衛生福利部食品藥物管理署委辦計畫

「精進無菌與新興生醫藥品品質管理接軌國際之研究」

新興生醫藥品 GMP 訓練活動(5)

日期：民國 110 年 11 月 3 日

主辦單位：衛生福利部食品藥物管理署

承辦單位：TPDA 社團法人中華無菌製劑協會

講 師 資 料

林宗儒　經　理/ 台南梁山工程顧問有限公司

時 間 表

時 間	內 容	講 師
13:00-13:30	報 到	
13:30-13:40	長 官 致 詞	TFDA 監管組代表
13:40-15:00	➢ ISO 14644 改版重點說明 • ISO 14644-1:2015 針對潔淨室分級之改版 • ISO 14644-2:2015 針對潔淨室監測之改版	林宗儒 經理
15:00-15:20	休 息	
15:20-16:40	➢ ATMP 作業級區之管理與監控 • 法規要求 • 設計規劃與管理實務	林宗儒 經理
16:40-17:00	交流討論 / 課後評估	

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ISO 14644改版重點說明與潔淨室管理

3-Nov-2021

林宗儒 Ken Lin

Persimmon Tainan
台南梁山工程顧問公司

110TPDA04030

OUTLINE

- ISO 14644改版重點說明
  - ISO 14644-1:2015針對潔淨室分級之改版
  - ISO 14644-2:2015針對潔淨室監測之改版
  - ISO 14644-3:2019針對HEPA洩漏測試之改版
- ATMP作業級區之管理與監控
  - 法規要求
  - 設計規劃與管理實務

ISO 14644改版重點說明與潔淨室管理

ISO 14644改版重點說明

What is ISO 14644?

- **ISO14644 consists of the following parts:**
  - Part 1: Classification of air cleanliness by particle concentration
    依據微粒濃度的分級
  - Part 2: Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration
    潔淨室微粒濃度的性能監控
  - Part 3: Test methods 測試方法
  - Part 4: Design, construction and start-up 設計、建造、啟用
  - Part 5: Operations 操作
  - Part 7: Separative devices (clean air hoods, gloveboxes, isolators and mini-environments) 隔離裝置
  - Part 8: Classification of air cleanliness by chemical concentration (ACC) 依據化學濃度的分級
  - Part 9: Classification of surface cleanliness by particle concentration依據微粒濃度的表面潔淨度分級
  - Part 10: Classification of surface cleanliness by chemical concentration 依據化學濃度的表面潔淨度分級

Why Do We Need To Know ISO 14644?

- PIC/S GMP Annex 1 (PE 009-15, 2021)
  - "**PRINCIPLE** …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."監控方法細節應參考其他如EN/ISO標準
  - "4. Clean rooms and clean air devices should be classified in accordance with EN ISO 14644-1. …" 依據ISO 14644-1進行分級
  - "5. …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." ISO 14644-1定義取樣位置與取樣量，與資料評估方法
  - "7. …EN ISO 14644-2 provides information on testing to demonstrate continued compliance with the assigned cleanliness classifications." ISO 14644-2提供檢測方法資訊

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What is ISO14644-1?

- **ISO14644-1 is one of the most used standards in Pharma and Electronics controlled environments** 製藥和電子管制環境中最常用的標準
  - ISO 14644-1 specifies classes of air cleanliness in terms of the number of particles expressed as a concentration in air volume. 以一定空氣體積下的微粒濃度，決定空氣潔淨度等級
  - It also specifies the standard method of testing to determine cleanliness class, including selection of sampling locations. 標準檢測方法/取樣位置的選擇

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Notable Areas of ISO14644-1 Change

- Number of Sample Locations 取樣位置的數量
- Particle Concentration Limit 微粒濃度限量
- Particle Counter Calibration 微粒計數器校正

ISO 14644-1 Key Changes and Interpretation (2015)

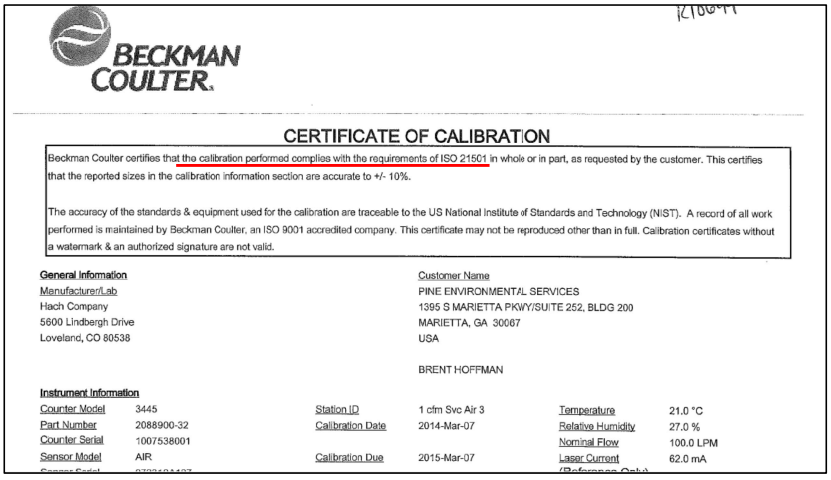
Change	Expectations
取消了使用5.0µm微粒限值對≤ISO5或更高等級的潔淨室進行分級的要求。	製造商應確保： • 對於≤ ISO 5區域的分級，應測量≥0.5µm的空氣微粒。 • 對於潔淨室> ISO 5的分類，應測量空氣微粒中的≥0.5µm和≥5.0µm的微粒。 • 應當對潔淨區域進行分級測試，以呈現「靜態」和「動態」的使用狀態。 在常規環控期間，應對≥0.5µm和≥5.0µm的微粒進行測量。
更改了決定樣品數量和位置的方法。	製造商應遵守改版之要求。

ISO 14644-1 Key Changes and Interpretation (2015)

Change	Expectations
製造商在分級測試之前必須執行的測試，現在需要參考ISO14644第3部分的“附錄A”。	在進行區域的分級測試之前，應執行以下測試： • 安裝的HEPA過濾器洩漏測試* • 氣流測量* • 壓差測量* • 氣流方向和可視化測試(Airflow direction and visualization) • 溫度 • 濕度 • 回復性測試(Recovery) • 圍堵洩漏測試(Containment leak)* [1] 標有*的項目應在往後的每個再分級(re-classification)事件之前先行確認。 應按照製造商和認證機構之間同意的邏輯和定義順序進行測試。 [1]與裝置的設計/操作相關。

ISO 14644-1 Key Changes and Interpretation (2015)

Change	Expectations
儀器準備和校正的規定要求，參照ISO 21501-4:2018	在使用前，應按照規範中所述對每個計數器執行無雜訊(zero count)檢查。 微粒監測設備應根據ISO 21501-4:2018進行校正。
免除對測量數據的統計處理。	製造商應遵守改版之要求。



BECKMAN COULTER

CERTIFICATE OF CALIBRATION

Beckman Coulter certifies that the calibration performed complies with the requirements of ISO 21501 in whole or in part, as requested by the customer. This certifies that the reported sizes in the calibration information section are accurate to +/- 10%.

The accuracy of the standards & equipment used for the calibration are traceable to the US National Institute of Standards and Technology (NIST). A record of all work performed is maintained by Beckman Coulter, an ISO 9001 accredited company. This certificate may not be reproduced other than in full. Calibration certificates without a watermark & an authorized signature are not valid.

General Information

Manufacturer/Lab
Hach Company
5600 Lindbergh Drive
Loveland, CO 80538

Customer Name
PINE ENVIRONMENTAL SERVICES
1395 S MARIETTA PKWY/SUITE 252, BLDG 200
MARIETTA, GA 30067
USA

BRENT HOFFMAN

Instrument Information

Counter Model	3445	Station ID	1 cfm Svc Air 3	Temperature	21.0 °C
Part Number	2088900-32	Calibration Date	2014-Mar-07	Relative Humidity	27.0 %
Counter Serial	1007538001			Nominal Flow	100.0 LPM
Sensor Model	AIR	Calibration Due	2015-Mar-07	Laser Current	62.0 mA

Number of Sample Locations

Area of zone [m2]	ISO 14644-1:1999	ISO 14644-1:2015
2	2	1
4	2	2
6	3	3
8	3	4
10	4	5
24	5	6
28	6	7
32	6	8
36	6	9
52	8	10
56	8	11
64	8	12
68	9	13
72	9	14
76	9	15
104	11	16
108	11	17
116	11	18
148	13	19
156	13	20
192	14	21
232	16	22
276	17	23
352	19	24
436	21	25
636	24	26
1000	32	27
>1000	n/a	See Formula A. 1

1999 Version

$N_L = \sqrt{A}$

where

N_L is the minimum number of sampling locations (rounded up to a whole number).

A is the area of the cleanroom or clean zone in square metres.

$$N_L = 27 \times \left(\frac{A\ m^2}{1000}\right)$$

ISO 14644 Establishment of Single Sample Volume Per Location

$$V_s = \frac{20}{C_{n,m}} \times 1\ 000$$

V_s is the minimum single sample volume per location, expressed in litres.

$C_{n,m}$ is the class limit (number of particles per cubic metre) for the largest considered particle size specified for the relevant class.

20 is the defined number of particles that could be counted if the particle concentration were at the class limit.

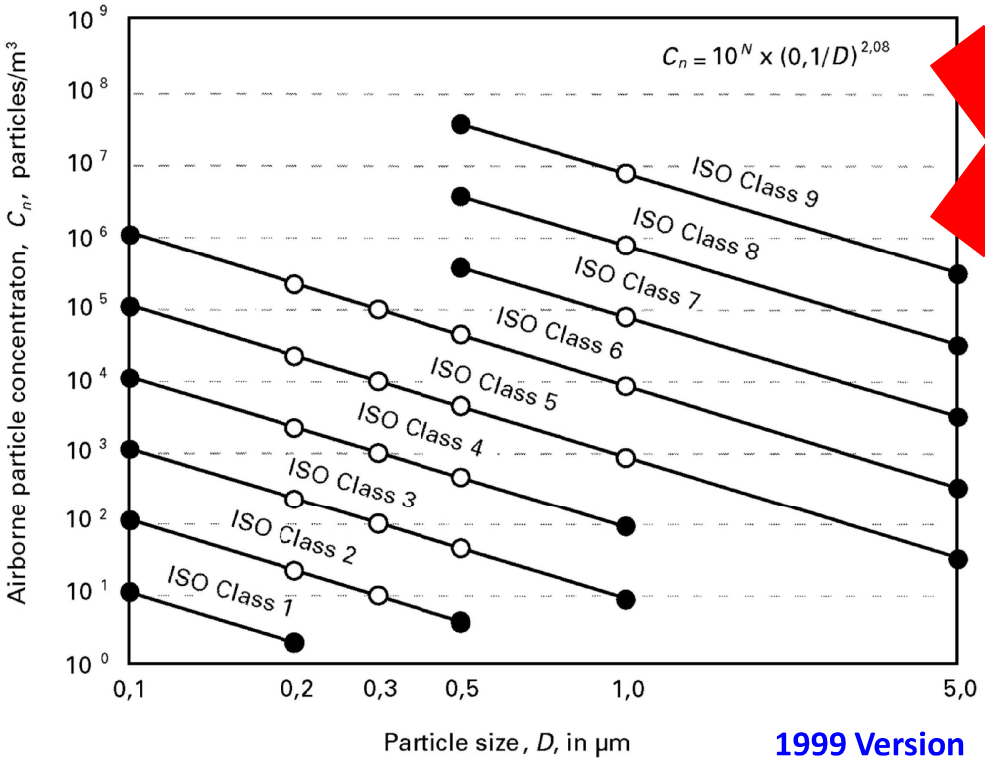
$$V_s = \frac{20}{20^*} \times 1000 = 1000\ L = 1\ m^3$$

*The ≥5µm particles limit for ISO 5

$$V_s = \frac{20}{2{,}900^{**}} \times 1000 = 6.9\ L \cong 0.007\ m^3 \cong 0.24\ ft^3 < 1 ft^3$$

* * The ≥5µm particles limit for ISO 7

ISO 14644 Classification Number



1999 Version

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ISO 14644 Classification Number

$$C_n = 10^N \times \left(\frac{0,1}{D}\right)^{2,08}$$

1999 Version

Cn is the maximum permitted concentration (in particles per cubic metre of air) of airborne particles that are equal to or larger than the considered particle size. Cn is rounded to the nearest whole number, using no more than three significant figures.

N is the ISO classification number, which shall not exceed a value of 9. Intermediate ISO classification numbers may be specified, with 0,1 the smallest permitted increment of N.

D is the considered particle size, in micrometres.

0,1 is a constant, with a dimension of micrometres.

$$20 = 10^N \times \left(\frac{0.1}{5}\right)^{2.08}$$

$10^N = 68373.47$

$Log10^N = Log68373.47$

$N = 4.834888 \rightarrow$ Grade A is ISO 4.8

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Particle Concentration Limit

Table 1 — Selected airborne particulate cleanliness classes for cleanrooms and clean zones

ISO classification number (*N*)	Maximum concentration limits (particles/m³ of air) for particles equal to and larger than the considered sizes shown below (concentration limits are calculated in accordance with equation (1) in 3.2)					
	0,1 µm	0,2 µm	0,3 µm	0,5 µm	1 µm	5 µm
ISO Class 1	10	2				
ISO Class 2	100	24	10	4		
ISO Class 3	1 000	237	102	35	8	
ISO Class 4	10 000	2 370	1 020	352	83	
ISO Class 5	100 000	23 700	10 200	3 520	832	29
ISO Class 6	1 000 000	237 000	102 000	35 200	8 320	293
ISO Class 7				352 000	83 200	2 930
ISO Class 8				3 520 000	832 000	29 300
ISO Class 9				35 200 000	8 320 000	293 000
NOTE Uncertainties related to the measurement process require that concentration data with no more than three significant figures be used in determining the classification level						

1999 Version

Particle Concentration Limit

Table 1 — ISO Classes of air cleanliness by particle concentration

ISO Class number (*N*)	Maximum allowable concentrations (particles/m³) for particles equal to and greater than the considered sizes, shown below[a]					
	0,1 µm	0,2 µm	0,3 µm	0,5 µm	1 µm	5 µm
1	*10*[b]	d	d	d	d	e
2	100	*24*[b]	*10*[b]	d	d	e
3	1 000	237	102	*35*[b]	d	e
4	10 000	2 370	1 020	352	*83*[b]	e
5	100 000	23 700	10 200	3 520	832	d, e, f
6	1 000 000	237 000	102 000	35 200	8 320	293
7	c	c	c	352 000	83 200	2 930
8	c	c	c	3 520 000	832 000	29 300
9[g]	c	c	c	35 200 000	8 320 000	293 000

[a] All concentrations in the table are cumulative, e.g. for ISO Class 5, the 10 200 particles shown at 0,3 µm include all particles equal to and greater than this size.

[b] These concentrations will lead to large air sample volumes for classification. Sequential sampling procedure may be applied; see Annex D.

[c] Concentration limits are not applicable in this region of the table due to very high particle concentration.

[d] Sampling and statistical limitations for particles in low concentrations make classification inappropriate.

[e] Sample collection limitations for both particles in low concentrations and sizes greater than 1 µm make classification at this particle size inappropriate, due to potential particle losses in the sampling system.

[f] In order to specify this particle size in association with ISO Class 5, the macroparticle descriptor M may be adapted and used in conjunction with at least one other particle size. (See C.7.)

[g] This class is only applicable for the in-operation state.

2015 Version

Instrument Calibration

- ISO 14644-1:2015 subsection A.2.2

A.2.2 Instrument calibration

The particle counter shall have a valid calibration certificate: the frequency and method of calibration should be based upon current accepted practice as specified in ISO 21501-4.
微粒計數器應有有效的校正證明書，依據ISO 21501-4之頻率與方法

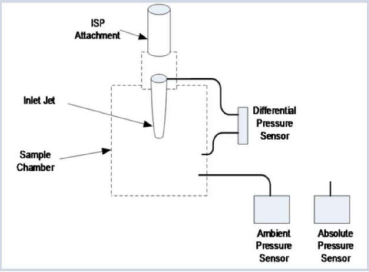
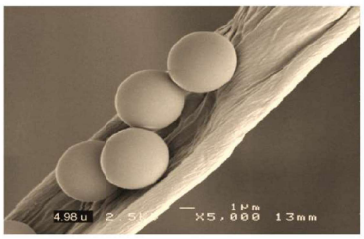
Note: Some particle counters cannot be calibrated to all of the required tests in ISO 21501-4. If this is the case, record the decision to use the counter in the test report.
若無法按照ISO 21501-4所有的檢測項目執行校正，在測試報告紀錄原因。

Instrument Calibration

- ISO 21501-4
  - "**Determination of particle size distribution—Single particle light interaction methods**" and specifically refers to the Light Scattering Aerosol Particle Counter (LSAPC).粒徑分佈的測定—單一微粒光干擾法，應用光散射氣膠微粒計數器LSAPC
  - *ISO 21501-4 provides a calibration procedure and verification method for airborne particle counters to minimize inaccurate measurements and reduce variations between different instruments.* 提供校正程序與確認方法，以減少測量不確定度與不同設備間的差異

Reference: https://www.pmeasuring.com/PMS/files/87/87e95f59-14f7-4b77-acb7-b0341a5aad97.pdf 110TPDA04030

Instrument Calibration

Test Items	ISO 21501-4 Calibration Requirements
Sampling Flow Rate 取樣流量 	The **standard uncertainty** of volumetric flow rate shall **be equal to or less than 5%.** **標準不確定度 ≤ 5%** *If the LSAPC does not have a flow rate control system this sub-clause does not apply, however the manufacturer shall specify the allowable limit of its flow rate of the LSAPC.* *沒有流量控制系統不適用，但仍須定出規格。*
Counting Efficiency 計數效率<與標準計數器的量測值的比率>  *Polystyrene latex spheres (PSLs)* 聚苯乙烯乳膠微粒	The counting efficiency shall be 50% ± 20% for calibration particles with a size close to the minimum.對於尺寸接近最小值的校正微粒，計數效率應為 50%±20%。 The counting efficiency shall be 100% ± 10% for calibration particles with a size of 1.5 to 2 times larger than the minimum detectable particle size.對於尺寸為最小可檢測粒徑 1.5 至 2 倍的校正微粒，計數效率應為 100%±10%。

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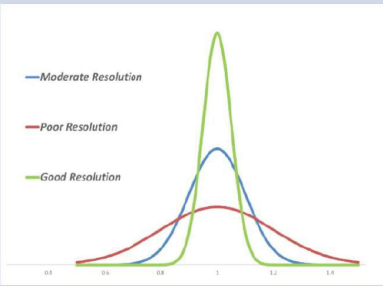
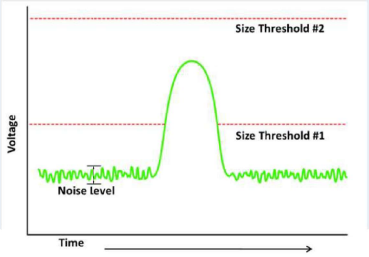
Reference: https://www.pmeasuring.com/PMS/files/87/87e95f59-14f7-4b77-acb7-b0341a5aad97.pdf 110TPDA04030

Instrument Calibration

Test Items	ISO 21501-4 Calibration Requirements
Resolution 分辨率<驗證儀器分辨粒徑微小差異的能力。> 	The size resolution shall be equal to or less than 15% for calibration particles of a size specified by the manufacturer. 對於製造商指定尺寸的校正微粒，尺寸分辨率應等於或小於 **15%**。
False Count Rate 錯誤計數率<zero count test> 	The false count rate is determined by measuring the particle number concentration in the unit of counts-per-cubic-meter at the minimum reported size range when sampling clean air. No Range Limits. 通過在取樣潔淨空氣時測量最小報告尺寸範圍內以每立方公尺計數為單位的粒子數濃度來確定的。

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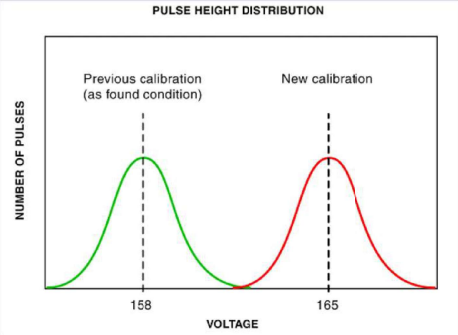
Reference: https://www.pmeasuring.com/PMS/files/87/87e95f59-14f7-4b77-acb7-b0341a5aad97.pdf 110TPDA04030

Instrument Calibration

Test Items	ISO 21501-4 Calibration Requirements
Particle Size Setting 微粒粒徑設定 	The error in the particle sizes shall be less or equal than 10%. 粒徑誤差應小於或等於**10%**。

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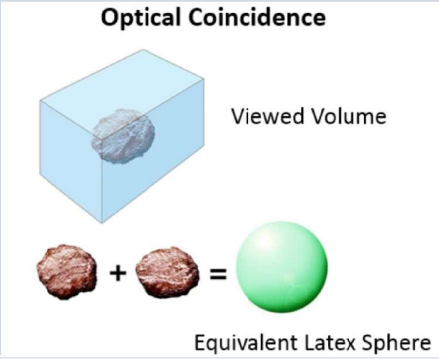
Reference: https://www.pmeasuring.com/PMS/files/87/87e95f59-14f7-4b77-acb7-b0341a5aad97.pdf 110TPDA04030

Instrument Calibration

Test Items	ADDITIONAL ISO 21501-4 Calibration Requirements
Coincidence Loss at Maximum Particle Concentration 最大微粒濃度的同時計數損失 	The coincidence loss, at the maximum measurable particle number concentration specified by the manufacturer, shall be ≤ 10%. 在製造商規定的最大可測量微粒濃度下，同時計數損失應≤ **10%**。
Maximum Particle Number Concentration 最大微粒數濃度	The value is calculated using the particle transit time through the laser beam and the instrument's flow rate. 該值是使用通過雷射光束的粒子傳輸時間與儀器的流速計算得出的。

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Reference: https://www.pmeasuring.com/PMS/files/87/87e95f59-14f7-4b77-acb7-b0341a5aad97.pdf 110TPDA04030

Instrument Calibration

Test Items	ADDITIONAL ISO 21501-4 Calibration Requirements
Sampling Time 取樣時間	The standard uncertainty in the duration of sampling time shall be ≤ ± 1%. **取樣持續時間內的標準不確定度應≤ ± 1%。**
Response Rate 反應率	The response rate of the LSAPC shall be ≤ 0.5%. **LSAPC 的反應率應≤ 0.5%。**

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ISO 14644-2 Key Changes and Interpretation (2015)

Change	Expectations
更改建議的再分級時間間距	製造商應確保： • 對於≤ ISO 5區域：再驗證的最大時間間隔為6個月。當該區域配備有連續監控設備時，如果連續監測的結果一直維持在指定的限量內，則6個月的時間間隔可以延長到12個月。 • 對於> ISO 5區域：再驗證的最大時間間隔為12個月。
有關進行監測的風險評估的附加規範	製造商應確保在其品質管理系統(QMS)中提到改版的要求。

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ISO 14644-2 Key Changes and Interpretation (2015)

Change	Expectations
減少了關於後續需要再分級的情況的規範	製造商應確保在以下任何一種情況下須進行裝置的再驗證。 • 完成修正不合規情況的矯正措施。 • 與當前性能規格有關的重大變更，例如實際應用的變更。變更的重要性應通過變更管理流程來確定。 • 會影響裝置運行的空氣流動的任何重大干擾。變更的重要性應通過變更管理流程來確定。 • 會嚴重影響裝置運行的特定維護保養(例如更換終端過濾器)。變更的重要性應通過變更管理流程來確定。

Notable Areas of ISO 14644-3 Change

- Removal of procedures relating to the classification of cleanrooms by airborne particles. (Refer to ISO14644-1) 刪除潔淨室的微粒分級 (回歸ISO14644-1規範)
- Updates to the procedures relating to installed filter system leakage testing, including changes and additions to the designated leak acceptance criteria. 更新HEPA安裝洩漏測試，包括指定洩漏的允收標準
- Changes in the specification requirements for test apparatus and a new procedure for a segregation test has been added. 變更測試設備規格要求與新增隔離測試程序

ISO 14644-3:2019 Revision

- 氣流可視化
  - 靜態條件下測試氣流的基本模式，動態條件下比照實際操作



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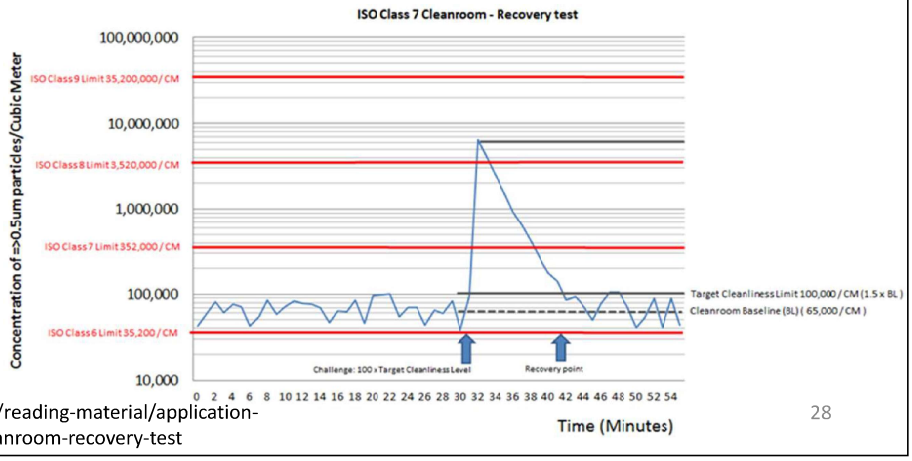
ISO 14644-3:2019 Revision

- 回復測試(recovery test; “Clean up” period)
  - 不建議單向氣流潔淨室進行回復測試，同時，回復測試應注意氣膠物質殘留而造成的污染。
  - 可使用100:1(不建議使用於ISO 8與ISO 9)或是10:1的回復時間測試



https://www.beckman.com/resources/reading-material/application-notes/conducting-the-iso-14644-3-cleanroom-recovery-test

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ISO 14644-3:2019 Revision

- HEPA安裝後洩漏測試：
  - 目的是確認掃描HEPA安裝正確，並不用於確定HEPA介質的效率；洩漏測試前，應進行風速確認；
  - 當用氣膠光度計法對HEPA測漏時，除一般的允收標準不大於0.01%，但對MPPS在99.95%至≤99.995%的HEPA，允收標準是不大於**0.1%**；

H14 (EN1822)
MERV19 (ASHRAE 52.2)
MPPS: ≥99.995%
DOP: ≥99.999%@0.3 μm

H13 (EN1822)
MERV17-18 (ASHRAE 52.2)
MPPS: ≥99.95%
DOP: ≥99.99%@0.3 μm

ISO 14644-3:2019 Revision

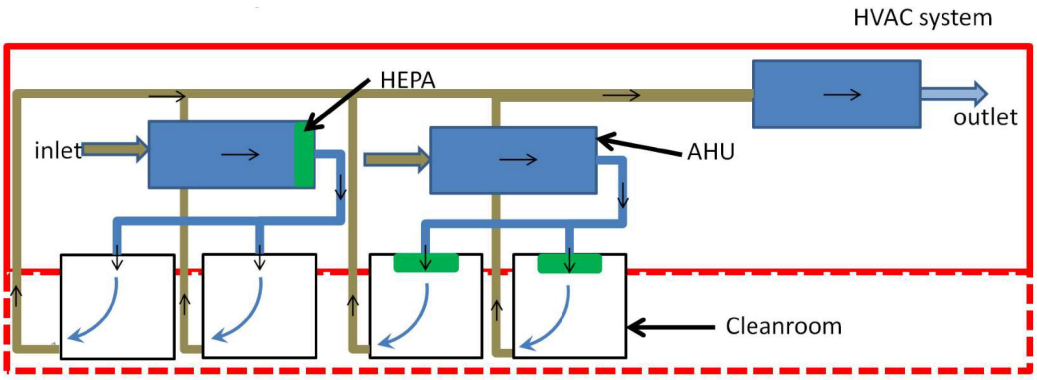
- HEPA安裝後洩漏測試(續)：
  - 上游氣膠濃度要求
    - 2005: 10mg/m³-100mg/m³
    - 2019: 1mg/m³-100mg/m³
    - 但表示，並不是所有光度計都適合1mg/m³的上游濃度挑戰（與靈敏度相關）
  - HEPA洩漏率測試時，掃描速度建議為5cm/s，掃描頭與送風面保持≤3cm的距離。

ISO 14644改版重點說明與潔淨室管理

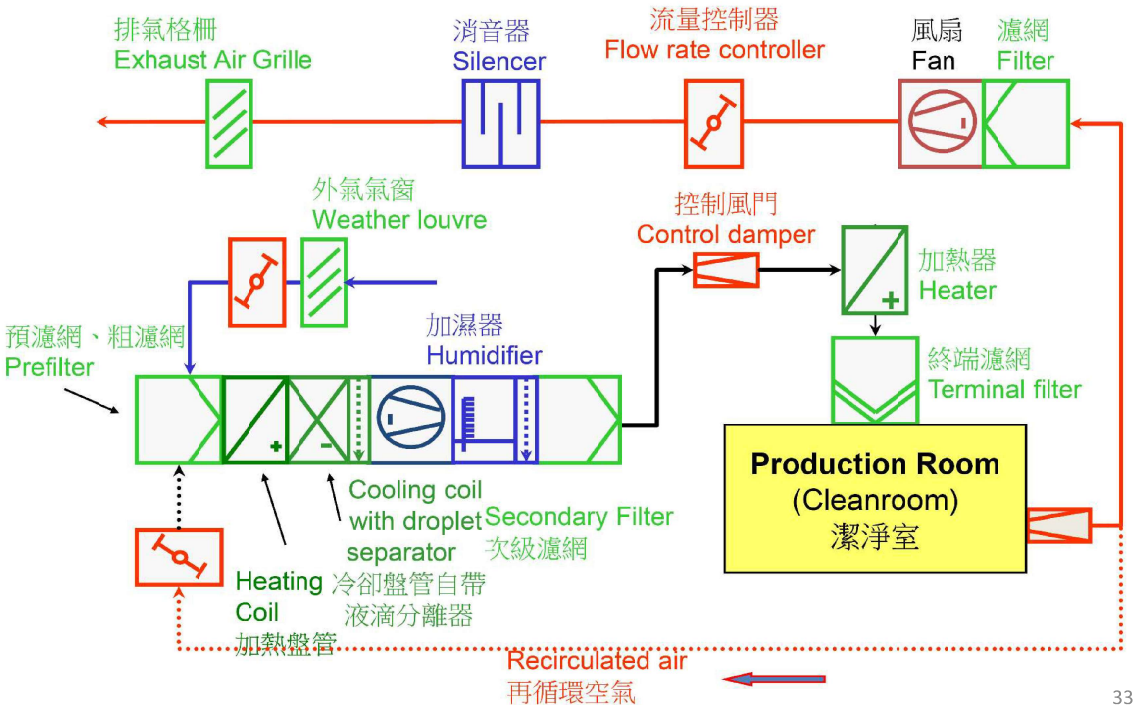
ATMP作業級區之管理與監控

Environment Control Utility

- Heating, ventilation and air-conditioning (HVAC) 加熱排風空調系統
- High-efficiency particulate air (HEPA) filter 高效率微粒空氣濾網
- Air-handling unit (AHU) 空調箱



典型的HVAC架構



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HVAC System

- HVAC設置目的在於：
  - 確保產品的品質
    - 於廠房設計階段考量，避免污染(contamination)與交叉污染(cross-contamination)發生。
  - 提供操作人員舒適之環境
    - 溫度與相對溼度的控制
    - 人員一旦在不舒適的環境下作業，就會容易脫落一些會造成環境與產品污染的微粒。

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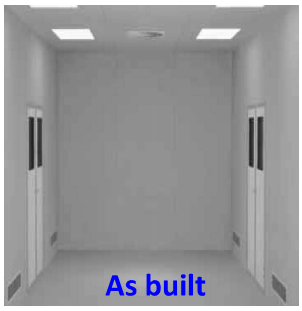
HVAC System Classification

在分級(classification)時，需要確認以下3種狀態：

- "As built" 竣工狀態
  - 淨空的房室，沒有任何設備與人員的存在。
- "At rest" 靜態
  - 設備可以運行，但是沒有操作人員存在。
- "In operation" 動態
  - 設備與人員處於例行的生產製程操作下。
  - 清除(Clean up)時間已完成確效。一般需要在15-20分鐘內，達到從該級區的動態規格回復到靜態的規格。



Annex 1 Classification And Monitoring

- **Clean room and clean air device classification**
  - Classified in accordance with EN ISO 14644-1

	Grade	Maximum permitted number of particles/m³ equal to or greater than the tabulated size			
		At rest		In operation	
		0.5μm	5.0μm	0.5μm	5.0μm
ISO 4.8	A	3,520	20	3,520	20
ISO 5	B	3,520	29	352,000	2,900
ISO 7	C	352,000	2,900	3,520,000	29,000
ISO 8	D	3,520,000	29,000	not defined	not defined

Annex 1 Classification And Monitoring

- **Clean room and clean air device monitoring**
  - Routinely monitored **in operation**
  - microbiological monitoring of clean areas during operation

	Recommended limits for microbial contamination [a]			
Grade	Air sample cfu/m³	Settle plates (diam. 90 mm), cfu/4 hours [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	-

Annex 1 Classification And Monitoring (Under Revision)

- **Qualification** of cleanrooms and clean air equipment should include:
  - Installed filter leakage and integrity testing.
  - Airflow measurement - Volume and velocity.
  - Air pressure difference measurement.
  - Airflow direction and visualization.
  - **Microbial airborne and surface contamination.**
  - Temperature measurement.
  - Relative humidity measurement.
  - Recovery testing.
  - Containment leak testing.

Annex 1 Classification And Monitoring (Under Revision)

- Cleanroom and clean air equipment **qualification**

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)]

- Clean room classification should be carried out in the "at rest" and "in operation" states.
- The "clean up" period should be determined during the classification of the rooms (guidance value of 15 to 20 minutes).

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Annex 1 Classification And Monitoring (Under Revision)

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

Grade	Air sample cfu/m³	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

No Glove Print

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Annex 1 Classification And Monitoring (Under Revision)

- 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	*

- The maximum time interval for **requalification** is
  - Grade A & B: 6 months
  - Grade C & D: 12 months

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Annex 1 Classification And Monitoring (Under Revision)

- **Environmental monitoring**

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

Grade	Maximum limits for particulates ≥ 0.5 µm/m^3		Maximum limits for particulates ≥ 5 µm/m^3	
	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)]

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Annex 1 Classification And Monitoring (Under Revision)

- 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 (1ft^3) per minute) so that all interventions, transient events and any system deterioration is captured. A級區微粒連續監控
- It is recommended that a similar system be used for Grade B area although the sample frequency may be decreased. B級區建議使用相同連續監控系統，但可減少取樣頻率

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Annex 1 Classification And Monitoring (Under Revision)

- Monitoring conditions such as frequency, sampling volume or duration, alert levels and action limits and corrective actions (including an investigation) should be established in each manufacturing area based on data generated during the initial qualification process, ongoing routine monitoring and periodic review of data. 應根據初始驗證程序、持續例行監測與數據定期審查所產生的數據在每個製造區域建立其監測條件，例如頻率、採樣量或持續時間、警戒值與行動界限以及矯正措施(包括調查)。

Annex 1 Classification And Monitoring (Under Revision)

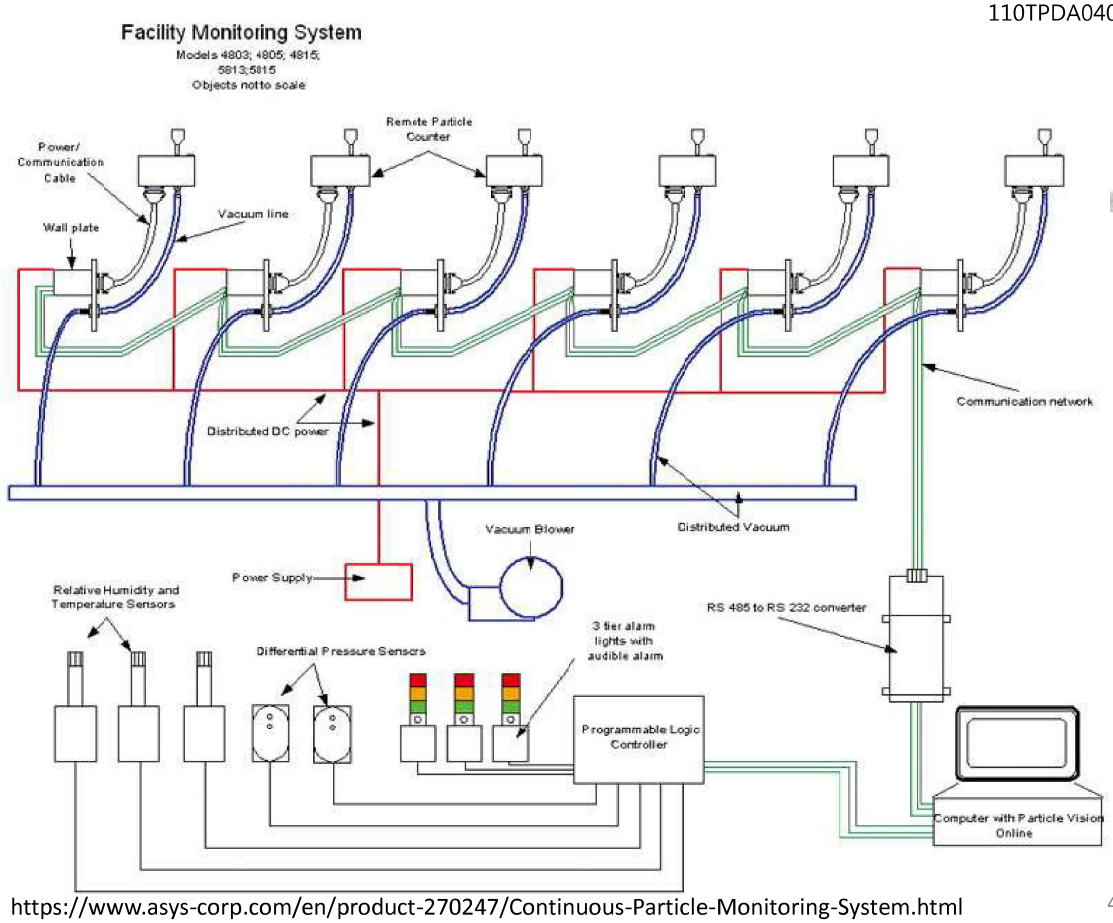
- Continuous viable air monitoring in the Grade A zone (e.g. air sampling or settle plates) should be undertaken for the full duration of critical processing, including equipment (aseptic set-up) assembly and filling operations. 在A級區整個關鍵製程期間必須連續監控微生物
- A similar approach should be considered for Grade B cleanrooms based on the risk of impact on the aseptic processing. 在影響無菌製程的風險考量下，B級潔淨室應當使用相同方法連續監控微生物

Annex 1 Classification And Monitoring (Under Revision)

- **Environmental and personnel monitoring-viable particles**

Table 7: Maximum action limits for viable particle contamination

Grade	Air sample cfu/m^3	Settle plates (diam. 90 mm) cfu/4 hours [a]	Contact plates (diam. 55mm), cfu/ plate [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	-



https://www.asys-corp.com/en/product-270247/Continuous-Particle-Monitoring-System.html

https://bakrona.ch/en/monitoring

Annex 1 Classification And Monitoring (Under Revision)

- 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. 人員手套必須每次關鍵操作後監控微生物，其餘表面則在作業結束後取樣
- Microbial **monitoring** of personnel in the Grade A zone and Grade B area should be performed to assess their aseptic behavior. A、B級區的作業人員必須監測其表面微生物

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Environment of Production Area

PIC/S GMP Annex 1

ISOLATOR TECHNOLOGY

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 it should be at least grade D.

使用隔離裝置(Isolator)可以在D級背景操作

PIC/S GMP不同作業的級區要求

Grade	Examples of operations for terminally sterilized product
A	Filling of products, when unusually at risk 當產品的充填處於異常風險時。
C	Preparation of solutions, when unusually at risk. Filling of products 當溶液的調製處於異常風險時。產品的充填。
D	Preparation of solutions and components for subsequent filling 供後續充填溶液的製備及組件之準備。

Grade	Examples of operations for aseptic preparations
A	Aseptic preparation and filling 無菌製備與充填。
C	Preparation of solutions to be filtered 待過濾溶液之製備。
D	Handling of components after washing 洗滌後之組件的處理。

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Environment of Production Area

PIC/S GMP Annex 2A

3.7 Positive pressure areas should be used to process sterile products, but negative pressure in specific areas at the point of exposure of pathogens is acceptable for containment reasons. Where negative pressure areas or BSCs are used for aseptic processing of materials with particular risks (e.g. pathogens), they should be surrounded by a positive pressure clean zone of **appropriate Grade**. These pressure cascades should be clearly defined and continuously monitored with appropriate alarm settings as defined by Annex 1. The design of such areas should be such that measures put in place to prevent release of material into the surrounding environment should not compromise sterility assurance level (SAL) of the product and vice versa.

用於特定風險無菌製程的負壓區域或是**BSC**，其背景應為適當級區之正壓區域。這些壓力梯度須明確定義並連續監控，如Annex 1所述。

Environment of Production Area

PIC/S GMP Annex 2A

3.11 Where **processes are not closed** and there is **exposure of the product to the immediate room environment without a subsequent microbial inactivation process**, (e.g. during additions of supplements, media, buffers, gasses, manipulations) appropriate environmental conditions should be applied. For aseptic manipulations parameters in line with Annex 1 (i.e. **Grade A with Grade B background**) should be applied. The environmental monitoring program should include testing and monitoring of non-viable contamination, viable contamination and air pressure differentials. The monitoring locations should be determined having regards to the QRM principles. The number of samples, volume, and frequency of monitoring, alert and action limits should be appropriate taking into account the QRM principles. Sampling methods should not pose a risk of contamination to the manufacturing operations. Where appropriate control is required in the process, temperature and relative humidity should be monitored. All environmental monitoring results should be trended.

在**非密閉**製程以及在**產品直接暴露**於間室環境且無後續的微生物去活化程序，環境條件應與Annex 1一致，**A/B級區**。

Environment of Production Area

PIC/S GMP Annex 2A

3.13 For **closed systems**, a lower classified area than Grade A in background Grade B might be acceptable based on the outcome of a QRM assessment. The appropriate level of air classification and monitoring should be determined having regard to the specific risks, considering the nature of the product, the manufacturing process and the equipment used. …

(a) The use of technologies as e.g. processing inside single use sterile disposable kits, or processing using closed, automated manufacturing platform or incubation in closed flasks, bags or fermenters **in Grade C may be acceptable** if adequate control measures are implemented to avoid the risk of microbial contamination and cross-contamination (e.g. appropriate control of materials, personnel flows and cleanliness). Particular attention should be paid if the materials are subsequently moved to a clean area of higher Grade.

(b) If the closed system can be shown to remain integral throughout the entire usage, a background of **Grade D** might be acceptable.

Requirements of Annex 1 regarding the provision of closed system should be considered.

對於**密閉系統**：

如製程在一次性拋棄式套組中操作、使用密閉/自動化生產裝置、或在無菌容器內培養，可以在**C級背景**作業

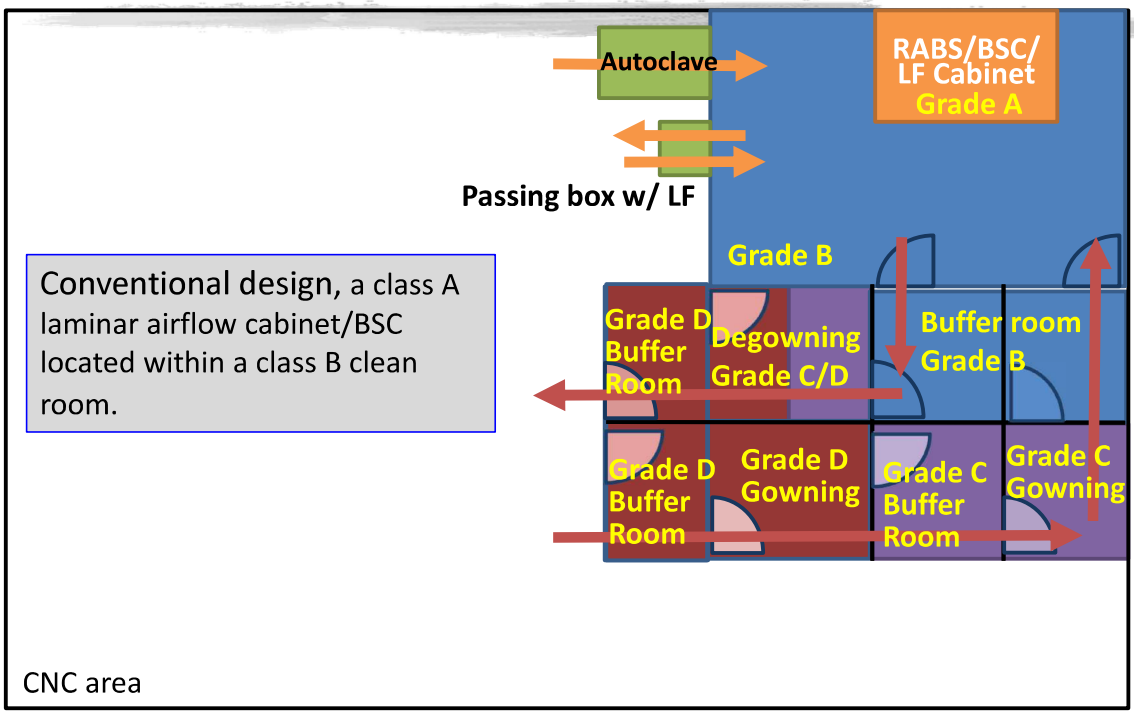
在整個操作期間可以確保密閉系統完整性，則可在**D級背景**作業。

Environment of Production Area

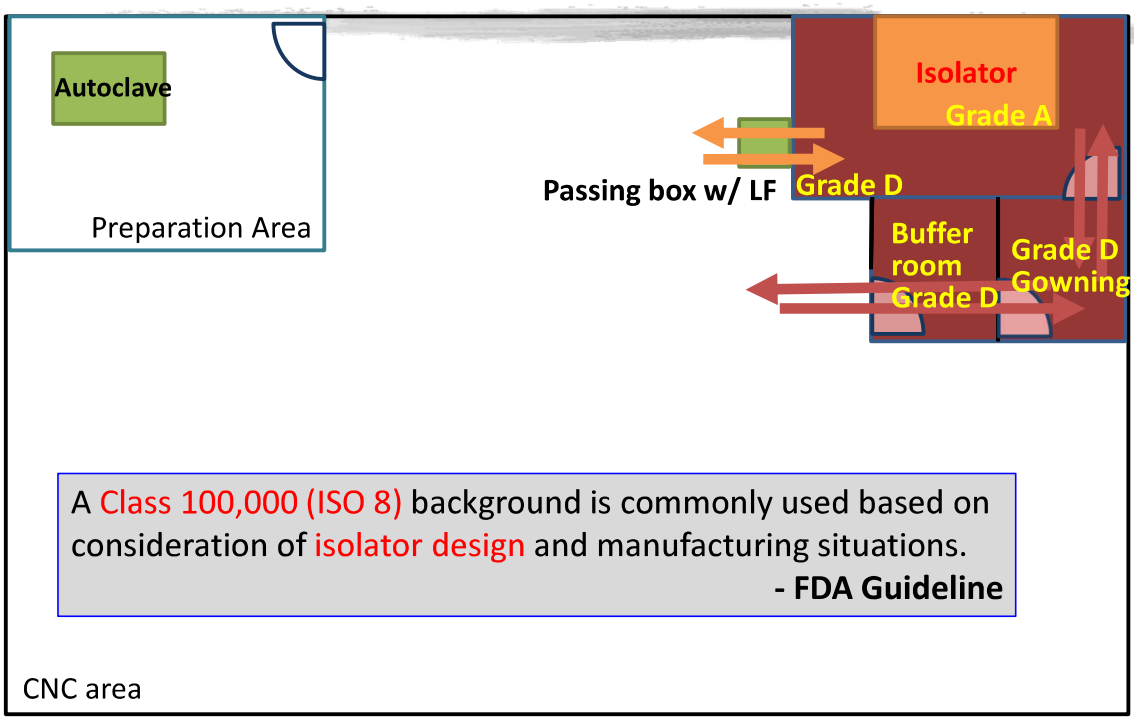
PDA TR62 Recommended Practices for Manual Aseptic Processes

- The supporting clean environment outside the critical zone is typically **ISO 7** when a UAFH or **BSC** is utilized for the manual process. 人工操作製程使用BSC，其背景一般為C級區
- Since air flows into the BSC from the surrounding environment, biosafety cabinets should be used only when worker safety from the material being handled is a meaningful concern. 氣流由周圍環境流入**BSC**中，因此，只有在處理材料對操作人員有安全疑慮時，才可以使用。

Environment of Production Area

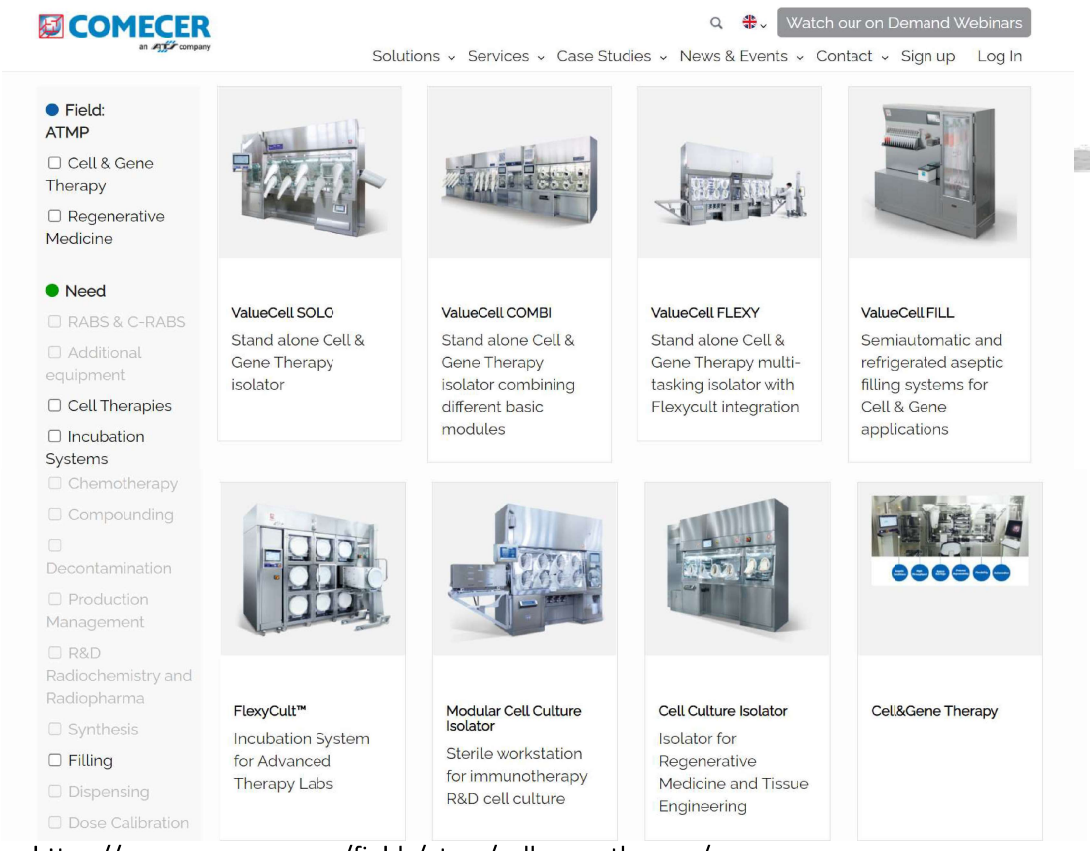


Environment of Production Area



A Class 100,000 (ISO 8) background is commonly used based on consideration of isolator design and manufacturing situations.

- FDA Guideline



https://www.comecer.com/fields/atmp/cell-gene-therapy/

潔淨室更衣需求

	PIC/S Grade D	PIC/S Grade C	PIC/S Grade A/B
Hair Cover	O	O	無菌頭罩應完全包覆頭髮和臉部毛髮；頭罩末端應塞入無菌套裝的領子內。
Beard and Moustache Cover	O	O	O
Suit	一般的保護套裝	腕部收緊及高領的單件式或兩件式褲套裝。衣著應無纖維或微粒異物釋出。	(滅菌的)防護衣無纖維或微粒物釋出，並阻擋由身體脫落的微粒。
Gloves*	X	X	滅菌、未沾粉末的橡皮或塑膠手套；衣袖應塞入手套內。
Shoes or Overshoes	適當消毒的鞋子或鞋套	滅菌過或消毒過的鞋子	滅菌的鞋子或鞋套；褲管底端應塞入鞋內。
Face Mask	X	X	滅菌面罩與眼罩

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潔淨室更衣需求

Gowning for Grade D

Gowning for Grade C

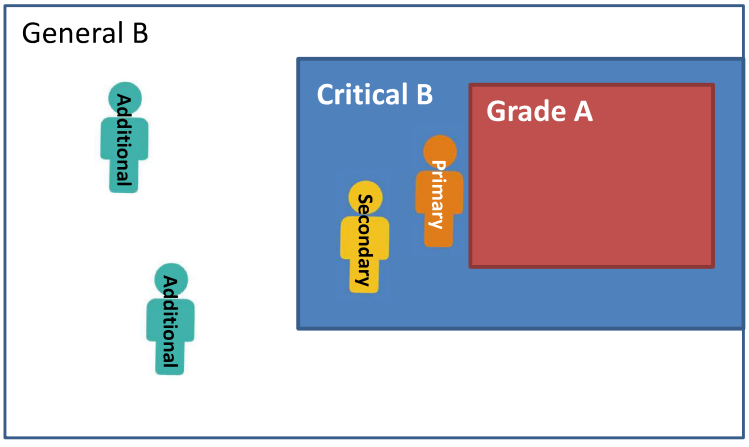
Gowning for Grade B

Manual Aseptic Process Design Principles in Unidirectional Air Flow Hoods

- Adequate space to perform the work. 足夠作業空間
- All exposed product and product-contacting components should continuously remain in First Air, i.e., the work location first in the path of HEPA-filtered air.
  產品暴露與產品接觸組件嚴格遵守最乾淨氣流(First Air)原則
- Aseptic manipulations should be made in First Air, not having passed over any other components or blocked by the operator's hands.
  無菌操作在最乾淨氣流下進行
- The operators should decontaminate or change their gloves on a frequent basis. 操作員的手套應時常消毒或更換

Manual Aseptic Process Design Principles in Unidirectional Air Flow Hoods

- The operators should work as a team. The primary operator(s) should perform all tasks inside the ISO 5 environment. The secondary operator(s) assists in the introduction/removal of items from the ISO 5 environment, and may assist the primary operator(s) with less critical tasks inside that environment. Additional support operator(s) may be necessary to support activities exclusively in the surrounding environment.
  團隊作業。



Manual Aseptic Process Design Principles in Unidirectional Air Flow Hoods

- The primary operator should wear sterile gloves and sleeves and never contact a non-sanitized or non-sterilized item. 主要操作員穿戴無菌手套與袖套，嚴禁接觸未經消毒或滅菌的物品
- The primary operator(s) performs the critical aseptic manipulations within the ISO 5 environment. The secondary operator(s) acts as a support person to minimize the potential of the primary operator touching non-sterile or non-disinfected surfaces. The hands of the primary operator should remain in the ISO 5 environment at all times. (There may be exceptions to this related to positron emission tomography products or radioactive products.) The secondary operator(s) should put on sterile gloves/sleeves prior to any activity inside the ISO 5 environment, or in transfers of items to/from the primary operator. Anytime the primary operator is required to leave the ISO 5 environment, gloves and sleeves (if appropriate) should either be changed or gloves should be re-sanitized prior to reentry to ISO 5. 主要操作執行關鍵無菌操作，次要操作員協助主要操作員儘量減少其接觸未經消毒或滅菌的物品的機會。主要操作員的手應始終保持在A級區中，離開A級區應更換手套/袖套，重新進入A級區時應消毒手套。次要操作員在A級區進行任何作業前，或是將物品移入移出設備時，應穿上無菌手套/袖套。

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Manual Aseptic Process Design Principles in Unidirectional Air Flow Hoods

- Sterilized items should be introduced to the ISO 5 area by aseptic removal of the final wrap around the item as it is being introduced. 已滅菌物品須脫去最後一層包裝後才能移入A級區
- Extra subassemblies and utensils should be sterilized and available for immediate use in the event a replacement is needed. 備用組件與器具應滅菌，並在需要更換時立即使用。
- Sterile tools and utensils should be employed wherever possible *to handle sterile materials during their processing,* rather than the direct contact with the operator gloves. There should be sterile supports or hangers for tools inside the ISO 5 environment in order to minimize contact between the tool and surfaces of the workspace. 應使用無菌工具或器具操作無菌材料，不能與操作員手套直接接觸。A級區的工具應有無菌支架或吊架，盡量減少工具與工作區表面接觸。
- The process should be designed so that samples can be taken with minimal risk of contamination. When withdrawing samples from a sterile container, it is preferable to take all desired samples from a container in a single step, and then subdivide that sample as required. Alternatively, the residual left in the original container post-production can be used as the test sample. The use of technologies such as sterile septum or connectors should be considered to minimize the risk during sampling. 採用污染風險最小的方式(無菌隔膜/無菌連接)進行取樣。無菌取樣需一次取樣，再依需求分樣；或用生產後的剩餘產品進行分析。

Manual Aseptic Process Design Principles in Unidirectional Air Flow Hoods

- Wherever possible materials being introduced into the process should be pre-measured into a tightly sealed container prior to sterilization and addition. 原料使用於製程時，在滅菌與添加之前，盡可能先秤好分裝於密封容器中
- Electrical equipment and controls pose a contamination risk and should be located outside the processing environment, if possible. If that is not possible a second operator (not the primary operator) should adjust equipment settings as necessary. Pay special attention to equipment which exhausts air (e.g., mixers, blenders, etc.) that could contaminate the environment. 電器設備與裝置存在污染風險，應安裝於製程區外。若不可行，則由次要操作員執行該設備之調整。應特別注意會排氣的設備(混合/攪拌器)
- Liquid transfers should be made using peristaltic pumps located outside the aseptic environment, rather than through the use of automatic pipettes, due to concerns regarding exhausted air. In order to minimize equipment movement and the risk of contamination, containers can be premarked to indicate the amount of material to transfer. 由於擔心排氣污染，應使用位於無菌環境外的蠕動泵進行液體轉移，而不是使用自動移液器。為了最大限度地減少設備移動和污染風險，容器可以預先標記以指示要轉移的材料量。

110TPDA04030

Manual Aseptic Process Design Principles in Unidirectional Air Flow Hoods

- Perform as much of the process inside the ISO 5 environment as possible in order to minimize the removal and reentry of in-process materials in suitable containers. This may require the placement of small equipment within the environment. 盡可能在A級區執行製程，並且儘量減少製程中原料在容器中的移進移出。這需要在A級區中放置小型設備。
- When containers of in-process materials must be removed from, and later returned to, the ISO 5 environment the containers should be aseptically wrapped in a pre-sterilized covering which should be properly removed and discarded prior to reentry. Alternatively, the exterior of the container(s) can be re-sanitized prior to reentry. 需要在A級區進出的裝有製程中原料之容器，應先包覆預先滅菌的覆蓋物，在重新進入A級區前正確取出並丟棄，或是容器外部可以在進入前重新消毒。
- Sanitize the operating environment when it is empty, and sanitize each nonsterilizable item/ equipment as it is first introduced and transferred into the next cleaner level of the aseptic processing environments. Do not introduce a large item into the environment in mid-process. **Note:** If sanitization of the operating environment/equipment is performed by the primary operator, sterile gloves/sleeves should be changed before aseptic manipulation of product is performed. 在操作環境淨空時執行消毒，以及針對不可滅菌的物品/設備首次移入與轉移到到更潔淨區域時進行消毒。不要在製程中移入大項物品。注意：若消毒是由主要操作員執行，則在無菌操作前必須更換手套/袖套。

Manual Aseptic Process Design Principles in Unidirectional Air Flow Hoods

- Product contact surfaces shall be sterilized. Sterility should be maintained with protective layers which can be removed as materials are transitioned to cleaner environments. 產品接觸面應進行滅菌。應使用保護層保持無菌狀態，當材料轉移到更清潔的環境時，保護層可以去除。
- Significant aseptic assembly in the processing environment should be avoided through the use of sterilized pre-assembled items. This will reduce the extent of manual assembly required. 通過使用經滅菌的預組裝物品，以避免在製程環境中進行大量無菌組裝。 這將減少所需的手動組裝的程度。
- Process steps not required to be aseptic should be performed outside the ISO 5 environment by other operator(s). 不需要無菌的製程步驟應由其他操作員在 A 級區之外執行。
- Once the process design has been established, it should be rehearsed several times and documented in air flow studies using all of the required items and placebo materials to refine the steps, location of items, etc. This ensures the process design is practical and reduces risk of contamination to a minimum. The use of engineering runs to develop the process is strongly encouraged. 當製程設計確立後，應多次演練並記錄下氣流研究，使用所有必需的物品與安慰劑物質以完善步驟、物品位置等。這確保了製程設計的實用性並將污染風險降至最低。強烈建議利用工程試製(engineering run)來開發製程。

Manual Aseptic Process Design Principles in Unidirectional Air Flow Hoods

- The manufacturing process should be documented in sufficient detail to allow operators to understand and conform to the desired practices. The secondary or support operator(s) should complete the batch record. 製造過程必須充分詳細地文件化以便操作員理解與遵守所需的規範。
- Environmental monitoring practices should be non-intrusive in order to avoid potential for contamination in the ISO 5 environment. Air sampling during processing may be performed with specially designed equipment that does not compromise the environment and may include settling plates. Surface monitoring should be performed using contact plates or swabs after processing has been completed. 環境監測不得干擾製程，以避免在A級環境中潛在的污染。製程中的空氣取樣可以使用不影響環境的專門設計設備進行，並可包括使用落菌培養皿。製程完成後，應使用培養品接觸或擦拭法進行表面監測。

Cleaning and Disinfection

- Cleaning is a critical step 清潔是關鍵步驟
  - Non-destructive mechanical action 非破壞性物理作用
  - Removes residues, soils, microorganisms 去除殘留物、塵土、微生物
- Allows for more effective disinfection 讓後續消毒更有效
- Spraying and Fogging vs. Manual Disinfection 噴霧與薰蒸 vs.人工消毒
- Cleaning removes contamination, disinfection destroys it 清潔去除污染物，消毒破壞污染物

Contamination Control

- **Keeping Contamination from Entering the Cleanroom**
- Choosing the **Appropriate Materials** for **Cleaning and Disinfecting**
- Using the Appropriate Materials in a **Consistent Manner**

Contamination Control

- Control what enters your environment
  - Viable and total particles
- Begin with items transferred into facility
  - Components, carts, personnel, tanks, tools, etc.
  - Defined entrance procedures
- Good control leads to less
  - Environmental Excursions
  - CAPA Investigations
  - Down time from production

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不同消毒位置之執行重點

打算清潔/消毒的表面	執行重點
櫃體與操作檯面	• 使用前與使用後都需要清潔。 • 清潔後用殺孢劑(sporicidal agent)處理。 • 消毒劑的使用方式：噴灑與擦拭。但要留意不得噴濕HEPA過濾器。 • 當殺孢劑處理後，需用70% IPA乾擦將殘留去除。
非產品接觸表面	• 如果鄰近於產品接觸表面要特別注意，小心的移除消毒劑殘留。避免消毒劑轉移到產品接觸表面。
非潔淨室結構表面 (桶槽、推車、層架、管路外表、監控取樣設備…等)	• 要留意難以清潔的位置：門的頂端、溝槽、軌道、對講機、桶槽/推車下方、輪子。**增加消毒劑接觸時間**。 • 清潔頻率要基於使用的級區，與對產品品質的影響而定。
工具	• 清潔/消毒程序端看工具使用的位置而定 • 盡可能滅菌處理。如果無法滅菌，就執行清潔、消毒程序後，再以酒精擦拭。
排水口、排水管	• 排水口不得設計在A級區與B級區。 • 盡可能加蓋。 • 排水管內部很難消毒(很難保證所有管路都浸到消毒劑、生物膜會阻礙消毒劑滲透且微生物滋長快)。 • 排水孔外部用殺孢劑消毒(漂白水、過氧化氫/過乙酸) • PDA TR No.70：「排水管很可能在管內組成生物膜，這將妨礙消毒劑穿透生物膜而接觸排水管表面。使用次氯酸鈉或過乙酸和過氧化氫消毒排水孔外部可見表面，能夠減少負荷菌，但預計這種負荷菌趨勢會在短時間內恢復。」。

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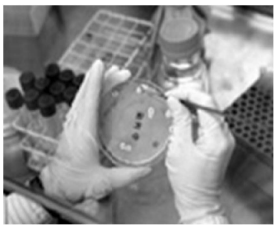
Cleanroom monitoring program

- 例行的監控計畫，是保證產品品質重要的一環。
- 額外的監控以及啟動條件，如；
  - 空調停機，再啟動
  - 過濾元件更換
  - 空調箱保養維護
  - 超出設定的規格

Cleanroom monitoring program

- 監控微粒與微生物污染
  - 監控位置及其數量的說明(圖示)、訂定邏輯，需要明訂在SOP或是計畫書中。
  - 足夠的取樣時間，以及適當的樣品大小
  - 取樣點的識別與標記
  - 定義樣品運送、儲存以及培養條件
  - 對應到SOP或計畫書的結果(監控方法/結果)
  - 定義各個不同功能或等級的潔淨室，其警戒界限和行動界限(alert and action limits)，以及相關作業
  - 取樣頻率
  - 趨勢分析



EM Sampling

- 如果取樣是由QC實驗室所負責，那麼，強烈建議，這些取樣程序必須要有QA的參與，並且需要定期的查核。
- 任何使用在檢品取樣過程的消毒程序或步驟(e.g. 針對取樣點的消毒)，必須證實不會影響檢品中的微生物數量。

EM Sampling

- 取樣必須由受訓合格的人員執行。且必須要使用無菌的器具，應用無菌的手法來取樣。
- 有時在取樣點同時確認環境條件是必須的。如，溫溼度、壓差。
- 取樣的時間必須被記錄。
- **在取樣地點以及檢測實驗室間的運送和儲存的責任歸屬，必須要有明確的SOP規範。**

EM Sampling

- 在取樣後，必須盡速執行檢品的檢測，除非有特殊規定(適當的確效/確認)。
- 如果檢品本身特性，在運送或儲存期間可能會長菌，那麼，必須要有SOP規範儲存的條件、時間與溫度，以確保不會因為儲存而影響結果的精確性。
- 儲存的條件必須要監控，其記錄必須要適當的保存。

Alert and Action Limits

- 行動界限(action limits)
  - 起始以法規值作為界限
  - 監控一段時間，累積資料後
    - 資料的第99百分位數
- 警界界限(alert limits)
  - 起始以法規值的80-70%作為界限
  - 監控一段時間，累積資料後
    - 資料的第95百分位數

取樣頻率 USP<1116>建議

Sampling Area/Location	Frequency of Sampling
Clean Room/RABS	
Critical zone (ISO 5 or better)	
Active air sampling	Each operational shift
Surface monitoring	At the end of the operation
Aseptic area adjacent critical zone	
All sampling	Each operating shift
Other nonadjacent aseptic areas	
All sampling	Once per day
Isolators	
Critical zone (ISO 5 or better)	
Active air sampling	Once per day
Surface monitoring	At the end of the campaign
Nonaseptic areas surrounding the isolator	
All sampling	Once per month

[a] All operators are aseptically gowned in these environments (with the exception of background environments for isolators). These recommendations do not apply to production areas for nonsterile products or other classified environments in which fully aseptic gowns are not donned.

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環控趨勢解釋說明

- **趨勢分析**

  來自日常的微生物環境監控計劃的數據，可以與時間、作業班次、設施等相關。定期評估這些資訊，以確定該計劃的狀態，以確定其是否處於適當的控制之下。趨勢分析用於幫助對經適當管制的環境的再驗證或維護和消毒計劃的決策。

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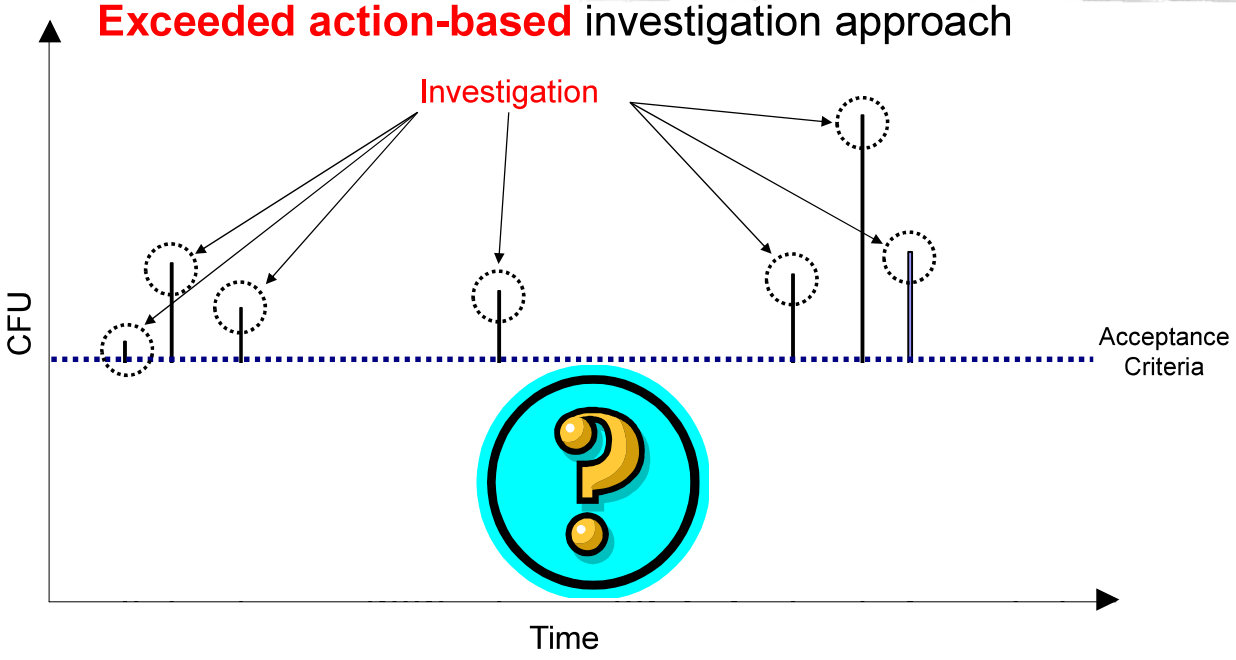
環控趨勢解釋說明

Exceeded action-based investigation approach



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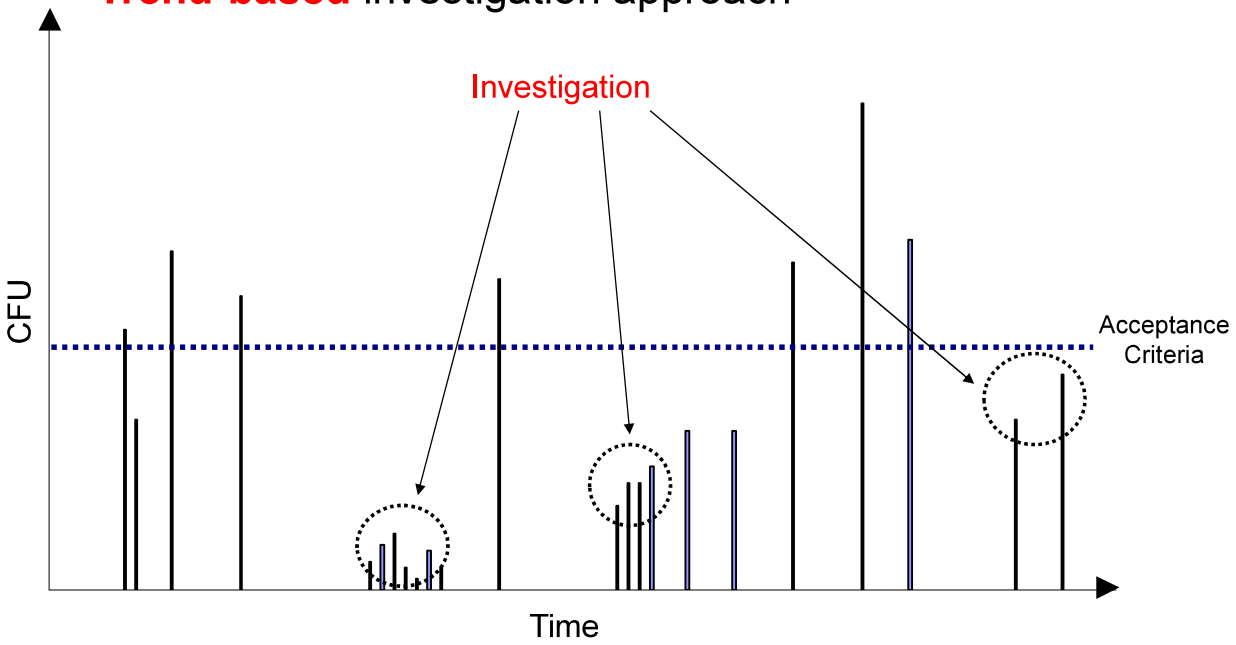
環控趨勢解釋說明

Trend-based investigation approach



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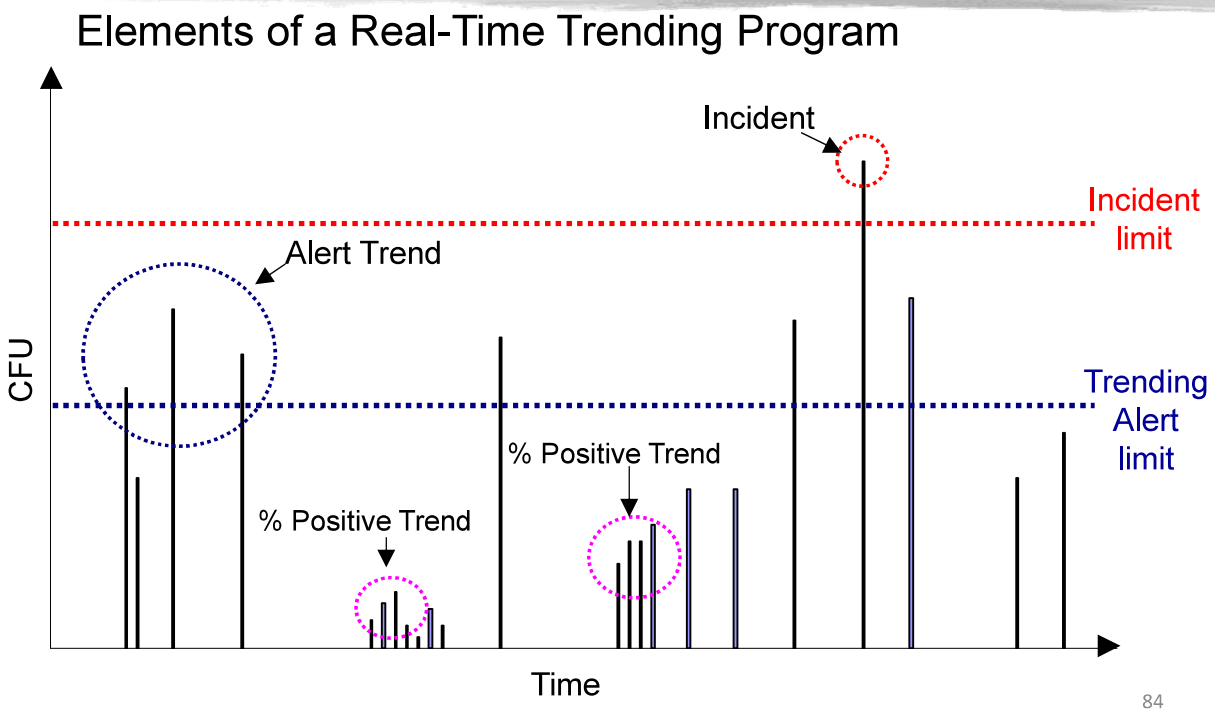
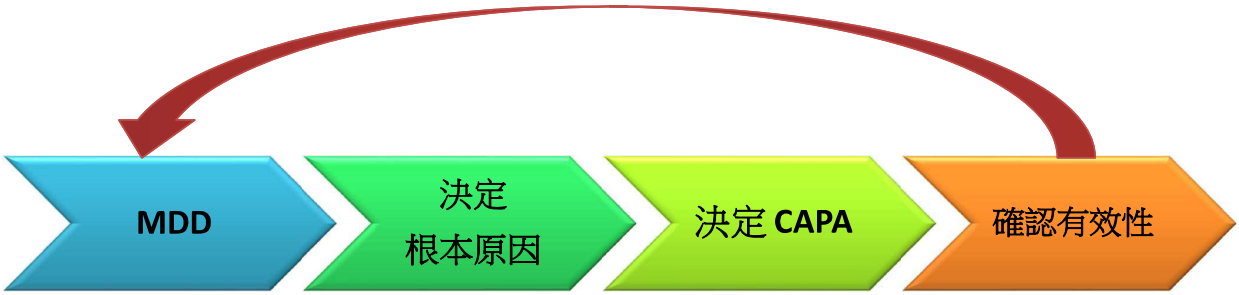
環控趨勢解釋說明

- 偶發事件 Incidents
  超出統計學的允收規格的離散事件。
- 警戒趨勢 Alert Trends
  非典型分佈，超過警戒值的趨勢。
- 陽性百分比趨勢 Percent Positive Trends (針對低負荷菌)
  陽性微生物取樣結果的非典型相對分佈(百分比)，被認為是重要的潛在相關事件。
- 菌叢趨勢 Microflora Trends (某些微生物種類的比率)
  非典型的微生物分佈，可能是由共同的污染來源有關。

環控趨勢解釋說明



Microbiological Data Deviations (MDD)



MDD 實驗室調查:
- ✓ 程序
- ✓ 檢品
- ✓ 菌株
- ✓ 培養基
- ✓ 儀器/設備
- ✓ 人員/訓練

1. 實驗室錯誤(無效的結果)
2. 分析上的變異
3. 產品異常
4. 不確定的原因

1. 重新執行檢測
2. 調查性的檢測
3. 依據SOP執行產品處置
4. 保留所有記錄，決定此批產品如何處置

- 持續的監控
- 數據收集
- 趨勢分析
- 年度產品回顧APR

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結果超出界限時的措施 …

- 當結果超出界限時，微生物鑑定應當被執行。
- 微生物的種類有時可以幫助判斷污染的來源，因為某一些典型的微生物是常見於水中、空氣或者是人員身上。
- 使用於生產現場的清潔劑(cleansing agent)與消毒劑(disinfectants)，不論是原液或稀釋液，都應該檢查其可能的污染。
- 針對環境監控結果異常，有時是因為清潔或消毒程序不足或不適當所造成。

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結果超出界限時的措施 …

- MDD結果的調查，至少要包含以下項目：
  - 審閱實驗室所進行的檢驗流程、相關記錄
  - 針對產品，進行額外的檢驗，確認原因
  - 審閱生產相關文件
  - 審閱維護/保養相關文件
  - 審閱清潔/消毒/滅菌(decontamination)相關文件
  - 審閱相關的物理與操作參數
    - 溫濕度、壓差、換氣回數、運轉時間…
    - 微粒與微生物監控數據、趨勢
  - 審閱人員監控資料

結果超出界限時的措施 …

- 矯正措施(Corrective action)可能包含下列項目：
  - 相關人員的再訓練
  - 增加取樣的頻率或是取樣量
  - 評估是否需要增加消毒或清潔的頻率

結果超出界限時的措施 …

- 再檢驗 (Repeat Test)
  - 此試驗是設計用來取代，經過調查的步驟已經被證實為無效的結果。
- 調查性檢驗 (Investigational Testing)
  - 此試驗的執行是用來輔助確認MDD的根本原因。調查性檢驗必須文件化且由實驗室主管所核准。由調查性檢驗所得的結果，僅可以用來確認MDD結果是否為有效的。
- 重新檢驗 (Retest)
  - 為使用已被核准的重新試驗計劃所執行的附加試驗。或可用於檢驗結果的判定。

Main Reference

- PIC/S GMP Guide PE 009-15 (Annexes) Annex 1, 2A/2B, May Frist, 2021.
- 2nd Targeted Consultation Document on Revision of PIC/S GMP Annex 1 (Manufacture of Sterile Products), 2020.
- PDA TR62 Recommended Practices for Manual Aseptic Processes. 2013.
- ISO, ISO 14644-1:2015, Cleanrooms and associated controlled environments – Part 1: Classification of air cleanliness by particle concentration.
- ISO, ISO 14644-2:2015, Cleanrooms and associated controlled environments – Part 2: Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration.

Persimmon Tainan
台南梁山工程顧問公司

Contact Me

- 林宗儒 Ken Lin
  Ken@persimmon.engineering

Thanks for your attention!

Questions?

http://meetmrholland.wordpress.com/2013/03/17/creative-meeting-design-foster-the-discussion/

意見調查表
及
課後測試

課程提問單