西藥藥品優良製造規範
（附則1：無菌藥品之製造）

PIC/S：Guide to Good Manufacturing Practice for Medicinal Products
（Annex 1 Manufacture of Sterile Medicinal Products）

(9 September 2022)

附則 1　無菌藥品的製造（Manufacture of Sterile Medicinal Products）

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

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

1.範圍 (Scope)	
無菌產品之製造涵蓋廣泛的無菌產品類型（包括原料藥、賦形劑、直接包裝材料及成品劑型）、包裝規格（由單一到多單元包裝）、製程（從高度自動化系統到手工製程）及技術 （例如生物技術、傳統小分子製造系統及密閉系統）。本附則提供的一般指引應被用於設計及控制所有無菌產品製造的廠房設施、設備、系統及程序，並使用品質風險管理（QRM） 原則，確保最終產品不受到微生物、微粒及內毒素/熱原的污染。	The manufacture of sterile products covers a wide range of sterile product types (active substance, excipient, primary packaging material and finished dosage form), packed sizes (single unit to multiple units), processes (from highly automated systems to manual processes) and technologies (e.g. biotechnology, classical small molecule manufacturing systems and closed systems). This Annex provides general guidance that should be used in the design and control of facilities, equipment, systems and procedures used for the manufacture of all sterile products applying the principles of Quality Risk Management (QRM), to ensure that microbial, particulate and endotoxin/pyrogen contamination is prevented in the final product.
QRM 完全適用於本文件各章節，通常不會於特定段落中再提及。在指出特定限量、頻率或範圍的地方，這些應被視為最低要求；之所以加以陳述，是基於監管經驗識別出且影響患者安全的歷史事件。	QRM applies to this document in its entirety and will not, normally, be referred to in specific paragraphs. Where specific limits or frequencies or ranges are specified, these should be considered as a minimum requirement. They are stated due to historical regulatory experience of issues that have been identified and have impacted the safety of patients.
本附則的目的是為無菌產品的製造提供指引。然而，一些原則及指引，如污染管制策略、廠房設施設計、潔淨室分級、驗證、確效、監測及人員著衣，可能用於支持其他非無菌產品的製造，例如管制及減少微生物、微粒及內毒素/熱原的污染也被認為重要的某些液劑、乳膏、軟膏及低負荷菌的生物中間產物。如果製造廠選擇將此指引應用於非無菌產品，則製造廠應清楚地記錄已應用哪些原則，並應證明符合這些原則。	The intent of the Annex is to provide guidance for the manufacture of sterile products. However, some of the principles and guidance, such as contamination control strategy, design of premises, cleanroom classification, qualification, validation, monitoring and personnel gowning, may be used to support the manufacture of other products that are not intended to be sterile such as certain liquids, creams, ointments and low bioburden biological intermediates, but where the control and reduction of microbial, particulate and endotoxin/pyrogen contamination is considered important. Where a manufacturer elects to apply guidance herein to non-sterile products, the manufacturer should clearly document which principles have been applied and acknowledge that compliance with those principles should be demonstrated.
2.原則 (Principle)	
2.1 為使微生物、微粒及內毒素/熱原的污染風險降到最低，無菌產品之製造應受制於特別的要求。下述關鍵領域應予以考慮:	2.1 The manufacture of sterile products is subject to special requirements in order to minimize risks of microbial, particulate and endotoxin/pyrogen contamination. The following key areas should be considered:
i. 廠房設施、設備與製程應經過適當設計，驗證及/或確效，並在適用的情況下，根據西藥藥品優良製造規範 （GMP） 的相關	i. Facility, equipment and process should be appropriately designed, qualified and/or validated and where applicable, subjected to

章節進行持續確認。應考慮使用適當的技術（例如限制進入屏障系統 (RABS)、隔離裝置、機器人系統、快速/替代方法及連續監測系統）以增加對產品的保護，使其免受來自諸如人員、原物料及周圍環境等潛在之外來內毒素/熱原、微粒及微生物的污染，並協助快速偵測環境及產品中的潛在污染物。	ongoing verification according to the relevant sections of the Good Manufacturing Practices (GMP) guide. The use of appropriate technologies (e.g. Restricted Access Barriers Systems (RABS), isolators, robotic systems, rapid/alternative methods and continuous monitoring systems) should be considered to increase the protection of the product from potential extraneous sources of endotoxin/pyrogen, particulate and microbial contamination such as personnel, materials and the surrounding environment, and assist in the rapid detection of potential contaminants in the environment and the product.
ii. 人員應具有充分的資格及經驗、訓練及行為，特別關注在製造、包裝及運銷過程中保護無菌產品所涉及的原則。	ii. Personnel should have adequate qualifications and experience, training and behaviour with a specific focus on the principles involved in the protection of sterile product during the manufacturing, packaging and distribution processes.
iii. 無菌產品製造的過程及監測系統應由具有適當製程、工程及微生物學知識的人員設計、試運轉、驗證、監測及定期審查。	iii. Processes and monitoring systems for sterile product manufacture should be designed, commissioned, qualified, monitored and regularly reviewed by personnel with appropriate process, engineering and microbiological knowledge.
iv. 原料及包裝材料應得到充分管制及測試，以確保其負荷菌及內毒素/熱原水準適合使用。	iv. Raw materials and packaging materials should be adequately controlled and tested to ensure that level of bioburden and endotoxin/pyrogen are suitable for use.
2.2 製程、設備、設施及製造活動應按照 QRM 原則進行管理，以提供主動識別、科學評估及管制潛在品質風險的方法。在使用替代方法的情況下，這些方法應有適當合理證明、風險評估及風險減輕的支持，並應符合本附則的旨意。首先，QRM 應運用於包括廠房設施、設備及流程的適當設計，然後是導入經過良好設計的程序，最後是監測系統的應用，以此作為證明設計及程序已正確實施並且繼續地表現符合預期。僅依靠監測或測試並不能保證無菌。	2.2 Processes, equipment, facilities and manufacturing activities should be managed in accordance with QRM principles to provide a proactive means of identifying, scientifically evaluating and controlling potential risks to quality. Where alternative approaches are used, these should be supported by appropriate rationale, risk assessment and mitigation, and should meet the intent of this Annex.In the first instance, QRM priorities should include appropriate design of the facility, equipment and processes, followed by the implementation of well-designed procedures, and finally application of monitoring systems as the element that demonstrates that the design and procedures have been correctly implemented and continue to perform in line with expectations.

	Monitoring or testing alone does not give assurance of sterility.
2.3 污染管制策略 (CCS) 應於全廠實施，以規範所有關鍵管制點並評估所有控制（設計、程序、技術及組織(程序 ICH Q7)上的）及監測措施的有效性，以管理藥品品質及安全的風險。 CCS 的整合策略應建立穩健的預防污染保證。CCS 應予積極審查，在適當的情況下進行更新，並應推動製造及管制方法的持續改善。其有效性應成為定期管理審查的一部分。如果現有的管制系統已經到位並得到適當的管理，這些系統可能不需要被取代，但應在 CCS 中引述，並且應了解相關聯系統之間的相互作用。	2.3 A Contamination Control Strategy (CCS) should be implemented across the facility in order to define all critical control points and assess the effectiveness of all the controls (design, procedural, technical and organisational) and monitoring measures employed to manage risks to medicinal product quality and safety. The combined strategy of the CCS should establish robust assurance of contamination prevention. The CCS should be actively reviewed and, where appropriate, updated and should drive continual improvement of the manufacturing and control methods. Its effectiveness should form part of the periodic management review. Where existing control systems are in place and are appropriately managed, these may not require replacement but should be referenced in the CCS and the associated interactions between systems should be understood.
2.4 污染控制以及為最大限度降低源自微生物、內毒素/熱原及微粒之污染風險而採取的步驟，它包括一系列相互關聯的事件及措施。這些通常是個別評估、管制及監測的，但它們的總體有效性應一併考慮。	2.4 Contamination control and steps taken to minimize the risk of contamination from microbial, endotoxin/pyrogen and particle sources includes a series of interrelated events and measures. These are typically assessed, controlled and monitored individually but their collective effectiveness should be considered together.
2.5 CCS 的建立需要詳細的技術及製程知識。潛在的污染源可歸因於微生物及細胞碎片（例如熱原、內毒素）以及微粒（例如玻璃及其他可目視及不可目視微粒）。 CCS 中要考慮的要素應包括（但不限於）：	2.5 The development of the CCS requires detailed technical and process knowledge. Potential sources of contamination are attributable to microbial and cellular debris (e.g. pyrogen, endotoxin) as well as particulate (e.g. glass and other visible and sub-visible particles). Elements to be considered within a CCS should include (but are not limited to):
i. 工廠及流程的設計，包括相關文件；	i. design of both the plant and processes including the associated documentation;
ii. 廠房設施及設備；	ii. premises and equipment;
iii. 組織與人事；	iii. personnel;
iv. 公用設施；	iv. utilities;

v. 原料管制—包括製程中管制；	v. raw material controls – including in-process controls;
vi. 產品容器及封蓋；	vi. product containers and closures;
vii. 供應商核准—諸如關鍵組件供應商、組件滅菌及一次性使用系統 (SUS) 以及關鍵服務提供商；	vii. vendor approval – such as key component suppliers, sterilisation of components and single use systems (SUS), and critical service providers;
viii. 委外活動及雙方之間關鍵資訊之取得/移轉的管理，例如委託滅菌服務；	viii. management of outsourced activities and availability/transfer of critical information between parties, e.g. contract sterilisation services;
ix. 製程風險管理；	ix. process risk management;
x. 製程確效；	x. process validation;
xi. 滅菌製程的確效；	xi. validation of sterilisation processes;
xii. 預防性維護保養—將設備、公用設施及廠房設施（計畫內及計畫外的維護保養）保養到確保沒有額外污染風險的標準；	xii. preventative maintenance – maintaining equipment, utilities and premises (planned and unplanned maintenance) to a standard that will ensure there is no additional risk of contamination;
xiii. 清潔及消毒；	xiii. cleaning and disinfection;
xiv. 監測系統—包括評估導入科學合理的替代方法以優化環境污染偵測的可行性；	xiv. monitoring systems - including an assessment of the feasibility of the introduction of scientifically sound, alternative methods that optimize the detection of environmental contamination;
xv. 預防機制—趨勢分析、詳細調查、根本原因確定、矯正及預防措施 (CAPA) 以及對綜合調查工具的需求；	xv. prevention mechanisms – trend analysis, detailed investigation, root cause determination, corrective and preventive actions (CAPA) and the need for comprehensive investigational tools;
xvi. 基於上述資訊的持續改進。	xvi. continuous improvement based on information derived from the above.
2.6 CCS 應考慮污染管制的所有面向，並進行持續及定期審查，從而在適當時更新製藥品質系統。對現有系統的變更應在實施前後評估對 CCS 的任何影響。	2.6 The CCS should consider all aspects of contamination control with ongoing and periodic review resulting in updates within the pharmaceutical quality system as appropriate. Changes to the systems in place should be assessed for any impact on the CCS before and after implementation.
2.7 製造廠應採取所有必要的步驟及預防措施，以確保在其設施內生產之產品的無菌性。無菌性或其他品質層面不得僅仰賴於最終製程或最終產品的檢驗。	2.7 The manufacturer should take all steps and precautions necessary to assure the sterility of the products manufactured within its facilities. Sole reliance for sterility or other quality aspects should not be placed on any terminal process or finished product test.
3. 製藥品質系統 (Pharmaceutical Quality System, PQS)	

3.1 無菌產品的製造是一項複雜的活動，需要特定的管制及措施來確保所生產產品的品質。因此，製造廠的 PQS 應涵蓋並解決無菌產品製造的具體要求，並確保所有活動都得到有效管制，從而將無菌產品中微生物、微粒及內毒素/熱原污染的風險降至最低。除了 GMP 指引(第一部分-藥品基本要求) 第 1 章詳述的 PQS 要求外，無菌產品製造的 PQS 還應確保：	3.1 The manufacture of sterile products is a complex activity that requires specific controls and measures to ensure the quality of products manufactured. Accordingly, the manufacturer's PQS should encompass and address the specific requirements of sterile product manufacture and ensure that all activities are effectively controlled so that the risk of microbial, particulate and endotoxin/pyrogen contamination is minimized in sterile products. In addition to the PQS requirements detailed in Chapter 1 of the GMP Guide (Part I – Basic Requirements for Medicinal Products), the PQS for sterile product manufacture should also ensure that:
i. 一個整合到產品全生命週期的有效風險管理系統，旨在減少微生物污染並確保製造之無菌產品的品質。	i. An effective risk management system is integrated into all areas of the product life cycle with the aim to minimize microbial contamination and to ensure the quality of sterile products manufactured.
ii. 製造廠對所製造之產品以及所採用的對產品品質有影響的設備、工程及製造方法具有足夠的知識及專長。	ii. The manufacturer has sufficient knowledge and expertise in relation to the products manufactured and the equipment, engineering and manufacturing methods employed that have an impact on product quality.
iii. 以正確識別及理解產品風險的方式進行程序、製程或設備失效的根本原因分析，從而實施適當的矯正及預防措施 (CAPA)。	iii. Root cause analysis of procedural, process or equipment failure is performed in such a way that the risk to product is correctly identified and understood so that suitable corrective and preventive actions (CAPA) are implemented.
iv. 風險管理應用於 CCS 的建立及維護，以識別、評估、減少/消除（如適用）及管制污染風險。風險管理應予文件化，並包括有關降低風險及接受殘留風險的決策理由。	iv. Risk management is applied in the development and maintenance of the CCS, to identify, assess, reduce/eliminate (where applicable) and control contamination risks. Risk management should be documented and should include the rationale for decisions taken in relation to risk reduction and acceptance of residual risk.
v. 高階管理層應有效監督整廠及產品生命週期的管制狀態。風險管理結果應定期審查，並在變更期間、在出現重大問題時以及在定期產品品質檢討時，將其結果作為持續品質管理的一部分。	v. Senior management should effectively oversee the state of control throughout the facility and product lifecycle. Risk management outcome should be reviewed regularly as part of the on-going quality management, during change, in the event of a significant emerging problem, and during the periodic product quality review.
vi. 與無菌產品的完成、儲存及運輸相關的過程不應損害無菌產品。應考慮的方面包括：容器完整性、污染及通過確保產品按照查驗登記的儲存條件進行儲存及維護來避免降解的風險。	vi. iProcesses associated with the finishing, storage and transport of sterile products should not compromise the sterile product. Aspects that should be considered include: container integrity, risks of contamination and avoidance of degradation by ensuring that products are stored and maintained in

	accordance with the registered storage conditions.
vii. 負責無菌產品認可/放行的人員可以適當地使用製造及品質資訊，並在無菌產品的製造及相關的關鍵品質屬性方面擁有足夠的知識及經驗。這是為了讓該等人員確定無菌產品是否按照查驗登記之規格及核准的製程製造及符合所要求的品質。	vii. Persons responsible for the certification/release of sterile products have appropriate access to manufacturing and quality information and possess adequate knowledge and experience in the manufacture of sterile products and the associated critical quality attributes. This is in order to allow such persons to determine if the sterile products have been manufactured in accordance with the registered specifications and approved process and are of the required quality.
3.2 所有不符合項目，例如無菌試驗失敗、環境監測偏差或偏離既定程序，都應在該批的認可/放行之前進行充分調查。調查應確定對製程及產品品質的潛在影響以及是否有任何其他製程或批次受到潛在影響。將某一產品或批次納入或排除在調查範圍內的原因應有明確的理由並記錄。	3.2 All non-conformities, such as sterility test failures, environmental monitoring excursions or deviations from established procedures should be adequately investigated before certification/release of the batch. The investigation should determine the potential impact upon process and product quality and whether any other processes or batches are potentially impacted. The reason for including or excluding a product or batch from the scope of the investigation should be clearly justified and recorded.
4.廠房設施 (Premises)	
4.1 無菌產品的製造應在適當的潔淨室中進行，人員進入潔淨室應通過更衣室，更衣室作為人員進入之氣鎖室，如同設備及原物料應經由的氣鎖室。潔淨室及更衣室應維持在適當的潔淨度標準，並提供已通過具適當效率之濾器的空氣。管制及監測應有科學合理證明，及應能有效評估潔淨室、氣鎖室及傳遞箱的環境狀態。	4.1 The manufacture of sterile products should be carried out in appropriate cleanrooms, entry to which should be through change rooms that act as airlocks for personnel and airlocks for equipment and materials. Cleanrooms and change rooms should be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency. Controls and monitoring should be scientifically justified and should effectively evaluate the state of environmental conditions of cleanrooms, airlocks and pass-through hatches.
4.2 組件的準備、產品的製備及充填等不同作業應在潔淨室或設施內採用適當技術面及操作面的隔離措施進行，以防止混雜及污染。	4.2 The various operations of component preparation, product preparation and filling should be carried out with appropriate technical and operational separation measures within the cleanroom or facility to prevent mix up and contamination.
4.3 使用限制性進入屏障系統（RABS）或隔離裝置有利於確保所需之環境條件，並將人員直接介入關鍵性區域導致之微生物污染降到最低。應於 CCS 評估採用前述設備。任何替代使用 RABS 或隔離裝置的方法應證明其合理性。	4.3 Restricted Access Barrier Systems (RABS) or isolators are beneficial in assuring required conditions and minimizing microbial contamination associated with direct human interventions in the critical zone. Their use should be considered in the

	CCS. Any alternative approaches to the use of RABS or isolators should be justified.
4.4 無菌產品的製造，區分成四個等級的潔淨室/區。	4.4 For the manufacture of sterile products there are four grades of cleanroom/zone.
A 級：高風險作業的關鍵區域，(例如，無菌作業線、充填區、膠塞貯盆、開口的直接包材或是執行受到第一手空氣保護的無菌連接等區域)。通常，此種環境由該處的氣流保護，像是在 RABS 或隔離裝置的單向氣流工作站。單向氣流的維持應予以證明並驗證可涵蓋整個 A 級區域。應透過廠房設施、設備、流程及程序設計，減少作業人員直接（例如，不透過屏障及手套孔技術）介入 A 級區域。	Grade A: The critical zone for high-risk operations (e.g. aseptic processing line, filling zone, stopper bowl, open primary packaging or for making aseptic connections under the protection of first air). Normally, such conditions are provided by a localised airflow protection, such as unidirectional airflow workstations within RABS or isolators. The maintenance of unidirectional airflow should be demonstrated and qualified across the whole of the grade A area. Direct intervention (e.g. without the protection of barrier and glove port technology) into the grade A area by operators should be minimized by premises, equipment, process and procedural design.
B 級：對於無菌製備及充填，B 級區作為 A 級區的背景環境(當該 A 級區不是隔離裝置時)。應連續監測壓差。在使用隔離裝置技術的情況下，可以考慮使用低於 B 級的潔淨室（參見第 4.20 點）。	Grade B: For aseptic preparation and filling, this is the background cleanroom for grade A (where it is not an isolator). Air pressure differences should be continuously monitored. Cleanrooms of lower grade than grade B can be considered where isolator technology is used (see paragraph 4.20).
C 級與 D 級：C 級與 D 級區的潔淨室係用於進行無菌充填產品製造中非關鍵性階段或作為隔離裝置之背景環境。最終滅菌產品的製備/充填作業亦可於該區域執行。（有關最終滅菌活動的具體細節，請參見第 8 節）。	Grade C and D: These are cleanrooms used for carrying out less critical stages in the manufacture of aseptically filled sterile products or as a background for isolators. They can also be used for the preparation/filling of terminally sterilised products. (See section 8 for the specific details on terminal sterilisation activities).
4.5 在潔淨室及關鍵區域內，所有暴露的表面均應平滑、不滲透且無破裂，使微粒或微生物的釋出或積聚降到最低。	4.5 In cleanrooms and critical zones, all exposed surfaces should be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particles or micro-organisms.
4.6 為減少粉塵的積聚及利於清潔，不應有難以有效清潔的凹處，因此應儘量減少突出的窗台、儲架、櫃子及設備。門的設計應避免無法清潔的凹處。因此，滑動門可能不合適。	4.6 To reduce accumulation of dust and to facilitate cleaning there should be no recesses that are difficult to clean effectively, therefore projecting ledges, shelves, cupboards and equipment should be kept to a minimum. Doors should be designed to avoid recesses that cannot be cleaned. Sliding doors may be undesirable for this reason.
4.7 潔淨室使用之材料，無論是用於房間的結構還是於房間內使用的物品，都應選擇儘量減少微粒的產生，且可容許重覆使用清潔劑、消毒劑及殺孢劑(如有使用時)。	4.7 Materials used in cleanrooms, both in the construction of the room and for items used within the room, should be selected to minimize generation of particles and to permit the repeated application of cleaning, disinfectant and sporicidal agents where used.

4.8 天花板應設計及密封以防止來自其上方空間的污染。	4.8 Ceilings should be designed and sealed to prevent contamination from the space above them.
4.9 在 A 級區及 B 級區應禁止使用水槽及排水設施。在其他潔淨室中，應在機器、水槽與排水設施之間安裝空氣阻斷裝置。較低等級的潔淨室內，其地板的排水設施應裝配捕集器或水封以從設計上防止逆流，並應定期清潔、消毒及維護。	4.9 Sinks and drains should be prohibited in the grade A and grade B areas. In other cleanrooms, air breaks should be fitted between the machine or sink and the drains. Floor drains in lower grade cleanrooms should be fitted with traps or water seals designed to prevent back flow and should be regularly cleaned, disinfected and maintained.
4.10 設備及原物料轉入及轉出潔淨室及關鍵區域是污染的最大潛在來源之一。任何可能損害潔淨室或關鍵區域潔淨度的活動應加以評估，如果無法完全消除，則應實施適當的管制。	4.10 The transfer of equipment and materials into and out of the cleanrooms and critical zones is one of the greatest potential sources of contamination. Any activities with the potential to compromise the cleanliness of cleanrooms or the critical zone should be assessed and if they cannot be eliminated, appropriate controls should be implemented.
4.11 原物料、設備及組件進入 A 級或 B 級區域之轉送應透過單向過程進行。可行時，物品應經過滅菌並通過密封於牆壁中的雙門滅菌器（例如通過雙門高壓滅菌器或去熱原烘箱/隧道）進入該區域。如果物品無法在轉移時進行滅菌，則應確效並實施可達到不會導入污染的相同目標之程序（例如，使用有效的轉移消毒過程、隔離裝置之快速轉移系統，或是氣體或液體原料用的細菌滯留過濾器）。自 A 級及 B 級區域移出的物品（例如原物料、廢棄物、環境樣品）應透過與轉入時不同之單向過程進行。如果無法達成，則應考慮基於時段切換的方法依程序進行移動（原物料進/出），並採取管制措施以避免對轉入物品造成潛在污染。	4.11 The transfer of materials, equipment, and components into the grade A or B areas should be carried out via a unidirectional process. Where possible, items should be sterilised and passed into these areas through double-ended sterilisers (e.g. through a double-door autoclave or depyrogenation oven/tunnel) sealed into the wall. Where sterilisation upon transfer of the items is not possible, a procedure which achieves the same objective of not introducing contamination should be validated and implemented, (e.g. using an effective transfer disinfection process, rapid transfer systems for isolators or, for gaseous or liquid materials, a bacteria-retentive filter). The removal of items from the grade A and B areas (e.g. materials, waste, environmental samples) should be carried out via a separate unidirectional process. If this is not possible, time-based separation of movement (incoming/exiting material) by procedure should be considered and controls applied to avoid potential contamination of incoming items.
4.12 氣鎖室應被設計及用於提供實體隔離，以將不同區域的微生物及微粒污染風險降到最低，並配置在不同等級之間供原物料及人員移動。可行時，供人員進出之氣鎖室應與供原物料移轉之氣鎖室分開。當無法做到這一點，則應考慮基於不同時段依程序分別進行人員或原物料的進出。氣鎖室應以過濾的空氣有效地沖洗，以確保能維持潔淨室之潔淨度等級。在靜態時，氣鎖室最後階段之潔淨度應與將進入之潔淨區的潔淨度等級相同（微生物及總微粒數）。進入與離開 B 級潔淨區，使用各自的更衣室是有必要的。當無法達成，則應考慮基於不同時段依程序分別	4.12 Airlocks should be designed and used to provide physical separation and to minimize microbial and particle contamination of the different areas and should be present for material and personnel moving between different grades. Wherever possible, airlocks used for personnel movement should be separated from those used for material movement. Where this is not practical, time-based separation of movement (personnel/material) by procedure should be considered. Airlocks should be flushed effectively with filtered air to ensure that the grade of the cleanroom is maintained. The final stage of the

進入/離開。當 CCS 指出具高污染風險，進入及離開生產區域應通過不同的更衣室。氣鎖室應設計如下：	airlock should, in the "at rest" state, be of the same cleanliness grade (viable and total particle) as the cleanroom into which it leads. The use of separate change rooms for entering and leaving the grade B area is desirable. Where this is not practical, time-based separation of activities (ingress/egress) by procedure should be considered. Where the CCS indicates that the risk of contamination is high, separate change rooms for entering and leaving production areas should be used. Airlocks should be designed as follows:
i. 人員氣鎖室：供人員進入更高潔淨度之區域（例如，從 D 級區到 C 級區再到 B 級區）。通常，洗手設備應只在更衣室的第一個階段提供，而不應設置在直接進入 B 級區的更衣室中。	i. Personnel airlocks: Areas of increasing cleanliness used for entry of personnel (e.g. from the grade D area to the grade C area to the grade B area). In general hand washing facilities should be provided only in the first stage of the changing room and not be present in changing rooms directly accessing the grade B area.
ii. 原物料氣鎖室：用於原物料及設備的轉送。	ii. Material airlocks: used for materials and equipment transfer.
a. 只有在轉送過程確效期間經過評估並已列入核准清單的原物料及設備，才能經氣鎖室或傳遞箱轉送到 A 級或 B 級區。用於 A 級區的設備及原物料在通過 B 級區時，應予以保護。任何需要例外轉送但未經核准的項目都應經預先核准。其核准應根據製造者的 CCS，實施及記錄適當的風險評估及緩解措施，並應包括由品質保證單位核准的特定消毒及監測計畫。	• Only materials and equipment that have been included on an approved list and assessed during validation of the transfer process, should be transferred into the grade A or grade B areas via an airlock or pass-through hatches. Equipment and materials (intended for use in the grade A area) should be protected when transiting through the grade B area. Any unapproved items that require transfer should be pre-approved as an exception. Appropriate risk assessment and mitigation measures should be applied and recorded as per the manufacturer's CCS and should include a specific disinfection and monitoring programme approved by quality assurance.
b. 傳遞箱應設計為用於保護較高等級的環境，例如主動供應經過濾的空氣進行有效沖洗。	• Pass-through hatches should be designed to protect the higher-grade environment, for example by effective flushing with an active filtered air supply.
c. 原物料或設備從較低等級或未分級區域移動到較高等級潔淨區，應進行與風險相稱並符合 CCS 的清潔及消毒。	• The movement of material or equipment from lower grade or unclassified area to higher grade clean areas should be subject to cleaning and disinfection commensurate with the risk and in line with the CCS.
4.13 對於傳遞箱及氣鎖室（用於原物料及人員），進出之門不應同時開啟。對於通往 A	4.13 For pass-through hatches and airlocks (for material and personnel), the entry and exit doors should not

級及 B 級區域的氣鎖室，應使用互鎖系統。對於通向 C 級及 D 級區域的氣鎖室，應至少使用視覺及/或聽覺警報系統。在需要保持區域隔離的情況下，應建立互鎖門關閉及打開之間的延遲時間。	be opened simultaneously. For airlocks leading to the grade A and grade B areas, an interlocking system should be used. For airlocks leading to grade C and D areas, a visual and/or audible warning system should be operated as a minimum. Where required to maintain area segregation, a time delay between the closing and opening of interlocked doors should be established.
4.14 在所有操作條件下，潔淨室應供應經過濾的空氣，並對較低等級的背景環境保持正壓及/或空氣的流動，並應有效的沖洗該區域。不同等級的相鄰潔淨室應具有最小 10 pa（指引值）的壓差。關鍵區域的保護措施應予特別注意。當需要圍堵某些物質，例如致病性的、高毒性的或放射性的產品、活的病毒或細菌原料時，則可能需要修改有關空氣供應及壓力的建議。修改可能包括配置正壓或負壓氣鎖室，以防止有害物質污染周圍區域。對於某些作業，設施（例如潔淨室及空調）的去污染及潔淨室排氣之處理可能是必須的。在圍堵時，又需要空氣流入關鍵區域的情況下，空氣來源應來自相同或更高等級的區域。	4.14 Cleanrooms should be supplied with a filtered air supply that maintains a positive pressure and/or an airflow relative to the background environment of a lower grade under all operational conditions and should flush the area effectively. Adjacent rooms of different grades should have an air pressure difference of a minimum of 10 Pascals (guidance value). Particular attention should be paid to the protection of the critical zone. The recommendations regarding air supplies and pressures may need to be modified where it is necessary to contain certain materials (e.g. pathogenic, highly toxic or radioactive products or live viral or bacterial materials). The modification may include positively or negatively pressurized airlocks that prevent the hazardous material from contaminating surrounding areas. Decontamination of facilities (e.g. the cleanrooms and the heating, ventilation, and air conditioning (HVAC) systems) and the treatment of air leaving a clean area, may be necessary for some operations. Where containment requires air to flow into a critical zone, the source of the air should be from an area of the same or higher grade.
4.15 潔淨室及區域內的空氣流動型態應可視化，以證明空氣不會從較低等級區域流到較高等級區域，並且空氣不會從較不潔淨的區域（例如地板）或通過作業人員或設備流向潔淨等級較高的區域，將污染轉移到潔淨等級較高的區域。如果需要使用單向氣流，則應進行可視化研究以確認其符合性（參見第 4.4 及 4.19 點）。當充填後，封閉的產品通過一個小出口轉送到相鄰較低等級的潔淨室，氣流可視化研究應證明該空氣不會從較低等級的潔淨室進入 B 級區域。如果空氣流動被證明對清潔區域或關鍵區域有污染風險，則應採取矯正措施，例如改善設計。空氣流動型態研究應於靜態及動態均執行（例如模擬作業人員的介入）。應保留空氣流動型態的錄影紀錄。在建立設施的環境監測計畫時，應文件化及參考空氣可視化研究的結果。	4.15 Airflow patterns within cleanrooms and zones should be visualised to demonstrate that there is no ingress from lower grade to higher grade areas and that air does not travel from less clean areas (such as the floor) or over operators or equipment that may transfer contamination to the higher-grade areas. Where unidirectional airflow is required, visualisation studies should be performed to determine compliance, (see paragraphs 4.4 & 4.19). When filled, closed products are transferred to an adjacent cleanroom of a lower grade via a small egress point, airflow visualization studies should demonstrate that air does not ingress from the lower grade cleanrooms to the grade B area. Where air movement is shown to be a contamination risk to the clean area or critical zone, corrective actions, such as design improvement, should be implemented.

	Airflow pattern studies should be performed both at rest and in operation (e.g. simulating operator interventions). Video recordings of the airflow patterns should be retained. The outcome of the air visualisation studies should be documented and considered when establishing the facility's environmental monitoring programme.
4.16 潔淨室之間及/或隔離裝置與其背景之間應安裝壓差計。在 CCS 中應考慮壓差的設定值及關鍵性。應連續監測及記錄被界定為關鍵處的壓差。應具備警報系統，以立即顯示及警告作業人員任何空氣供應上的失靈或壓差降低（當其低於被界定為關鍵的設定限值時）。警報信號不應在未經評估的情況下被忽略，並且應該有一個程序來說明發出警報信號時要採取的步驟。如果警報設定了延遲通報，則應以 CCS 對其進行評估及合理證明。其他區域的壓差則應定期監測及記錄。	4.16 Indicators of air pressure differences should be fitted between cleanrooms and/or between isolators and their background. Set-points and the criticality of air pressure differences should be considered within the CCS. Air pressure differences identified as critical should be continuously monitored and recorded. A warning system should be in place to instantly indicate and warn operators of any failure in the air supply or reduction of air pressure differences (below set limits for those identified as critical). The warning signal should not be overridden without assessment and a procedure should be available to outline the steps to be taken when a warning signal is given. Where alarm delays are set, these should be assessed and justified within the CCS. Other air pressure differences should be monitored and recorded at regular intervals.
4.17 設施的設計應允許從 A 級及 B 級區域以外的地方觀察生產活動（例如，通過窗戶或遠端攝影機，可以看到該區域及過程的全貌，以允許在不進入的情況下進行觀察及監督）。在設計新設施或整建現有設施時應考慮這一要求。	4.17 Facilities should be designed to permit observation of production activities from outside the grade A and B areas (e.g. through the provision of windows or remote cameras with a full view of the area and processes to allow observation and supervision without entry). This requirement should be considered when designing new facilities or during refurbishment of existing facilities.
屏障技術	**Barrier Technologies**
4.18 隔離裝置或 RABS 是不同的技術，與其相關聯的製程，應設計為將 A 級環境與周圍房間的環境隔離以提供保護。製程中，物品進入或移出所帶來的危害應降到最低，並由高性能轉送技術或經過確效的系統提供支持，這些系統可牢靠地防止污染並適用於所相應的技術（指隔離裝置或 RABS）。	4.18 Isolators or RABS, which are different technologies, and the associated processes, should be designed to provide protection through separation of the grade A environment from the environment of the surrounding room. The hazards introduced from entry or removal of items during processing should be minimized and supported by high capability transfer technologies or validated systems that robustly prevent contamination and are appropriate for the respective technology.
4.19 所用技術及製程的設計應確保在關鍵區域維持適當的條件，以在操作過程中保護暴露的產品。	4.19 The design of the technology and processes used should ensure appropriate conditions are maintained in the critical zone to protect the exposed product during operations.
i. 隔離裝置：	i. Isolators:

a. 開放式隔離裝置的設計應確保 A 級條件，在關鍵區域受到第一手空氣保護，且在製造過程中以單向氣流掠過暴露的產品才再排離。	a. The design of open isolators should ensure grade A conditions with first air protection in the critical zone and unidirectional airflow that sweeps over and away from exposed products during processing.
b. 密閉式隔離裝置的設計應確保 A 級條件，在製造過程中對暴露的產品提供適當保護。在進行簡單操作的密閉式隔離裝置中，氣流可能不是完全單向的。但是，任何擾流型式的氣流都不應增加暴露產品的污染風險。如果整個生產線都涵蓋在密閉式隔離裝置中，則應確保在 A 級條件下，關鍵區域受到第一手空氣保護，並且在製造過程中以單向氣流掠過暴露產品才再排離。	b. The design of closed isolators should ensure grade A conditions with adequate protection for exposed products during processing. Airflow may not be fully unidirectional in closed isolators where simple operations are conducted. However, any turbulent airflow should not increase risk of contamination of the exposed product. Where processing lines are included in closed isolators, grade A conditions should be ensured with first air protection in the critical zone and unidirectional airflow that sweeps over and away from exposed products during processing.
c. 負壓隔離裝置僅應在認為必須對產品（例如放射性藥品）進行圍堵時使用，並且應採取特定的風險控制措施以確保關鍵區域不受影響。	c. Negative pressure isolators should only be used when containment of the product is considered essential (e.g. radiopharmaceutical products) and specialized risk control measures should be applied to ensure the critical zone is not compromised.
ii. 限制進入屏障系統 (RABS)：	ii. RABS:
RABS 的設計應確保 A 級條件，在關鍵區域具有單向氣流及第一手空氣的保護。應維持從關鍵區域到背景環境的正向氣流。	The design of RABS should ensure grade A conditions with unidirectional airflow and first air protection in the critical zone. A positive airflow from the critical zone to the supporting background environment should be maintained.
4.20 隔離裝置或 RABS 的背景環境應確保將污染轉移的風險降至最低。	4.20 The background environment for isolators or RABS should ensure the risk of transfer of contamination is minimized.
i. 隔離裝置：	i. Isolators:
a. 開放式隔離裝置的背景環境一般應至少為 C 級。密閉式隔離裝置的背景應至少為 D 級。背景分級應基於風險評估決定，並在 CCS 中闡明其合理性。	a. The background environment for open isolators should generally correspond to a minimum of grade C. The background for closed isolators should correspond to a minimum of grade D. The decision on the background classification should be based on risk assessment and justified in the CCS.
b. 在對隔離裝置的 CCS 進行風險評估時的主要考慮因素應包括（但不限於）：生物去污染程序、自動化程度、手套操作可能危及關鍵製程點的“第一手空氣”保護的影響、可能損失屏障裝置/手套完整性的影響、使用的轉送機制及作業(諸如	b. Key considerations when performing the risk assessment for the CCS of an isolator should include (but are not limited to); the bio-decontamination programme, the extent of automation, the impact of glove manipulations that may potentially compromise ‘first air’

可能需要在對隔離裝置進行最終生物去污染之前打開門的安裝或維護)。當識別出有額外的製程風險時，除非在 CCS 中適當證明合理性，應考慮使用更高等級的背景。	protection of critical process points, the impact of potential loss of barrier/glove integrity, transfer mechanisms used and activities such as set-up or maintenance that may require the doors to be opened prior to the final bio-decontamination of the isolator. Where additional process risks are identified, a higher grade of background should be considered unless appropriately justified in the CCS.
c. 應進行開放式隔離裝置交界處之空氣流動型態的研究，以證明沒有空氣侵入。	c. Airflow pattern studies should be performed at the interfaces of open isolators to demonstrate the absence of air ingress.
ii. RABS：	ii. RABS:
用於無菌製備的 RABS 的背景環境應至少為 B 級，並且應進行空氣流動型態研究以證明介入期間沒有空氣侵入，適用時，應包括門的開口處。	The background environment for RABS used for aseptic processing, should correspond to a minimum of grade B and airflow pattern studies should be performed to demonstrate the absence of air ingress during interventions, including door openings if applicable.
4.21 用於手套系統（指隔離裝置及 RABS）的材料，應證明具有適當的機械及化學耐受性。手套更換頻率應界定在 CCS 中。	4.21 The materials used for glove systems (for both isolators and RABS) should be demonstrated to have appropriate mechanical and chemical resistance. The frequency of glove replacement should be defined within the CCS.
i. 隔離裝置：	i. Isolators:
a. 對於隔離裝置，手套系統的洩漏測試應使用可證明適用於其任務及重要性的方法進行。應按界定的時間間隔進行測試。 一般來說，手套完整性測試頻率應最少在每批次或連續批生產（campaign）的開始及結束時進行。根據經過確效的連續批生產（campaign）時間長度，可能需要額外的手套完整性測試。手套完整性監測應包括與每次使用及在任何可能影響系統完整性的操作後所進行的目視檢查。對於生產單一單元或小批量的人工無菌製備活動，完整性確認的頻率可能基於其他標準，例如在每一個製造時段的開始及結束時。	a. For isolators, leak testing of the glove system should be performed using a methodology demonstrated to be suitable for the task and criticality. The testing should be performed at defined intervals. Generally glove integrity testing should be performed at a minimum frequency of the beginning and end of each batch or campaign. Additional glove integrity testing may be necessary depending on the validated campaign length. Glove integrity monitoring should include a visual inspection associated with each use and following any manipulation that may affect the integrity of the system. For manual aseptic processing activities where single unit or small batch sizes are produced, the frequency of integrity verification may be based on other criteria, such as the beginning and end of each manufacturing session.
b. 隔離裝置系統的完整性/洩漏測試應按界定的時間間隔進行。	b. Integrity / leak testing of isolator systems should be performed at defined intervals.
ii. RABS：	ii. RABS:

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

	of the product or materials being handled. Appropriate cleanliness levels in the "at rest" and "operational" states should be maintained.
4.24 潔淨室及潔淨空氣設備應使用符合附則 15 要求的方法進行驗證。潔淨室驗證（包括分級）應與操作過程的環境監測清楚區分。	4.24 Cleanrooms and clean air equipment should be qualified using methodology in accordance with the requirements of Annex 15. Cleanroom qualification (including classification) should be clearly differentiated from operational environmental monitoring.
4.25 潔淨室及潔淨空氣設備驗證是評估潔淨室或潔淨空氣設備符合其界定之等級及預期用途的整體過程。作為附則 15 的驗證要求的一部分，潔淨室及潔淨空氣設備的驗證應包括（如果與裝置的設計/操作相關時）：	4.25 Cleanroom and clean air equipment qualification is the overall process of assessing the level of compliance of a classified cleanroom or clean air equipment with its intended use. As part of the qualification requirements of Annex 15, the qualification of cleanrooms and clean air equipment should include (where relevant to the design/operation of the installation):
i. 安裝之過濾系統的洩漏及完整性測試，	i. installed filter system leakage and integrity testing,
ii. 氣流測試 -風量及風速，	ii. airflow tests - volume and velocity,
iii. 壓差測試，	iii. air pressure difference test,
iv. 氣流方向測試及其可視化，	iv. airflow direction test and visualisation,
v. 浮游微生物及表面污染，	v. microbial airborne and surface contamination,
vi. 溫度量測測試，	vi. temperature measurement test,
vii. 相對濕度測試，	vii. relative humidity test,
viii. 回復性測試，	viii. recovery test,
ix. 圍堵洩漏測試。	ix. containment leak test.
潔淨室及潔淨空氣設備的驗證可參考 ISO 14644 系列標準。	Reference for the qualification of the cleanrooms and clean air equipment can be found in the ISO 14644 series of standards.
4.26 潔淨室分級是潔淨室驗證的一部分，是一種透過測量潔淨室或潔淨空氣設備的總微粒濃度，再針對其規格評估空氣潔淨度等級的方法。分級應排定時間執行，以避免對製程或產品品質產生任何影響。例如，初始分級應在模擬操作期間進行，而再分級則在模擬操作期間或在無菌製程模擬 （APS） 期間進行。	4.26 Cleanroom classification is part of the cleanroom qualification and is a method of assessing the level of air cleanliness against a specification for a cleanroom or clean air equipment by measuring the total particle concentration. Classification activities should be scheduled and performed in order to avoid any impact on process or product quality. For example, initial classification should be performed during simulated operations and reclassification performed during simulated operations or during aseptic process simulation (APS).
4.27 對於潔淨室分級，應測量等於或大於 0.5 及 5 μm 的微粒總數。該測量應根據表 1 中規定的限值同時在靜態及在模擬的動態中進行。	4.27 For cleanroom classification, the total of particles equal to or greater than 0.5 and 5 μm should be measured. This measurement should be performed both at rest and in simulated operations in accordance with the limits specified in Table 1.
表 1：用於分級的最大容許總微粒濃度	Table 1: Maximum permitted total particle concentration for classification

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

(a) 依據 CCS 或歷史趨勢，分級時可以考慮包括 5μm 微粒。

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

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

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

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

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

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

4.29 潔淨室分級應在“靜態”及“動態”狀態下進行。

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

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

i. The definition of “at rest” state is the condition whereby the installation of all the utilities is complete including any functioning HVAC, with the main manufacturing equipment installed as specified but not operating and without personnel present in the room.

ii. “動態”狀態的定義：潔淨室的安裝已完成、HVAC 系統全部運行、設備已安裝並在製造廠界定的操作模式下運轉，且有最大人數在場執行或模擬日常操作的情況。

ii. The definition of “in operation” state is the condition where the installation of the cleanroom is complete, the HVAC system fully operational, equipment installed and functioning in the manufacturer’s defined operating mode with the maximum number of personnel present

	performing or simulating routine operational work.
iii. 應在完成操作及清線/清潔活動後的“清除”期間達到上表 1 中所訂“靜態”總微粒限值。“清除”期間（指引值為小於 20 分鐘）應在房間驗證期間確定與記錄。作業中斷時，應依程序執行，以重新回復到已驗證的潔淨狀態。	iii. The total particle limits given in Table 1 above for the “at rest” state should be achieved after a “clean up” period on completion of operations and line clearance/cleaning activities. The "clean up" period (guidance value of less than 20 minutes) should be determined during the qualification of the rooms, documented and adhered to in procedures to reinstate a qualified state of cleanliness if disrupted during operation.
4.30 單向氣流系統供應的風速應在驗證計畫書中明確證明，包括風速測量的位置。風速應予設計、測量及保持，以確保在工作位置有適當的單向空氣流動為產品及開放組件提供保護（例如，發生高風險操作處以及產品及/或組件暴露處）。除非 CCS 另有科學證明，單向氣流系統應在工作位置提供 0.36 – 0.54 m/s 範圍（指引值）內的均勻風速。氣流可視化研究應與風速測量相關。	4.30 The speed of air supplied by unidirectional airflow systems should be clearly justified in the qualification protocol including the location for air speed measurement. Air speed should be designed, measured and maintained to ensure that appropriate unidirectional air movement provides protection of the product and open components at the working position (e.g. where high-risk operations occur and where product and/or components are exposed). Unidirectional airflow systems should provide a homogeneous air speed in a range of 0.36 – 0.54 m/s (guidance value) at the working position, unless otherwise scientifically justified in the CCS. Airflow visualization studies should correlate with the air speed measurement.
4.31 潔淨室的微生物污染程度作為潔淨室驗證的一部分。採樣點的數量應基於文件化的風險評估以及從房間分級、氣流可視化研究以及該區域將要執行的製程與操作的知識所獲得的結果而定。每個級區於驗證期間微生物污染的最大限量見表 2。驗證應包括“靜態”及“動態”兩種狀態。	4.31 The microbial contamination level of the cleanrooms should be determined as part of the cleanroom qualification. The number of sampling locations should be based on a documented risk assessment and the results obtained from room classification, air visualization studies and knowledge of the process and operations to be performed in the area. The maximum limits for microbial contamination during qualification for each grade are given in Table 2. Qualification should include both “at rest” and “in operation” states.
表 2：驗證期間最大容許微生物污染程度	Table 2: Maximum permitted microbial contamination level during qualification

級區	空氣樣品 CFU/m^3	落菌培養皿 (直徑 90 mm) CFU/4 小時 (a)	接觸培養皿 (直徑 55 mm) CFU/培養皿
A	無生長		
B	10	5	5
C	100	50	25
D	200	100	50

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

(a) 落菌培養皿應在操作期間暴露並在最多 4 小時	(a) Settle plates should be exposed for the duration of

後依需要更換。暴露時間應基於復甦研究，且不應使所用的培養基脫水。	operations and changed as required after a maximum of 4 hours. Exposure time should be based on recovery studies and should not allow desiccation of the media used.
註 1：表中針對特定級區列出的所有方法都應用於驗證該特定級區的區域。如果未使用列表中的任何一種方法，或使用了替代方法，則應適當證明所採用的方法是合理的。	Note 1: All methods indicated for a specific grade in the table should be used for qualifying the area of that specific grade. If one of the methods tabulated is not used, or alternative methods are used, the approach taken should be appropriately justified.
註 2：在整份文件中使用 CFU 作為限量的單位。如果使用不同的或新的技術以不同於 CFU 的方式呈現結果，則製造廠應科學地證明該限量的合理性，並在可能的情況下將其與 CFU 相關聯。	Note 2: Limits are applied using CFU throughout the document. If different or new technologies are used that present results in a manner different from CFU, the manufacturer should scientifically justify the limits applied and where possible correlate them to CFU.
註 3：對於人員著衣驗證，應採用表 6 中對接觸培養皿及手套指印的限量。	Note 3: For the qualification of personnel gowning, the limits given for contact plates and glove prints in Table 6 should apply.
註 4：取樣方法不應對製造作業造成污染風險。	Note 4: Sampling methods should not pose a risk of contamination to the manufacturing operations.
4.32 潔淨室及潔淨空氣設備的再驗證應按照規定的程序定期進行。再驗證至少應包括以下內容：	4.32 The requalification of cleanrooms and clean air equipment should be carried out periodically following defined procedures. The requalification should include at a minimum the following:
i. 潔淨室分級（總微粒濃度），	i. cleanroom classification (total particle concentration),
ii. 最終過濾器的完整性測試，	ii. integrity test of final filters,
iii. 風量測量，	iii. airflow volume measurement,
iv. 房室間壓差的確認，	iv. verification of air pressure difference between rooms, and
v. 風速測試	v. air velocity test
（註：對於 B、C 及 D 級，風速測試應根據風險評估進行，並文件化為 CCS 的一部分。但是，對於提供單向氣流的充填區（例如，當充填最終滅菌產品時，或為 A 級區及 RABS 的背景時），風速測試是需要的。對於具有非單向氣流的級區，應以回復性測試的測量替代風速測試）。	(Note: For grade B, C and D the air velocity test should be performed according to a risk assessment documented as part of the CCS. However, it is required for filling zones supplied with unidirectional airflow (e.g. when filling terminally sterilised products or background to grade A and RABS). For grades with non-unidirectional airflow, a measurement of recovery testing should replace velocity testing).
A 級區及 B 級區再驗證的最長時間間隔為 6 個月。	The maximum time interval for requalification of grade A & B areas, is 6 months.
C 級區及 D 級區再驗證的最長時間間隔為 12 個月。	The maximum time interval for requalification of grade C & D areas, is 12 months.

在為矯正不符合規定的設備或設施狀況而實施的補救措施完成後，或在變更設備、設施或製程後(當其適用時)，還應進行至少包括上述試驗的適當再驗證。變更的重要性應由變更管理過程來決定。要考慮的變更範例包括但不限於以下內容：	Appropriate requalification consisting of at least the above tests should also be carried out following completion of remedial action implemented to rectify an out of compliance equipment or facility condition or after changes to equipment, facility or processes as appropriate. The significance of a change should be determined through the change management process. Examples of changes to be considered include but are not limited to the following:
i. 氣流的干擾會影響裝置的運轉。	i. interruption of air movement which affects the operation of the installation,
ii. 改變潔淨室的設計或 HVAC 系統的操作設定參數。	ii. ii. change in the design of the cleanroom or of the operational setting parameters of the HVAC system,
iii. 影響裝置運轉的特殊維護（例如更換最終過濾器）。	iii. special maintenance which affects the operation of the installation (e.g. change of final filters).
消毒	**Disinfection**
4.33 潔淨室的消毒特別重要。應按照書面程序對其進行徹底清潔及消毒。為使消毒有效，應事先進行清潔以去除表面污染。清潔程序應有效去除消毒劑的殘留。應使用一種以上的消毒劑，藉由不同作用方式，以確保其組合使用可有效的對抗細菌及真菌。消毒應包括定期使用殺孢劑。應定期進行監測，以評估消毒程序的有效性並偵測常在菌類型的變化（例如，微生物對目前使用的消毒方案具耐受性）。	4.33 The disinfection of cleanrooms is particularly important. They should be cleaned and disinfected thoroughly in accordance with a written programme. For disinfection to be effective, prior cleaning to remove surface contamination should be performed. Cleaning programmes should effectively remove disinfectant residues. More than one type of disinfecting agent should be employed to ensure that where they have different modes of action, their combined usage is effective against bacteria and fungi. Disinfection should include the periodic use of a sporicidal agent. Monitoring should be undertaken regularly in order to assess the effectiveness of the disinfection programme and to detect changes in types of microbial flora (e.g. organisms resistant to the disinfection regime currently in use).
4.34 消毒過程應經過確效。確效研究應證明消毒劑以特定使用方式在該表面材料類型上或具有代表性的材料（證明合理的情況下）之適用性及有效性，並應支持所製備溶液開封後使用的有效期限。	4.34 The disinfection process should be validated. Validation studies should demonstrate the suitability and effectiveness of disinfectants in the specific manner in which they are used and on the type of surface material, or representative material if justified, and should support the in-use expiry periods of prepared solutions.
4.35 A 級及 B 級區域使用的消毒劑及清潔劑在使用前應是無菌的。依照 CCS 的決定，C 級及 D 級區域中使用的消毒劑也可能需要是無菌的。如果消毒劑及清潔劑是由無菌產品製造廠稀釋/製備，則應以防止污染的方式進行，並應監測微生物污染。稀釋液應保存在事先清潔過的容器中（並在可行的情況下進行滅菌），並且只能在規定的期限內儲存。如果使用“市售現成”之消毒劑及清潔劑在成功完	4.35 Disinfectants and detergents used in grade A and grade B areas should be sterile prior to use. Disinfectants used in grade C and D may also be required to be sterile where determined in the CCS. Where the disinfectants and detergents are diluted / prepared by the sterile product manufacturer, this should be done in a manner to prevent contamination and they should be monitored for microbial contamination. Dilutions should be kept in

成適當的供應商驗證後，可以接受分析證明書或符合性證明書的結果。	previously cleaned containers (and sterilized where applicable) and should only be stored for the defined period. If the disinfectants and detergents are supplied “ready-made” then results from certificates of analysis or conformance can be accepted subject to successful completion of the appropriate vendor qualification.
4.36 當對潔淨室及相關表面使用燻蒸或氣相消毒（例如氣相過氧化氫）時，應了解並確效任何燻蒸劑及分散系統的有效性。	4.36 Where fumigation or vapour disinfection (e.g. Vapour-phase Hydrogen Peroxide) of cleanrooms and associated surfaces are used, the effectiveness of any fumigation agent and dispersion system should be understood and validated.
5 設備 (Equipment)	
5.1 應提供設備設計的書面詳細說明（視情況可包括製程及設備儀表圖示）。這應為初始驗證文件的一部分並須持續更新。	5.1 A written, detailed description of the equipment design should be available (including process and instrumentation diagrams as appropriate). This should form part of the initial qualification package and be kept up to date.
5.2 設備的監測需求應在開發初期於“使用者需求規格”中明訂，並在驗證時予以確認。應確認製程及設備的警報事件並評估其趨勢，應基於其關鍵程度來決定警報的評估頻率（關鍵警報須立即審查）。	5.2 Equipment monitoring requirements should be defined in “user requirements specifications” during early stages of development, and confirmed during qualification. Process and equipment alarm events should be acknowledged and evaluated for trends. The frequency at which alarms are assessed should be based on their criticality (with critical alarms reviewed immediately).
5.3 設備、配件及支援服務之設計與安裝，應儘可能使其作業、維護保養及修理能在潔淨區外執行。如果維護保養必須在潔淨室內進行，且在該維修工作期間未維持所要求之潔淨度及/或無菌性的標準者，則應考慮採取預防措施，例如只限指定人員進入工作區域、制定明確規範的工作計畫書及維護保養程序等，還應考慮額外的清潔、消毒及環境監測。倘設備需要滅菌者，應儘可能在完成組裝後為之。	5.3 As far as practicable, equipment, fittings and services should be designed and installed so that operations, maintenance, and repairs can be performed outside the cleanroom. If maintenance has to be performed in the cleanroom, and the required standards of cleanliness and/or asepsis cannot be maintained, then precautions such as restricting access to the work area to specified personnel, generation of clearly defined work protocols and maintenance procedures should be considered. Additional cleaning, disinfection and environmental monitoring should also be considered. If sterilisation of equipment is required, it should be carried out, wherever possible, after complete reassembly.
5.4 清潔程序應經確效，使其能夠：	5.4 The cleaning process should be validated to be able to:
i. 清除任何會對所用消毒劑的有效性產生不利影響的殘留物或碎屑。	i. remove any residue or debris that would detrimentally impact the effectiveness of the disinfecting agent used,
ii. 在清潔程序中及消毒前儘量減少產品的化學、微生物及微粒污染。	ii. minimize chemical, microbial and particulate contamination of the product during the process and prior to disinfection.

5.5 對於無菌製程，直接及間接接觸產品的組件都應進行滅菌。直接接觸產品的組件是指有產品通過的組件，例如充填針或泵。間接接觸產品組件是指不與產品接觸但可能與其他已滅菌品表面接觸的設備組件，其無菌性對整體產品的無菌性至關重要（例如，膠塞貯盆與導軌，以及已滅菌組件等已滅菌物品）。	5.5 For aseptic processes, direct and indirect product contact parts should be sterilised. Direct product contact parts are those that the product passes through, such as filling needles or pumps. Indirect product contact parts are equipment parts that do not contact the product, but may come into contact with other sterilised surfaces, the sterility of which is critical to the overall product sterility (e.g. sterilised items such as stopper bowls and guides, and sterilised components).
5.6 所有設備，如滅菌器、空氣處理系統（包括空氣過濾）及水系統都應經過驗證、監測及有計劃地維護保養。維護保養完成後，經核可方可恢復使用。	5.6 All equipment such as sterilisers, air handling systems (including air filtration) and water systems should be subject to qualification, monitoring and planned maintenance. Upon completion of maintenance, their return to use should be approved.
5.7 對產品無菌性至關重要的設備進行計劃外維護保養時，其對產品無菌性的潛在影響應進行評估並予以記錄。	5.7 Where unplanned maintenance of equipment critical to the sterility of the product is to be carried out, an assessment of the potential impact to the sterility of the product should be performed and recorded.
5.8 輸送帶不得通過介於 A 級或 B 級區與較低空氣潔淨度之作業區間的隔板/隔牆，除非該輸送帶本身是持續地滅菌的（例如：在滅菌的隧道中）。	5.8 A conveyor belt should not pass through a partition between a grade A or B area and a processing area of lower air cleanliness, unless the belt itself is continually sterilised (e.g. in a sterilising tunnel).
5.9 微粒計數器，包括採樣管，應經過驗證。對於管徑及彎曲半徑，應考慮製造商建議的規格。除非有正當理由，否則其管長通常不應超過 1 公尺，並且應儘量減少彎曲的次數。應使用具短取樣管的手提式微粒計數器進行潔淨度分級。單向氣流系統中，應使用等速採樣頭（isokinetic sample heads）。它們應以適當方向安置並盡可能靠近關鍵位置，以確保樣本具有代表性。	5.9 Particle counters, including sampling tubing, should be qualified. The manufacturer's recommended specifications should be considered for tube diameter and bend radii. Tube length should typically be no longer than 1m unless justified and the number of bends should be minimized. Portable particle counters with a short length of sample tubing should be used for classification purposes. Isokinetic sampling heads should be used in unidirectional airflow systems. They should be oriented appropriately and positioned as close as possible to the critical location to ensure that samples are representative.
6 公用設施 (Utilities)	
6.1 公用設施系統其管制的性質及程度應與該公用設施相關的產品品質風險相稱。其影響應經由風險評估確定，並將其文件化作為 CCS 的一部分。	6.1 The nature and extent of controls applied to utility systems should be commensurate with the risk to product quality associated with the utility. The impact should be determined via a risk assessment and documented as part of the CCS.
6.2 一般來說，有較高風險的公用設施如下：	6.2 In general, higher risk utilities are those that:
i. 直接接觸產品的公用設施，例如用於洗滌及潤洗的水、用於滅菌的氣體及蒸汽，	i. directly contact product e.g. water for washing and rinsing, gases and steam for sterilisation,
ii. 最終將成為產品一部分的接觸物，	ii. contact materials that will ultimately become part of the product,
iii. 其接觸面會與產品接觸者，	iii. contact surfaces that come into contact with the

	product,
iv. 其它直接影響產品者。	iv. otherwise directly impact the product.
6.3 公用設施的設計、安裝、驗證、操作、維護及監測應確保公用設施系統如預期運作。	6.3 Utilities should be designed, installed, qualified, operated, maintained and monitored in a manner to ensure that the utility system functions as expected.
6.4 高風險公用設施的關鍵參數及關鍵品質屬性的結果應定期進行趨勢分析，以確保系統維持適當能力。	6.4 Results for critical parameters and critical quality attributes of high risk utilities should be subject to regular trend analysis to ensure that system capabilities remain appropriate.
6.5 公用設施系統的安裝紀錄應在該系統的整個生命週期內予以保存。此類紀錄應包括現行圖及示意圖、建築材料清單及系統規格。通常，重要資訊包括以下項目：	6.5 Records of utility system installation should be maintained throughout the system's life-cycle. Such records should include current drawings and schematic diagrams, construction material lists and system specifications. Typically, important information includes attributes such as:
i. 管道流向、坡度、直徑及長度，	i. pipeline flow direction, slopes, diameter and length,
ii. 桶槽及容器的詳細資訊，	ii. tank and vessel details,
iii. 閥門、過濾器、排水管、採樣點及使用點，	iii. valves, filters, drains, sampling and user points,
6.6 管線、管道及其他公用設施不應出現在潔淨室中。如果不可避免，則其安裝應使其不產生凹處、未密封的開口及難以清潔的表面。管線的安裝應允許其外表面的清潔及消毒。	6.6 Pipes, ducts and other utilities should not be present in cleanrooms. If unavoidable, then they should be installed so that they do not create recesses, unsealed openings and surfaces which are difficult to clean. Installation should allow cleaning and disinfection of outer surface of the pipes.
水系統	**Water systems**
6.7 水處理設施及輸送系統，應經設計、建造、安裝、試運轉、驗證、監測及維護保養以防止微生物污染並確保具有適當品質的可靠水源。應採取措施將微粒、微生物污染/增殖及內毒素/熱原存在的風險降至最低（例如有斜度的管道以提供完全排水及避免盲管）。如果系統中包含過濾器，則應特別注意對其進行監測及維護保養。所產製的水應符合現行相關藥典的個論。	6.7 Water treatment plant and distribution systems should be designed, constructed, installed, commissioned, qualified, monitored and maintained to prevent microbiological contamination and to ensure a reliable source of water of an appropriate quality. Measures should be taken to minimize the risk of presence of particulates, microbial contamination/proliferation and endotoxin/pyrogen (e.g. sloping of piping to provide complete drainage and the avoidance of dead legs). Where filters are included in the system, special attention should be given to their monitoring and maintenance. Water produced should comply with the current monograph of the relevant Pharmacopeia.
6.8 水系統應經過驗證及確效，以保持適當的物理、化學及微生物管制程度，同時要考慮到季節變化的影響。	6.8 Water systems should be qualified and validated to maintain the appropriate levels of physical, chemical and microbial control, taking the effect of seasonal variation into account.
6.9 在輸水系統管線中水流應保持亂流，以儘量減少微生物粘附及隨後形成生物膜的風險。應在驗證期間確定流速並定期監測。	6.9 Water flow should remain turbulent through the pipes in water distribution systems to minimize the risk of microbial adhesion, and subsequent biofilm

	formation. The flow rate should be established during qualification and be routinely monitored.
6.10 注射用水 (WFI) 應使用符合驗證過程中規定規格的水生產，並以微生物生長風險最小的方式儲存及輸送（例如在 70 ℃ 以上恆定循環）。WFI 應透過蒸餾或等同於蒸餾的純化製程生產。這可能包括逆滲透搭配其他適當的技術，例如電去離子 (EDI)、超過濾或奈米過濾。	6.10 Water for injections (WFI) should be produced from water meeting specifications that have been defined during the qualification process, stored and distributed in a manner which minimizes the risk of microbial growth (e.g. by constant circulation at a temperature above 70°C). WFI should be produced by distillation or by a purification process that is equivalent to distillation. This may include reverse osmosis coupled with other appropriate techniques such as electrodeionization (EDI), ultrafiltration or nanofiltration.
6.11 WFI 儲桶配備疏水性細菌滯留通氣過濾器時，過濾器不應成為污染源，並且在安裝前及使用後測試過濾器的完整性。應採取管制措施（例如加熱）以防止過濾器上形成冷凝水。	6.11 Where WFI storage tanks are equipped with hydrophobic bacteria retentive vent filters, the filters should not be a source of contamination and the integrity of the filter tested before installation and after use. Controls should be in place to prevent condensation formation on the filter (e.g. by heating).
6.12 為儘量減少生物膜形成的風險，水系統的滅菌、消毒或再生應按照預定的時間表進行，並且作為超出限值或規格後的補救措施。使用化學品對水系統進行消毒後，應執行經過確效的潤洗/沖洗程序，並應在消毒/再生後對水進行測試。在水系統恢復使用之前，其化學試驗結果應獲得核准，且其微生物/內毒素結果應在使用本系統中的水所生產的批次產品被認可/放行前經確認符合規格並獲得核准。	6.12 To minimize the risk of biofilm formation, sterilisation, disinfection or regeneration of water systems should be carried out according to a predetermined schedule and as a remedial action following out-of-limit or specification results. Disinfection of a water system with chemicals should be followed by a validated rinsing/flushing procedure. Water should be tested after disinfection/regeneration. Chemical testing results should be approved before the water system is returned to use and microbiological/endotoxin results verified to be within specification and approved before batches manufactured using water from the system are considered for certification/release.
6.13 應執行定期持續的水系統化學及微生物監測，以確保水持續符合藥典規格。警戒值應以初始驗證數據為基礎，然後根據隨後的再驗證、例行監測及調查期間獲得的數據定期重新評估。應對持續監測數據進行審查，以識別出系統在性能上的任何不利趨勢。採樣計畫應反映 CCS 的要求，並應在指定的時間間隔內涵蓋所有出水口及使用點，以確保定期獲取有代表性的水樣進行分析。採樣計畫應基於驗證數據，且應考慮潛在最差狀況的採樣位置，並應確保每天至少包含一個用於製造過程的代表性水樣。	6.13 Regular ongoing chemical and microbial monitoring of water systems should be performed to ensure that the water continues to meet compendial expectations. Alert levels should be based on the initial qualification data and thereafter periodically reassessed on data obtained during subsequent re-qualifications, routine monitoring, and investigations. Review of ongoing monitoring data should be carried out to identify any adverse trend in system performance. Sampling programmes should reflect the requirements of the CCS and should include all outlets and points of use, at a specified interval, to ensure that representative water samples are obtained for analysis on a regular basis. Sample plans should be based on the qualification data, should consider the

	potential worst case sampling locations and should ensure that at least one representative sample is included every day of the water that is used for manufacturing processes.
6.14 偏離警戒值應予文件化及審查，並調查以確定該偏離是否為單一（獨立的）事件，或者其結果是否顯示存在不良趨勢或系統劣化。每次偏離行動值都應調查，以確定可能的根本原因以及由於使用該水而對產品品質及製造過程的任何潛在影響。	6.14 Alert level excursions should be documented and reviewed, and include an investigation to determine whether the excursion is a single (isolated) event or if results are indicative of an adverse trend or system deterioration. Each action limit excursion should be investigated to determine the probable root causes and any potential impact on the quality of products and manufacturing processes as a result of the use of the water.
6.15 WFI 系統應包括連續監測系統，例如總有機碳 (TOC) 及導電度，因為與非連續採樣相比，這些系統可以更好地指示整體系統性能。傳感器設置的位置應基於風險。	6.15 WFI systems should include continuous monitoring systems such as Total Organic Carbon (TOC) and conductivity, as these may give a better indication of overall system performance than discrete sampling. Sensor locations should be based on risk.
蒸汽作為直接滅菌劑	**Steam used as a direct sterilising agent**
6.16 純蒸汽（清潔蒸汽）產生器的給水應適當純化。純蒸汽產生器的設計、驗證及操作方式應確保產生的蒸汽品質符合界定的化學及內毒素標準。	6.16 Feed water to a pure steam (clean steam) generator should be appropriately purified. Pure steam generators should be designed, qualified and operated in a manner to ensure that the quality of steam produced meets defined chemical and endotoxin levels.
6.17 用於直接滅菌的蒸汽應具有合適的品質，並且不應含有可能導致產品或設備污染的添加物。對於提供純蒸汽直接對材料或產品接觸表面（例如多孔硬質高壓滅菌器裝載）進行滅菌的純蒸汽產生器，其蒸汽冷凝水應符合現行相關藥典 WFI 的個論（蒸汽冷凝水不強制要求微生物測試）。應制定適當的取樣計劃，以確保定期獲得具有代表性的純蒸汽進行分析。用於滅菌的純蒸汽在其他的品質方面則應根據經過確效的參數定期評估。這些參數應包括以下（除非另有合理理由）：不凝氣體、乾燥度及過熱度。	6.17 Steam used as a direct sterilising agent should be of suitable quality and should not contain additives at a level which could cause contamination of product or equipment. For a generator supplying pure steam used for the direct sterilisation of materials or product-contact surfaces (e.g. porous / hard-good autoclave loads), steam condensate should meet the current monograph for WFI of the relevant Pharmacopeia (microbial testing is not mandatory for steam condensate). A suitable sampling schedule should be in place to ensure that representative pure steam is obtained for analysis on a regular basis. Other aspects of the quality of pure steam used for sterilisation should be assessed periodically against validated parameters. These parameters should include the following (unless otherwise justified): non-condensable gases, dryness value (dryness fraction) and superheat.
氣體及真空系統	**Gases and vacuum systems**
6.18 與產品/主要容器表面直接接觸的氣體應具有適當的化學、微粒及微生物的品質。包括油及水含量等所有相關參數應予規定，並考慮氣體的用途、類型及氣體產生系統的設計；	6.18 Gases that come in direct contact with the product/primary container surfaces should be of appropriate chemical, particulate and microbial quality. All relevant parameters, including oil and

如另有現行相關藥典的個論或產品品質要求，亦應符合之。	water content, should be specified, taking into account the use and type of the gas, the design of the gas generation system and, where applicable, comply with the current monograph of the relevant Pharmacopeia or the product quality requirement.
6.19 無菌製程中使用的氣體應在使用點通過滅菌級過濾器（孔徑最大為 0.22 μm）進行過濾。如果過濾器以批次為基礎使用（例如，用於過濾覆蓋無菌充填產品的氣體）或作為產品容器的通氣過濾器，則應對過濾器進行完整性測試，並將結果作為批次認可/放行過程的一部分進行審查。位於最末段的滅菌過濾器之後的任何傳輸管道或管線都應進行滅菌。當氣體用於製程中時，應在使用點定期對氣體進行微生物監測。	6.19 Gases used in aseptic processes should be filtered through a sterilising grade filter (with a nominal pore size of a maximum of 0.22 μm) at the point of use. Where the filter is used on a batch basis (e.g. for filtration of gas used for overlay of aseptically filled products) or as product vessel vent filter, then the filter should be integrity tested and the results reviewed as part of the batch certification/release process. Any transfer pipework or tubing that is located after the final sterilising grade filter should be sterilised. When gases are used in the process, microbial monitoring of the gas should be performed periodically at the point of use.
6.20 當真空或壓力系統的回流對產品構成潛在風險，該系統關閉時應有防止回流的機制。	6.20 Where backflow from vacuum or pressure systems poses a potential risk to the product, there should be mechanism(s) to prevent backflow when the vacuum or pressure system is shut off.
加熱、冷卻及液壓系統	**Heating and cooling and hydraulic systems**
6.21 與液壓、加熱及冷卻系統相關的主要設備項目，應盡可能位於充填室外。應有適當的管制措施來圍堵與系統流體相關的任何溢出及/或交叉污染。	6.21 Major items of equipment associated with hydraulic, heating and cooling systems should, where possible, be located outside the filling room. There should be appropriate controls to contain any spillage and/or cross contamination associated with the system fluids.
6.22 這些系統的任何洩漏可能對產品構成風險，都應該是可偵測的（例如洩漏指示系統）。	6.22 Any leaks from these systems that would present a risk to the product should be detectable (e.g. an indication system for leakage).
7 組織與人事 (Personnel)	
7.1 製造廠在無菌產品的製造及檢驗應確保有足夠的適當人員，適當的資格、訓練及經驗，以及在製造作業所使用的任何特定製造技術，以確保符合適用於製造及處理無菌產品的 GMP。	7.1 The manufacturer should ensure that there are sufficient appropriate personnel, suitably qualified, trained and experienced in the manufacture and testing of sterile products, and any of the specific manufacturing technologies used in the site's manufacturing operations, to ensure compliance with GMP applicable to the manufacture and handling of sterile products.
7.2 應僅有所需之最少人員可在潔淨室。應在初始驗證及 APS 等活動中確定、記錄及考慮潔淨室作業人員的最大數量，以免影響無菌保證。	7.2 Only the minimum number of personnel required should be present in cleanrooms. The maximum number of operators in cleanrooms should be determined, documented and considered during activities such as initial qualification and APS, so as not to compromise sterility assurance.
7.3 所有人員，包括從事清潔、維修保養、監測及進入潔淨室的人員，都應接受定期訓練、	7.3 All personnel including those performing cleaning, maintenance, monitoring and those that access

著衣驗證及與有關正確製造無菌產品之規範的評估。該訓練應包含衛生以及微生物學的基本原理，還應特別關注潔淨室的作業、污染管制、無菌技術及無菌產品的保護（針對進入 B 級潔淨室及/或介入 A 級潔淨區的作業人員）以及如果產品不能達到無菌時，可能對患者造成的潛在安全影響。訓練應基於人員工作的職能及場地的關鍵程度。	cleanrooms should receive regular training, gowning qualification and assessment in disciplines relevant to the correct manufacture of sterile products. This training should include the basic elements of microbiology and hygiene, with a specific focus on cleanroom practices, contamination control, aseptic techniques and the protection of sterile products (for those operators entering the grade B cleanrooms and/or intervening into grade A) and the potential safety implications to the patient if the product is not sterile. The level of training should be based on the criticality of the function and area in which the personnel are working.
7.4 進入 A 級及 B 級區域的人員應接受無菌更衣及無菌行為的訓練。無菌更衣程序的遵循性應予評估確認，並至少每年定期再評估確認，且應包括目視及微生物評估（採用的監測位置，包括如戴手套的手指、前臂、胸部及頭罩（面罩/前額）等。其預期的限值參見第 9.30 點）。應僅限於已通過更衣評估並參加過成功的 APS 之適當合格人員，可不受監督進入正在或將要進行無菌操作的 A 級及 B 級區域。	7.4 The personnel accessing grade A and B areas should be trained for aseptic gowning and aseptic behaviours. Compliance with aseptic gowning procedures should be confirmed by assessment and periodic reassessment at least annually, and should involve both visual and microbial assessment (using monitoring locations such as gloved fingers, forearms, chest and hood (facemask / forehead). See paragraph 9.30 for the expected limits). The unsupervised access to the grade A and grade B areas where aseptic operations are or will be conducted should be restricted to appropriately qualified personnel, who have passed the gowning assessment and have participated in a successful APS.
7.5 未符合資格認證之人員不得進入作業中的 B 級潔淨室或 A 級區。如果在特殊情況下有此需要，製造廠應制定書面程序，概述將未符合資格認證之人員帶入 B 級及 A 級區域的過程。在未符合資格認證人員的活動期間，由製造廠授權的人員應對其進行監督，並應評估這些活動對區域潔淨度的影響。這些人員的進入應根據 PQS 進行評估及記錄。	7.5 Unqualified personnel should not enter grade B cleanrooms or grade A in operation. If needed in exceptional cases, manufacturers should establish written procedures outlining the process by which unqualified personnel are brought into the grade B and A areas. An authorized person from the manufacturer should supervise the unqualified personnel during their activities and should assess the impact of these activities on the cleanliness of the area. Access by these persons should be assessed and recorded in accordance with the PQS.
7.6 應建立取消人員在潔淨室工作資格或取消其不受監督進入潔淨室資格的系統，這是基於多方面的考慮，這包括持續的評估及/或來自人員監測規劃中識別出的不良趨勢及/或涉及 APS 失敗。一旦被取消資格，在允許作業人員進一步參與無菌操作之前，應完成再訓練及資格再認證。對於會進入 B 級潔淨室或對 A 級區進行介入的作業人員，其再認證應考慮包括參與過一次成功的 APS。	7.6 There should be systems in place for the disqualification of personnel from working in or given unsupervised entry into cleanrooms that is based on aspects including ongoing assessment and/or identification of an adverse trend from the personnel monitoring programme and/or after being implicated in a failed APS. Once disqualified, retraining and requalification should be completed before permitting the operator to have any further involvement in aseptic practices. For operators

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

且還在其規定的保持時間內，並且在使用前還要經過目視檢查以確保包裝是完整的。可重複使用的服裝（包括眼罩），如果發現損壞，應予以更換，或以驗證試驗期間所確定的預定頻率予以更換。服裝的驗證應考慮任何必要的服裝測試要求，包括僅通過目視檢查可能無法識別的服裝損壞。	for cleanliness and integrity immediately prior to and after gowning. Gown integrity should also be checked upon exit. For sterilised garments and eye coverings, particular attention should be taken to ensure they have been subject to the sterilisation process, are within their specified hold time and that the packaging is visually inspected to ensure it is integral before use. Reusable garments (including eye coverings) should be replaced if damage is identified, or at a set frequency that is determined during qualification studies. The qualification of garments should consider any necessary garment testing requirements, including damage to garments that may not be identified by visual inspection alone.
7.12 選擇的衣著應能限制由於作業人員的移動而釋出脫落物。	7.12 Clothing should be chosen to limit shedding due to operators' movement.
7.13 每一潔淨等級區所要求之典型衣著，其說明如下：	7.13 A description of typical clothing required for each cleanliness grade is given below:
i. B 級（包括進入/介入 A 級區）：在無菌衣更衣前應穿著專用的適當服裝（參見第 7.14 點）。在穿戴經過滅菌的衣服時，應戴上經適當滅菌的、未沾粉末的橡皮或塑膠手套。無菌頭套應將所有毛髮（包括面部毛髮）包覆起來，如果其與服裝的其餘部分是分開的，則應將其末端塞入無菌服的領子內。應佩戴無菌面罩及無菌眼罩（例如護目鏡）以覆蓋及包覆所有面部皮膚，並防止液滴及微粒脫落。應穿著適當的滅菌鞋類（例如套靴）。褲管底端應塞在鞋內。衣服的袖口應塞進第二雙無菌手套中，該手套應戴在穿無菌衣時戴的那雙手套上。此類防護服應儘量減少纖維或微粒的脫落，並可將由身體脫落的微粒保留在防護服內。服裝的微粒脫落性及微粒保留效率應在服裝驗證試驗期間予以評估。服裝的包裝及摺疊方式應允許作業人員在不接觸服裝外表面的情況下穿上，並防止其接觸到地板。	i. Grade B (including access / interventions into grade A): appropriate garments that are dedicated for use under a sterilised suit should be worn before gowning (see paragraph 7.14). Appropriately sterilised, non-powdered, rubber or plastic gloves should be worn while donning the sterilised garments. Sterile headgear should enclose all hair (including facial hair) and where separate from the rest of the gown, it should be tucked into the neck of the sterile suit. A sterile facemask and sterile eye coverings (e.g. goggles) should be worn to cover and enclose all facial skin and prevent the shedding of droplets and particles. Appropriate sterilised footwear (e.g. over-boots) should be worn. Trouser legs should be tucked inside the footwear. Garment sleeves should be tucked into a second pair of sterile gloves worn over the pair worn while donning the gown. The protective clothing should minimize shedding of fibres or particles and retain particles shed by the body. The particle shedding and the particle retention efficiencies of the garments should be assessed during the garment qualification. Garments should be packed and folded in such a way as to allow operators to don the gown without contacting the outer surface of the garment and to prevent the garment from touching the floor.
ii. C 級：頭髮，面部及口部所有蓄留之鬍鬚，應予覆蓋。應穿著在腕部收緊及高領的單件式或兩件式褲套裝，及適當且	ii. Grade C: Hair, beards and moustaches should be covered. A single or two-piece trouser suit gathered at the wrists and with high neck and

經過消毒的鞋子或鞋套。衣著應可儘量減少纖維及微粒的脫落。	appropriately disinfected shoes or overshoes should be worn. They should minimize the shedding of fibres and particles.
iii. D 級：頭髮，面部及口部所有蓄留之鬍鬚，應予覆蓋。應穿著一般保護套裝及適當消毒的鞋子或鞋套。為避免任何來自潔淨區外的污染物，應採取適當的措施。	iii. Grade D: Hair, beards and moustaches should be covered. A general protective suit and appropriately disinfected shoes or overshoes should be worn. Appropriate measures should be taken to avoid any ingress of contaminants from outside the clean area.
iv. 即使在 C 級及 D 級區，進行由 CCS 所界定的具有污染風險的活動時，可能會需要額外穿戴手套及口罩。	iv. Additional gowning including gloves and facemask may be required in grade C and D areas when performing activities considered to be a contamination risk as defined by the CCS.
7.14 潔淨室著衣應在適當潔淨等級的更衣室內進行，以確保防護服的潔淨度可以被維持。廠外衣著包括襪子在內(個人內衣除外），不應帶入直接通往 B 級及 C 級區域的更衣室中。在進入 B 級及 C 級更衣室之前，應穿著覆蓋手臂及腿部全長的一件式或兩件式廠服，以及覆蓋足部的廠襪。廠服及廠襪不應對更衣區或製程存在污染風險。	7.14 Cleanroom gowning should be performed in change rooms of an appropriate cleanliness grade to ensure gown cleanliness is maintained. Outdoor clothing including socks (other than personal underwear) should not be brought into changing rooms leading directly to grade B and C areas. Single or two-piece facility trouser suits, covering the full length of the arms and the legs, and facility socks covering the feet, should be worn before entry to change rooms for grades B and C. Facility suits and socks should not present a risk of contamination to the gowning area or processes.
7.15 每個進入 B 級或 A 級區的作業人員在每次進入時，都應穿上適當尺寸的乾淨、經滅菌的防護服裝（包括眼罩及口罩）。無菌服在一個輪班期間內，更換之前的最長穿戴時間應作為服裝驗證的一部分予以界定。	7.15 Every operator entering grade B or A areas should gown into clean, sterilised protective garments (including eye coverings and masks) of an appropriate size at each entry. The maximum period for which the sterilised gown may be worn before replacement during a shift should be defined as part of the garment qualification.
7.16 作業期間應定期消毒手套。如果服裝及手套損壞並存在任何污染產品的風險，應立即更換。	7.16 Gloves should be regularly disinfected during operations. Garments and gloves should be changed immediately if they become damaged and present any risk of product contamination.
7.17 可重複使用的潔淨區衣著應在與生產作業充分隔離的洗衣房中清洗，應使用經過驗證的程序，確保衣著在重複的洗衣過程中不會損壞及/或被纖維或微粒污染。所使用的洗衣設施不應引入污染或交叉污染的風險。衣著的不當處理及使用可能會損壞纖維並增加微粒脫落的風險。洗滌後及包裝前，應目視檢查服裝的損壞及其清潔度。服裝管理過程應作為服裝驗證計畫的一部分進行評估及訂定，並應包括洗衣及滅菌的次數上限。	7.17 Reusable clean area clothing should be cleaned in a laundry facility adequately segregated from production operations, using a qualified process ensuring that the clothing is not damaged and/or contaminated by fibres or particles during the repeated laundry process. Laundry facilities used should not introduce risk of contamination or cross-contamination. Inappropriate handling and use of clothing may damage fibres and increase the risk of shedding of particles. After washing and before packing, garments should be visually inspected for damage and visual cleanliness. The garment

	management processes should be evaluated and determined as part of the garment qualification programme and should include a maximum number of laundry and sterilisation cycles.
7.18 在潔淨區的活動如對生產過程不重要，則應儘量減少，特別是在無菌作業進行時。人員的移動應緩慢、受控且有序的，以避免由於過度劇烈的活動而造成微粒及微生物的過度脫落。執行無菌操作的作業人員應全程遵循無菌操作技術，以防止氣流變化，從而將品質較低的空氣引入關鍵區域。鄰接關鍵區域的移動應予以限制，並應避免單向氣流(第一手空氣)的路徑受阻。對氣流可視化研究的回顧應被視為訓練計畫的一部分。	7.18 Activities in clean areas that are not critical to the production processes should be kept to a minimum, especially when aseptic operations are in progress. Movement of personnel should be slow, controlled and methodical to avoid excessive shedding of particles and organisms due to over-vigorous activity. Operators performing aseptic operations should adhere to aseptic technique at all times to prevent changes in air currents that may introduce air of lower quality into the critical zone. Movement adjacent to the critical zone should be restricted and the obstruction of the path of the unidirectional (first air) airflow should be avoided. A review of airflow visualisation studies should be considered as part of the training programme.
8 生產及特定技術 (Production and Specific Technologies)	
最終滅菌產品	**Terminally sterilised products**
8.1 組件及原物料的製備至少應在 D 級潔淨室中進行，以降低微生物、內毒素/熱原及微粒污染的風險，使產品適合滅菌。當產品處於高風險或異常風險的微生物污染中(例如，產品會促進微生物生長，產品必須在充填前長時間保存，或產品大部分未在密閉容器中加工），則至少應在 C 級環境中製備。軟膏劑、乳膏劑、懸液劑及乳劑的製備在最終滅菌前應至少在 C 級環境中進行。	8.1 Preparation of components and materials should be performed in at least a grade D cleanroom in order to limit the risk of microbial, endotoxin/pyrogen and particle contamination, so that the product is suitable for sterilisation. Where the product is at a high or unusual risk of microbial contamination (e.g. the product actively supports microbial growth, the product must be held for long periods before filling or the product is not processed mostly in closed vessels), then preparation should be carried out in at least a grade C environment. Preparation of ointments, creams, suspensions and emulsions should be carried out in at least a grade C environment before terminal sterilisation. Specific guidance regarding terminally sterilised veterinary medicinal products can be found within Annex 4 of the GMP Guide.
8.2 直接包裝容器及組件應使用經過確效的程序清潔，以確保微粒、內毒素/熱原及負荷菌的污染被適當控制。	8.2 Primary packaging containers and components should be cleaned using validated processes to ensure that particle, endotoxin/pyrogen and bioburden contamination is appropriately controlled.
8.3 最終滅菌產品的充填，應至少在 C 級環境中進行。	8.3 Filling of products for terminal sterilisation should be carried out in at least a grade C environment.
8.4 當經過 CCS 確認產品存在異常的環境污染風險，例如，充填作業緩慢、容器為廣口、或在密封前必須暴露數秒鐘以上之時間，則產品應在 A 級區充填，充填背景至少為 C 級。	8.4 Where the CCS identifies that the product is at an unusual risk of contamination from the environment because, for example, the filling operation is slow, the containers are wide necked or are necessarily exposed for more than a few seconds before closing, then the

	product should be filled in grade A with at least a grade C background.
8.5 半製品溶液的操作應包括過濾步驟，於可能的情況下，在充填到最終產品的容器之前使用微生物滯留過濾器以減少負荷菌及微粒之含量；並且在製備及充填之間應訂定容許的最長時間。	8.5 Processing of the bulk solution should include a filtration step with a microorganism retaining filter, where possible, to reduce bioburden levels and particles prior to filling into the final product containers and there should be a maximum permissible time between preparation and filling.
8.6 表 3 中提供在不同級區的作業範例。	8.6 Examples of operations to be carried out in the various grades are given in Table 3
表 3：製備及加工最終滅菌之作業及級區範例 **A 級區** - 當產品的充填處於異常風險時。 **C 級區** - 當溶液的調製處於異常風險時。 - 產品的充填。 **D 級區** - 供後續充填溶液的製備及組件之準備。	Table 3: Examples of operations and grades for terminally sterilised preparation and processing operations **Grade A** - Filling of products, when unusually at risk. **Grade C** - Preparation of solutions, when unusually at risk. - Filling of products. **Grade D** - Preparation of solutions and components for subsequent filling.
無菌製備及操作	**Aseptic preparation and processing**
8.7 應明確界定無菌製程。應識別、評估及適當管制與無菌製程相關的風險以及要求。工廠的 CCS 應明確界定這些管制措施的允收標準、監控要求及其有效性審查。應描述及實施管制這些風險的方法及程序。應正式記錄被接受的殘留風險。	8.7 The aseptic process should be clearly defined. The risks associated with the aseptic process, and any associated requirements, should be identified, assessed and appropriately controlled. The site's CCS should clearly define the acceptance criteria for these controls, requirements for monitoring and the review of their effectiveness. Methods and procedures to control these risks should be described and implemented. Accepted residual risks should be formally documented.
8.8 無菌環境的製備過程中，在所有作業階段（包括半製品在滅菌之前及之後的階段），以及直到產品被密封在最終容器，應根據藥廠的 CCS 採取預防措施，以儘量減少微生物、內毒素/熱原及微粒之污染。潔淨室中應儘量減少容易產生微粒及纖維的材料存在。	8.8 Precautions to minimize microbial, endotoxin/pyrogenic and particle contamination should be taken, as per the site's CCS, during the preparation of the aseptic environment, during all processing stages (including the stages before and after bulk product sterilisation), and until the product is sealed in its final container. The presence of materials liable to generate particles and fibres should be minimized in cleanrooms.
8.9 在可能的情況下，應考慮使用 RABS、隔離裝置或其他系統等設備，以減少對 A 級區之關鍵介入的需要，並將污染風險降至最低。也可以考量機器人及製程自動化的技術來消除直接人為的關鍵介入（例如乾熱隧道、凍乾機自動裝載、原位滅菌）。	8.9 Where possible, the use of equipment such as RABS, isolators or other systems, should be considered in order to reduce the need for critical interventions into grade A and to minimize the risk of contamination. Robotics and automation of processes can also be considered to eliminate direct human critical interventions (e.g. dry heat tunnel, automated lyophilizer loading, sterilisation in place).
8.10 表 4 列出在各種級區環境下進行的作業範例。	8.10 Examples of operations to be carried out in the various environmental grades are given in Table 4.

表 4：在各種不同級區從事無菌製備及加工作業之範例

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

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

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

8.11 對於最終配方無法過濾的無菌產品，應考慮以下因素：	8.11 For sterile products where the final formulation cannot be filtered, the following should be considered
i. 所有與產品及組件接觸的設備在使用前都應進行滅菌。	i. all product and component contact equipment should be sterilised prior to use,
ii. 所有原料或半製品均應滅菌並以無菌操作方式添加。	ii. all raw materials or intermediates should be sterilised and aseptically added,
iii. 待分裝之溶液或半製品應滅菌。	iii. bulk solutions or intermediates should be sterilised.
8.12 與產品直接或間接接觸的已滅菌設備、組件及輔助物品之拆封、組裝及準備，應被視為無菌操作，並在具有 B 級背景的 A 級區中進行。無菌產品的充填線組裝及充填應視為無菌操作，並在具有 B 級背景的 A 級區中進行。在使用隔離裝置的情況下，背景應符合第 4.20 點。	8.12 The unwrapping, assembly and preparation of sterilised equipment, components and ancillary items with direct or indirect product contact should be treated as an aseptic process and performed in grade A with a grade B background. The filling line set-up and filling of the sterile product should be treated as an aseptic process and performed in grade A with a grade B background. Where an isolator is used, the background should be in accordance with paragraph 4.20.
8.13 無菌產品如軟膏、乳膏、懸液劑及乳劑等的製備及充填，當產品及成分暴露在環境中且產品不經後續過濾（通過滅菌級過濾器）或最終滅菌時，應在具有 B 級背景的 A 級區中進行。當使用隔離裝置或 RABS 時，背景應符合第 4.20 點。	8.13 Preparation and filling of sterile products such as ointments, creams, suspensions and emulsions should be performed in grade A with a grade B background when the product and components are exposed to the environment and the product is not subsequently filtered (via a sterilising grade filter) or terminally sterilised. Where an isolator or RABS is used, the background should be in accordance with paragraph 4.20.
8.14 無菌連接應在具有 B 級背景的 A 級區中進行，以減少環境的任何潛在污染，除非隨後進行原位滅菌或使用內建無菌的連接裝置進行。內建無菌連接裝置的設計應降低污染風險。	8.14 Aseptic connections should be performed in grade A with a grade B background unless subsequently sterilised in place or conducted with intrinsic sterile connection devices that minimize any potential contamination from the immediate environment. Intrinsic sterile connection devices should be designed to mitigate risk of contamination.
當使用隔離裝置，其背景應符合第 4.20 點。應適當評估無菌連接並確認其有效性。有關內建無菌連接裝置的要求，參見第 8.129 及 8.130 點。	Where an isolator is used, the background should be in accordance with paragraph 4.20. Aseptic connections should be appropriately assessed and their effectiveness verified. For requirements regarding intrinsic sterile connection devices, see paragraphs 8.129 and 8.130.
8.15 應透過工程設計方法儘量減少無菌操作（包括非內建的無菌連接裝置），例如將設備預先組裝並滅菌。當可行時，與產品接觸的管路及設備應預先組裝並原位滅菌。	8.15 Aseptic manipulations (including non-intrinsic sterile connection devices) should be minimized through the use of engineering design solutions such as preassembled and sterilised equipment. Whenever feasible, product contact piping and equipment should be pre-assembled, and sterilised in place.
8.16 應有核准清單，列出在生產過程中可能發生	8.16 There should be an authorized list of allowed and

且經允許及驗證的介入（包括常規及矯正性之介入）（參見第 9.34 點）。應仔細設計介入，以確保有效降低環境、過程及產品的污染風險。設計介入的過程應包括考慮對氣流、關鍵表面及產品的任何影響。應儘可能使用工程解決方案，以儘量減少作業人員在介入期間的動作。應全程遵守無菌技術，包括適當使用無菌的工具進行操作。應首先通過風險管理及 APS 對列出常規性及矯正性的介入類型以及如何執行它們的程序，進行評估並保持最新。應只有在特殊情況下才可使用未驗證的介入措施，並適當考慮與介入措施相關的風險且獲得品質部門的授權。介入的細節應根據製造廠的 PQS 進行風險評估、記錄及全面調查。任何未驗證的介入措施都應由品質部門進行徹底評估，並納入批次處置之考量。	qualified interventions, both inherent and corrective, that may occur during production (see paragraph 9.34). Interventions should be carefully designed to ensure that the risk of contamination of the environment, process and product is effectively minimized. The process of designing interventions should include the consideration of any impact on air-flows and critical surfaces and products. Engineering solutions should be used whenever possible to minimize incursion by operators during the intervention. Aseptic technique should be observed at all times, including the appropriate use of sterile tools for manipulations. The procedures listing the types of inherent and corrective interventions, and how to perform them, should be first evaluated via risk management and APS and be kept up to date. Non-qualified interventions should only be used in exceptional circumstances, with due consideration of the risks associated with the intervention and with the authorisation of the quality unit. The details of the intervention conducted should be subject to risk assessment, recorded and fully investigated under the manufacturer's PQS. Any non-qualified interventions should be thoroughly assessed by the quality department and considered during batch disposition.
8.17 介入及停機應記錄在批次紀錄中。每條生產線停機或介入都應在批次紀錄中充分記錄，包括相關的時間、事件持續時間及參與的作業人員（參見第 9.34 點）。	8.17 Interventions and stoppages should be recorded in the batch record. Each line stoppage or intervention should be sufficiently documented in batch records with the associated time, duration of the event, and operators involved (ref to paragraph 9.34).
8.18 無菌製備及操作的各工程期間應儘量縮短，並限制在經界定及確效的最長時間內，包括：	8.18 The duration of each aspect of aseptic preparation and processing should be minimized and limited to a defined and validated maximum time, including:
i. 設備、組件及容器的清潔、乾燥及滅菌之間的保持時間；	i. the holding time between equipment, component, and container cleaning, drying and sterilisation;
ii. 已滅菌之設備、組件及容器在使用前及充填/組裝期間的保持時間；	ii. the holding time for sterilised equipment, components, and containers before use and during filling/assembly;
iii. 已去污染之環境的保持時間（例如在 RABS 或隔離裝置使用前）；	iii. the holding time for a decontaminated environment, such as the RABS or isolator before use;
iv. 從產品製備開始到滅菌或通過微生物滯留濾器過濾(適用時)，再到無菌充填過程結束的時間。考慮到產品成分及規定的儲存方法，每種產品應分別界定最長允許時間；	iv. the time between the start of the preparation of a product and its sterilisation or filtration through a microorganism-retaining filter (if applicable), through to the end of the aseptic filling process There should be a maximum permissible time for each product that takes into account its composition and the prescribed method of storage;
v. 已滅菌產品在充填前的保持時間；	v. the holding time for sterilised product prior to

	filling;
vi. 無菌操作時間；	vi. the aseptic processing time;
vii. 充填時間。	vii. the filling time.
8.19 應由在無菌操作方面具有特定專業知識的人員定期觀察無菌作業（包括 APS），以確認作業的正確執行，包括作業人員在潔淨室中的行為，並糾正所見之不適當操作。	8.19 Aseptic operations (including APS) should be observed on a regular basis by personnel with specific expertise in aseptic processing to verify the correct performance of operations including operator behaviour in the cleanroom and address inappropriate practices if detected.
無菌產品的完成	**Finishing of sterile products**
8.20 開口的直接容器應保持在具適當背景（如第 4.20 點所述）的 A 級條件下。對於部分封塞的小瓶或預充填式的注射容器，請參閱第 8.126 點。	8.20 Open primary packaging containers should be maintained under grade A conditions with the appropriate background for the technology as described in paragraph 4.20. For partially stoppered vials or prefilled syringes (see paragraph 8.126).
8.21 最終容器應採用經過適當確效的方法密封。	8.21 Final containers should be closed by appropriately validated methods.
8.22 當最終容器以熔封方式密封時，例如：吹製-充填-密封（BFS）、成型-充填-密封（FFS）、小容量及大容量注射用袋（SVP & LVP）、玻璃或塑膠安瓿，應評估並確定影響密封完整性的各關鍵參數及變數，並在操作過程中有效地控制與監測。玻璃安瓿、BFS 單元及小容量容器（≤100 ml）應使用經確效的方法進行 100% 完整性測試。大容量容器（>100 ml），在符合科學正當性且有數據證明現有製程的一致性及嚴謹的製程控制下，減少取樣可能是可以接受的。應該注意的是，目視檢查不被認為是可接受的完整性測試方法。	8.22 Where final containers are closed by fusion, e.g. Blow-Fill-Seal (BFS), Form-Fill-Seal (FFS), Small and Large Volume Parenteral (SVP & LVP) bags, glass or plastic ampoules, the critical parameters and variables that affect seal integrity should be evaluated, determined, effectively controlled and monitored during operations. Glass ampoules, BFS units and small volume containers (≤100 ml) closed by fusion should be subject to 100% integrity testing using validated methods. For large volume containers (>100 ml) closed by fusion, reduced sampling may be acceptable where scientifically justified and based on data demonstrating the consistency of the existing process, and a high level of process control. It should be noted that visual inspection is not considered as an acceptable integrity test method.
8.23 使用熔封以外之方式密封的產品，應取樣並以確效的方法檢查其完整性。測試頻率應基於所使用之容器及密封系統的知識與經驗。應使用符合科學正當性的抽樣計畫。樣品量應基於供應商管理、包裝組件規格及製程知識等資訊。	8.23 Samples of products using systems other than fusion should be taken and checked for integrity using validated methods. The frequency of testing should be based on the knowledge and experience of the container and closure systems being used. A scientifically justified sampling plan should be used. The sample size should be based on information such as supplier management, packaging component specifications and process knowledge.
8.24 真空下密封的容器，應在認可/放行前之一段界定的適當時間後及架儲期間，測試其真空度的維持。	8.24 Containers sealed under vacuum should be tested for maintenance of vacuum after an appropriate pre-determined period prior to certification/release and during shelf life.
8.25 容器密封完整性的確效，應考慮可能對容器	8.25 The container closure integrity validation should take

完整性產生負面影響的任何運輸或裝運需求（例如，減壓或極端溫度）。	into consideration any transportation or shipping requirements that may negatively impact the integrity of the container (e.g. by decompression or extreme temperatures).
8.26 如果用於小瓶捲縮封蓋的設備會產生大量微粒，則應採取防止微粒污染的措施，例如將設備放置在配備適當抽氣的實體隔離工作站。	8.26 Where the equipment used to crimp vial caps can generate large quantities of non-viable particle, measures to prevent particle contamination such as locating the equipment at a physically separate station equipped with adequate air extraction should be taken.
8.27 無菌充填產品的小瓶封蓋，可使用滅菌瓶蓋進行無菌操作，或在無菌操作區外進行潔淨操作。採用後者時，小瓶離開無菌操作區之前應受到 A 級條件的保護；之後，封塞的小瓶應以 A 級空氣保護，直到完成鋁蓋捲縮為止。供應 A 級空氣的背景環境至少應符合 D 級區要求。當封蓋是人工作業，則應在適當設計的隔離裝置中的 A 級條件下，或在具有 B 級背景的 A 級區進行。	8.27 Vial capping of aseptically filled products can be undertaken as an aseptic process using sterilised caps or as a clean process outside the aseptic processing area. Where the latter approach is adopted, vials should be protected by grade A conditions up to the point of leaving the aseptic processing area, and thereafter stoppered vials should be protected with a grade A air supply until the cap has been crimped. The supporting background environment of grade A air supply should meet at least grade D requirements. Where capping is a manual process, it should be performed under grade A conditions either in an appropriately designed isolator or in grade A with a grade B background.
8.28 當無菌充填產品的封蓋是採提供 A 級空氣保護的潔淨操作時，小瓶之膠塞有漏塞或置放離位者，應在封蓋前移除。另，應具備經適當驗證的自動方法檢測膠塞高度。	8.28 Where capping of aseptically filled sterile product is conducted as a clean process with grade A air supply protection, vials with missing or displaced stoppers should be rejected prior to capping. Appropriately qualified, automated methods for stopper height detection should be in place.
8.29 當封蓋作業站需要人員介入時，應採用適當的技術性及（程序 ICH Q7）上的措施防止直接接觸小瓶，使污染降到最低。RABS 及隔離裝置可能有助於確保所需條件。	8.29 Where human intervention is required at the capping station, appropriate technological and organizational measures should be used to prevent direct contact with the vials and to minimize contamination. RABS and isolators may be beneficial in assuring the required conditions.
8.30 所有已充填的注射用產品容器都應個別檢查外來污染或其他缺陷。缺陷分類及嚴重程度應在驗證期間根據風險與歷史知識決定。需要考慮的因素包括但不限於缺陷對患者及給藥途徑的潛在影響。應該對不同的缺陷類型進行分類並分析批次的表現。當批次缺陷數量異於日常生產時（依據例行及趨勢數據），應進行調查。應建立並維護缺陷資料庫（defect library），該資料庫收集所有已知的缺陷分類。缺陷資料庫應使用於生產和品保人員的教育訓練。初始檢查合格的容器於後續抽樣及檢查，不應發現嚴重缺陷。後續發現任何嚴重缺陷都應啟動調查，因其顯示初始檢查過程可能失敗。	8.30 All filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. Defect classification and criticality should be determined during qualification and based on risk and historical knowledge. Factors to consider include, but are not limited to, the potential impact of the defect to the patient and the route of administration. Different defect types should be categorized and batch performance analysed. Batches with unusual levels of defects, when compared with routine defect numbers for the process (based on routine and trend data), should be investigated. A defect library should be generated and maintained which captures all known classes of defects. The defect library should be used for

	the training of production and quality assurance personnel. Critical defects should not be identified during any subsequent sampling and inspection of acceptable containers. Any critical defect identified subsequently should trigger an investigation as it indicates a possible failure of the original inspection process.
8.31 當以人工進行檢查時，應在適當且經管制的照明與背景條件下進行。檢查速率應適當管制和驗證。執行檢查的作業人員應至少每年接受一次目視檢查驗證（如果平時有戴眼鏡者於驗證時應佩戴矯正鏡片）。驗證作業應使用取自製造廠缺陷資料庫套組的適當樣品，並考慮最差狀況（例如檢查時間、產品經由輸送帶系統傳送給作業人員的產線速度、容器尺寸或疲勞度），並應考量包括視力檢查。應儘量減少作業人員的分心，並應在檢查時經常進行適當時間的休息。	8.31 When inspection is performed manually, it should be conducted under suitable and controlled conditions of illumination and background. Inspection rates should be appropriately controlled and qualified. Operators performing the inspection should undergo visual inspection qualification (whilst wearing corrective lenses, if these are normally worn) at least annually. The qualification should be undertaken using appropriate samples from the manufacturer's defect library sets and taking into consideration worst case scenarios (e.g. inspection time, line speed where the product is transferred to the operator by a conveyor system, container size or fatigue) and should include consideration of eyesight checks. Operator distractions should be minimized and frequent breaks, of an appropriate duration, should be taken from inspection.
8.32 當使用自動方法檢查時，其程序應確效，證明可以檢出可能影響產品品質或安全性的已知缺陷，且其檢出能力應等同或優於人工檢查方法。設備的性能應在啟動前和整個批次中定期使用具有代表性的缺陷品進行挑戰。	8.32 Where automated methods of inspection are used, the process should be validated to detect known defects (which may impact product quality or safety) and be equal to, or better than, manual inspection methods. The performance of the equipment should be challenged using representative defects prior to start up and at regular intervals throughout the batch.
8.33 應記錄檢查的結果，並對缺陷類型和數量進行趨勢分析。也應依據統計學原理對各種缺陷類型的不合格比例進行趨勢分析。當觀察到不良趨勢時，應評估對市場產品的影響以作為調查的一部分。	8.33 Results of the inspection should be recorded and defect types and numbers trended. Reject levels for the various defect types should also be trended based on statistical principles. Impact to product on the market should be assessed as part of the investigation when adverse trends are observed.
滅菌	**Sterilisation**
8.34 可行時，最終產品應使用經過確效與管制的滅菌程序進行最終滅菌，因為這比經過確效與管制的無菌過濾製程及/或無菌操作提供了更高的無菌保證程度。當產品不可能進行最終滅菌，則應考慮使用無菌操作後的最終熱處理，並結合無菌操作以提高無菌保證程度。	8.34 Where possible, finished product should be terminally sterilised, using a validated and controlled sterilisation process, as this provides a greater assurance of sterility than a validated and controlled sterile filtration process and/or aseptic processing. Where it is not possible for a product to undergo terminal sterilisation, consideration should be given to using post-aseptic processing terminal heat treatment, combined with aseptic process to give improved sterility assurance.
8.35 滅菌設備與滅菌週期/程式的選擇、設計與位置，應基於科學原則以及證明滅菌過程可	8.35 The selection, design and location of the equipment and cycle/programme used for sterilisation should be

再現及可信賴的數據。應界定所有參數，關鍵者應予管控、監測並記錄。	based on scientific principles and data which demonstrate repeatability and reliability of the sterilisation process. All parameters should be defined, and where critical, these should be controlled, monitored and recorded.
8.36 所有滅菌過程應予確效。確效研究應考慮產品成分、儲存條件，以及從開始準備待滅菌產品或原物料到滅菌之間的最長時間。在採用任何滅菌過程之前，其對產品及設備的適用性，以及每種裝載的全部待滅物品每次都能達到預期滅菌條件的效能，應藉由物理量測及適當時搭配生物指示劑（BI），進行確效。為有效滅菌，產品全部及設備與組件的所有表面均應受到必要的處理，且相關程序應予設計以確保達到此目的。	8.36 All sterilisation processes should be validated. Validation studies should take into account the product composition, storage conditions and maximum time between the start of the preparation of a product or material to be sterilised and its sterilisation. Before any sterilisation process is adopted, its suitability for the product and equipment, and its efficacy in consistently achieving the desired sterilising conditions in all parts of each type of load to be processed should be validated notably by physical measurements and where appropriate by Biological Indicators (BI). For effective sterilisation, the whole of the product, and surfaces of equipment and components should be subject to the required treatment and the process should be designed to ensure that this is achieved.
8.37 當採用的產品滅菌方法未在現行版的藥典中描述，或用於非單純水溶液的產品時，應特別注意。在可能的情況下，加熱滅菌是首選方法。	8.37 Particular attention should be given when the adopted product sterilisation method is not described in the current edition of the Pharmacopoeia, or when it is used for a product which is not a simple aqueous solution. Where possible, heat sterilisation is the method of choice.
8.38 應為所有滅菌製程建立確效的裝載型式，各裝載型式應定期再確效。最大及最小裝載也應被視為整體裝載確效策略的一部分。	8.38 Validated loading patterns should be established for all sterilisation processes and load patterns should be subject to periodic revalidation. Maximum and minimum loads should also be considered as part of the overall load validation strategy.
8.39 應基於風險按預定的時間間隔檢討及確認滅菌過程的有效性。加熱滅菌週期應以被認為是最差狀況的裝載型式，最低再確效頻率至少每年一次。其他裝載型式應依 CCS 中證明合理的頻率進行確效。	8.39 The validity of the sterilizing process should be reviewed and verified at scheduled intervals based on risk. Heat sterilization cycles should be revalidated with a minimum frequency of at least annually for load patterns that are considered worst case. Other load patterns should be validated at a frequency justified in the CCS.
8.40 應建立並遵守所有滅菌過程的例行操作參數，例如：物理參數及裝載型式。	8.40 Routine operating parameters should be established and adhered to for all sterilisation processes, e.g. physical parameters and loading patterns.
8.41 應有適當機制來偵測不符合確效參數的滅菌週期。應調查任何失敗的或偏離確效程序的滅菌作業（例如：較長或較短的加熱階段）。	8.41 There should be mechanisms in place to detect a sterilisation cycle that does not conform to the validated parameters. Any failed sterilisation or sterilisation that deviated from the validated process (e.g. have longer or shorter phases such as heating cycles) should be investigated.
8.42 在適當位置放置合適 BI 應被視為支持滅菌	8.42 Suitable BIs placed at appropriate locations should be

過程確效的一種附加方法。 BI 應根據製造商的說明書進行儲存及使用。當 BI 用於支持確效及/或監控滅菌過程（例如環氧乙烷滅菌），對每一個滅菌週期應進行陽性對照測試。如果使用 BI，則應採取嚴格的預防措施以避免將微生物污染轉移到製造或其他測試過程中。不應僅用 BI 結果推翻其他關鍵參數及製程設計要素。	considered as an additional method to support the validation of the sterilisation process. BIs should be stored and used according to the manufacturer's instructions. Where BIs are used to support validation and/or to monitor a sterilisation process (e.g. with ethylene oxide), positive controls should be tested for each sterilisation cycle. If BIs are used, strict precautions should be taken to avoid transferring microbial contamination to the manufacturing or other testing processes. BI results in isolation should not be used to override other critical parameters and process design elements.
8.43 BI 的可靠性很重要。應驗證 BI 供應商，且應控制其運輸及儲存條件，避免損害 BI 品質。在使用新的 BI 批次之前，應確認該批次之指示微生物的數量、純度及鑑別。對於其他關鍵參數，例如 D 值與 Z 值，通常可以使用合格供應商提供的批次證明書。	8.43 The reliability of BIs is important. Suppliers should be qualified and transportation and storage conditions should be controlled in order that BI quality is not compromised. Prior to use of a new batch/lot of BIs, the population, purity and identity of the indicator organism of the batch/lot should be verified. For other critical parameters, e.g. D-value, Z-value, the batch certificate provided by the qualified supplier can normally be used.
8.44 應有明確的方法區分未滅菌及已滅菌的產品、設備及組件。用於盛裝產品、其他設備及/或組件之籃子或托盤等器具應清楚地標明（或以電子方式追蹤）產品名稱、批號以及是否已滅菌。當合適時，可以使用如高壓滅菌膠帶或輻射指示劑之類的指示劑來標示該批次（或子批次材料、組件、設備）是否已經過滅菌處理。然而，這些指示劑僅顯示已經歷滅菌過程；它們並不表示產品為無菌或達到要求的無菌保證程度。	8.44 There should be a clear means of differentiating products, equipment and components, which have not been subjected to the sterilisation process from those which have. Equipment such as baskets or trays used to carry products, other items of equipment and/or components should be clearly labelled (or electronically tracked) with the product name and batch number and an indication of whether or not it has been sterilised. Indicators such as autoclave tape, or irradiation indicators may be used, where appropriate, to indicate whether or not a batch (or sub-batch material, component, equipment) has passed through a sterilisation process. However, these indicators show only that the sterilisation process has occurred; they do not indicate product sterility or achievement of the required sterility assurance level.
8.45 每次滅菌操作都應有滅菌紀錄。每一個週期都應該有唯一的標識碼。應審查及核准滅菌紀錄的符合性，以作為批次認可/放行程序的一部分。	8.45 Sterilisation records should be available for each sterilisation run. Each cycle should have a unique identifier. Their conformity should be reviewed and approved as part of the batch certification/release procedure.
8.46 需要時，原物料、設備及組件應以適用於特定材質之確效方法進行滅菌。滅菌後應提供適當的保護以防止再次污染。如果滅菌物品在滅菌後不立即使用，則應使用適當密封的包裝儲存，並應建立最長保持時間。在證明合理的情況下，多層無菌包裝的組件，如果無菌包裝的完整性及構造可讓作業人員在將	8.46 Where required, materials, equipment and components should be sterilised by validated methods appropriate to the specific material. Suitable protection after sterilisation should be provided to prevent recontamination. If sterilised items are not used immediately after sterilisation, these should be stored

物品轉移到 A 級的過程易於消毒（例如，通過使用多層無菌包裝，每次從較低級區轉移到較高級區時可逐層去除），則不須儲存於潔淨室。如果以密封包裝達到保護，則該包裝作業應在滅菌前進行。	using appropriately sealed packaging and a maximum hold time should be established. Where justified, components that have been packaged with multiple sterile packaging layers need not be stored in a cleanroom if the integrity and configuration of the sterile pack allows the items to be readily disinfected during transfer by operators into grade A (e.g. by the use of multiple sterile coverings that can be removed at each transfer from lower to higher grade). Where protection is achieved by containment in sealed packaging, this packaging process should be undertaken prior to sterilisation.
8.47 如果原物料、設備、組件和輔助物品在密封包裝中進行滅菌後轉移到 A 級區，則應使用適當確效的方法（例如，氣鎖室或傳遞箱）進行，同時消毒密封包裝的外部表面。還應考慮使用快速傳送對接口技術。應證明這些方法可有效控制 A 級區及 B 級區域的潛在污染風險，同樣，應證明將物品移入 B 級區及 A 級區的消毒程序，可有效地將包裝上的任何污染降至可接受程度。	8.47 Where materials, equipment, components and ancillary items are sterilised in sealed packaging and then transferred into grade A, this should be done using appropriate validated methods (for example, airlocks or pass-through hatches) with accompanying disinfection of the exterior of the sealed packaging. The use of rapid transfer port technology should also be considered. These methods should be demonstrated to effectively control the potential risk of contamination of the grade A and grade B areas and, likewise, the disinfection procedure should be demonstrated to be effective in reducing any contamination on the packaging to acceptable levels for entry of the item into the grade B and grade A areas.
8.48 對密封於包裝或容器中的原物料、設備、組件和輔助物品進行滅菌時，應驗證其包裝能將微粒、微生物、內毒素/熱原或化學污染的風險降至最低，且適用於所選的滅菌方法。包裝密封的程序應予確效。確效應考慮無菌保護屏障系統的完整性、滅菌前的最長保持時間及已滅菌物品的最長架儲期。使用前應檢查每件已滅菌物品之無菌保護屏障系統的完整性。	8.48 Where materials, equipment, components and ancillary items are sterilised in sealed packaging or containers, the packaging should be qualified for minimizing the risk of particulate, microbial, endotoxin/pyrogen or chemical contamination, and for compatibility with the selected sterilisation method. The packaging sealing process should be validated. The validation should consider the integrity of the sterile protective barrier system, the maximum hold time before sterilisation and the maximum shelf life assigned to the sterilised items. The integrity of the sterile protective barrier system for each of the sterilised items should be checked prior to use.
8.49 對於非直接或非間接接觸產品，且為無菌操作所必須，但不能滅菌的原物料、設備、組件及輔助物品，應有有效且經確效的消毒及轉送程序。這些物品一經消毒，應加以保護以防止再次污染。這些物品及其他代表潛在污染的途徑，應涵蓋在環境監測計畫中。	8.49 For materials, equipment, components and ancillary items that are not a direct or indirect product contact part and are necessary for aseptic processing but cannot be sterilised, an effective and validated disinfection and transfer process should be in place. These items, once disinfected, should be protected to prevent recontamination. These items, and others representing potential routes of contamination, should be included in the environmental monitoring programme.

加熱滅菌	**Sterilisation by heat**
8.50 應使用具有適當準確度及精確度的設備，以電子或紙本的方式記錄每一個加熱滅菌週期。系統的控制及監測儀器應具有保障措施及/或冗餘配置，以檢測不符合確效參數要求的週期，並中止或判定該週期失敗（例如，使用雙重控制/雙探針連接到獨立的控制及監測系統）。	8.50 Each heat sterilisation cycle should be recorded either electronically or by hardcopy, using equipment with suitable accuracy and precision. The system should have safeguards and/or redundancy in its control and monitoring instrumentation to detect a cycle not conforming to the validated cycle parameter requirements and abort or fail this cycle (e.g. by the use of duplex/double probes connected to independent control and monitoring systems).
8.51 用於控制及/或記錄的溫度探針的位置應在確效期間確定，並根據系統設計進行選擇，以便正確記錄並代表例行滅菌週期條件。應設計確效研究來證明系統控制及記錄的探針位置的合適性，並應包括在確效期間使用位於相同位置的獨立監測探針確認這些探針的功能及位置。	8.51 The position of the temperature probes used for controlling and/or recording should be determined during the validation and selected based on system design and in order to correctly record and represent routine cycle conditions. Validation studies should be designed to demonstrate the suitability of system control and recording probe locations, and should include the verification of the function and location of these probes by the use of an independent monitoring probe located at the same position during validation.
8.52 在開始計算滅菌時間之前，整個裝載應達到要求的溫度。在裝載內使用參考探針控制的滅菌週期，應特別考慮，確保裝載探針的溫度在週期開始前，控制在規定的溫度範圍內。	8.52 The whole of the load should reach the required temperature before measurement of the sterilising time-period starts. For sterilisation cycles controlled by using a reference probe within the load, specific consideration should be given to ensuring the load probe temperature is controlled within defined temperature range prior to cycle commencement.
8.53 加熱滅菌週期的高溫階段完成後，應採取預防措施，以防止滅菌裝載物在冷卻過程中被污染。任何與產品或滅菌物料接觸的冷卻液體或氣體都應經過滅菌。	8.53 After completion of the high temperature phase of a heat sterilisation cycle, precautions should be taken against contamination of a sterilised load during cooling. Any cooling liquid or gas that comes into contact with the product or sterilised material should be sterilised.
8.54 在核准以參數放行的情況下，應有穩健的系統運用於產品生命週期內確效及製程例行監控。該系統應予定期審查。附則 17 提供關於參數放行的進一步指導。	8.54 In those cases where parametric release has been authorized, a robust system should be applied to the product lifecycle validation and the routine monitoring of the manufacturing process. This system should be periodically reviewed. Further guidance regarding parametric release is provided in Annex 17.
濕熱滅菌	**Moist heat sterilisation**
8.55 濕熱滅菌可以使用蒸汽（直接或間接接觸）達成，但也包括其他系統，例如超熱水系統（噴淋或浸泡週期），可用於可能被其他滅菌週期設計造成破損的容器（例如吹製-充填-密封的容器、塑膠軟袋）。	8.55 Moist heat sterilisation can be achieved using steam, (direct or indirect contact), but also includes other systems such as superheated water systems (cascade or immersion cycles) that could be used for containers that may be damaged by other cycle designs (e.g. Blow-Fill-Seal containers, plastic bags).
8.56 除密封於容器中的產品外，待滅菌的物品應是乾燥的，並用可允許空氣移除及蒸汽滲	8.56 The items to be sterilised, other than products in sealed containers, should be dry, packaged in a protective

透，且防止滅菌後再次污染的保護性屏障系統進行包裝。從滅菌器中取出後，所有裝載的物品都應是乾燥的。應通過目視檢查確認裝載的乾燥度，作為滅菌過程允收標準的一部分。	barrier system which allows removal of air and penetration of steam and prevents recontamination after sterilisation. All loaded items should be dry upon removal from the steriliser. Load dryness should be confirmed by visual inspection as a part of the sterilisation process acceptance.
8.57 對於多孔物品滅菌週期（硬質物品），應監控並記錄過程的時間、溫度及壓力。每件滅菌物品從高壓滅菌器中取出時，應檢查是否有損壞、包裝材料完整性以及濕氣。任何發現不符合預期用途的物品都應移出製造區域並進行調查。	8.57 For porous cycles (hard goods), time, temperature and pressure should be used to monitor the process and be recorded. Each sterilised item should be inspected for damage, packaging material integrity and moisture on removal from the autoclave. Any item found not to be fit for purpose should be removed from the manufacturing area and an investigation performed.
8.58 能夠進行預真空滅菌週期的高壓滅菌器，應在整個滅菌期間記錄滅菌艙排水口的溫度。適當時也可以使用裝載探針，但控制系統應保持與裝載確效時相關。對於原位蒸汽滅菌系統，在整個滅菌期間應記錄適當之冷凝水排放點的溫度。	8.58 For autoclaves capable of performing prevacuum sterilisation cycles, the temperature should be recorded at the chamber drain throughout the sterilisation period. Load probes may also be used where appropriate but the controlling system should remain related to the load validation. For steam in place systems, the temperature should be recorded at appropriate condensate drain locations throughout the sterilisation period.
8.59 多孔週期的確效應包括計算平衡時間、暴露時間、壓力及溫度的相關性以及滅菌期間的最低/最高溫度範圍。液體週期的確效應包括溫度、時間及/或 F_0。關鍵製程參數應符合規定的限值（包括適當的容許偏差），並作為滅菌確效及例行滅菌週期可接受標準的一部分。	8.59 Validation of porous cycles should include a calculation of equilibration time, exposure time, correlation of pressure and temperature and the minimum/maximum temperature range during exposure. Validation of fluid cycles should include temperature, time and/or F0. Critical processing parameters should be subject to defined limits (including appropriate tolerances) and be confirmed as part of the sterilisation validation and routine cycle acceptance criteria.
8.60 當真空階段是週期的一部分或系統在滅菌後恢復到低於滅菌器周圍環境的壓力時，應定期（通常每週）對滅菌器進行洩漏測試。	8.60 Leak tests on the steriliser should be carried out periodically (normally weekly) when a vacuum phase is part of the cycle or the system is returned, post-sterilisation, to a pressure lower than the environment surrounding the steriliser.
8.61 當滅菌過程包括空氣移除時（例如高壓滅菌器中的多孔裝載、凍乾艙），應充分保證在滅菌前及滅菌過程中去除空氣。對於高壓滅菌器，這應該包括空氣移除測試週期（通常每天進行）或使用空氣檢測系統。待滅菌的裝載設計應支持有效的空氣去除，及易於排水以防止冷凝水的積聚。	8.61 There should be adequate assurance of air removal prior to and during sterilisation when the sterilisation process includes air purging (e.g. porous autoclave loads, lyophilizer chambers). For autoclaves, this should include an air removal test cycle (normally performed on a daily basis) or the use of an air detector system. Loads to be sterilised should be designed to support effective air removal and be free draining to prevent the build-up of condensate.
8.62 應通過適當的週期設計及控制，例如設定正確的壓力、加熱與冷卻的速率以及裝載型式，以防止最終滅菌的軟質容器的變形及損	8.62 Distortion and damage of non-rigid containers that are terminally sterilised, such as containers produced by Blow-Fill-Seal or Form-Fill-Seal technologies, should

壞（例如由吹製-充填-密封或成型-充填-密封技術生產的容器）。	be prevented by appropriate cycle design and control (for instance setting correct pressure, heating and cooling rates and loading patterns).
8.63 當原位蒸汽處理系統用於滅菌時（例如用於固定管道、容器及凍乾機艙體），系統應經過適當設計及確效，確保系統的所有部分都經過所需的處理。在例行使用過程中，應在適當位置監測系統的溫度、壓力及時間，以確保所有區域都得到有效且可重複的滅菌。在初始及定期確效期間，這些位置應被證明具代表性，且與升溫最慢的位置相關。經原位蒸汽滅菌的系統，應該保持完整性，並且當操作需要時，在使用前保持正壓，或配備滅菌級空氣過濾器。	8.63 Where steam in place systems are used for sterilisation (e.g. for fixed pipework, vessels and lyophilizer chambers), the system should be appropriately designed and validated to assure all parts of the system are subjected to the required treatment. The system should be monitored for temperature, pressure and time at appropriate locations during routine use to ensure all areas are effectively and reproducibly sterilised. These locations should be demonstrated as being representative of, and correlated with, the slowest to heat locations during initial and routine validation. Once a system has been sterilised by steam in place, it should remain integral and where operations require, maintained under positive pressure or otherwise equipped with a sterilising vent filter prior to use.
8.64 使用超熱水作為傳熱介質的液體裝載週期中，熱水應持續地接觸所有要求的點位。初始驗證研究應包括整個裝載的溫度測繪。應對設備進行例行檢查，以確保噴嘴（入水處）沒有堵塞，且排水管沒有碎屑。	8.64 In fluids load cycles where superheated water is used as the heat transfer medium, the heated water should consistently reach all of the required contact points. Initial qualification studies should include temperature mapping of the entire load. There should be routine checks on the equipment to ensure that nozzles (where the water is introduced) are not blocked and drains remain free from debris.
8.65 超熱水的高壓滅菌器中對液體裝載的滅菌確效應包括整個裝載的溫度測繪與熱滲透以及再現性研究。裝載物的所有部分應均勻加熱，並在規定的時間內達到要求的溫度。例行溫度監測的探針應與驗證過程中確定的最差狀況位置相關聯。	8.65 Validation of the sterilisation of fluids loads in a superheated water autoclave should include temperature mapping of the entire load and heat penetration and reproducibility studies. All parts of the load should heat up uniformly and achieve the desired temperature for the specified time. Routine temperature monitoring probes should be correlated to the worst case positions identified during the qualification process.
乾熱滅菌	**Dry heat sterilisation**
8.66 乾熱滅菌利用高溫空氣或氣體對產品或物品進行滅菌。乾熱滅菌特別適用於以熱去除難消除的耐熱污染物，例如內毒素/熱原，通常用於製備無菌充填的組件。當在既定限度內例行操作時，產品、組件或設備所暴露之時間及溫度的組合應產生合乎需要且可再現的致死率及/或內毒素/熱原的去活化/去除水準。該過程可以在烘箱中或在連續隧道過程中進行，例如用於玻璃容器的滅菌及去熱原。	8.66 Dry heat sterilisation utilizes high temperatures of air or gas to sterilise a product or article. Dry heat sterilisation is of particular use in the thermal removal of difficult-to-eliminate thermally robust contaminants such as endotoxin/pyrogen and is often used in the preparation of components for aseptic filling. The combination of time and temperature to which product, components or equipment are exposed should produce an adequate and reproducible level of lethality and/or endotoxin/pyrogen inactivation/removal when operated routinely within the established limits. The process may be operated in an oven or in a continuous tunnel

	process, e.g. for sterilisation and depyrogenation of glass containers.
8.67 乾熱滅菌/去熱原隧道的配置應維持適當的壓差及氣流，確保氣流保護 A 級滅菌區的完整性及性能。應評估壓差曲線圖。應評估任何氣流變化的影響，以確保維持加熱曲線。供應到隧道的所有空氣都應至少通過 HEPA 過濾器，並且應進行定期測試（至少每半年一次）以證明空氣過濾器的完整性。任何與已滅菌組件接觸的隧道組件都應進行適當的滅菌或消毒。在確效及/或例行處理期間應考慮的關鍵製程參數應包括但不限於：	8.67 Dry heat sterilisation/depyrogenation tunnels should be configured to ensure that airflow protects the integrity and performance of the grade A sterilising zone by maintaining appropriate pressure differentials and airflow through the tunnel. Air pressure difference profiles should be assessed. The impact of any airflow change should be assessed to ensure the heating profile is maintained. All air supplied to the tunnel should pass through at least a HEPA filter and periodic tests (at least biannually) should be performed to demonstrate air filter integrity. Any tunnel parts that come into contact with sterilised components should be appropriately sterilised or disinfected. Critical process parameters that should be considered during validation and/or routine processing should include, but are not limited to:
i. 輸送帶速度或滅菌區內的停留時間，	i. belt speed or dwell time within the sterilising zone,
ii. 溫度 - 最低及最高溫度，	ii. temperature – minimum and maximum temperatures,
iii. 物料/物品的熱滲透，	iii. heat penetration of the material/article,
iv. 熱分佈/均勻性，	iv. heat distribution/uniformity,
v. 由熱分佈及熱滲透研究相關的壓差曲線所確定的氣流。	v. airflows determined by air pressure difference profiles correlated with the heat distribution and penetration studies.
8.68 當使用熱處理作為任何組件或與產品接觸的設備/原物料的去熱原製程的一部分時，應進行確效研究以證明該製程提供了合適的 F_h 值並使內毒素濃度至少降低 3 $\log_{10}$。當達到這一標準時，不用額外的要求來證明滅菌效果。	8.68 When a thermal process is used as part of the depyrogenation process for any component or product contact equipment/material, validation studies should be performed to demonstrate that the process provides a suitable F_h value and results in a minimum 3 $\log_{10}$ reduction in endotoxin concentration. When this is attained, there is no additional requirement to demonstrate sterilisation in these cases.
8.69 確效時應使用加入內毒素的容器，並應透過全面核算對該容器進行謹慎管理。容器應代表正常生產所用的材料（涉及包裝材料的組成、孔隙率、尺寸、額定容量）。還應證明內毒素的含量及回收效率。	8.69 Containers spiked with endotoxin should be used during validation and should be carefully managed with a full reconciliation performed. Containers should be representative of the materials normally processed (in respect to composition of the packaging materials, porosity, dimensions, nominal volume). Endotoxin quantification and recovery efficiency should also be demonstrated.

8.70 乾熱烘箱通常用於直接包裝材料、起始原料或原料藥滅菌或去熱原，但也可用於其他製程。除非保持包裝的完整性，否則在整個滅菌及滅菌後的保持過程中，乾熱烘箱對潔淨度等級相對較低的潔淨區應保持正壓。所有進入烘箱的空氣都應通過 HEPA 過濾器。在驗證及/或例行操作中應考慮的關鍵製程參數應包括但不限於：	8.70 Dry heat ovens are typically employed to sterilise or depyrogenate primary packaging components, starting materials or active substances but may be used for other processes. They should be maintained at a positive pressure relative to lower grade clean areas throughout the sterilisation and post sterilisation hold process unless the integrity of the packaging is maintained. All air entering the oven should pass through a HEPA filter. Critical process parameters that should be considered in qualification and/or routine processing should include, but are not limited to:
i. 溫度，	i. temperature,
ii. 暴露期間/時間，	ii. exposure period/time,
iii. 艙室壓力（用於維持相對高壓），	iii. chamber pressure (for maintenance of over pressure),
iv. 風速，	iv. air speed,
v. 烘箱內的空氣品質，	v. air quality within the oven,
vi. 物料/物品的熱滲透（加熱緩慢的各點），	vi. heat penetration of material/article (slow to heat spots),
vii. 熱分佈/均勻性，	vii. heat distribution/uniformity,
viii. 待滅菌/去熱原物品的裝載型式及配置，包括最小及最大裝載量。	viii. load pattern and configuration of articles to be sterilised/depyrogenated including minimum and maximum loads.
輻射滅菌	**Sterilisation by radiation**
8.71 輻射滅菌主要用於對熱敏感的原物料及產品的滅菌。紫外線照射不是可接受的滅菌方法。有關游離輻射滅菌的指引詳見附則 12。	8.71 Sterilisation by radiation is used mainly for the sterilisation of heat sensitive materials and products. Ultraviolet irradiation is not an acceptable method of sterilisation. Guidance regarding ionising radiation sterilisation can be found within Annex 12.
8.72 確效過程應確保已考量產品密度及包裝等變數的影響。	8.72 Validation procedures should ensure that the effects of variation in density of the product and packages are considered.
環氧乙烷滅菌	**Sterilisation with ethylene oxide**
8.73 本方法應只用在沒有其他方法可用的情形。在製程確效期間，應證明環氧乙烷(EO)對產品無損害及其除氣所容許的條件與時間，可將任何殘留的環氧乙烷氣體及其反應產物減低至該類產品或原物料所界定之允許限量。	8.73 This method should only be used when no other method is practicable. During process validation, it should be shown that there is no damaging effect on the product and that the conditions and time allowed for degassing result in the reduction of any residual ethylene oxide (EO) gas and reaction products to defined acceptable limits for the given product or material.

8.74 氣體與微生物細胞直接接觸是必要的，應採取預防措施以避免微生物可能被包覆在諸如晶體或乾燥的蛋白質等物質中。包裝材料的性質、孔隙率及數量會顯著影響滅菌過程。	8.74 Direct contact between gas and microbial cells is essential, precautions should be taken to avoid the presence of organisms likely to be enclosed in material such as crystals or dried protein. The nature, porosity and quantity of packaging materials can significantly affect the process.
8.75 暴露於氣體之前，應使原物料與製程所需的濕度及溫度達到平衡。使用蒸汽對裝載物進行滅菌前的溼度調整，蒸汽應具有適當的品質；在滅菌前達到該狀態所需的時間，應依相對需求加以均衡，縮減至最短。	8.75 Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process. Where steam is used to condition the load for sterilisation, it should be of an appropriate quality. The time required for this should be balanced against the opposing need to minimize the time before sterilisation.
8.76 每一個滅菌週期都應使用適當的生物指示劑進行監控，並將適當數量的測試單元分佈在整個裝載中的特定位置，這些位置在確效期間已被證明是最差狀況。	8.76 Each sterilisation cycle should be monitored with suitable BIs, using the appropriate number of test units distributed throughout the load at defined locations that have been shown to be worst case locations during validation.
8.77 滅菌製程確效及日常監控應考慮的關鍵製程參數，包括但不限於：	8.77 Critical process parameters that could be considered as part of the sterilisation process validation and routine monitoring include, but are not limited to:
i. EO 氣體濃度，	i. EO gas concentration,
ii. 壓力，	ii. pressure,
iii. 使用的 EO 氣體量，	iii. amount of EO gas used,
iv. 相對濕度，	iv. relative humidity,
v. 溫度，	v. temperature,
vi. 暴露時間。	vi. exposure time.
8.78 滅菌後，裝載物應通氣以使 EO 氣體及/或其反應產物從包裝產品中釋出到預定水準。通氣過程可在滅菌器內及/或單獨的通氣艙或通氣室內進行。通氣階段應作為整體 EO 滅菌製程確效的一部分進行確效。	8.78 After sterilisation, the load should be aerated to allow EO gas and/or its reaction products to desorb from the packaged product to predetermined levels. Aeration can occur within a steriliser chamber and/or in a separate aeration chamber or aeration room. The aeration phase should be validated as part of the overall EO sterilisation process validation.
對無法在最終容器中滅菌的產品進行過濾滅菌	**Filter sterilisation of products which cannot be sterilised in their final container**
8.79 如果產品不能在其最終容器中滅菌，溶液或液體應通過無菌之滅菌級過濾器滅菌（過濾器孔徑最大為 0.22 μm，經過適當確效可獲得無菌濾液），並且隨後無菌充填到先前已滅菌的容器中。所用過濾器的選擇應確保其與產品相容並符合上市許可中的說明（參見第 8.135 點）。	8.79 If the product cannot be sterilised in its final container, solutions or liquids should be sterilised by filtration through a sterile sterilising grade filter (with a nominal pore size of a maximum of 0.22 μm that has been appropriately validated to obtain a sterile filtrate) and subsequently aseptically filled into a previously sterilised container. The selection of the filter used should ensure that it is compatible with the product and as described in the marketing authorization (see paragraph 8.135).
8.80 可以在製程中的多個點使用合適之減少負荷菌的預過濾器及/或滅菌級過濾器，以確保	8.80 Suitable bioburden reduction prefilters and/or sterilising grade filters may be used at multiple points

在最終滅菌過濾器前之液體的負荷菌低於管制標準。由於無菌過濾製程與其他滅菌製程相比具潛在額外風險，因此，通過儘可能靠近充填點的無菌滅菌級過濾器所進行之額外過濾，應視為整個 CCS 的一部分。	during the manufacturing process to ensure a low and controlled bioburden of the liquid prior to the final sterilising filter. Due to the potential additional risks of a sterile filtration process, as compared with other sterilisation processes, an additional filtration through a sterile sterilising grade filter, as close to the point of fill as possible, should be considered as part of an overall CCS.
8.81 過濾系統組件的選擇及其在過濾系統內的相互連接及排列，包括預過濾器，應基於產品的關鍵品質屬性，並經過合理證明與記錄。過濾系統應儘量減少纖維及微粒的產生，不會導致或促成不可接受的雜質/不純物限量，或具有以其他方式改變產品品質及效能的特性。同樣地，過濾器特性應與液體相容，並且不受待過濾產品的不利影響。應評估產品成分的吸附性及過濾器成分被萃出/浸出（參見第 8.135 點）。	8.81 The selection of components for the filtration system and their interconnection and arrangement within the filtration system, including pre-filters, should be based on the critical quality attributes of the product, justified and documented. The filtration system should minimize the generation of fibres and particles, not cause or contribute to unacceptable levels of impurities, or possess characteristics that otherwise alter the quality and efficacy of the product. Similarly, the filter characteristics should be compatible with the fluid and not be adversely affected by the product to be filtered. Adsorption of product components and extraction/leaching of filter components should be evaluated (see paragraph 8.135).
8.82 過濾系統的設計應：	8.82 The filtration system should be designed to:
i. 允許在經過確效的製程參數範圍內操作；	i. allow operation within validated process parameters;
ii. 保持濾液的無菌性；	ii. maintain the sterility of the filtrate;
iii. 儘量減少最末端滅菌級過濾器及產品最終充填之間所需的無菌連接數量；	iii. minimize the number of aseptic connections required between the final sterilising grade filter and the final filling of the product;
iv. 需要時，允許執行清潔程序；	iv. allow cleaning procedures to be conducted as necessary;
v. 允許進行必要的滅菌程序，包括原位滅菌。；	v. allow sterilisation procedures, including sterilisation in place, to be conducted as necessary;
vi. 允許在過濾之前及之後對 0.22 μm 最終滅菌級過濾器進行原位完整性測試，最好是一個密閉系統。應選擇原位完整性測試方法，以避免對產品品質產生任何不利影響。	vi. permit in-place integrity testing, of the 0.22 μm final sterilising grade filter, preferably as a closed system, both prior to, and following filtration as necessary. In-place integrity testing methods should be selected to avoid any adverse impact on the quality of the product.
8.83 液體的無菌過濾應根據相關藥典要求進行確效。確效可以按產品的不同含量或差異進行分組，但應針對最差的情況進行。分組的理由應該合理並文件化。	8.83 Sterile filtration of liquids should be validated in accordance with relevant Pharmacopeia requirements. Validation can be grouped by different strengths or variations of a product but should be done under worst case conditions. The rationale for grouping should be justified and documented.
8.84 在過濾器確效期間，應儘可能使用待過濾的產品執行滅菌級過濾器的細菌滯留試驗。如果要過濾的產品不適合用於細菌滯留測試，	8.84 During filter validation, wherever possible, the product to be filtered should be used for bacterial retention testing of the sterilising grade filter. Where the product

則應證明適合的替代產品用於該試驗之合理性。細菌滯留試驗中使用的挑戰微生物應有合理證明。	to be filtered is not suitable for use in bacterial retention testing, a suitable surrogate product should be justified for use in the test. The challenge organism used in the bacterial retention test should be justified.
8.85 確效時應考慮及建立過濾參數，應包括但不限於：	8.85 Filtration parameters that should be considered and established during validation should include, but are not limited to:
i. 用於過濾器完整性測試的潤濕液：	i. The wetting fluid used for filter integrity testing:
• 應根據過濾器製造商的建議或待過濾液體。應建立適當的完整性測試值規格。	• It should be based on the filter manufacturer's recommendation or the fluid to be filtered. The appropriate integrity test value specification should be established.
• 如果此系統用非產品的液體進行沖洗或原位完整性測試，應採取適當措施以避免對產品品質產生任何有害影響。	• If the system is flushed or integrity tested in-situ with a fluid other than the product, appropriate actions are taken to avoid any deleterious effect on product quality.
ii. 過濾製程條件包括：	ii. Filtration process conditions including:
• 液體預過濾後的保持時間及對生物負荷菌的影響，	• fluid pre-filtration holding time and effect on bioburden,
• 過濾器預處理，必要時使用液體，	• filter conditioning, with fluid if necessary,
• 最長的過濾時間/過濾器與液體接觸的總時間，	• maximum filtration time/total time filter is in contact with the fluid,
• 最大操作壓力，	• maximum operating pressure,
• 流速，	• flow rate,
• 最大過濾量，	• maximum filtration volume,
• 溫度，	• temperature,
• 過濾已知體積的半製品溶液所需的時間及過濾器上、下游的壓差。	• the time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter.
8.86 應實施例行製程管制以確保遵守經確效的過濾參數。關鍵製程參數的結果應包含在批次紀錄中，包括但不限於過濾已知體積之半製品溶液所需的最短時間，及過濾器上、下游的壓差。 製造過程中關鍵參數的任何顯著差異應予記錄與調查。	8.86 Routine process controls should be implemented to ensure adherence to validated filtration parameters. Results of critical process parameters should be included in the batch record, including but not limited to the minimum time taken to filter a known volume of bulk solution and pressure difference across the filter. Any significant difference from critical parameters during manufacturing should be documented and investigated.
8.87 滅菌過濾器組裝應在使用前通過完整性測試進行確認（使用前、滅菌後完整性測試或稱PUPSIT），以檢查使用前過濾器在準備過程所造成的損壞及完整性損失。用於對液體進行滅菌的滅菌級過濾器，應在使用後先進行非破壞性完整性測試，再從其濾殼(housing)中取出過濾器。完整性測試過程應進行確效，測試結果應與確效期間所建立之過濾器的微生物滯留能力相關。使用的測試實例包括起泡點、擴散流、水侵入或持壓測	8.87 The integrity of the sterilised filter assembly should be verified by integrity testing before use (pre-use post sterilisation integrity test or PUPSIT), to check for damage and loss of integrity caused by the filter preparation prior to use. A sterilising grade filter that is used to sterilise a fluid should be subject to a non-destructive integrity test post-use prior to removal of the filter from its housing. The integrity test process should be validated and test results should correlate to the microbial retention capability of the filter

試。由於製程限制（例如過濾非常少量的溶液），滅菌後 PUPSIT 可能並不總是可行，這是被認可的。在這些情況下，可以採取替代方法，前提是已經進行了徹底的風險評估，並且通過實施適當的控制措施來降低非完整的(non-integral)過濾系統的任何風險，以達到合規性。在此類風險評估中要考慮的要點應包括但不限於：	established during validation. Examples of tests that are used include bubble point, diffusive flow, water intrusion or pressure hold test. It is recognized that PUPSIT may not always be possible after sterilisation due to process constraints (e.g. the filtration of very small volumes of solution). In these cases, an alternative approach may be taken providing that a thorough risk assessment has been performed and compliance is achieved by the implementation of appropriate controls to mitigate any risk of a non-integral filtration system. Points to consider in such a risk assessment should include but are not limited to:
i. 深入了解及管制過濾器滅菌製程，以確保將過濾器損壞的可能性降至最低。	i. in depth knowledge and control of the filter sterilisation process to ensure that the potential for damage to the filter is minimized,
ii. 深入了解及管制供應鏈，包括：	ii. in depth knowledge and control of the supply chain to include:
• 受委託的滅菌廠，	• contract sterilisation facilities,
• 明確的運輸機制，	• defined transport mechanisms,
• 已滅菌過濾器的包裝，防止在運輸及儲存過程中損壞過濾器。	• packaging of the sterilised filter, to prevent damage to the filter during transportation and storage.
iii. 深入的製程知識，例如：	iii. in depth process knowledge such as:
• 特定產品類型，包括微粒負荷量以及是否存在影響過濾器完整性數值的風險，例如改變完整性測試值的可能性，從而防止在使用後過濾器完整性測試期間檢測到非完整的過濾器；以及	• the specific product type, including particle burden and whether there exists any risk of impact on filter integrity values, such as the potential to alter integrity-testing values and therefore prevent the detection of a non-integral filter during a post-use filter integrity test; and
• 在最末端滅菌級過濾器之前執行預過濾及製程步驟，即可在滅菌過濾之前去除微粒負荷並使產品澄清。	• pre-filtration and processing steps, prior to the final sterilising grade filter, which would remove particle burden and clarify the product prior to the sterile filtration.
8.88 關鍵無菌氣體及空氣通氣之過濾器（與產品的無菌性直接相關）的完整性應在使用後通過測試確認，且濾芯應保留在過濾器組合或濾殼中。	8.88 The integrity of critical sterile gas and air vent filters (that are directly linked to the sterility of the product) should be verified by testing after use, with the filter remaining in the filter assembly or housing.
8.89 非關鍵空氣或氣體通氣過濾器的完整性應在適當的時間間隔進行確認及記錄。如果氣體過濾器使用時間較長，則應在安裝時及更換前進行完整性測試。應根據風險規定及監控最長使用時間（例如，可行時，考慮最多使用次數及允許的熱處理/滅菌週期次數）。	8.89 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, integrity testing should be carried out at installation and prior to replacement. The maximum duration of use should be specified and monitored based on risk (e.g. considering the maximum number of uses and heat treatment/ sterilisation cycles permitted as applicable).
8.90 對於氣體過濾，應避免濾芯或過濾設備遭受非預期的受潮或潤濕。	8.90 For gas filtration, unintended moistening or wetting of the filter or filter equipment should be avoided.

8.91 如果滅菌過濾製程已被確效為由多個過濾器組成之系統以達到特定液體的無菌性，則此過濾系統被認為是單一的滅菌單元，系統內的所有過濾器在使用後應通過完整性測試。	8.91 If the sterilising filtration process has been validated as a system consisting of multiple filters to achieve the sterility for a given fluid, the filtration system is considered to be a single sterilising unit and all filters within the system should satisfactorily pass integrity testing after use.
8.92 在冗餘過濾系統中（其中第二個冗餘滅菌級過濾器作為支援，但經確效的滅菌製程只需要一個過濾器），應進行主要滅菌級過濾器的使用後完整性測試，如果證明是完整的，則不需要對冗餘（支援）過濾器進行使用後完整性測試。但是，如果第一個過濾器的使用後完整性測試失敗，則應對第二個（冗餘）過濾器進行使用後完整性測試，同時進行調查及風險評估，以確定導致第一個過濾器測試失敗的原因。	8.92 In a redundant filtration system (where a second redundant sterilising grade filter is present as a backup but the sterilising process is validated as only requiring one filter), post-use integrity test of the primary sterilising grade filter should be performed and if demonstrated to be integral, then a post-use integrity test of the redundant (backup) filter is not necessary. However, in the event of a failure of the post-use integrity test on the primary filter, post-use integrity test on the secondary (redundant) filter should be performed, in conjunction with an investigation and risk assessment to determine the reason for the primary filter test failure.
8.93 負荷菌樣品應從半製品中，以及在緊鄰最末端無菌過濾前取出。如果使用了冗餘的過濾裝置，則應在第一個過濾器之前進行。取樣系統的設計應避免引入污染。	8.93 Bioburden samples should be taken from the bulk product and immediately prior to the final sterile filtration. In case where a redundant filtration set-up is used, it should be taken prior to the first filter. Systems for taking samples should be designed so as not to introduce contamination.
8.94 液體滅菌級過濾器應在單一批次製程後丟棄，同一過濾器不應連續使用超過一個工作日，除非這種使用已確效。	8.94 Liquid sterilising grade filters should be discarded after the processing of a single batch and the same filter should not be used continuously for more than one working day unless such use has been validated.
8.95 如果產品的連續製造已在 CCS 中得到適當證明及確效，過濾器使用者應：	8.95 Where campaign manufacture of a product has been appropriately justified in the CCS and validated, the filter user should:
i. 評估並記錄特定液體的無菌過濾製程中，過濾器使用時間相關的風險；	i. assess and document the risks associated with the duration of filter use for the sterile filtration process for a given fluid;
ii. 進行並記錄有效的確效及驗證研究，以證明特定無菌過濾製程及特定液體的過濾器使用的持續時間不會影響最末端滅菌級過濾器的性能或濾液品質；	ii. conduct and document effective validation and qualification studies to demonstrate that the duration of filter use for a given sterile filtration process and for a given fluid does not compromise performance of the final sterilising grade filter or filtrate quality;
iii. 記錄過濾器的最長確效使用時間並予以管制，以確保過濾器的使用不超過確效的最長持續時間。應保留這些管制紀錄；	iii. document the maximum validated duration of use for the filter and implement controls to ensure that filters are not used beyond the validated maximum duration. Records of these controls should be maintained;
iv. 實施管制措施以確保被液體或清潔劑殘留物污染、或以任何其他方式被認為有缺陷的過濾器不會被使用。	iv. implement controls to ensure that filters contaminated with fluid or cleaning agent residues, or considered defective in any other way, are

	removed from use.
成型-充填-密封 (FFS)	**Form-Fill-Seal (FFS)**
8.96 用於最終滅菌產品的 FFS 機器的條件應符合本附則第 8.3 及 8.4 點的環境要求。用於無菌製造的 FFS 機器的條件應符合本附則第 8.10 點的環境要求。	8.96 The conditions for FFS machines used for terminally sterilised products should comply with the environmental requirements of paragraphs 8.3 and 8.4 of this Annex. The conditions for FFS machines used in aseptic manufacture should comply with the environmental requirements of paragraph 8.10 of this Annex.
8.97 組件製造、供應及處理過程中，應透過適當的管制將 FFS 製程中使用之包裝膜的污染降至最低。由於包裝膜的關鍵性，應實施程序以確保所提供的包裝膜符合界定的規格並具有適當的品質，包括材料厚度及強度、微生物及微粒污染的限量、完整性及相關的印刷圖文。 應在 PQS 中定義、管制包裝膜及相關組件的採樣頻率、負荷菌，以及可行時，內毒素/熱原限量，並在 CCS 中加以考慮。	8.97 Contamination of the packaging films used in the FFS process should be minimized by appropriate controls during component fabrication, supply and handling. Due to the criticality of packaging films, procedures should be implemented to ensure that the films supplied meet defined specifications and are of the appropriate quality, including material thickness and strength, microbial and particulate contamination, integrity and artwork, as relevant. The sampling frequency, the bioburden and, where applicable, endotoxin/pyrogen levels of packaging films and associated components should be defined and controlled within the PQS and considered in the CCS.
8.98 應特別注意了解及評估設備的操作，包括組裝、充填、密封及切割等製程，以便對關鍵製程參數能適當的了解、確效、管制及監測。	8.98 Particular attention should be given to understanding and assessing the operation of the equipment, including set-up, filling, sealing and cutting processes, so that critical process parameters are understood, validated, controlled and monitored appropriately.
8.99 任何與產品接觸的氣體，例如：給容器充氣或用於覆蓋產品的氣體應儘可能於靠近使用點處適當的過濾。應根據第 6.18 及 6.19 點定期確認所用氣體的品質及氣體過濾系統的有效性。	8.99 Any product contact gases, e.g. those used to inflate the container or used as a product overlay, should be appropriately filtered, as close to the point of use as possible. The quality of gases used and the effectiveness of gas filtration systems should be verified periodically in accordance with paragraphs 6.18 and 6.19.
8.100 FFS 驗證期間的管制措施應與 CCS 保持一致。需要考慮的面向包括但不限於：	8.100 The controls identified during qualification of FFS should be in alignment with the CCS. Aspects to be considered include but are not limited to:
i. 確定關鍵區域的界線，	i. determination of the boundaries of the critical zone,
ii. 環境管制及監測，包括機器及它所在的背景，	ii. environmental control and monitoring, both of the machine and the background in which it is placed,
iii. 人員著裝要求，	iii. personnel gowning requirements,
iv. 產品充填線及過濾系統的完整性測試（相關時），	iv. integrity testing of the product filling lines and filtration systems (as relevant),
v. 批次或充填活動的持續時間，	v. duration of the batch or filling campaign,
vi. 包裝膜的管制，包括對包裝膜去污染或滅菌的任何要求，	vi. control of packaging films, including any requirements for film decontamination or sterilisation,

vii. 必要時對設備進行原位清潔及原位滅菌，	vii. cleaning-in-place and sterilisation-in-place of equipment as necessary,
viii. 機器操作、設定及警報管理（相關時）。	viii. machine operation, settings and alarm management (as relevant).
8.101 FFS 的關鍵製程參數應在設備驗證期間確定，並應包括但不限於：	8.101 Critical process parameters for FFS should be determined during equipment qualification and should include, but are not limited to:
i. 根據經過確效的參數設定統一的包裝尺寸及切割；	i. settings for uniform package dimensions and cutting in accordance with validated parameters;
ii. 設定、維護及監測經過確效相關的成型溫度（包括預熱及冷卻）、成型時間及壓力；	ii. setting, maintenance and monitoring of validated forming temperatures (including pre-heating and cooling), forming times and pressures as relevant;
iii. 設定、維護及監測已確效相關的密封溫度、整個密封範圍的密封溫度均勻性、密封時間及壓力；	iii. setting, maintenance and monitoring of validated sealing temperatures, sealing temperature uniformity across the seal, sealing times and pressures as relevant;
iv. 環境及產品溫度；	iv. environmental and product temperature;
v. 批次特定之包裝的密封強度及均一性測試；	v. batch-specific testing of package seal strength and uniformity;
vi. 設定以達到正確的充填量、速度及充填均一性；	vi. settings for correct filling volumes, speeds and uniformity;
vii. 任何附加印刷（批次編碼）、凹凸壓花的設定，以確保單元完整性不受影響；	vii. settings for any additional printing (batch coding), embossing or debossing to ensure that unit integrity is not compromised;
viii. 充填容器完整性測試的方法及參數（參見第 8.22 點）。	viii. methods and parameters for integrity testing of filled containers (see paragraph 8.22).
8.102 在生產過程中應採用適當的程序來確認、監測及記錄 FFS 關鍵製程參數及設備操作。	8.102 Appropriate procedures for the verification, monitoring and recording of FFS critical process parameters and equipment operation should be applied during production.
8.103 操作程序應描述如何偵測、矯正成型及密封的問題。被拒用的單元或密封問題應予記錄及調查。	8.103 Operational procedures should describe how forming and sealing issues are detected and rectified. Rejected units or sealing issues should be recorded and investigated.
8.104 應根據風險制定適當的維護程序，包括對每一單元密封有效性之關鍵模具的維護及檢查計劃。任何被識別出有潛在產品品質問題的議題都應予記錄及調查。	8.104 Appropriate maintenance procedures should be established based on risk, and include maintenance and inspection plans for tooling critical to the effectiveness of unit sealing. Any issues identified that indicate a potential product quality concern should be documented and investigated.
吹製-充填-密封(BFS)	**Blow-Fill-Seal**
8.105 用於製造最終滅菌產品的吹製-充填-密封設備應安裝在至少 D 級環境中。充填點的條件應符合第 8.3 及 8.4 點的環境要求。	8.105 Blow-Fill-Seal equipment used for the manufacture of products which are terminally sterilised should be installed in at least a grade D environment. The conditions at the point of fill should comply with the environmental requirements of paragraphs 8.3 and 8.4.

8.106 BFS 用於無菌製程：	8.106 BFS used for aseptic processing:
i. 用於無菌充填的穿梭式設備，型坯對環境是開放的，因此型坯擠出、吹出塑形及密封的關鍵區域應滿足 A 級條件。充填環境的設計及維護應滿足 A 級條件靜、動態之微生物及總微粒的限值。	i. For shuttle type equipment used for aseptic filling, the parison is open to the environment and therefore the areas where parison extrusion, blow-moulding and sealing take place should meet grade A conditions at the critical zones. The filling environment should be designed and maintained to meet grade A conditions for viable and total particle limits both at rest and when in operation.
ii. 用於無菌充填的旋轉式設備，型坯通常一旦成型就成為密閉環境，型坯內的充填環境的設計及維護應滿足 A 級條件靜、動態之微生物及總微粒的限值。	ii. For rotary-type equipment used for aseptic filling, the parison is generally closed to the environment once formed, the filling environment within the parison should be designed and maintained to meet grade A conditions for viable and total particle limits both at rest and when in operation.
iii. 設備應至少安裝在 C 級環境中，前提是使用 A/B 級衣著。在 C 級區域對穿著 A/B 級衣著的作業人員進行微生物監測時，應按照風險管理原則進行，並考慮到作業人員所從事活動所適用的限值及監測頻率。	iii. The equipment should be installed in at least a grade C environment, provided that grade A/B clothing is used. The microbiological monitoring of operators wearing grade A/B clothing in a grade C area, should be performed in accordance with risk management principles, and the limits and monitoring frequencies applied with consideration of the activities performed by these operators.
8.107 由於聚合物在操作過程中的擠出及切割會產生微粒，以及 BFS 設備關鍵充填區的尺寸限制，因此不預期對 BFS–設備的總微粒進行動態監測。但是，應提供數據來證明設備的設計可確保充填製程環境的關鍵區域在動態下滿足 A 級條件。	8.107 Due to the generation of particles from polymer extrusion and cutting during operation, and the restrictive size of critical filling zones of BFS equipment, in operation monitoring of total particle for BFS equipment is not expected. However, data should be available to demonstrate that the design of the equipment ensures that critical zones of the filling process environment would meet grade A conditions in operation.
8.108 BFS 製程的微生物環境監測應基於風險，並根據本附則第 9 節進行設計。應在關鍵製程的整個過程中進行動態微生物監測，包括設備組裝。對於旋轉式 BFS 設備，可能無法監控關鍵充填區。	8.108 Viable environmental monitoring of BFS processes should be risk-based, and designed in accordance with section 9 of this Annex. In operation viable monitoring should be undertaken for the full duration of critical processing, including equipment assembly. For rotary-type BFS equipment, it is acknowledged that monitoring of the critical filling zone may not be possible.
8.109 環境管制及監測計畫應考慮 BFS 製程產生的移動部件與複雜的氣流路徑以及製程中高熱輸出的影響，（例如，通過使用氣流可視化研究及/或其他等效研究）。 環境監測計畫還應考慮空氣過濾器配置、空氣	8.109 The environmental control and monitoring programme should take into consideration the moving parts and complex airflow paths generated by the BFS process and the effect of the high heat outputs of the process, (e.g. through the use of airflow

過濾器完整性、冷卻系統完整性（參見第 6.21 點）、設備設計及驗證等因素。	visualization studies and/or other equivalent studies). Environmental monitoring programmes should also consider factors such as air-filter configuration, air-filter integrity, cooling systems integrity (see paragraph 6.21), equipment design and qualification.
8.110 模製容器的擠出、成型或密封過程中與容器關鍵表面接觸的空氣或其他氣體應經適當過濾。應根據第 6.18 及 6.19 點定期確認所用氣體的品質及氣體過濾系統的有效性。	8.110 Air or other gases that make contact with critical surfaces of the container during extrusion, formation or sealing of the moulded container should undergo appropriate filtration. The quality of gas used and the effectiveness of gas filtration systems should be verified periodically in accordance with paragraphs 6.18 and 6.19.
8.111 聚合物顆粒的儲存、取樣及輸配系統應通過適當的設計、管制及維護，來防止聚合物顆粒的微粒及微生物污染。	8.111 Particulate and microbial contamination of the polymer granulate should be prevented by appropriate design, control, and maintenance of the polymer granulate storage, sampling and distribution systems.
8.112 應了解擠出系統為模製容器提供適當無菌保證的能力並予確效。 原料聚合物的取樣頻率，負荷菌、以及可行時內毒素/熱原的限量應在 PQS 中界定及管制，並在 CCS 中加以考慮。	8.112 The capability of the extrusion system to provide appropriate sterility assurance for the moulded container should be understood and validated. The sampling frequency, the bioburden and, where applicable, endotoxin/pyrogen levels of the raw polymer should be defined and controlled within the PQS and considered in the CCS.
8.113 相關時，應在充填程序中清楚界定及描述要求停止充填及/或擠出、成型與密封，以及在需要時對充填機進行再滅菌的介入措施，並包含在 APS 中（參見第 9.34、9.35 及 9.36 點）。	8.113 Interventions requiring cessation of filling and/or extrusion, moulding and sealing and, where required, re-sterilisation of the filling machine should be clearly defined and described in the filling procedure, and included in the APS as relevant (see paragraphs 9.34, 9.35 and 9.36).
8.114 BFS 驗證期間確定的管制措施應與廠內的 CCS 保持一致。需要考慮的面向包括但不限於：	8.114 The controls identified during qualification of BFS should be in alignment with the site's CCS. Aspects to be considered include but are not limited to:
i. 確定關鍵區域的界線，	i. determination of the boundaries of the critical zone,
ii. 環境管制及監測，包括機器及它所在的背景。	ii. environmental control and monitoring, both of the machine and the background in which it is placed,
iii. 人員著裝要求，	iii. personnel gowning requirements,
iv. 產品充填線及過濾系統的完整性測試（相關時），	iv. integrity testing of the product filling lines and filtration systems (as relevant),
v. 批次或連續充填活動的時間，	v. duration of the batch or filling campaign,
vi. 管制聚合物顆粒，包括輸配系統及關鍵擠出溫度，	vi. control of polymer granulate, including distribution systems and critical extrusion temperatures,
vii. 必要時對設備進行原位清潔及原位滅菌，	vii. cleaning-in-place and sterilisation-in-place of equipment as necessary,
viii. 機器操作、設定及警報管理（相關時）。	viii. machine operation, settings and alarm management (as relevant).

8.115 BFS 的關鍵製程參數應在設備驗證期間確定，應包括但不限於：	8.115 Critical process parameters for BFS should be determined during equipment qualification and should include, but are not limited to:
i. 產品管路及充填針（心軸）的原位清潔及原位滅菌；	i. clean-in-place and sterilisation-in-place of product pipelines and filling needles (mandrels);
ii. 擠出參數的設定、維護及監控，包括溫度、速度及擠出喉部型坯厚度的設定；	ii. setting, maintenance and monitoring of extrusion parameters, including temperature, speed and extruder throat settings for parison thickness;
iii. 型坯溫度的設定、維護及監測，包括產品安定性所需的冷卻速率；	iii. setting, maintenance and monitoring of mould temperatures, including rate of cooling where necessary for product stability;
iv. 添加到模製單元之輔助組件的製備及滅菌，例如瓶蓋；	iv. preparation and sterilisation of ancillary components added to the moulded unit, e.g. bottle caps;
v. 相關時，關鍵之擠出、轉移及充填區域的環境管制、清潔、滅菌及監控；	v. environmental control, cleaning, sterilisation and monitoring of the critical extrusion, transfer and filling areas as relevant;
vi. 在容器的關鍵點測試批次特定的包裝壁厚度；	vi. batch-specific testing of package wall-thickness at critical points of the container;
vii. 設定以達到正確的充填量、速度及充填均一性；	vii. settings for correct filling volumes, speeds and uniformity;
viii. 設定任何附加的印刷（批次資訊）、凹版或凸版壓花，以確保包裝單元的完整性及品質不受影響；	viii. settings for any additional printing (batch coding), embossing or debossing to ensure that unit integrity and quality is not compromised;
ix. 所有充填容器經 100%完整性測試的方法及參數（參見第 8.22 點）；	ix. methods and parameters for integrity testing of 100% of all filled containers (see paragraph 8.22);
x. 設定用於去除充填單元周圍之廢塑料（毛邊去除）的切割器或銑模。	x. settings for cutters or punches used to remove waste plastic surrounding filled units (flash removal).
8.116 在生產過程中應採用適當的程序來確認、監測及記錄 BFS 關鍵製程參數與設備操作。	8.116 Appropriate procedures for the verification, monitoring and recording of BFS critical process parameters and equipment operation should be applied during production.
8.117 作業程序應描述如何檢測及矯正吹製、成型與密封問題。應記錄及調查被拒用單元或密封問題。	8.117 Operational procedures should describe how blowing, forming and sealing issues are detected and rectified. Rejected units or sealing issues should be recorded and investigated.
8.118 如果 BFS 製程包括添加組件到模製容器（例如，為 LVP 瓶添加蓋子），這些組件應適當去污染，並使用潔淨的、受管控的流程添加到製程中。	8.118 Where the BFS process includes the addition of components to moulded containers (e.g. addition of caps to LVP bottles), these components should be appropriately decontaminated and added to the process using a clean, controlled process.
i. 對於無菌製程，應在 A 級條件下添加組件，並使用預先滅菌的組件，以確保關鍵表面的無菌性。	i. For aseptic processes, the addition of components should be performed under grade A conditions, to ensure the sterility of critical surfaces, using pre-sterilised components.

ii. 對於最終滅菌的產品，最終滅菌製程確效應確保組件及模製容器之間所有關鍵產品路徑的無菌性，包括滅菌期間未潤濕的區域。	ii. For terminally sterilised products, the validation of terminal sterilisation processes should ensure the sterility of all critical product pathways between the component and moulded container, including areas that are not wetted during sterilisation.
iii. 應建立及確效測試程序，以確保組件及模製容器的有效密封。	iii. Testing procedures should be established and validated to ensure the effective sealing of components and moulded containers.
8.119 應根據風險制定適當的維護程序，包括對單元密封、完整性及無菌性關鍵品項的維護及檢查計畫。	8.119 Appropriate maintenance procedures should be established based on risk, and include maintenance and inspection plans for items critical to unit sealing, integrity and sterility.
8.120 用於形成容器的模具被認為是關鍵設備，對模具的任何變更或修改都應執行成品容器完整性的評估，並且評估的結果應經由確效支持。任何被識別出有潛在影響產品品質的議題，都應記錄並進行調查。	8.120 The moulds used to form containers are considered critical equipment and any changes or modification to moulds should result in an assessment of finished product container integrity, and where the assessment indicates, should be supported by validation. Any issues identified that indicate a potential product quality concern should be documented and investigated.
凍乾	**Lyophilization**
8.121 凍乾是一個關鍵的製程步驟，所有可能影響產品或原物料無菌性的活動，都需要被視為滅菌產品無菌製程的延伸。凍乾設備及其製程的設計應確保產品或原物料在凍乾過程中保持無菌性，藉由避免凍乾產品從充填到完成凍乾過程之間的微生物和微粒污染。所有線上的管制措施應由藥廠的 CCS 決定。	8.121 Lyophilization is a critical process step and all activities that can affect the sterility of the product or material need to be regarded as extensions of the aseptic processing of the sterilised product. The lyophilization equipment and its processes should be designed to ensure that product or material sterility is maintained during lyophilization by preventing microbial and particle contamination between the filling of products for lyophilization, and completion of lyophilization process. All control measures in place should be determined by the site's CCS.
8.122 凍乾機及相關設備（例如托盤、小瓶的支撐環）的滅菌應經確效，並在 APS 時對滅菌週期與使用之間的保持時間做適當的挑戰（參見第 9.33 點）。對凍乾機應根據系統設計定期滅菌。應在維護或清潔後進行重新滅菌。應保護已滅菌的凍乾機及相關設備不受污染。	8.122 The sterilisation of the lyophilizer and associated equipment (e.g. trays, vial support rings) should be validated and the holding time between the sterilisation cycle and use appropriately challenged during APS (see paragraph 9.33). The lyophilizer should be sterilised regularly, based on system design. Re-sterilisation should be performed following maintenance or cleaning. Sterilised lyophilizers and associated equipment should be protected from contamination after sterilisation.
8.123 凍乾機與相關的產品轉移，及裝載/卸載區域的設計應儘可能減少作業人員的介入。凍乾機滅菌的頻率應根據設計及使用過程中與系統污染相關的風險來確定。人工裝載或卸載且沒有屏障技術分離的凍乾機應	8.123 Lyophilizers and associated product transfer and loading/unloading areas should be designed to minimize operator intervention as far as possible. The frequency of lyophilizer sterilisation should be determined based on the design and risks related to

在每次裝載前進行滅菌。對於由自動化系統裝載及卸載或由密閉屏障系統保護的凍乾機，應證明滅菌頻率之合理性，並文件化作為 CCS 的一部分。	system contamination during use. Lyophilizers that are manually loaded or unloaded with no barrier technology separation should be sterilised before each load. For lyophilizers loaded and unloaded by automated systems or protected by closed barrier systems, the frequency of sterilisation should be justified and documented as part of the CCS.
8.124 在滅菌後及凍乾過程中應保持凍乾機的完整性。用於保持凍乾機完整性的過濾器應在每次使用該系統前進行滅菌，其完整性測試結果應作為批次認可/放行的一部分。艙室的真空/洩漏完整性測試的頻率應予文件化，應規定容許滲入凍乾機的最大空氣量，並在每個滅菌週期開始時檢查。	8.124 The integrity of the lyophilizer should be maintained following sterilisation and during lyophilization. The filter used to maintain lyophilizer integrity should be sterilised before each use of the system and its integrity testing results should be part of the batch certification/release. The frequency of vacuum/leak integrity testing of the chamber should be documented and the maximum permitted leakage of air into the lyophilizer should be specified and checked at the start of every cycle.
8.125 應定期檢查凍乾托盤確保無變形或損壞。	8.125 Lyophilization trays should be checked regularly to ensure that they are not misshapen or damaged.
8.126 裝載（及卸載，在凍乾物尚未密封且暴露的情況下）設計的考慮要點包括但不限於：	8.126 Points to consider for the design of loading (and unloading, where the lyophilized material is still unsealed and exposed), include but are not limited to:
i. 應規定凍乾機內的裝載型式並予文件化。	i. The loading pattern within the lyophilizer should be specified and documented.
ii. 將部分封閉的容器轉送到凍乾機時，應始終在 A 級條件下進行，並以儘量減少作業人員直接介入的方式進行處理。應使用輸送帶系統或移動式轉送系統（例如潔淨空氣轉運車、移動式單向氣流工作站）等技術，以確保用於部分封閉容器的轉送系統能維持其潔淨度。或者，經確效的情況下，在 A 級區密封且在 B 級區不會重新打開的托盤，可用於保護部分封塞的小瓶（例如適當封閉的盒子）。	ii. The transfer of partially closed containers to a lyophilizer should be undertaken under grade A conditions at all times and handled in a manner designed to minimize direct operator intervention. Technologies such as conveyor systems or portable transfer systems (e.g. clean air transfer carts, portable unidirectional airflow workstations) should be used to ensure that the cleanliness of the system used to transfer the partially closed containers is maintained. Alternatively, where supported by validation, trays closed in grade A and not reopened whilst in the grade B area may be used to protect partially stoppered vials (e.g. appropriately closed boxes).
iii. 運輸裝置及裝載區的通風不應對氣流型態產生不利影響。	iii. Airflow patterns should not be adversely affected by transport devices and venting of the loading zone.
iv. 未密封的容器（例如部分封塞的小瓶）應保持在 A 級條件下，通常應通過實體屏障技術或任何其他適當措施與作業人員隔開。	iv. Unsealed containers (such as partially stoppered vials) should be maintained under grade A conditions and should normally be separated from operators by physical barrier technology or any other appropriate measures.
v. 如果在打開凍乾機艙室之前產品屬於未	v. Where seating of the stoppers is not completed

完成封塞狀態，則從凍乾機中取出的產品在隨後的處理過程中應保持在 A 級條件下。	prior to opening the lyophilizer chamber, product removed from the lyophilizer should remain under grade A conditions during subsequent handling.
vi. 裝載及卸載凍乾機時使用的器具（例如托盤、袋子、定位裝置、鑷子）應是無菌的。	vi. Utensils used during loading and unloading of the lyophilizer (e.g. trays, bags, placing devices, tweezers) should be sterile.
密閉系統	**Closed systems**
8.127 使用密閉系統可以降低來自鄰近環境的微生物、微粒及化學污染的風險。密閉系統應始終設計為減少人工操作的需求及相關風險。	8.127 The use of closed systems can reduce the risk of microbial, particle and chemical contamination from the adjacent environment. Closed systems should always be designed to reduce the need for manual manipulations and the associated risks.
8.128 確保用於無菌製程之密閉系統的所有與產品接觸表面的無菌性至關重要。用於無菌製程之任何密閉系統的設計及選擇，應確保能維持無菌狀態。在末端滅菌級過濾器之後，無菌設備（例如管線/管路）與滅菌產品路徑的連接應設計為無菌連接（例如通過內建無菌連接裝置）。	8.128 It is critical to ensure the sterility of all product contact surfaces of closed systems used for aseptic processing. The design and selection of any closed system used for aseptic processing should ensure maintenance of sterility. Connection of sterile equipment (e.g. tubing/pipework) to the sterilised product pathway after the final sterilising grade filter should be designed to be connected aseptically (e.g. by intrinsic sterile connection devices).
8.129 應採取適當措施確保無菌連接中使用組件的完整性。實現這一目標的方法應在 CCS 中確定及記錄。當存在損害產品無菌性風險時，應考慮進行適當的系統完整性測試。供應商評估應包括可能導致系統喪失無菌性之潛在失敗模式相關數據的整理。	8.129 Appropriate measures should be in place to ensure the integrity of components used in aseptic connections. The means by which this is achieved should be determined and captured in the CCS. Appropriate system integrity tests should be considered when there is a risk of compromising product sterility. Supplier assessment should include the collation of data in relation to potential failure modes that may lead to a loss of system sterility.
8.130 密閉系統所處的背景環境應基於其設計及所採取的製程。對於無菌製程且該系統的完整性可能受到損害的任何風險，該系統應位於 A 級區。如果可以證明系統在每次使用時都保持完整（例如通過壓力測試及/或監控），那麼可以使用較低的級區。應徹底評估級區之間的任何轉送（參見第 4.10 點）。若密閉系統有打開需求時（例如，半製品製造線的維護），則應在適合該原物料的級區進行（例如，用於最終滅菌製程的 C 級區，或用於無菌製程的 A 級區）或進一步清潔及消毒（如為無菌製程則應滅菌）。	8.130 The background environment in which closed systems are located should be based on their design and the processes undertaken. For aseptic processing and where there are any risks that system integrity may be compromised, the system should be located in grade A. If the system can be shown to remain integral at every usage (e.g. via pressure testing and/or monitoring) then a lower classified area may be used. Any transfer between classified areas should be thoroughly assessed (see paragraph 4.10). If the closed system is opened (e.g. for maintenance of a bulk manufacturing line) then this should be performed in a classified area appropriate to the materials (e.g. grade C for terminal sterilisation processes, or grade A for aseptic processing) or be subject to further cleaning and disinfection (and sterilisation in case of aseptic processes).

一次性使用系統 (SUS)	Single use systems (SUS)
8.131 SUS 是用於製造無菌產品的技術，可替代重複使用的設備。SUS 可以是單一組件，也可以由多個組件組成，例如袋子、過濾器、管線、連接器、閥門、儲存瓶及傳感器。一次性使用系統應設計為減少對人為操作的需求及人工介入的複雜性。	8.131 SUS are those technologies used in manufacture of sterile products which are used as an alternative to reusable equipment. SUS can be individual components or made up of multiple components such as bags, filters, tubing, connectors, valves, storage bottles and sensors. Single use systems should be designed to reduce the need for manipulations and complexity of manual interventions.
8.132 有些與 SUS 相關的特定風險，應作為 CCS 的一部分進行評估。這些風險包括但不限於：	8.132 There are some specific risks associated with SUS which should be assessed as part of the CCS. These risks include but are not limited to:
i. 產品與產品接觸表面之間的相互作用（如吸附，或浸出與萃取），	i. the interaction between the product and product contact surface (such as adsorption, or leachables and extractables),
ii. 相較於固定的可重複使用系統之脆弱本質，	ii. the fragile nature of the system compared with fixed reusable systems,
iii. 增加人工操作(包括系統的檢查與處理)與連接的數量及複雜性，	iii. the increase in the number and complexity of manual operations (including inspection and handling of the system) and connections made,
iv. 組裝的複雜性，	iv. the complexity of the assembly,
v. 滅菌級過濾器使用前及使用後完整性測試的性能（參見第 8.87 點），	v. the performance of the pre- and post-use integrity testing for sterilising grade filters (see paragraph 8.87),
vi. 存在孔洞及洩漏的風險，	vi. the risk of holes and leakage,
vii. 打開外包裝時可能危及系統，	vii. the potential for compromising the system at the point of opening the outer packaging,
viii. 微粒污染的風險。	viii. the risk of particle contamination.
8.133 SUS 的滅菌製程應經過確效，並證明對系統性能無不利影響。	8.133 Sterilisation processes for SUS should be validated and shown to have no adverse impact on system performance.
8.134 一次性使用系統(包括滅菌)供應商的評估，對於這些系統的選擇及使用至關重要。對於無菌 SUS，無菌保證的確認應為供應商驗證的一部分，並且應在接收時，檢查每一個單元的滅菌證據。	8.134 Assessment of suppliers of disposable systems including sterilisation is critical to the selection and use of these systems. For sterile SUS, verification of sterility assurance should be performed as part of the supplier qualification and evidence of sterilisation of each unit should be checked on receipt.
8.135 產品與產品接觸表面的吸附及反應性應在製程條件下進行評價。	8.135 The adsorption and reactivity of the product with product contact surfaces should be evaluated under process conditions.
8.136 應評價 SUS 的可萃取物及可浸出物的概貌，以及對產品品質的任何影響，特別是由聚合物材料製成的一次性使用系統。應對每一組件進行評估，以評價可萃取物概貌數據的適用性。對於被認為可浸出物有高風險的組件，包括可能吸收製程物質或與其接觸時間較長的組件，應考慮對可浸出物概貌研究的評估，包括安全性問題。	8.136 The extractable and leachable profiles of the SUS and any impact on the quality of the product especially where the system is made from polymer-based materials should be evaluated. An assessment should be carried out for each component to evaluate the applicability of the extractable profile data. For components considered to be at high risk from leachables, including those that may absorb processed

如果應用模擬的製程條件，則應準確反映實際製程，並具有科學依據。	materials or those with extended material contact times, an assessment of leachable profile studies, including safety concerns, should be taken into consideration. If applying simulated processing conditions, these should accurately reflect the actual processing conditions and be based on a scientific rationale.
8.137 SUS 應設計為在預期作業條件下的整個製程中保持完整性。如果在例行製程或運輸過程中可能會暴露在更極端的條件下(例如冷凍及解凍過程)，則必須注意一次性使用組件的結構完整性。這應包括確認內建的無菌連接裝置（熱封及機械式密封）在這些條件下保持完整。	8.137 SUS should be designed to maintain integrity throughout processing under the intended operational conditions. Attention to the structural integrity of the single use components is necessary where these may be exposed to more extreme conditions (e.g. freezing and thawing processes) either during routine processing or transportation. This should include verification that intrinsic sterile connection devices (both heat sealed and mechanically sealed) remain integral under these conditions.
8.138 應根據產品及其製程的風險或關鍵性，為 SUS 建立及實施允收標準。接收時，應檢查每件 SUS，以確保它們是按照核准的規格製造、供應和運送的。使用前應對外包裝（例如外部紙箱、產品袋的外觀）、標籤打印及附加文件（例如合格證書及滅菌證明）進行目視檢查，並文件化。	8.138 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 sterilisation) should be carried out and documented prior to use.
8.139 SUS 的關鍵人工處理作業，例如組裝及連接，應受到適當的管制，並在 APS 期間進行確認。	8.139 Critical manual handling operations of SUS such as assembly and connections should be subject to appropriate controls and verified during APS.

9 環境與製程監測 (Environmental & process monitoring)

概述	**General**
9.1 藥廠的環境及製程監測計畫是整體 CCS 的一部分，是用於監測將微生物及微粒污染風險降至最低的管制措施。應該注意的是，將監測系統的每個要項（微生物、浮游微粒及 APS）分開之後的個別可靠性是有限的，所以不應被個別地考量為無菌狀態指標。當一起考量時，其結果有助於確認它們所監測之系統的設計、確效及操作的可靠性。	9.1 The site's environmental and process monitoring programme forms part of the overall CCS and is used to monitor the controls designed to minimize the risk of microbial and particle contamination. It should be noted that the reliability of each of the elements of the monitoring system (viable, non-viable and APS) when taken in isolation is limited and should not be considered individually to be an indicator of asepsis. When considered together, the results help confirm the reliability of the design, validation and operation of the system that they are monitoring.
9.2 該計畫通常由以下要項組成：	9.2 This programme is typically comprised of the following elements:

i. 環境監測—總微粒；	i. environmental monitoring – total particle;
ii. 環境及人員監測—微生物；	ii. environmental and personnel monitoring – viable particle;
iii. 溫度、相對濕度及其他特定性質；	iii. temperature, relative humidity and other specific characteristics;
iv. APS（僅限於無菌製造之產品）。	iv. APS (aseptically manufactured product only).
9.3 來自這些系統之資訊應使用於例行批次認可/放行以及製程檢討或調查期間之定期評估。這適用於最終滅菌及無菌製程，但是，其影響的嚴重程度可能因產品及製程類型而異。	9.3 The information from these systems should be used for routine batch certification/release and for periodic assessment during process review or investigation. This applies for both terminal sterilisation and aseptic processes, however, the criticality of the impact may differ depending upon the product and process type.
環境與製程監測	**Environmental and process monitoring**
9.4 應建立文件化的環境監測計畫。環境監測計畫的目的是：	9.4 An environmental monitoring programme should be established and documented. The purpose of the environmental monitoring programme, is to:
i. 確保潔淨室及潔淨空氣設備依設計及法規要求，以持續提供適當的空氣潔淨度環境。	i. Provide assurance that cleanrooms and clean air equipment continue to provide an environment of appropriate air cleanliness, in accordance with design and regulatory requirements.
ii. 有效地偵測出對於環境限值的偏離，以啟動對於產品品質風險的調查及評估。	ii. Effectively detect excursions from environmental limits triggering investigation and assessment of risk to product quality.
應執行風險評估以建立全面的環境監測計畫，亦即採樣位置、監測頻率、監測方法以及培養條件（例如：時間、溫度、好氧及/或厭氧條件）。執行這些風險評估應基於以下的詳細知識：投入製程的原物料及最終產品、設施、設備、特定製程及步驟的關鍵性、所涉及之操作、例行監測數據、於驗證期間所獲得之監測數據以及從環境中所分離出來之代表性菌叢的知識。	Risk assessments should be performed in order to establish this comprehensive environmental monitoring programme, i.e. sampling locations, frequency of monitoring, monitoring methods and incubation conditions (e.g. time, temperature(s), aerobic and/or anaerobic conditions). These risk assessments should be conducted based on detailed knowledge of; the process inputs and final product, the facility, equipment, the criticality of specific processes and steps, the operations involved, routine monitoring data, monitoring data obtained during qualification and knowledge of typical microbial flora isolated from the environment.
該風險評估應包含確定關鍵監測位置，亦即在製程中如有微生物存在則可能會對產品品質產生影響的位置（例如：A 級區、無菌作業區以及與 A 級區直接交界的 B 級區）。還應考量納入空氣可視化研究等其他資訊。這些風險評估應予定期審查，以確認藥廠環境監測計畫的有效性。應考量將監測計畫納入藥廠之整體趨勢分析與 CCS 範圍中。	The risk assessment should include the determination of critical monitoring locations, those locations where the presence of microorganisms during processing may have an impact upon product quality, (e.g. grade A, aseptic processing areas and the grade B areas that directly interface with the grade A area). Consideration of other information such as air visualisation studies should also be included. These risk assessments should be reviewed regularly in order to confirm the effectiveness of the site's environmental monitoring programme. The

	monitoring programme should be considered in the overall context of the trend analysis and the CCS for the site.
9.5 對潔淨室、潔淨空氣設備以及人員之日常監測，應在所有關鍵製程階段的動態中執行，包括設備組裝。	9.5 Routine monitoring of cleanrooms, clean air equipment and personnel should be performed in operation throughout all critical stages of processing, including equipment set-up.
9.6 諸如溫度及相對濕度等其他特性，應控制在符合產品/製程/人員需求的範圍內，並支持所界定之潔淨度標準（例如：A 級區或 B 級區）的維持。	9.6 Other characteristics, such as temperature and relative humidity, should be controlled within ranges that align with product/processing/personnel requirements and support maintenance of defined cleanliness standards (e.g. grade A or B).
9.7 對於 A 級區的監測應能證明關鍵操作過程中無菌製程條件的維持。應在對於無菌的設備表面、容器、封蓋以及產品造成最高污染風險的位置執行監測。為了在關鍵區域獲得可靠數據，監測位置的選擇以及採樣裝置的方向與定位應合理且適當。	9.7 The monitoring of grade A should demonstrate the maintenance of aseptic processing conditions during critical operations. Monitoring should be performed at locations posing the highest risk of contamination to the sterile equipment surfaces, containers, closures and product. The selection of monitoring locations and the orientation and positioning of sampling devices should be justified and appropriate to obtain reliable data from the critical zones.
9.8 採樣方法不應對製造作業造成污染風險。	9.8 Sampling methods should not pose a risk of contamination to the manufacturing operations.
9.9 應對微生物及總微粒監測的結果設定適當的警戒水準及行動限量。最大總微粒行動限量描述於表 5，最大微生物行動限量描述於表 6。但是，可採用基於數據的趨勢、製程本質或於 CCS 決定之更嚴格的行動限量。微生物及總微粒警戒水準的建立均應基於潔淨室驗證的測試結果，並基於持續的趨勢數據予以定期審查。	9.9 Appropriate alert levels and action limits should be set for the results of viable and total particle monitoring. The maximum total particle action limits are described in Table 5 and the maximum viable particle action limits are described in Table 6. However, more stringent action limits may be applied based on data trending, the nature of the process or as determined within the CCS. Both viable and total particle alert levels should be established based on results of cleanroom qualification tests and periodically reviewed based on ongoing trend data.
9.10 A 級區（僅總微粒）、B 級區、C 級區以及 D 級區之警戒水準的設定，應能使不良趨勢（例如：事件的次數或顯示環境管制劣化的個別事件）被偵測出並予解決。	9.10 Alert levels for grade A (total particle only) grade B, grade C and grade D should be set such that adverse trends (e.g. a numbers of events or individual events that indicate a deterioration of environmental control) are detected and addressed.
9.11 監測程序中應明訂趨勢分析方法。趨勢應包含，但不限於：	9.11 Monitoring procedures should define the approach to trending. Trends should include, but are not limited to:
i. 越來越多的偏離行動限量或警戒水準；	i. increasing numbers of excursions from action limits or alert levels;
ii. 連續偏離警戒水準；	ii. consecutive excursions from alert levels;

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

表 5：被允許之總微粒監測的最大濃度。

級區	≧0.5μm/m³ 粒子的最大限量		≧5 μm/m³ 粒子的最大限量	
	靜態	動態	靜態	動態
A	3 520	3 520	29	29
B	3 520	352 000	29	2 930
C	352 000	3520 000	2 930	29 300
D	3 520 000	未預先訂定[a]	29 300	未預先訂定[a]

Table 5: Maximum permitted total particle concentration for monitoring.

Grade	Maximum limits for total particle ≥ 0.5 μm/m³		Maximum limits for total particle ≥ 5 μm/m³	
	at rest	in operation	at rest	In operation
A	3 520	3 520	29	29
B	3 520	352 000	29	2 930

C	352 000	352 000	2 930	29 300
D	3 520 000	Not predetermined [a]	29 300	Not predetermined [a]

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

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

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

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

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

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

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

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

9.17 A 級區之 ≥0.5 及 ≥5 μm 的微粒應予連續監測，並以合適之採樣流速（至少每分鐘 28 L [1ft^3]），以偵測所有介入、短暫突發事件以及任何的系統劣化。系統應經常將每個個別的樣本結果與警戒水準及行動限量相比對，這樣的頻率可以識別出任何潛在的偏差並即時回應。如果超過警戒水準，則應啟動警報。作業程序中應界定警報時所需採取的行動，包括考慮額外的微生物監測。

9.17 The grade A area should be monitored continuously (for particles ≥0.5 and ≥5 μm) and with a suitable sample flow rate (at least 28 litres (1ft^3) per minute) so that all interventions, transient events and any system deterioration is captured. The system should frequently correlate each individual sample result with alert levels and action limits at such a frequency that any potential excursion can be identified and responded to in a timely manner. Alarms should be triggered if alert levels are exceeded. Procedures should define the actions to be taken in response to alarms including the consideration of additional microbial monitoring.

9.18 雖然在 B 級區的採樣頻率可能可以降低，但仍建議使用類似的系統。B 級區應以適當的取樣量及頻率執行監測，以使監測程序能夠偵測出任何增加的污染及系統劣化程度。如果超過警戒水準，則警報應會被啟動。

9.18 It is recommended that a similar system be used for the grade B area although the sample frequency may be decreased. The grade B area should be monitored at such a frequency and with suitable sample size that the programme captures any increase in levels of contamination and system deterioration. If alert levels are exceeded, alarms should be triggered.

9.19 監測系統的選擇應考量製造作業中所使用之原物料（例如：包含活微生物、粉末狀產品或放射性藥品）所可能增加之生物、化學或輻射危害的任何風險。	9.19 The selection of the monitoring system should take into account any risk presented by the materials used in the manufacturing operation (e.g. those involving live organisms, powdery products or radiopharmaceuticals) that may give rise to biological, chemical or radiation hazards.
9.20 對於製程中出現污染物而且可能損壞微粒計數器或呈現危害（例如：活微生物、粉末狀產品以及輻射危害）的情況，其所採用的頻率及策略應確保在暴露於風險前、後之環境等級。應考量增加微生物監測，以確保製程的全面監測。此外，應於模擬操作期間執行監測。這類操作應以適當的時間間隔執行，並明訂於 CCS 中。	9.20 In the case where contaminants are present due to the processes involved and would potentially damage the particle counter or present a hazard (e.g. live organisms, powdery products and radiation hazards), the frequency and strategy employed should be such as to assure the environmental classification both prior to and post exposure to the risk. An increase in viable particle monitoring should be considered to ensure comprehensive monitoring of the process. Additionally, monitoring should be performed during simulated operations. Such operations should be performed at appropriate intervals. The approach should be defined in the CCS.
9.21 使用自動化系統所採集之監測樣本量，通常依所使用之系統的採樣速率而定。樣本量不需與用於潔淨室及潔淨空氣設備之正式分級的樣本量相同。監測樣本量之合理性應經證明。	9.21 The size of monitoring samples taken using automated systems will usually be a function of the sampling rate of the system used. It is not necessary for the sample volume to be the same as that used for formal classification of cleanrooms and clean air equipment. Monitoring sample volumes should be justified.
環境及人員監測—微生物	**Environmental and personnel monitoring – viable particle**
9.22 應於執行無菌操作的場所頻繁地使用諸如落菌培養皿、定量空氣採樣器、手套、工作服以及表面採樣工具（例如：擦拭及接觸培養皿）等的組合方法監測微生物。所使用之採樣方法應於 CCS 中證明其合理性，且應證明不會對 A 級區及 B 級區氣流型態產生不利影響。潔淨室及設備表面應於操作結束時予以監測。	9.22 Where aseptic operations are performed, microbial monitoring should be frequent using a combination of methods such as settle plates, volumetric air sampling, glove, gown and surface sampling (e.g. swabs and contact plates). The method of sampling used should be justified within the CCS and should be demonstrated not to have a detrimental impact on grade A and B airflow patterns. Cleanroom and equipment surfaces should be monitored at the end of an operation.
9.23 在非執行正常製造作業期間（例如：消毒後、開始製造前、批次完成及停工期之後）的潔淨室內，以及未使用之相關房間內，也應執行微生物監測，以偵測可能影響潔淨室內管制的潛在污染事件。在發生意外事件時，可以使用額外的採樣位置來確認矯正措施（例如：清潔及消毒）的有效性。	9.23 Viable particle monitoring should also be performed within the cleanrooms when normal manufacturing operations are not occurring (e.g. post disinfection, prior to start of manufacturing, on completion of the batch and after a shutdown period), and in associated rooms that have not been used, in order to detect potential incidents of contamination which may affect the controls within the cleanrooms. In case of an incident, additional

	sample locations may be used as a verification of the effectiveness of a corrective action (e.g. cleaning and disinfection).
9.24 A 級區的關鍵製程應全程持續監測微生物（例如：以空氣採樣器或落菌培養皿），包括設備無菌組裝及關鍵製程。應基於影響無菌製程之風險考量，對 B 級區潔淨室採用類似的方法。監測的執行方式應能偵測出所有介入、短暫突發事件以及任何系統劣化，並避免因監測操作的介入而導致任何風險。	9.24 Continuous viable air monitoring in grade A (e.g. air sampling or settle plates) should be undertaken for the full duration of critical processing, including equipment (aseptic set-up) assembly and critical processing. A similar approach should be considered for grade B cleanrooms based on the risk of impact on the aseptic processing. The monitoring should be performed in such a way that all interventions, transient events and any system deterioration would be captured and any risk caused by interventions of the monitoring operations is avoided.
9.25 風險評估應依所執行之作業及與關鍵區的鄰近程度，來評估人員監測的位置、類型及頻率。監測應包含在製程中定期對人員採樣。對人員採樣應以不會危及製程之方式進行。應特別考量在參與關鍵介入之後（可根據介入程度監測工作服相關部位，但至少一定要監測手套）及每次離開 B 級區潔淨室之人員的監測（手套及工作服）。當在關鍵介入之後對手套執行監測時，應在繼續工作之前更換外層手套。當在關鍵介入後需要監測工作服時，應在潔淨室內進行後續作業前更換工作服。	9.25 A risk assessment should evaluate the locations, type and frequency of personnel monitoring based on the activities performed and the proximity to critical zones. Monitoring should include sampling of personnel at periodic intervals during the process. Sampling of personnel should be performed in such a way that it will not compromise the process. Particular consideration should be given to monitoring personnel following involvement in critical interventions (at a minimum gloves, but may require monitoring of areas of gown as applicable to the process) and on each exit from the grade B cleanroom (gloves and gown). Where monitoring of gloves is performed after critical interventions, the outer gloves should be replaced prior to continuation of activity. Where monitoring of gowns is required after critical interventions, the gown should be replaced before further activity in the cleanroom.
9.26 應對在 A 級區及 B 級區的人員執行微生物監測。對於本質是人工操作之作業（例如：無菌調配或充填），其所增加的風險應導致加強工作服的微生物監測，並在 CCS 中證明其合理性。	9.26 Microbial monitoring of personnel in the grade A and grade B areas should be performed. Where operations are manual in nature (e.g. aseptic compounding or filling), the increased risk should lead to enhanced emphasis placed on microbial monitoring of gowns and justified within the CCS.
9.27 當由製造人員執行例行性監測時，應接受品質單位的定期監督（亦請參見第 8.19 點）。	9.27 Where monitoring is routinely performed by manufacturing personnel, this should be subject to regular oversight by the quality unit (refer also to paragraph 8.19).
9.28 製造廠應考量採用合適的替代監測系統，例如快速方法，以加快偵測微生物污染問題並降低產品風險。在經確效證明與已建立之方法等同或更佳後，可以採用這些快速且自動	9.28 The adoption of suitable alternative monitoring systems such as rapid methods should be considered by manufacturers in order to expedite the detection of microbiological contamination

化的微生物監測方法。	issues and to reduce the risk to product. These rapid and automated microbial monitoring methods may be adopted after validation has demonstrated their equivalency or superiority to the established methods.
9.29 應充分了解所使用之採樣方法及設備，且應備有作業程序以供正確操作與解讀所得結果。應可取得對於所選用採樣方法之回收效率的支持性數據。	9.29 Sampling methods and equipment used should be fully understood and procedures should be in place for the correct operation and interpretation of results obtained. Supporting data for the recovery efficiency of the sampling methods chosen should be available.
9.30 微生物污染的行動限量如表 6 所示	9.30 Action limits for viable particle contamination are shown in Table 6

表 6：微生物污染的最大行動限量

等級	空氣樣品 CFU /m^3	落菌培養皿（直徑 90 mm） CFU /4 小時[(a)]	接觸培養皿 (直徑55 mm), CFU / plate [(b)]	手套指印，包括雙手 5指 CFU/手套
A	無生長[(c)]			
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

Table 6: Maximum action limits for viable particle contamination

Grade	Air sample cfu/m^3	Settle plates (diam. 90 mm) CFU/4 hours [(a)]	Contact plates (diam. 55mm), CFU/ plate [(b)]	Glove print, Including 5 fingers on both hands CFU/ glove
A	No growth[(c)]			
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

(a) 落菌培養皿應在作業期間（包括設備組裝）暴露於 A 級區及 B 級區，並在最多 4 小時之後依需要進行更換（暴露時間應基於包含回收研究在內的確效，且不應對所使用之培養基的適用性產生任何負面影響）。 ▪ 對於 C 級區及 D 級區，其暴露時間（最多 4 小時）及頻率應基於 QRM。 ▪ 個別落菌培養皿的暴露時間可以少於 4 小時。	(a) - Settle plates should be exposed in grade A and B areas for the duration of operations (including equipment set-up) and changed as required after a maximum of 4 hours (exposure time should be based on validation including recovery studies and it should not have any negative effect on the suitability of the media used). ▪ For grade C and D areas, exposure time (with a maximum of 4 hours) and frequency should be based on QRM. ▪ Individual settle plates may be exposed for less than 4 hours.
(b) 接觸培養皿限量適用於 A 級區及 B 級區內的設備、房間及工作服表面。C 級區及 D 級區通常不需要例行的工作服監測，這取決於該區域功能而定。	(b) Contact plate limits apply to equipment, room and gown surfaces within the grade A and grade B areas. Routine gown monitoring is not normally required for grade C and D areas, depending on their function.
(c) 應注意，對於 A 級區內的任何長菌情形都應予調查。	(c) It should be noted that for grade A, any growth should result in an investigation.
註 1：應注意上表所列出的監測方法類型僅是舉例，也可以使用其他方法，其前提是可符合為產品可能被污染之整個關鍵製程提供資訊的目的（例如：無菌生產線組裝、無菌製程、充填及凍乾機裝載）。	Note 1: It should be noted that the types of monitoring methods listed in the table above are examples and other methods can be used provided they meet the intent of providing information across the whole of the critical process where product may be contaminated (e.g. aseptic

	line set-up, aseptic processing, filling and lyophilizer loading).
註 2：在整份文件中使用 CFU 作為限量的單位。當使用不同的或新的技術以不同於 CFU 的方式呈現結果時，製造廠應科學地證明被應用之限量的合理性，並在可能的情況下將其與 CFU 相關聯。	Note 2: Limits are applied using CFU throughout the document. If different or new technologies are used that present results in a manner different from CFU, the manufacturer should scientifically justify the limits applied and where possible correlate them to CFU.
9.31 在 A 級區及 B 級區被偵測出來的微生物，應鑑別到種，並評估此類微生物對產品品質（對所涉及之每一批次）及整體管制狀態的潛在影響。對於 C 級區及 D 級區，亦應考量對於在超出行動限量或警戒水準等場合所偵測到的、或在微生物分離後所得到的諸如可形成孢子之微生物與黴菌等難予管制之微生物的鑑別；且以足夠的頻率來維持對於這些區域之當前典型菌叢的了解。	9.31 Microorganisms detected in the grade A and grade B areas should be identified to species level and the potential impact of such microorganisms on product quality (for each batch implicated) and overall state of control should be evaluated. Consideration should also be given to the identification of microorganisms detected in grade C and D areas (for example where action limits or alert levels are exceeded) or following the isolation of organisms that may indicate a loss of control, deterioration in cleanliness or that may be difficult to control such as spore-forming microorganisms and moulds and at a sufficient frequency to maintain a current understanding of the typical flora of these areas.
無菌製程模擬 (APS)（亦稱為培養基充填）	**Aseptic process simulation (APS) (also known as media fill)**
9.32 對於無菌操作管制之有效性的定期確認應包含 APS(使用無菌營養培養基及/或替代物代替產品)。APS 不應被視為是確效該無菌製程或該無菌製程之各層面的主要方法。無菌製程之有效性應透過製程設計、遵守製藥品質系統與製程管制、教育訓練以及評估監測數據來確認。適當的營養培養基及/或替代物之選擇應基於其模擬產品於製程中具無菌性風險的產品實質特性之評估。對於諸如以無菌生產的半固體、粉末、固形物、微球體、微脂體以及產品被冷卻或被加熱或被凍乾等其他劑型，在製程階段可能有會間接影響任何被引入之污染微生物的生存能力時，應儘可能開發代表該項操作的近似替代程序。在諸如緩衝劑等替代物被使用為 APS 的一部分時，該替代物不應抑制任何潛在污染物的生長。	9.32 Periodic verification of the effectiveness of the controls in place for aseptic processing should include an APS using a sterile nutrient media and/or surrogate in place of the product. The APS should not be considered as the primary means to validate the aseptic process or aspects of the aseptic process. The effectiveness of the aseptic process should be determined through process design, adherence to the pharmaceutical quality system and process controls, training, and evaluation of monitoring data. Selection of an appropriate nutrient media and/or surrogate should be made based on the ability of the media and/or surrogate to imitate physical product characteristics assessed to pose a risk to product sterility during the aseptic process. Where processing stages may indirectly impact the viability of any introduced microbial contamination, (e.g. aseptically produced semi-solids, powders, solid materials, microspheres, liposomes and other formulations where product is cooled or heated or lyophilized), alternative procedures that represent the operations as closely as possible should be developed. Where surrogate materials, such as buffers, are used in parts of the

	APS, the surrogate material should not inhibit the growth of any potential contamination.
9.33 APS 應儘可能模擬例行無菌製程，且包含所有關鍵性製造步驟，尤其是：	9.33 The APS should imitate as closely as possible the routine aseptic manufacturing process and include all the critical manufacturing steps, specifically:
i. APS 應評估被使用於製程之原物料在滅菌及去污染行程後直到容器被密封之前被執行的所有無菌操作。	i. The APS should assess all aseptic operations performed subsequent to the sterilisation and decontamination cycles of materials utilised in the process to the point where the container is sealed.
ii. 對於不可過濾的產品，任何額外的無菌步驟均應經過評估。	ii. For non-filterable formulations, any additional aseptic steps should be assessed.
iii. 當無菌製造是在惰性氣體環境下執行時，除非意圖執行厭氧模擬，否則應於製程模擬時以空氣取代惰性氣體。	iii. Where aseptic manufacturing is performed under an inert atmosphere, the inert gas should be substituted with air in the process simulation unless anaerobic simulation is intended.
iv. 當製程需要添加無菌粉末時，盛裝可被接受之替代物的容器應與被評價之製程所用的容器相同。	iv. Processes requiring the addition of sterile powders should use an acceptable surrogate material in the same containers as those used in the process under evaluation.
v. 應避免分開模擬個別的單元操作（例如：涉及無菌粉末之乾燥、混合、粉碎及細分的製程）。採取任何個別模擬均應文件化佐證其合理性，並確保個別模擬的總和持續全面地涵蓋整個製程。	v. Separate simulations of individual unit operations (e.g. processes involving drying, blending, milling and subdivision of a sterile powder) should be avoided. Any use of individual simulations should be supported by a documented justification and ensure that the sum total of the individual simulations continues to fully cover the whole process.
vi. 凍乾產品的製程模擬程序應代表整個無菌製程鏈，包括充填、運送、裝載、在艙室停留(chamber dwell)的代表性期間、卸載與密封等經合理界定並予文件化的最差狀況操作參數 。	vi. The process simulation procedure for lyophilized products should represent the entire aseptic processing chain including filling, transport, loading, a representative duration of the chamber dwell, unloading and sealing under specified, documented and justified conditions representing worst case operating parameters.
vii. 除了可能影響污染物存活性或復甦外，凍乾製程模擬應模擬製程的所有層面。例如：應避免溶液沸騰或凍結。在確定 APS 設計時，要考量的因素包括(合適時)： • 使用空氣替代氮氣或其他製程氣體來破真空， • 重現凍乾機在滅菌與使用之間的最長時間間隔， • 重現過濾與凍乾之間的最長期間，以及 • 最差狀況下的量化，例如：裝載最大數量的托盤、重現艙室(chamber) 開放於環境中的最長裝載期間。	vii. The lyophilization process simulation should mimic all aspects of the process, except those that may affect the viability or recovery of contaminants. For instance, boiling-over or actual freezing of the solution should be avoided. Factors to consider in determining APS design include, where applicable: • the use of air to break vacuum instead of nitrogen or other process gases, • replicating the maximum interval between sterilisation of the lyophilizer and its use, • replicating the maximum period of time between filtration and lyophilization, and

	• quantitative aspects of worst-case situations, e.g. loading the largest number of trays, replicating the longest duration of loading where the chamber is open to the environment.
9.34 APS 應考量在正常生產及最差狀況下已知會發生的各種無菌操作及介入，且考量下列事項：	9.34 The APS should take into account various aseptic manipulations and interventions known to occur during normal production as well as worst-case situations, and take into account the following:
i. 代表該例行製程的常規及矯正性介入，應以與例行無菌製程相似的方式及頻率執行。	i. Inherent and corrective interventions representative of the routine process should be performed in a manner and frequency similar to that during the routine aseptic process.
ii. APS 中之介入的內容及頻率，應基於對產品無菌性造成風險之評估。	ii. The inclusion and frequency of interventions in the APS should be based on assessed risks posed to product sterility.
9.35 APS 不應被用於證明那些造成非必要污染風險之作業的正當性。	9.35 APS should not be used to justify practices that pose unnecessary contamination risks.
9.36 在制定 APS 計畫時，應考量下列事項：	9.36 In developing the APS plan, consideration should be given to the following:
i. 識別涵蓋相關變因之最差狀況的條件，例如：容器尺寸、作業線速度及對製程的影響。評估的結果應能證明所選變因的合理性。	i. Identification of worst case conditions covering the relevant variables, such as container size and line speed, and their impact on the process. The outcome of the assessment should justify the variables selected.
ii. 確定用於確效之容器/封蓋組合的代表性尺寸。當製程相等性經科學證明合理時，可以考量使用涵括法或矩陣法來確效相同容器/封蓋組合的不同產品。	ii. Determining the representative sizes of container/closure combinations to be used for validation. Bracketing or matrix approach may be considered for validation of the same container/closure configuration for different products where process equivalence is scientifically justified.
iii. 無菌產品及設備在無菌製程中暴露的最大允許保持時間。	iii. Maximum permitted holding times for sterile product and equipment exposed during the aseptic process.
iv. 每個容器的充填量應足以確保培養基接觸到所有可能直接污染無菌產品之所有設備及組件的表面，且應提供足夠的頂部空間以支持潛在微生物的生長，並確保在檢查期間可以偵測到混濁度。	iv. The volume filled per container, which should be sufficient to ensure that the media contacts all equipment and component surfaces that may directly contaminate the sterile product. The volume used should provide sufficient headspace to support potential microbial growth and ensure that turbidity can be detected during inspection.
v. 除非意圖模擬厭氧，否則須使用空氣替代例行無菌製程中所使用的任何惰性氣體。在這些情況下，應考量將偶爾的厭氧模擬納入整體確效策略的一部分（參見第 9.33 點第 iii 項）。	v. The requirement for substitution of any inert gas used in the routine aseptic manufacturing process by air unless anaerobic simulation is intended. In these situations, inclusion of occasional anaerobic simulations as part of the

	overall validation strategy should be considered (see paragraph 9.33 point iii).
vi. 所選定的營養培養基應能供相關藥典所描述之指定對照微生物及代表性環境分離菌(representative local isolates)的生長。	vi. The selected nutrient media should be capable of growing a designated group of reference microorganisms as described by the relevant pharmacopeia and suitably representative local isolates.
vii. 偵測微生物污染的方法應科學地證明其合理性，以確保可靠地偵測到污染。	vii. The method of detection of microbial contamination should be scientifically justified to ensure that contamination is reliably detected.
viii. 製程模擬應有足夠的時間，以挑戰製程、執行介入的作業人員、輪班以及為無菌產品製造提供適當條件之製備環境的能力。	viii. The process simulation should be of sufficient duration to challenge the process, the operators that perform interventions, shift changes and the capability of the processing environment to provide appropriate conditions for the manufacture of a sterile product.
ix. 在製造廠執行不同的或延長的班次時，應設計 APS 以獲取與那些班次相關、且經評估會對產品無菌性造成風險的因素，例如作業人員可以出現在潔淨室中的最長時間。	ix. Where the manufacturer operates different or extended shifts, the APS should be designed to capture factors specific to those shifts that are assessed to pose a risk to product sterility, for example the maximum duration for which an operator may be present in the cleanroom.
x. 模擬正常無菌製造中斷之生產怠工情形（例如換班、重新填裝給料容器、導入附加設備）。	x. Simulating normal aseptic manufacturing interruptions where the process is idle (e.g. shift changeovers, recharging dispensing vessels, introduction of additional equipment)
xi. 確保依照例行生產要求執行環境監測，並貫徹於整個製程模擬期間。	xi. Ensuring that environmental monitoring is conducted as required for routine production, and throughout the entire duration of the process simulation.
xii. 在應用連續批次製造時，例如使用屏障技術或製造無菌原料藥，應考量設計及執行製程模擬，以便模擬連續批次製造之開始與結束的相關風險，並證明該期間不造成任何風險。	xii. Where campaign manufacturing occurs, such as in the use of Barrier Technologies or manufacture of sterile active substances, consideration should be given to designing and performing the process simulation so that it simulates the risks associated with both the beginning and the end of the campaign and demonstrating that the campaign duration does not pose any risk.
xiii. 執行“生產後或連續的 APS”之結果，可被用作額外的保證或調查目的；然而，它們的使用應在 CCS 中證明其合理性，且不應取代例行的 APS。如果使用，則應證明任何殘留的產品不會對任何潛在微生物污染的回收產生負面影響。	xiii. The performance of "end of production or campaign APS" may be used as additional assurance or investigative purposes; however, their use should be justified in the CCS and should not replace routine APS. If used, it should be demonstrated that any residual product does not negatively impact the recovery of any potential microbial contamination.
9.37 對於無菌原料藥，其批量應大到足以代表例	9.37 For sterile active substances, batch size should be

行操作及在最差狀況下的模擬介入操作，並涵蓋所有可能與無菌產品接觸的表面。此外，所有模擬物（替代物或生長培養基）均應評估其微生物。模擬物應足以滿足被模擬製程的評估，且不應影響微生物的回收。	large enough to represent routine operation, simulate intervention operation at the worst case, and cover all surfaces that may come into contact with the sterile product. In addition, all the simulated materials (surrogates or growth medium) should be subjected to microbial evaluation. The simulation materials should be sufficient to satisfy the evaluation of the process being simulated and should not compromise the recovery of micro-organisms.
9.38 APS 的執行應作為初始確效的一部分，至少要有 3 次連續成功的模擬試驗，且涵蓋可能會涉及無菌製程的所有工作輪班，以及經評估會對產品無菌保證有影響的操作實務、設施、服務或設備之任何重大修改(例如：HVAC 系統及設備的修改、製程變更、輪班次數及人員數量、主要設施關閉)。通常，每一無菌製程、每一充填線以及每一輪班班次均應每年重複兩次（約每六個月一次）APS（定期再確效）。每位作業人員每年至少應參與一次成功的 APS。應考量在停工之前的最後一批之後、在長時間沒有使用之前、以及在生產線除役或搬遷之前執行 APS。	9.38 APS should be performed as part of the initial validation, with at least three consecutive satisfactory simulation tests that cover all working shifts that the aseptic process may occur in, and after any significant modification to operational practices, facilities, services or equipment which are assessed to have an impact on the sterility assurance of the product (e.g. modification to the HVAC system, equipment, changes to process, number of shifts and numbers of personnel, major facility shut down). Normally, APS (periodic revalidation) should be repeated twice a year (approximately every six months) for each aseptic process, each filling line and each shift. Each operator should participate in at least one successful APS annually. Consideration should be given to performing an APS after the last batch prior to shut down, before long periods of inactivity or before decommissioning or relocation of a line.
9.39 在人工操作（例如：無菌調製或充填）的情況下，每一類型容器、容器封蓋及一序列的設備均應予執行初始確效，應在每位作業人員參與下執行連續 3 次成功的 APS，且每位作業人員大約每 6 個月應以一次 APS 再確效。APS 的批量應模擬例行無菌製造作業使用的批量。	9.39 Where manual operation (e.g. aseptic compounding or filling) occurs, each type of container, container closure and equipment train should be initially validated with each operator participating in at least 3 consecutive successful APS and revalidated with one APS approximately every 6 months for each operator. The APS batch size should mimic that used in the routine aseptic manufacturing process.
9.40 APS 操作（充填）的單元數應足以有效地模擬無菌製造作業中具代表性的所有活動。CCS 中應清楚地闡釋充填單元數之合理性。通常，至少要充填 5,000 到 10,000 單元。對於小批量（例如：小於 5,000 單元），其 APS 的容器數應至少等於生產批次的數量。	9.40 The number of units processed (filled) for APS should be sufficient to effectively simulate all activities that are representative of the aseptic manufacturing process. Justification for the number of units to be filled should be clearly captured in the CCS. Typically, a minimum of 5000 to 10000 units are filled. For small batches (e.g. those under 5000 units), the number of containers for APS should at least equal the size of the production batch.
9.41 已充填的 APS 單元應在培養前予以振搖、旋	9.41 Filled APS units should be agitated, swirled or

轉或倒置，以確保培養基與容器的所有內表面接觸。來自 APS 的所有容器封蓋完整之單元均應予以培養及評估，包含有外觀缺陷的單元或經過非破壞性製程管制檢查的單元。如果單元在製程模擬期間被丟棄且未培養，則這些單元應與例行充填期間被丟棄的單元相當；並且僅當與生產 SOP 所明確規定必須丟棄之相同情況時（即介入類型、生產線位置、移除特定單元數），才可移除該單元。在任何情況下，於培養基充填介入期間被移除的單元都不應多於生產期間被移除的單元。例如包含在例行生產期間的組裝過程後或在特定類型之介入後必須移除的單元。為了充分了解製程及評估無菌組裝或強制性生產線清理期間的污染風險，這些單元通常會被單獨培養，並可能不包含在 APS 的允收標準中。	inverted before incubation to ensure contact of the media with all interior surfaces in the container. All integral units from the APS should be incubated and evaluated, including units with cosmetic defects or those which have gone through non-destructive in-process control checks. If units are discarded during the process simulation and not incubated, these should be comparable with units discarded during a routine fill, and only if production SOPs clearly specify that units must be removed under the same circumstances (i.e. type of intervention; line location; specific number of units removed). In no case should more units be removed during a media fill intervention than would be cleared during a production run. Examples may include those that must be discarded during routine production after the set-up process or following a specific type of intervention. To fully understand the process and assess contamination risks during aseptic setup or mandatory line clearances, these units would typically be incubated separately, and would not necessarily be included in the acceptance criteria for the APS.
9.42 如果製程包含與產品接觸表面接觸但隨後即被丟棄的原物料（例如產品沖洗液），則被丟棄的原物料應該用營養培養基模擬且當作 APS 的一部分予以培養，除非可以清楚地證明廢棄過程不會影響產品的無菌性。	9.42 Where processes include materials that contact the product contact surfaces but are then discarded (e.g. product flushes), the discarded material should be simulated with nutrient media and be incubated as part of the APS, unless it can be clearly demonstrated that this waste process would not impact the sterility of the product.
9.43 已充填的 APS 單元應在透明容器中培養，以確保可目視偵測微生物生長。當產品容器不透明（例如：琥珀色玻璃、不透明塑料）時，可以使用相同構造的透明容器替代，以幫助偵測污染。當無法以相同構造之透明容器替代時，則應開發及確效合適的微生物生長偵測方法。可行時，被從受污染單元中所分離出來的微生物應予鑑別到種，以幫助確定可能的污染物來源。	9.43 Filled APS units should be incubated in a clear container to ensure visual detection of microbial growth. Where the product container is not clear (e.g. amber glass, opaque plastic), clear containers of identical configuration may be substituted to aid in the detection of contamination. When a clear container of identical configuration cannot be substituted, a suitable method for the detection of microbial growth should be developed and validated. Microorganisms isolated from contaminated units should be identified to the species level when practical, to assist in the determination of the likely source of the contaminant.
9.44 如無延遲之必要，則已充填的 APS 單元應立即培養，以達到潛在污染的最可能復甦。培養條件及培養時程的選擇應經過科學闡釋及確效，以提供適當程度的微生物污染偵測靈	9.44 Filled APS units should be incubated without unnecessary delay to achieve the best possible recovery of potential contamination. The selection of the incubation conditions and duration should be

敏度。	scientifically justified and validated to provide an appropriate level of sensitivity of detection of microbial contamination.
9.45 培養完成後：	9.45 On completion of incubation:
i. 已充填的 APS 單元應由受過適當偵測微生物污染之訓練且經資格驗證的人員檢查。檢查應在利於識別任何微生物污染的條件下執行。	i. Filled APS units should be inspected by personnel who have been appropriately trained and qualified for the detection of microbiological contamination. Inspection should be conducted under conditions that facilitate the identification of any microbial contamination.
ii. 已充填單元的樣品應接種適當範圍的對照菌種及具適當代表性的環境分離菌，以執行陽性對照。	ii. Samples of the filled units should undergo positive control by inoculation with a suitable range of reference organisms and suitably representative local isolates.
9.46 目標應該是零生長。任何受到污染的單元應判定 APS 失敗，且應採取下列措施：	9.46 The target should be zero growth. Any contaminated unit should result in a failed APS and the following actions should be taken:
i. 調查並確定最可能的根本原因；	i. an investigation to determine the most probable root cause(s);
ii. 確定及執行適當的矯正措施；	ii. determination and implementation of appropriate corrective measures;
iii. 應執行足夠次數（通常至少 3 次）之成功的、連續重複的 APS，以證明該製程已回復到管制狀態；	iii. a sufficient number of successful, consecutive repeat APS (normally a minimum of 3) should be conducted in order to demonstrate that the process has been returned to a state of control;
iv. 及時審查自前次成功的 APS 以來與無菌生產有關之所有適當紀錄； a) 審查結果應包含對自上次成功的 APS 以來所製造批次中所潛在之無菌偏離的風險評估。 b) 所有未放行到市場的其他批次均應納入調查範圍。任何有關其放行狀態的決定均應考量調查結果。	iv. a prompt review of all appropriate records relating to aseptic production since the last successful APS; a) The outcome of the review should include a risk assessment of potential sterile breaches in batches manufactured since the last successful APS. b) All other batches not released to the market should be included in the scope of the investigation. Any decision regarding their release status should consider the investigation outcome.
v. 製程模擬失敗之後，該生產線所製造之所有產品均應予隔離，直到製程模擬失敗已被成功解決；	v. all products that have been manufactured on a line subsequent to a process simulation failure should be quarantined until a successful resolution of the process simulation failure has occurred;
vi. 如果根本原因調查顯示失敗與作業人員的活動有關，則應採取措施以限制作業人員的活動，直到已重新完成訓練及資格驗證；	vi. where the root cause investigation indicates that the failure was related to operator activity, actions to limit the operator's activities, until retrained and requalified, should be taken;
vii. 只有成功地完成再確效後才可恢復生產。	vii. production should resume only after

	completion of successful revalidation.
9.47 所有 APS 的運行應予完整文件化且包含已處理單元（例如：已充填的單元數、已培養及未培養的單元數）的數量調和。文件中應包含已充填及未培養單元數量的合理說明。在 APS 過程中執行的所有介入均應予記錄，包括每次介入的開始及結束時間以及所涉及的人員。所有微生物監測數據以及其他測試數據均應記錄於 APS 批次紀錄中。	9.47 All APS runs should be fully documented and include a reconciliation of units processed (e.g. units filled, incubated and not incubated). Justification for filled and non-incubated units should be included in the documentation. All interventions performed during the APS should be recorded, including the start and end time of each intervention and the involved person. All microbial monitoring data as well as other testing data should be recorded in the APS batch record.
9.48 應僅在有書面程序要求商業批次同樣處理的情況下，才可中止 APS 的行程。在這種情況下，應有文件化的調查。	9.48 An APS run should be aborted only under circumstances in which written procedures require commercial lots to be equally handled. An investigation should be documented in such cases.
9.49 在下列情況下，無菌製程應重複初始的確效：	9.49 An aseptic process should be subject to a repeat of the initial validation when:
i. 已長時間未操作該特定的無菌製程；或	i. the specific aseptic process has not been in operation for an extended period of time; or
ii. 製程、設備、程序或環境發生的變化可能會影響無菌製程，或增加新的產品容器或容器-封蓋組合。	ii. there is a change to the process, equipment, procedures or environment that has the potential to affect the aseptic process or an addition of new product containers or container-closure combinations.
10 品質管制 (Quality Control ,QC)	
10.1 應有在微生物學、無菌保證及製程知識方面經適當訓練及經驗的人員，以支持製造作業之設計、環境監測管理，及評估微生物相關事件對於無菌產品安全性之影響的任何調查。	10.1 There should be personnel available with appropriate training and experience in microbiology, sterility assurance and knowledge of the processes to support the design of the manufacturing activities, environmental monitoring regime and any investigation assessing the impact of microbiologically linked events to the safety of the sterile product.
10.2 當監測作業及/或 CCS 指出有需要時，原料、組件及產品之規格應包含微生物、微粒及內毒素/熱原限量之要求。	10.2 Specifications for raw materials, components and products should include requirements for microbial, particulate and endotoxin/pyrogen limits when the need for this has been indicated by monitoring and/or by the CCS.
10.3 對於每一批次無菌充填的產品及最終滅菌的產品皆應執行負荷菌分析，並將其結果視為最終批次審查的一部分。緊接末端滅菌級過濾器或最終滅菌製程前之負荷菌應規定其限量，該限量與要採用之滅菌方法的效能有關。所採樣品應代表最差狀況（例如在保持時間之終點）。對於最終滅菌產品其參數設定為過度滅菌者，負荷菌應在適當排定之時間間隔監測。	10.3 The bioburden assay should be performed on each batch for both aseptically filled product and terminally sterilised products and the results considered as part of the final batch review. There should be defined limits for bioburden immediately before the final sterilising grade filter or the terminal sterilisation process, which are related to the efficiency of the method to be used. Samples should be taken to be representative of the worst case scenario (e.g. at the end of hold time). Where

	overkill sterilisation parameters are set for terminally sterilised products, bioburden should be monitored at suitable scheduled intervals.
10.4 對於經許可以參數放行之產品，應制定已充填產品於滅菌行程前負荷菌監測之支持性計畫，且應對每一批次執行負荷菌分析。滅菌前充填單元之取樣位置應基於最差狀況並能代表該批。在負荷菌試驗期間所發現之任何微生物均應予鑑別，並確定其對滅菌製程有效性的影響。合適時，應監測內毒素/熱原含量。	10.4 For products authorised for parametric release, a supporting pre-sterilisation bioburden monitoring programme for the filled product prior to initiating the sterilisation cycle should be developed and the bioburden assay should be performed for each batch. The sampling locations of filled units before sterilisation should be based on a worst case scenario and be representative of the batch. Any organisms found during bioburden testing should be identified and their impact on the effectiveness of the sterilising process determined. Where appropriate, the level of endotoxin/pyrogen should be monitored.
10.5 最終產品的無菌試驗，應僅被認為是一系列確保無菌性之關鍵控制下的最後措施。它不能用於確保不符合其設計、程序或確效參數之產品的無菌性。該測試應依產品加以確效。	10.5 The sterility test applied to the finished product should only be regarded as the last in a series of critical control measures by which sterility is assured. It cannot be used to assure sterility of a product that does not meet its design, procedural or validation parameters. The test should be validated for the product concerned.
10.6 無菌試驗應在無菌條件下執行。無菌試驗所抽取之樣品應代表整個批次，尤其應包含取自該批次中被認為最具污染風險之部分的樣品，例如：	10.6 The sterility test should be performed under aseptic conditions. Samples taken for sterility testing should be representative of the whole of the batch but should in particular include samples taken from parts of the batch considered to be most at risk of contamination, for example:
i. 對於經無菌充填之產品，其樣品應包含在該批次之開始與結束時的產品。另應基於風險進行額外取樣(例如：在重大介入後所充填之產品)。	i. For products which have been filled aseptically, samples should include containers filled at the beginning and end of the batch. Additional samples, e.g. taken after critical interventions should be considered based on risk.
ii. 對於以最終容器形式加熱滅菌之產品，其所取樣品應能代表最差狀況的位置（例如：在每一裝載之潛在的最冷或加熱最慢的部位）。	ii. For products which have been heat sterilised in their final containers, samples taken should be representative of the worst case locations (e.g. the potentially coolest or slowest to heat part of each load).
iii. 對於經凍乾的產品，其樣品應取自不同的凍乾裝載。	iii. For products which have been lyophilized, samples taken from different lyophilization loads.
註：如果在製造過程產生子批次（例如：最終滅菌產品），則應從每個子批次中抽取無菌試驗用樣品，並對每個子批次樣品執行無菌試驗。另應考量對其他最終產品試驗項目分別執行試驗。	Note: Where the manufacturing process results in sub-batches (e.g. for terminally sterilised products) then sterility samples from each sub-batch should be taken and a sterility test for each sub-batch performed. Consideration should also be given to performing separate testing for other finished product tests.
10.7 某些產品可能由於架儲期太短，以致無法在	10.7 For some products it may not be possible to obtain

放行前完成無菌試驗以獲得無菌試驗結果。在這些情況下，應採用額外的製程設計與額外的監測，及/或替代檢驗方法以降低被識別出來的風險，並對此進行評估與記錄。	a sterility test result prior to release because the shelf life of the product is too short to allow completion of a sterility test. In these cases, the additional considerations of design of the process and additional monitoring and/or alternative test methods required to mitigate the identified risks should be assessed and documented.
10.8 用於試驗前對無菌試驗樣品外部表面去污染的任何過程（例如：氣化過氧化氫、紫外線），不應對試驗方法之靈敏度或樣品的可靠性產生負面影響。	10.8 Any process (e.g. Vaporized Hydrogen Peroxide, Ultra Violet) used to decontaminate the external surfaces of sterility samples prior to testing should not negatively impact the sensitivity of the test method or the reliability of the sample.
10.9 用於產品檢驗的培養基在使用前應依相關藥典執行品質管制檢驗。用於環境監測及 APS 的培養基在使用前應使用經過科學證明及指定的對照微生物，並包含具適當代表性的環境分離菌執行生長效能試驗。培養基品質管制檢驗通常應由終端使用者執行。任何依賴委外檢驗或供應商檢驗的培養基都應證明其合理性，並且應徹底考量在這種情況下的運輸及裝運條件。	10.9 Media used for product testing should be quality control tested according to the related Pharmacopeia before use. Media used for environmental monitoring and APS should be tested for growth promotion before use, using a scientifically justified and designated group of reference microorganisms and including suitably representative local isolates. Media quality control testing should normally be performed by the end user. Any reliance on outsourced testing or supplier testing of media should be justified and transportation and shipping conditions should be thoroughly considered in this case.
10.10 級區之環境監測數據與趨勢數據應作為產品批次核定/放行的一部分予以審查。應有書面程序描述當發現環境監測數據超出趨勢或超出既定限值時所應採取的措施。對於短架儲期產品，可能無法取得製造當時的環境數據；在這些情況下，其符合性應包含對最新可用數據的審查。這些產品的製造廠應考量使用快速/替代之方法。	10.10 Environmental monitoring data and trend data generated for classified areas should be reviewed as part of product batch certification/release. A written procedure should be available that describes the actions to be taken when data from environmental monitoring are found out of trend or exceeding the established limits. For products with short shelf life, the environmental data for the time of manufacture may not be available; in these cases, the compliance should include a review of the most recent available data. Manufacturers of these products should consider the use of rapid/alternative methods.
10.11 當快速及自動化微生物方法被使用於一般製造目的時，這些方法應針對相關產品或製程執行確效。	10.11 Where rapid and automated microbial methods are used for general manufacturing purposes, these methods should be validated for the product(s) or processes concerned.

詞彙 (*Glossary)*	
氣鎖室—用於維持相鄰房間（通常具有不同空氣潔淨度標準）之氣壓管制且有互鎖門的封閉空間。氣鎖室之目的是在於防止微粒物質及微生物污染物從管制程度較低的區域進入管制程度較高	Airlock – An enclosed space with interlocked doors, constructed to maintain air pressure control between adjoining rooms (generally with different air cleanliness standards). The intent of an airlock is to

的區域。	preclude ingress of particle matter and microorganism contamination from a lesser controlled area.
行動限量—對於諸如微生物或浮游微粒限量等的既定相關數值；當超過該限量時，應啟動適當調查，並依調查結果採取矯正措施。	Action limit – An established relevant measure (e.g. microbial, or airborne particle limits) that, when exceeded, should trigger appropriate investigation and corrective action based on the investigation.
警戒水準—對於在正常操作條件及確效狀態下之微生物或浮游微粒濃度等的潛在性漂移，發出早期警告的既定相關數值；它不一定會為矯正措施提供基礎，但會啟動適當的監視及後續行動，以解決潛在的問題。警戒水準是基於例行的及經過驗證的趨勢數據所建立的，並被定期審查。警戒水準可以基於不良趨勢、超出所設定之限值的個別偏離以及重複事件等多個參數予以建立。	Alert level – An established relevant measure (e.g. microbial, or airborne particle levels) giving early warning of potential drift from normal operating conditions and validated state, which does not necessarily give grounds for corrective action but triggers appropriate scrutiny and follow-up to address the potential problem. Alert levels are established based on routine and qualification trend data and are periodically reviewed. The alert level can be based on a number of parameters including adverse trends, individual excursions above a set limit and repeat events.
無菌製備/製程—在受控環境中處理無菌產品、容器及/或設備；在該環境中對空氣供應、原物料以及人員進行管理，以防止微生物、內毒素/熱原以及微粒污染。	Aseptic preparation/processing – The handling of sterile product, containers and/or devices in a controlled environment in which the air supply, materials and personnel are regulated to prevent microbial, endotoxin/pyrogen and particle contamination.
無菌製程模擬(APS)—對整個無菌製程的模擬，以確認該製程確保產品無菌性的能力。包括與例行製造相關的所有無菌操作，例如：必要時的設備組裝、調配、充填、凍乾及密封等製程。	Aseptic Process Simulation (APS) – A simulation of the entire aseptic manufacturing process in order to verify the capability of the process to assure product sterility. Includes all aseptic operations associated with routine manufacturing, e.g. equipment assembly, formulation, filling, lyophilization and sealing processes as necessary.
無菌狀態—經由使用無菌工作區，並以防範暴露的無菌產品受到微生物污染的方式執行作業所達到的管制狀態。	Asepsis – A state of control attained by using an aseptic work area and performing activities in a manner that precludes microbial contamination of the exposed sterile product.
細菌滯留試驗—該試驗用於確效過濾器是否可以從氣體或液體中去除細菌。該試驗通常使用標準微生物(例如：最低濃度為 10^7 cfu/cm^2 的 *Brevundimonas diminuta*)來執行。	Bacterial retention testing – This test is performed to validate that a filter can remove bacteria from a gas or liquid. The test is usually performed using a standard organism, such as Brevundimonas diminuta at a minimum concentration of 10^7 Colony Forming Units/cm^2.
屏障—將無菌操作區（通常為 A 級區）與其背景環境隔離，以提供該區保護的實體隔離物。此類系統之部分或全部經常使用稱為 RABS 或隔離裝置的屏障技術。	Barrier – A physical partition that affords aseptic processing area (usually grade A) protection by separating it from the background environment. Such systems frequently use in part or totally the Barrier Technologies known as RABS or isolators.
負荷菌—與人員、製造環境(空氣及表面)、設	Bioburden – The total number of microorganisms

備、產品包裝、原料（包括水）、製程中原物料或最終產品等相關之微生物的總數。	associated with a specific item such as personnel, manufacturing environments (air and surfaces), equipment, product packaging, raw materials (including water), in-process materials, or finished products.
生物去污染—以殺孢子化學藥劑去除活性負荷菌的過程。	Bio-decontamination - A process that eliminates viable bioburden via use of sporicidal chemical agents.
生物指示劑 (BI)—被接種到合適之介質（例如：溶液、容器或封蓋）上的定量微生物，並放置在滅菌器內或裝載內或房間內之位置，以確定物理性或化學性滅菌或消毒週期的效率。挑戰微生物的選定是依其對給定製程的抵抗性來選擇及確效的。由進料批次的 D 值、微生物計數及純度來確定 BI 的品質。	Biological Indicators (BI) – A population of microorganisms inoculated onto a suitable medium (e.g. solution, container or closure) and placed within a steriliser or load or room locations to determine the sterilisation or disinfection cycle efficacy of a physical or chemical process. The challenge microorganism is selected and validated based upon its resistance to the given process. Incoming lot D-value, microbiological count and purity define the quality of the BI.
吹製-充填-密封 (BFS)— 一種將可熱塑顆粒成型為容器，充填產品，然後在連續、整合、自動操作中密封的技術。兩種最常見的 BFS 機器類型是穿梭型（型坏切割）及迴轉型(密封型坏)。	Blow-Fill-Seal (BFS) – A technology in which containers are formed from a thermoplastic granulate, filled with product, and then sealed in a continuous, integrated, automatic operation. The two most common types of BFS machines are the Shuttle type (with Parison cut) and the Rotary type (Closed Parison).
時段切換製造—在界定的時段內，嚴格遵守既定且經過確效的管制措施，依序製造一系列批次的相同產品。	Campaign manufacture – A manufacture of a series of batches of the same product in sequence in a given period of time with strict adherence to established and validated control measures.
級區—包含多個潔淨室的區域（參見潔淨室定義）。	Classified area – An area that contains a number of cleanrooms (see cleanroom definition).
清潔—去除污染物(例如：產品殘留物或消毒劑殘留物)的過程。	Cleaning – A process for removing contamination e.g. product residues or disinfectant residues.
潔淨區—具有明確的微粒及微生物潔淨度標準的區域，通常包含多個相連的潔淨室。	Clean area – An area with defined particle and microbiological cleanliness standards usually containing a number of joined cleanrooms.
潔淨室—經設計、維護及管制，以防止藥品受到微粒及微生物污染的作業室。這樣的作業室會被指定且可重複地符合適當的空氣潔淨度。	Cleanroom – A room designed, maintained, and controlled to prevent particle and microbial contamination of drug products. Such a room is assigned and reproducibly meets an appropriate air cleanliness level.
潔淨室分級—一種經由量測總微粒濃度，然後依潔淨室或潔淨空氣設備之規格，來評估其空氣潔淨度的方法。	Cleanroom classification – A method of assessing the level of air cleanliness against a specification for a cleanroom or clean air equipment by measuring the total particle concentration.
潔淨室驗證—一種評估被分級之潔淨室或潔淨空氣設備是否符合其預期用途的方法。	Cleanroom qualification – A method of assessing the level of compliance of a classified cleanroom or clean air equipment with its intended use.

密閉系統—產品不暴露於周圍環境的系統。例如：可經由使用管線或管子相互連接的半製品容器（例如桶或袋）作為一個系統來實現；當用於無菌產品的情況下，整個系統於連接後進行滅菌。例如（但不限於），在原料藥製造中可見的大規模可重複使用的系統，或在生物藥品製造中可見的拋棄式袋子及歧管系統。在操作結束之前，密閉系統不得被打開。在本附則中所使用的術語"密閉系統"並不指 RABS 或隔離裝置等系統。	Closed system – A system in which the product is not exposed to the surrounding environment. For example, this can be achieved by the use of bulk product holders (such as tanks or bags) that are connected to each other by pipes or tubes as a system, and where used for sterile products, the full system is sterilised after the connections are made. Examples of these can be (but are not limited to) large scale reusable systems, such as those seen in active substance manufacturing, or disposable bag and manifold systems, such as those seen in the manufacture of biological products. Closed systems are not opened until the conclusion of an operation. The use of the term "closed systems" in this Annex does not refer to systems such as RABS or isolator systems.
菌落形成單位 (CFU)— 一個微生物學的術語，描述源自一種或多種微生物之單一可被偵測的菌落。對於液體樣品，菌落形成單位通常以 CFU/ml 表示；對於空氣樣品，則為 CFU/m^3；對於在諸如落菌培養皿或接觸培養皿等固體介質等樣品，則通常以 CFU/樣品表示。	Colony Forming Unit (CFU) – A microbiological term that describes a single detectable colony that originates from one or more microorganisms. Colony forming units are typically expressed as CFU per ml for liquid samples, CFU per m^3 for air sample and CFU per sample for samples captured on solid medium such as settle or contact plates.
污染—在生產、抽樣、包裝或重新包裝、儲存或運輸過程中，將具微生物性質的雜質/不純物（微生物的數量及類型、熱原）或外來微粒物質被非期望地引入原物料、半製品/中間產品、原料藥或藥品之內或之上，它們可能對產品品質造成不利影響。	Contamination – The undesired introduction of impurities of a microbiological nature (quantity and type of microorganisms, pyrogen), or of foreign particle matter, into or onto a raw material, intermediate, active substance or drug product during production, sampling, packaging or repackaging, storage or transport with the potential to adversely impact product quality.
污染管制策略 (CCS) — 對微生物、內毒素/熱原以及微粒之一套計畫性的管制，源自對於當前產品及製程的瞭解，以確保製程性能及產品品質。其管制可以包含與原料藥、賦形劑與藥品物料及組件、設施及設備操作條件、製程中管制、最終產品規格，以及與監測及管制相關的方法與頻率。	Contamination Control Strategy (CCS) – A planned set of controls for microorganisms, endotoxin/pyrogen and particles, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to active substance, excipient and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.
矯正性介入—在無菌製程中用以矯正或調整的介入。它們在例行的無菌製程中不以設定的頻率發生。其例子包含清除組件堵塞、止漏、調整傳感器以及更換設備組件等。	Corrective intervention – An intervention that is performed to correct or adjust an aseptic process during its execution. These may not occur at a set frequency in the routine aseptic process. Examples include such as clearing component jams, stopping leaks, adjusting sensors, and replacing equipment

	components.
關鍵表面—可能直接接觸或直接影響無菌產品或其容器或其封蓋的表面。關鍵表面應於製造作業開始前使成為無菌，並於整個製程中保持無菌性。	Critical surfaces – Surfaces that may come directly into contact with, or directly affect, a sterile product or its containers or closures. Critical surfaces are rendered sterile prior to the start of the manufacturing operation, and sterility is maintained throughout processing.
關鍵區—在無菌操作區內，產品與關鍵表面被暴露於環境中的位置。	Critical zone – A location within the aseptic processing area in which product and critical surfaces are exposed to the environment.
關鍵性介入—在關鍵區之矯正性或常規性介入。	Critical intervention – An intervention (corrective or inherent) into the critical zone.
D 值—將有存活力的生物體數量減到原始數量之 10%所需的滅菌參數值（持續期間或吸收劑量）。	D-value – The value of a parameter of sterilisation (duration or absorbed dose) required to reduce the number of viable organisms to 10 per cent of the original number.
盲管—長度大於其管線內徑 3 倍的非循環管線（其內的流體可能保持靜止）。	Dead leg – Length of non-circulating pipe (where fluid may remain static) that is greater than 3 internal pipe diameters.
除役—當製程、設備或潔淨室被停用且不再被使用的狀態。	Decommission – When a process, equipment or cleanroom are closed and they will not be used again.
去污染—從一個區域、標的物或人體去除或減少任何污染物（化學物質、廢棄物、殘留物或微生物）的整個過程。其所使用的去污染方法（例如：清潔、消毒、滅菌）應經選擇及確效，以達到適合該項被去污染標的之預定用途的潔淨度程度。亦請參見生物去污染。	Decontamination – The overall process of removal or reduction of any contaminants (chemical, waste, residue or microorganisms) from an area, object, or person. The method of decontamination used (e.g. cleaning, disinfection, sterilisation) should be chosen and validated to achieve a level of cleanliness appropriate to the intended use of the item decontaminated. See also Bio-decontamination.
去熱原—被設計用以將熱原物質（例如：內毒素）移除或去活化到規定之最小量的程序。	Depyrogenation – A process designed to remove or inactivate pyrogenic material (e.g. endotoxin) to a specified minimum quantity.
消毒—對微生物之結構或代謝功能進行不可逆的處理，以減少菌數達到適合於界定目的之程序。	Disinfection – The process by which the reduction of the number of microorganisms is achieved by the irreversible action of a product on their structure or metabolism, to a level deemed to be appropriate for a defined purpose.
內毒素—存在於革蘭氏陰性菌細胞壁中的熱原性產物（亦即：脂多醣）。內毒素可導致接受注射之患者出現從發燒到死亡的反應。	Endotoxin – A pyrogenic product (i.e. lipopolysaccharide) present in the Gram negative bacterial cell wall. Endotoxin can lead to reactions in patients receiving injections ranging from fever to death.
平衡時間—從對照量測點達滅菌溫度開始，至裝載內所有點位均達到滅菌溫度所經過的時間。	Equilibration time – Period which elapses between the attainment of the sterilisation temperature at the reference measurement point and the attainment of the sterilisation temperature at all points within the load.
可萃取物—在暴露於極端條件之適當溶劑下，從	Extractables - Chemical entities that migrate from the

製程設備表面轉移進入被加工之產品或原物料中的化學成分。	surface of the process equipment, exposed to an appropriate solvent at extreme conditions, into the product or material being processed.
第一手空氣—在接觸暴露的產品和產品接觸表面之前沒有被干擾，因而在到達關鍵區之前不太有受污染可能的過濾空氣。	First Air – Refers to filtered air that has not been interrupted prior to contacting exposed product and product contact surfaces with the potential to add contamination to the air prior to reaching the critical zone.
過濾器完整性測試—確認過濾器（產品、氣體或 HVAC 的過濾器）保持其截留特性，且在其處理、安裝或製程中沒有被損壞的測試。	Filter Integrity test - A test to confirm that a filter (product, gas or HVAC filter) retain their retentive properties and have not been damaged during handling, installation or processing.
成型-充填-密封(FFS) — 一種自動充填製程，通常用於最終滅菌產品。該製程係將包材薄膜經連續式平面滾輪(flat roll)壓出來以成型直接容器，並同時將產品充填入該容器，再將已充填的直接容器密封的連續製程。FFS 製程可以使用單網系統(single web system)（該製程係將單一的薄膜平面滾輪纏繞在自身周圍以形成一個空腔）或雙網系統(dual web system)（該製程係將兩個薄膜平面滾輪放在一起以形成一個空腔），該類製程通常借助於真空模具或加壓氣體。其所形成的空腔被充填、密封並切成段。該薄膜通常由聚合物材料、聚合物塗層或其他合適的材料所組成。	Form-Fill-Seal (FFS) –An automated filling process, typically used for terminally sterilised products, which constructs the primary container out of a continuous flat roll of packaging film while simultaneously filling the formed container with product and sealing the filled containers in a continuous process. FFS processes may utilize a single web system (where a single flat roll of film is wrapped around itself to form a cavity), or a dual web system (where two flat rolls of film are brought together to form a cavity), often with the aid of vacuum moulds or pressurised gases. The formed cavity is filled, sealed and cut into sections. Films typically consist of a polymeric material, polymeric coated foil or other suitable material.
更衣(著衣)驗證— 以初始及定期的計畫，確立個人穿著整套工作服之能力。	Gowning qualification – A programme that establishes, both initially and on a periodic basis, the capability of an individual to don the complete gown.
A 級空氣供應—所供應之過濾空氣經驗證符合 A 級區總微粒品質，但不需要對該空氣執行連續總微粒監測或符合 A 級區微生物監測限量。專用於保護封蓋尚未經捲縮的全塞小瓶。	Grade A air supply – Air which is passed through a filter qualified as capable of producing grade A total particle quality air, but where there is no requirement to perform continuous total particle monitoring or meet grade A viable monitoring limits. Specifically used for the protection of fully stoppered vials where the cap has not yet been crimped.
HEPA 過濾器—依相關國際標準所規定之高效率微粒空氣過濾器。	HEPA filter – High efficiency particulate air filter specified in accordance with a relevant international standard.
常規的介入—無菌製程不可分割的一部分，是組建(set-up)、例行操作及/或監測（例如：無菌組裝、容器補充、環境採樣）所需的介入。常規的介入是執行無菌製程之程序或工作指示要求的所需介入。	Inherent interventions – An intervention that is an integral part of the aseptic process and is required for either set-up, routine operation and/or monitoring (e.g. aseptic assembly, container replenishment, environmental sampling). Inherent interventions are required by procedure or work instruction for the execution of the aseptic process.
內建無菌連接裝置—在連接過程中降低污染風險	Intrinsic sterile connection device – A device that

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

人工無菌操作—由作業人員對於裝有無菌產品之開放式容器，以人工調製、充填、置放及/或密封的無菌製程。	Manual aseptic processing– An aseptic process where the operator manually compounds, fills, places and /or seals an open container with sterile product.
作業人員—參與操作作業的任何個人，包括生產線組建、充填、維護或與製造活動相關的其他人員。	Operator - Any individual participating in the processing operation, including line set-up, filling, maintenance, or other personnel associated with manufacturing activities.
過度滅菌—足以將具最小 D 值為 1 分鐘的微生物，至少減少 12 個 **$\log_{10}$** 的過程。	Overkill sterilisation – A process that is sufficient to provide at least a 12 log10 reduction of microorganisms having a minimum D-value of 1 minute.
型坯—將聚合物由 BFS 機器擠出的"管"狀物，再由該"管"狀物形成容器。	Parison – The "tube" of polymer extruded by the BFS machine from which containers are formed.
傳遞艙—與氣鎖室同義（參見氣鎖室定義），但通常尺寸較小。	Pass-through hatch – Synonymous with airlock (see airlock definition) but typically smaller in size.
患者—人類或動物，包括臨床試驗的參與者。	Patient – Human or animal including participants in a clinical trial.
無菌操作後的終端熱處理— 一種在無菌操作後採用的終端濕熱過程，它已被證明可提供≤10^{-6} 的無菌保證程度，但無法滿足蒸汽滅菌的要求（例如：$F_0 \geq 8$ 分鐘）。這也可能有利於對無法經由過濾去除之病毒的破壞。	Post-aseptic processing terminal heat treatment– A terminal moist heat process employed after aseptic processing which has been demonstrated to provide a sterility assurance level (SAL) ≤10^{-6} but where the requirements of steam sterilisation (for example, F0≥8 min) are not fulfilled. This may also be beneficial in the destruction of viruses that may not be removed through filtration.
熱原—接受注射之患者會引起發熱反應的物質。	Pyrogen – A substance that induces a febrile reaction in patients receiving injections;
快速轉移系統/接頭 (RTP)—用於將物品轉移入 RABS 或隔離裝置內的系統，以將關鍵區域的風險降至最低。一個例子是帶有 alpha/beta 端口的快速轉移容器。	Rapid Transfer System/Port (RTP) – A System used for the transfer of items into RABS or isolators that minimizes the risk to the critical zone. An example would be a rapid transfer container with an alpha/beta port.
原料—用於生產無菌產品的任何成分，包括那些可能不會出現在最終藥品中的成分。	Raw material – Any ingredient intended for use in the manufacture of a sterile product, including those that may not appear in the final drug product.
限制進入屏障系統(RABS)—提供封閉的但非完全密封的環境，滿足規定的空氣品質條件（用於 A 級區無菌操作），並使用硬質壁板及經整合的手套將其內部與周圍潔淨室環境隔開之系統。RABS 的內表面使用殺孢劑消毒及去污染。作業人員使用手套、半套裝、RTP 及其他經整合的傳輸端口來執行操作或將原物料傳送到 RABS 內部。依其設計，門很少被打開(只有在嚴格的預定義的條件下)。	Restricted Access Barrier System (RABS) – System that provides an enclosed, but not fully sealed, environment meeting defined air quality conditions (for aseptic processing grade A), and using a rigid-wall enclosure and integrated gloves to separate its interior from the surrounding cleanroom environment. The inner surfaces of the RABS are disinfected and decontaminated with a sporicidal agent. Operators use gloves, half suits, RTPs and other integrated transfer ports to perform manipulations or convey materials to the interior of the RABS. Depending on the design, doors are rarely opened, and only under strictly pre-defined

	conditions.
一次性使用系統 (SUS)—與產品接觸的組件僅被使用一次的系統，以取代可被重複使用的設備，諸如不銹鋼的傳輸管線或待分/包裝產品容器等。在本文件中，SUS 涵蓋那些使用於無菌產品製造過程，且通常是由諸如袋子、過濾器、管線、連接器、儲存瓶以及傳感器等拋棄式組件所組成。	Single Use Systems (SUS) – Systems in which product contact components are used only once to replace reusable equipment such as stainless steel transfer lines or bulk containers.SUS covered in this document are those that are used in manufacturing processes of sterile products and are typically made up of disposable components such as bags, filters, tubing, connectors, storage bottles and sensors.
殺孢劑—當以足夠的濃度使用時，可以在規定的接觸時間內破壞細菌及真菌孢子的藥劑。它們被預期會殺死所有的營養型微生物。	Sporicidal agent – An agent that destroys bacterial and fungal spores when used in sufficient concentration for specified contact time. It is expected to kill all vegetative microorganisms.
無菌產品—在本指引中，無菌產品係指一種或多種經過滅菌的組成物在無菌條件下，並最終組成之無菌原料藥或無菌產品。這些組成物包含最終藥品的容器、封蓋塞及組件。或經由最終滅菌製程使變成無菌的產品。	Sterile Product – For purpose of this guidance, sterile product refers to one or more of the sterilised elements exposed to aseptic conditions and ultimately making up the sterile active substance or finished sterile product. These elements include the containers, closures, and components of the finished drug product. Or, a product that is rendered sterile by a terminal sterilisation process.
滅菌級過濾器—在經過適當確效後，可以從液體或氣體中去除所規定之挑戰微生物而產出無菌濾出物一種過濾器。此類過濾器的孔徑通常等於或小於 0.22 μm。	Sterilising grade filter – A filter that, when appropriately validated, will remove a defined microbial challenge from a fluid or gas producing a sterile effluent. Usually such filters have a pore size equal or less than 0.22 μm.
最終滅菌—在產品的最終容器中使用致死的滅菌劑或條件，以達到事先訂定的 10^{-6} 或更佳的無菌保證程度（SAL）（例如：理論上存在單一個有存活力的微生物的機率或在被滅菌總單元中等於或小於 1×10^{-6}（百萬分之一）單元。	Terminal Sterilisation – The application of a lethal sterilising agent or conditions to a product in its final container to achieve a predetermined sterility assurance level (SAL) of 10^{-6} or better (e.g. the theoretical probability of there being a single viable microorganism present on or in a sterilised unit is equal to or less than 1×10^{-6} (one in a million)).
亂流—空氣不是單向流動的。潔淨室中的亂流空氣應經由氣流混合稀釋以沖洗潔淨室，並確保維持可接受的空氣品質。	Turbulent airflow – Air that is not unidirectional. Turbulent air in cleanrooms should flush the cleanroom via mixed flow dilution and ensure maintenance of acceptable air quality.
單向氣流—以穩定且均勻的方式，並以足夠的速度在單一方向上移動的氣流，可重複地將微粒從關鍵操作區或檢驗區帶走。	Unidirectional airflow – An airflow moving in a single direction, in a robust and uniform manner, and at sufficient speed, to reproducibly sweep particles away from the critical processing or testing area.
單向氣流(UDAF)櫃—提供過濾單向氣流的櫥櫃型機械裝置（以前稱為層流單元或 LAF）。	Unidirectional Airflow (UDAF) unit – A cabinet supplied with filtered unidirectional airflow (previously referred to as a Laminar Airflow Unit or LAF).
最差狀況— 一組包含操作限制量及各種情境、並涵蓋標準作業程序內最有可能導致製程或產品失敗的條件（當與理想條件相較時），這些條件	Worst case – A set of conditions encompassing processing limits and circumstances, including those within standard operating procedures, that pose the

最有可能，但不一定總是導致產品或製程失敗。	greatest chance of process or product failure (when compared with ideal conditions). Such conditions have the highest potential to, but do not necessarily always result in product or process failure.
水系統—用於生產、儲存及配送水的系統，其水質通常符合特定藥典等級（例如純水及注射用水(WFI)）。	Water system – A system for producing, storing and distributing water, usually compliant to a specific pharmacopeia grade (e.g. purified water and water for injection (WFI)).
Z 值—導致生物指示劑 D 值發生 10 倍變化的溫差。	Z-value – The temperature difference that leads to a 10-fold change in the D-value of the biological indicators.