Purity
7.6 Radiochemical Identity and Purity
7.7 Chemical Purity
7.8 Total Mass of the Active Pharmaceutical Ingredient and Specific Activity
7.9 Bacterial Endotoxin
7.10 Sterility

TFDA：斷層掃描用正子放射同位素優良調製作業指引，2019

四、調製與製程管制

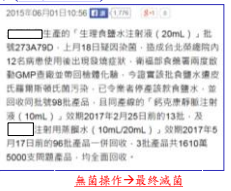
(十)製程確認：

4. 如果調製正子放射同位素品項為中華藥典、美國藥典或歐洲藥典等公定書收錄者，則其製程確認品質規格必須符合中華藥典、美國藥典或歐洲藥典等公定書基準。如果所調製的正子放射同位素品項未列於中華藥典、美國藥典或歐洲藥典等公定書，則此製程確認之品質規格項目必須包括：

1. 放射化學鑑別與純度
2. 放射核種鑑別與純度
3. 含量
4. 無菌性(注射劑)
5. 細菌內毒素含量(注射劑)
6. 酸鹼值
7. 性狀
8. 立體化學純度(如果適用)
9. 殘留溶劑
10. 合成或純化過程使用到的其他有毒化學物質
11. 立體化學純度(如果適用)
12. 安定劑或保藏劑的有效濃度(如果適用)
13. 不純物(包括前驅物、已知中間產物、副產物或已知分解產物)。

無菌保證

- 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

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

- 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，找出污染根本原因，改善後再確效

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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

- Terminal Sterilization – The application of a lethal sterilizing agent or conditions to a product within a sealed container to achieve a predetermined sterility assurance level (SAL) of 10^{-6} or better (i.e. the theoretical probability of there being a single viable microorganism present on or in a sterilized unit is equal to or less than 1 x 10^{-6} (one in a million).

-- PIC/S GMP Annex 1 Glossary

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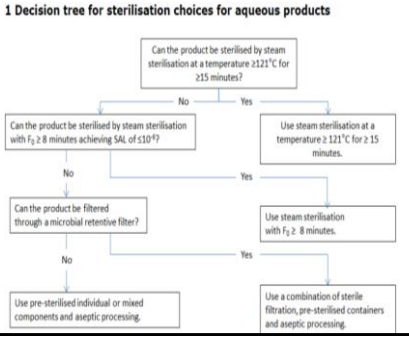
選擇適當的滅菌方法

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



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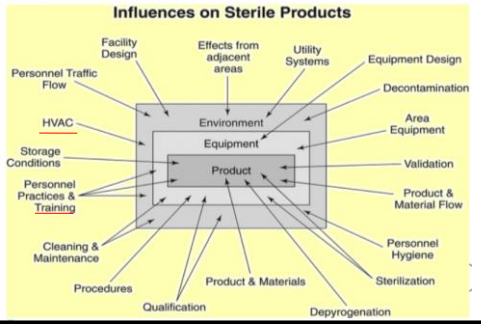
影響無菌產品品質的 因素 - USP 41 <1211>
製藥廠的 污染管制策略Contamination Control Strategy(CCS)



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1. 3 潔淨室的分級、驗證與環境監測

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斷層掃描用正子放射同位素優良調製作業指引
二、設施與設備

(二) 正子放射性同位素的化學合成、純化、最終過濾前的配方調配等作業之工作區不得低於C級。最終產品之除菌過濾與分裝必須於A級無菌工作區 (如層流操作台或隔離箱)進行。潔淨室級區定義如下表： *(除菌過濾：非無菌端在C區？隔離箱=Isolator？)*

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

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Annex 3
廠房設施及設備 -無菌生產

25. 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。

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。 *(是否需要負壓緩衝室sink airlock?)*

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。

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。

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Annex 1, 2020 draft
潔淨室分級

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.

(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	
	at rest	in operation	at rest	in operation
A	3 520	3 520	Not applicable	Not applicable
B	3 520	352 000	Not applicable	2 900
C	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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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.

- *潔淨空氣設備：Isolator, BSC...*
- *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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微生物限量

4.33 The microbial concentration of the cleanrooms should be determined as part of the cleanroom qualification.

（潔淨室驗證時須檢測微生物）

The number of sampling locations should be based on a documented risk assessment, including the results of the classification, air visualization studies and knowledge of the process and operations to be performed in the area.

(取樣位置：根據風險評估，包括分級、氣流視覺化、製程知識)

The maximum limits for microbial contamination during qualification for each grade are given in Table 2. Qualification should include both at rest and in operation states.

（微生物限量驗證：靜態與動態都要執行）

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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)

4.35 Other characteristics, such as temperature and relative humidity, should be controlled within ranges that align with product/processing requirements and support maintenance of defined cleanliness standards (e.g. Grade A or B).

(溫、溼度管制範圍：應配合產品、製程需求，與潔淨環境之維護)

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1.3.1 環境監測計畫

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斷層掃描用正子放射同位素優良調製作業指引
二、設施與設備

(二)必須定期對潔淨區域執行微生物及空氣懸浮粒子監測。

考量輻射線的危害，執行最終產品除菌過濾與分裝之無菌工作區，其落下菌監控得在每日首批作業前開始執行，且應涵蓋無菌組裝及動態作業；　*(落下菌應可全程監測)*

懸浮粒子及浮游菌依風險評估定期確認。

這些程序必須以文書規範。應記錄依據這些程序執行的監測結果以及不符規範時的矯正措施。

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環境監測計畫
風險評估

9.4 Risk assessments should be performed in order to establish a comprehensive environmental monitoring program, i.e. sampling locations, frequency of monitoring, monitoring method used and incubation conditions (e.g. time, temperature(s), aerobic and/or anaerobic conditions).

(環境監測計畫：取樣點，監測頻率，監測方法，培養條件)

These risk assessments should be conducted based on detailed knowledge of; the process inputs and final product, the facility, equipment, specific processes, the operations involved, historical monitoring data, monitoring data obtained during qualification and knowledge of typical microbial flora isolated from the environment. Consideration of other information such as air visualization studies should also be included.

(風險評估項目：製程的細部知識、歷史監測數據、典型環境菌、氣流)

These risk assessments should be reviewed regularly in order to confirm the effectiveness of the site's environmental monitoring program. The monitoring program should be considered in the overall context of the trend analysis and the CCS for the site. *(定期檢討，趨勢分析)*

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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)

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.

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)

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)

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)

其他考量

9.7 Sampling methods should not pose a risk of contamination to the manufacturing operations.

(環境監測不得造成生產作業被汙染的風險)

9.13 Results from environmental monitoring should be considered when reviewing batch documentation for finished product batch certification.

(產品放行)

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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))

38

無菌作業 II & III

2.1 無菌作業的考量要點 (避免人工介入的汙染)

39

3.二、設施與設備

斷層掃描用正子放射同位素優良調製作業指引

(六) 調製正子放射同位素產品的無菌過濾膜匣與無菌容器應於無菌層流操作台內組裝。 *(調製、過濾、充填都在A級區？)*

- 操作人員必須穿著潔淨的工作服；手部伸入無菌層流操作台之前，應戴上手套並消毒。 *(應穿著B或C級區服裝？)*
- 覆蓋及開啟無菌物品的保護封套必須在無菌層流操作台內操作。無菌組件移出無菌層流操作台前應置於密封容器內。*(製程結束後移出？)*
- 最終產品容器*(primary container/closure?)*、過濾套組*(filter assembly?)*、過濾膜匣*(capsule? cartridge? housing?)*及注射針頭*(filling needle ?)*都必須為無菌、可拋棄式及僅供單次使用。 *(整套設備都是SUS？)*
- 過濾膜匣組裝到最終產品容器後，仍必須保持該組裝套組的無菌狀態。任何套組接觸到非無菌表面而有破壞無菌性之虞時，必須更換該套組。 *(整個製程為無菌作業？)*
- 在插入最終產品容器前，瓶口橡皮塞必須用70%乙醇或異丙醇等消毒劑擦拭，並讓其在無菌層流操作台中自然揮發。

(無菌操作還需要消毒嗎？消毒方法驗證/確效)

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Table 5: Examples of operations and grades for aseptic preparation and processing operation

Grade A	Critical zone for - Aseptic assembly of filling equipment. - Connections made under aseptic conditions (where sterilized product contact surfaces are exposed) that are post the final sterilizing filter. These connections should be sterilized by steam-in-place whenever feasible. - Aseptic compounding and mixing. - Replenishment of sterile bulk product, containers and closures. - Removal and cooling of unprotected (e.g. with no packaging) items from sterilizers. - Staging and conveying of sterile primary packaging components. - Aseptic filling, sealing of containers such as ampoules, vial closure, transfer of open or partially stoppered vials. - Loading of a lyophilizer.
Grade B	Background support for the Grade A zone (when not in an isolator). - Transport, while protected from the surrounding environment, of equipment, components and ancillary items for introduction into the Grade A zone.
Grade C	- Preparation of solutions to be filtered including weighing.
Grade D	- Cleaning of equipment. - Handling of components, equipment and accessories after washing. - Assembly of cleaned components, equipment and accessories prior to sterilization. - Assembly of closed and sterilized SUS using intrinsic aseptic connectors.

Annex 1 無菌製程

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closed/open RABS, Isolator；機械手臂，自動化)

8.13 The unwrapping, assembly and preparation of sterilized equipment, components and ancillary items and the preparation and filling of the sterile product should be treated as an aseptic process and performed in a Grade A zone with a Grade B background. Where an isolator or RABS is used, the background should be in accordance with paragraphs 4.21 & 4.22.

(RABS, open/ closed Isolator的背景環境：B，C，D)

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降低汙染風險

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)

密閉系統

8.118 It is critical to ensure the sterility of all product contact surfaces of closed systems used for aseptic processing. The design and selection of any closed system used for aseptic processing should ensure maintenance of sterility. Connection of sterile equipment (e.g. tubing / pipework) to the sterilized product pathway after the final sterilizing filter should be designed to be connected aseptically (e.g. by intrinsic aseptic connectors or fusion systems).

(確保密閉系統內部的無菌性，使用無菌接頭連結)

8.119 Appropriate measures should be in place to ensure the integrity of components used in aseptic connections. The means by which this is achieved should be determined and captured in the CCS. Appropriate system integrity tests should be considered when there is a risk of compromising product sterility. Supplier assessment should include the collation of data in relation to potential failure modes that may lead to a loss of system sterility.*(確保連結組件的無菌：完整性試驗，供應商評估)，(作業背景：A，或C如果完整性無虞)*

單次使用系統

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

8.122 There are some specific risks associated with SUS which should be assessed as part of the CCS. These risks include but are not limited to:

i. The interaction between the product and product contact surface (such as adsorption, or the formation of leachables and extractables).
ii. The fragile nature of the system compared to fixed reusable systems.
iii. The increase in the number and complexity of manual operations (including inspection and handling of the system) and connections made.
iv. The complexity of the assembly.
v. The performance of the pre-use integrity test for sterilizing grade filters (refer to paragraph 8.88)
vi. The risk of holes and leakage.
vii. The potential for compromising the system at the point of opening the outer packaging.
viii. The risk of particulate contamination.

(交互作用，脆弱性，增加複雜的人工操作，組裝複雜性，過濾器執行使用前的IT，洩漏孔洞，打開外包裝的影響，微粒子汙染)

單次使用系統

8.124 Assessment of suppliers of disposable systems including sterilization is critical to the selection and use of these systems. For sterile SUS, verification of sterility should be performed as part of the supplier qualification and on receipt and use of each unit.

(供應商評估：無菌性確認，滅菌確效)

8.128 Acceptance criteria should be established and implemented for SUS corresponding to the risks or criticality of the products and its processes. On receipt, each piece of SUS should be checked to ensure that they have been manufactured, supplied and delivered in accordance with the approved specification. A visual inspection of the outer packaging (e.g. appearance of exterior carton, product pouches), label printing, and review of attached documents (e.g. certificate of conformance and proof of sterilization) should be carried out and documented prior to use.

(允收標準：COA，COC規格確認，外觀檢查)

四、調製與製程管制
無菌操作人員的訓練、驗證、授權

（八）所有無菌操作，包括組裝無菌組件、調製、過濾與處理無菌溶液，必須由定期通過無菌操作驗證的合格人員執行。

無菌操作技術是以培養基充填模擬測試進行確效；利用微生物生長培養基取代正子放射同位素溶液，以模擬無菌組件連接及過濾的無菌操作過程。模擬程序結束後，輕搖產品容器， 使充填的培養基接觸容器內部所有表面。含培養基容器置於30~35˚C、20~25˚C或其他適當溫度培養14天以上，期間定期檢查是否有微生物生長。容器內培養基沒有微生物生長為通過測試的標準。

初始的無菌製程或新的操作人員必須分三日執行並通過模擬測試三次。

每位合格操作人員每年必須執行並通過模擬測試至少一次。無菌製程每年必須執行並通過模擬測試至少兩次。只要該無菌製程有明顯變更（例如人員、組件或設備的變更）以及有跡象顯示無法維持產品無菌，就必須執行培養基充填模擬測試。

(APS：包括生產線以及人員驗證)

無菌區工作人員訓練
Annex 1

7.4 All personnel including those performing cleaning, maintenance, monitoring and those that access cleanrooms should receive regular training, gowning qualification and assessment in disciplines relevant to the correct manufacture of sterile products.

(經常性訓練，更衣驗證，遵守無菌操作規定)

This training should include the basic elements of microbiology, hygiene, with a specific focus on cleanroom practices, contamination control, aseptic techniques and the protection of sterile products (for those operators entering the Grade B cleanrooms and/or intervening into the Grade A zone) and the potential safety implications to the patient if product is not sterile.*(訓練內容：微生物，個人衛生，潔淨室作業，管制汙染，無菌技術，保護無菌產品，產品遭汙染的潛在影響)*

The level of training should be based on the criticality of the function and area in which the personnel are working.

(訓練程度：根據工作職責的重要性)

3.人工無菌操作的考量要點
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)

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)

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)

潔淨服 - C、D級區

Grade C: Hair, beards and moustaches should be covered. A single or two-piece trouser suit gathered at the wrists and with high neck and appropriately disinfected shoes or overshoes should be worn. They should minimize the shedding of fibres and particulate matter.

(口罩，高領單件或兩件式潔淨服，消毒的鞋子)

Grade D: Hair, beards and moustaches should be covered. A general protective suit and appropriately disinfected shoes or overshoes should be worn. Appropriate measures should be taken to avoid any ingress of contaminants from outside the clean area.

(口罩，一般保護式潔淨服，消毒的鞋子)

7.13 Clothing should be chosen to prevent shedding due to operators moving excessively (when cold) or sweating (when hot).

(穿著舒適的衣服材質)

無菌衣的保護效果

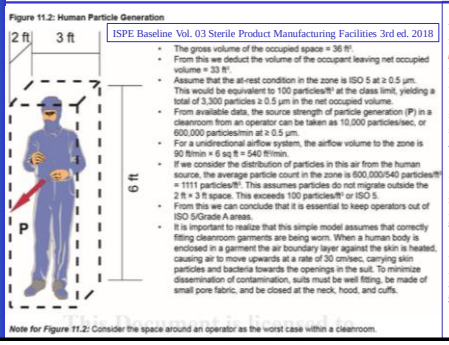

Figure 11.2: Human Particle Generation

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

2. 2 無菌過濾與濾膜完整性

四、調製與製程管制

（七）注射用正子放射同位素溶液必須使用無菌過濾膜除菌，並以無菌操作充填入一無菌、無熱原的容器中。所有使用於無菌過濾程序的原料、容器與封蓋及其它材料的操作過程，均必須在適當控制的環境下採用無菌操作技術為之。

-- 斷層掃描用正子放射同位素優良調製作業指引

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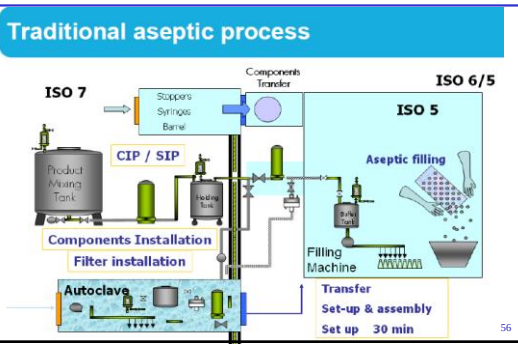
傳統的無菌製程設計



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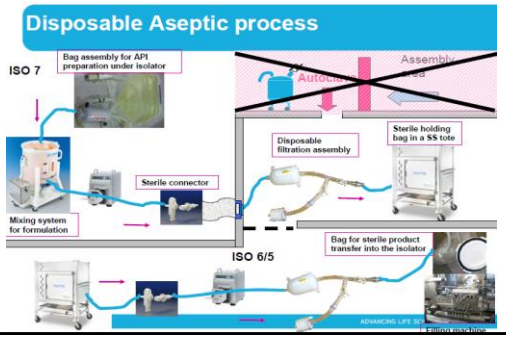
拋棄式單次使用的無菌製程設計



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過濾系統設計

8.84 The filtration system should be designed to:

i. Allow operation within validated process parameters. *(可操作的確效參數)*

ii. Maintain the sterility of the filtrate. *(保持過濾液的無菌性)*

iii. Minimize the number of aseptic connections required between the sterilizing filter and the final filling of the product. *(減少無菌連結)*

iv. Allow cleaning procedures to be conducted as necessary. *(可清潔)*

v. Allow sterilization procedures, including sterilization in place, to be conducted as necessary. *(可原位滅菌)*

vi. Permit in-place integrity testing, of the 0.22 µm sterilizing filter, preferably as a closed system, prior to filtration as necessary. In-place integrity testing methods should be selected to avoid any adverse impact on the quality of the product.*(密閉系統的原位完整性試驗)*

Annex 1

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過濾參數

8.87 Filtration parameters that should be considered and established in validation and monitored in routine processing should include, but are not limited to:

(過濾的關鍵參數需要確效以及例行的監測)

i. The wetting fluid used for filter integrity testing should be based on the filter manufacturer's recommendation or the fluid to be filtered. The appropriate integrity test value specification should be established.

(潤濕液：產品、WFI、其他；建立適當的IT值)

ii. If the system is flushed or integrity tested in-situ with a fluid other than the product, appropriate actions are taken to avoid any deleterious effect on product quality.

(使用非產品之沖洗液：避免破壞產品品質)

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過濾參數

iii. Filtration process conditions including:

- Fluid pre-filtration holding time and effect on bioburden. *(過濾前存放時間與對負荷菌的影響)*
- Filter conditioning, with fluid if necessary. *(調解：控溫、預潤溫、沖洗)*
- Maximum filtration time/total time filter is in contact with fluid. *(與產品接觸時間)*
- Maximum operating pressure. *(最大操作壓力)*
- Flow rate. *(流速)*
- Maximum filtration volume. *(最大過濾體積)*
- Temperature. *(溫度)*
- The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter. *(已知容量的過濾時間，壓差)*

Note: Results of these checks should be included in the batch record. Any significant difference in parameters from those validated to those observed during routine manufacturing should be noted and investigated.

(紀錄於批次紀錄：管制範圍，偏差調查)

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完整性測試 (一)

8.88 The integrity of the sterilized filter assembly should be verified by integrity testing before use, to check for damage and loss of integrity caused by the filter preparation prior to use. A sterilizing grade filter that is used to sterilize a fluid should be subject to a non-destructive integrity test post-use prior to removal of the filter from its housing. Test results should correlate to the microbial retention capability of the filter established during validation.

(密閉系統、非破壞性、原位完整性試驗，與微生物滯留試驗比對)

Examples of tests that are used include bubble point, diffusive flow, water intrusion or pressure hold test *(四種測試方法)*

完整性測試 (二)

8.88 … It is recognized that pre-use post sterilization integrity testing (PUPSIT) may not always be possible after sterilization due to process constraints (e.g. the filtration of very small volumes of solution). In these cases, an alternative approach may be taken providing that a thorough risk assessment has been performed and compliance is achieved by the implementation of appropriate controls to mitigate any risk of non-sterility. Points to consider in such a risk assessment should include but are not be limited to

(PUPSIT：滅菌後使用前的完整性測試)

完整性測試 (三)

8.88 (cont.)

i. In depth knowledge and control of the sterilization process to ensure that the potential for damage to the filter is minimized. *(了解滅菌過程)*

ii. ii. In depth knowledge and control of the supply chain to include:
- Contract sterilization facilities. *(供應鏈)*
- Defined transport mechanisms.
- Packaging of the sterilized filter, to prevent damage to the filter during transportation and storage.

iii. In depth process knowledge such as: *(了解製程)*
- The specific product type, including particulate burden and whether there exists any risk of impact on filter integrity values, such as the potential to alter integrity testing values and therefore prevent the detection of a non-integral filter during a post-use filter integrity test.
- Pre-filtration and processing steps, prior to the sterilizing filter, which would remove particulate burden and clarify the product prior to the sterile filtration.

通氣過濾器完整性測試

8.89 The integrity of critical sterile gas and air vent filters (that are directly linked to the sterility of the product) should be verified by testing after use, with the filter remaining in the filter assembly.

(關鍵氣體過濾器：使用後測；非關鍵氣體過濾器：定期測)

8.90 The integrity of non-critical air or gas vent filters should be confirmed and recorded at appropriate intervals.

Where gas filters are in place for extended periods such as vent filters, integrity testing should be carried out pre and post-use. The maximum duration of use should be specified and monitored based on risk (e.g. considering the maximum number of uses and sterilization cycles permitted).

(長期使用的非關鍵通氣過濾器(如WFI儲存桶)使用前、後測，訂定最長使用期限)

連續亞批次的調製/過濾

8.96 Where campaign manufacture of a product has been appropriately justified in the CCS and validated, the filter user should:

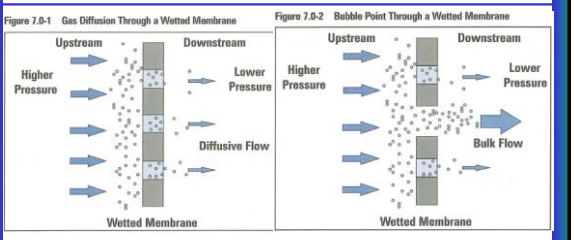
i. Assess and document the risks associated with the duration of filter use for the sterile filtration process for a given fluid. *(評估過濾風險)*

ii. Conduct and document effective validation and qualification studies to demonstrate that the duration of filter use for a given sterile filtration process and for a given fluid does not compromise performance of the sterilizing filter or filtrate quality. *(過濾系統驗證，過濾製程確效)*

iii. Document the maximum validated duration of use for the filter and implement controls to ensure that filters are not used beyond the validated maximum duration. Records of these controls should be maintained. *(確效最過濾器最長的使用時間)*

iv. Implement controls to ensure that filters contaminated with fluid or cleaning agent residues, or considered defective in any other way, are removed from use. *(確保被污染或有瑕疵的過濾器不被使用)*

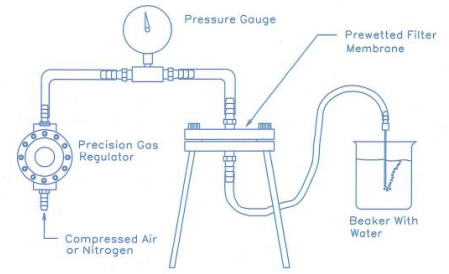
Integrity Testing 原理 --PDA TR26



- Figure 7.0-1 illustrates gas diffusion through the wetted membrane pores at pressures where the wetting fluid is held in the pores by capillary forces.
- Figure 7.0-2 illustrates gas flow through the membrane at a pressure exceeding the bubble point and the wetting fluid is expelled from the largest pores.

人工氣泡試驗

Figure B-1 Typical Manual Bubble Point Test Equipment



考量要點

- The following are points to consider when performing the bubble point test manually:
  - Pressure should be increased slowly in a stepwise manner. *(逐步加壓)*
  - Allow pressure to stabilize at each step in the pressure increase. The true bubble point value may be overshot if pressure is increased too rapidly. The test cannot be repeated without rewetting the membrane. *(穩壓後再加壓，避免氣泡點驟升，重試濾膜需先再潤濕)*
  - Minimize downstream connections and avoid kinking the downstream tubing. *(減少下游連接，可避免管路扭曲)*
  - Check for leaks in the system. *(檢查系統有無洩漏)*

考量要點

- Clearly define the bubble point as bulk air flow. The most common error is misidentifying bubbles that are not the result of bulk flow. Some bubbles will appear as a result of diffusion across the wetted membrane. Free-flowing air is the indication, not the first bubble. *(定義起泡點：自由流動的氣體)*
- Manually performed bubble point test determination can be subjectively different from one operator to another; therefore, operators should be properly trained to conduct the test and to interpret the test results. *(人工測試偏向主觀，須經適當訓練)*
- Keep upstream volume to a minimum. With extremely high upstream volumes, longer stabilization between pressure increases may be required. *(降低上游液體體積，液量大穩壓時間長)*
- Maintain the temperature within the specified range. *(控制適當溫度範圍)*

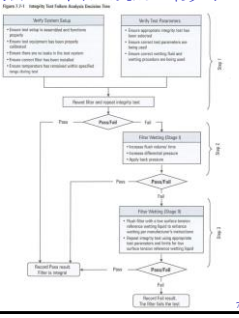
議題K：滅菌過濾器的完整性試驗

PDA Points to Consider for Aseptic Processing Part 2, May 2016

問題：滅菌過濾器使用後的完整性試驗，如果初次失敗，最多可再執行幾次？

建議：

- 在PDA*技術報告第26號：液體的無菌過濾*的建議，包括在過濾器用戶地點試驗三次的細部過程。
- 在用戶地點失敗三次後，建議提送過濾器給過濾器製造商進一步調查與測試。
- PDA TR26 Figure 7.1.1 Integrity Test Failure Analysis Decision Tree



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議題K：滅菌過濾器的完整性試驗

理論

- 初次失敗後，可採用漸進的矯正方式來決定完整性試驗是假的或是真的失敗。
- 大部分過濾器失敗是整片過濾模基質的不當潤濕，例如產品殘留，溫度變動，沖洗壓力等。重新潤濕可確定是否為假失敗。
- 如果第二次仍失敗，通常建議使用低表面張力的液體，如水/溶劑混合物，沖洗液體過濾器，決定潤濕問題是否為主要問題。
- 用戶地點第三次試驗失敗後，宜檢送過濾器給廠商進行完整調查。濾器製造商有專家、工具與方法來決定過濾器完整性試驗失敗是否為真正的失敗與造成失敗的真正原因。

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2. 3無菌充填與封蓋

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四、調製與製程管制

-- 斷層掃描用正子放射同位素優良調製作業指引 --

（九）製程管制應包含並確保中間產品受到管制，直到完成中間產品的檢驗或其他的確認工作，或收到必要的核准並登錄為止。
（管制項目，檢驗時間）

(十) 製程確認： *(Process Verification)*

1. 必須每年至少一次確認所制訂的製程、電腦程式、設備及設施能調製符合 既定規格的正子放射同位素產品。 *(再驗證&再確效)*

3. 新的調製程序或任何製程、電腦程式、原料規格的改變有可能影響產品的鑑別、品質或純度時，在獲得許可之前，應進行連續三批次的製程確認。 *（風險評估 & 變更管理）*

5. 如為連續亞批次的調製 (正子放射同位素之放射性核種半衰期25分鐘者) 應確認開始與最終亞批產物的均質性。
(調製均質性 & 含量均一度)

核准的介入動作

8.17 There should be an authorized list of allowed interventions, both inherent and corrective, that may occur during production. The procedures listing the types of inherent and corrective interventions, and how to perform them, should be updated, as necessary to ensure consistency with the actual manufacturing activities. In the event that an unauthorized intervention is required, details of the intervention conducted should be recorded and fully assessed under the manufacturer's PQS.
(核准的介入表單，必要的與矯正的介入，規範介入細節，定期更新)

8.19 Aseptic operations (including APS) should be observed at a regular basis by personnel with specific expertise in aseptic processing to verify the correct performance of operations and address inappropriate practices if detected.
(由無菌作業專家經常觀察無菌操作人員的作業是否正確)

--Annex 1

訂定可容許的最長作業時間與放置時間

8.18 The duration of each aspect of aseptic preparation and processing should be limited to a defined and validated maximum time, including:

i. The holding time between equipment, component, and container cleaning, drying and sterilization. *(清潔到乾燥到滅菌)*
ii. The holding time for sterilized equipment, components, and containers before use and during filling/assembly. *(滅菌到使用)*
iii. The holding time for a decontaminated environment, such as the RABS and isolator before and during filling /assembly. *(環境消毒到使用)*
iv. The time between the start of the preparation of a product and its sterilization or filtration through a microorganism-retaining filter (if applicable), through to the end of the aseptic filling process. There should be a maximum permissible time for each product that takes into account its composition and the prescribed method of storage. *(每種產品可允許的從調製到無菌充填最長作業時間)*
v. The holding time for sterilized product prior to filling. *(已滅菌產品到充填)*
vi. The aseptic processing time. *(無菌作業時間)*
vii. The filling time. *(充填時間)*
viii. The maximum exposure time of sterilized containers and closures in the critical processing zone (including filling) prior to closure.*(已滅菌容器封蓋密封前曝露時間)*

容器密封

8.21 Containers should be closed by appropriately validated methods.

Containers closed by fusion, e.g. Blow-fill-seal (BFS), Form-Fill-Seal (FFS), Small and Large Volume Parenteral (SVP & LVP) bags, glass or plastic ampoules, should be subject to 100% integrity testing.
(使用經確效的密封方法，完整性試驗：熔封法100%)

Samples of containers closed by other methods should be taken and checked for integrity using validated methods. The frequency of testing should be based on the knowledge and experience of the container and closure systems being used. A scientifically valid sampling plan should be utilized. The sample size should be based on information such as supplier approval, packaging component specifications and process knowledge.*(其他密封法：取樣計畫，取樣量與代表性；完整性試驗方法確效)*

It should be noted that visual inspection alone is not considered as an acceptable integrity test method.
(不接受僅使用目視法來判定容器密封完整性)

無菌封蓋與潔淨封蓋

8.25 Vial capping can be undertaken as an aseptic process using sterilized caps or as a clean process outside the aseptic core. Where the latter approach is adopted, vials should be protected by Grade A conditions up to the point of leaving the aseptic processing area, and thereafter stoppered vials should be protected with a Grade A air supply until the cap has been crimped. *(潔淨封蓋：提供A級空氣保護封蓋作業)*

Where capping is a manual process it should be performed under Grade A conditions either in an appropriately designed isolator or into Grade A zone with a Grade B background.
(人工封蓋：僅能在A/B級區)

8.26 Where capping of aseptically filled sterile product is conducted as a clean process with Grade A air supply protection, vials with missing or displaced stoppers should be rejected prior to capping. Appropriately qualified, automated methods for stopper height detection should be in place. *(潔淨封蓋：需配備自動檢測與排除封蓋不良品的設備)*

異物檢查

8.29 All filled containers of parenteral products should be inspected individually for extraneous contamination or other defects.

Defect classification and criticality should be determined during qualification and based on risk and historical knowledge. Factors to consider include, but are not limited to, the potential impact of the defect to the patient and the route of administration. Different defect types should be categorized and batch performance analysed. Batches with unusual levels of defects, when compared with routine defect numbers for the process (based on historical and trend data), should lead to an investigation.
(每支注射劑都需目視檢查；不良品分類、分級；每批紀錄，設定允收標準；偏差調查)

A defect library should be generated and maintained which captures all known classes of defects. The defect library should be used for the training of production and quality assurance personnel. Critical defects should not be identified during any subsequent sampling and inspection of acceptable containers. Any critical defect identified should trigger an investigation as it indicates a possible failure of the original inspection process.
(不良品標準庫，用於訓練與校正，QA抽檢，再檢查)

在單向氣流櫃的人工無菌操作設計原則
PDA TR62 Recommended Practices for Manual Aseptic Processes, 2013

- 操作環境： UAFH
  - 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

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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

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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。

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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。

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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。

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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

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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。

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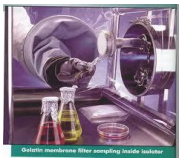
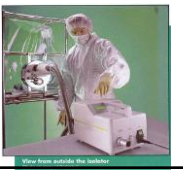
環境監控

- 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。





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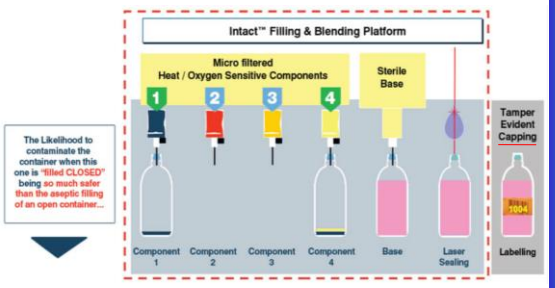
密閉無菌容器
http://medinstill.com/



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謝謝聆聽！

Q & A

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