

附則 1 無菌藥品的製造

(MANUFACTURE OF STERILE MEDICINAL PRODUCTS)

原則 (PRINCIPLE)	
<p>The manufacture of sterile products is subject to special requirements in order to minimise risks of microbiological contamination, and of particulate and pyrogen contamination. Much depends on the skill, training and attitudes of the personnel involved. Quality Assurance bears a particularly great importance and this type of manufacture must strictly follow carefully established and validated methods of preparation and procedure. Sole reliance for sterility or other quality aspects must not be placed on any terminal process or finished product test.</p>	<p>為要使微生物的污染以及微粒和熱原污染的風險降到最低，無菌產品的製造應遵從特別的要求。大部分的要求取決於參與人員的技術、訓練和態度。品質保證有特別大的重要性，且這種型式的製造應嚴格依循謹慎建立並經確效的製備方法與程序。無菌性或其他品質層面之信賴度不得僅置於最終製程或最終產品的測試上。</p>
<p><i>Note: The present guidance does not lay down detailed methods for determining the microbiological and particulate cleanliness of air, surfaces, etc. Reference is made to other compendia such as the EN/ISO Standards.</i></p>	<p>註：本準則(附則)並未規定關於測定空氣、表面等之微生物的及微粒的潔淨度之詳細方法。請參考其他的規範，例如 EN/ISO 標準。</p>
概述 (GENERAL)	
<p>1. The manufacture of sterile products should be carried out in clean areas, entry to which should be through airlocks for personnel and/or for equipment and materials. Clean areas should be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency.</p>	<p>1. 無菌產品的製造應在潔淨區中執行，人員及/或設備與原物料進入該潔淨區，應分別經由各該氣鎖室。潔淨區應維持在適當的潔淨度標準，並供應通過具適當效率之濾器的空氣。</p>
<p>2. The various operations of component preparation, product preparation and filling should be carried out in separate areas within the clean area. Manufacturing operations are divided into two categories; firstly those where the product is terminally sterilised, and secondly those which are conducted aseptically at some or all stages.</p>	<p>2. 組件的準備、產品的製備及充填之不同作業應在潔淨區內之個別的區域中為之。製造作業劃分成兩類；第一類，其產品係經最終滅菌，以及第二類，其產品在製程中的某些階段或全部階段係以無菌技術執行。</p>

<p>3. Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate environmental cleanliness level in the operational state in order to minimise the risks of particulate or microbial contamination of the product or materials being handled.</p>	<p>3. 無菌產品之製造，其潔淨區是按要求的環境特徵分級。為使處理中之產品或原物料的微粒或微生物污染之風險降到最低，每一個製造作業在操作狀態中均要有一個適當的環境潔淨度水準。</p>
<p>In order to meet “in operation” conditions these areas should be designed to reach certain specified air-cleanliness levels in the “at-rest” occupancy state. The “at-rest” state is the condition where the installation is complete with production equipment installed and operating but with no operating personnel present. The “in operation” state is the condition where the installation is functioning in the defined operating mode with the specified number of personnel working.</p>	<p>為要符合動態的條件，這些區域應經設計，使其達到在靜態時之經界定的一定空氣潔淨度水準。靜態是指該生產設施已完成生產設備之安裝並在運轉中，但無操作人員在場之狀態。動態是指該生產設施正在有特定數目之操作人員在場工作之界定的操作模式中運轉的狀態。</p>
<p>The “in operation” and “at rest” states should be defined for each clean room or suite of clean rooms.</p>	<p>對於每一間潔淨室或每一套 (suite) 潔淨室，皆應界定其“動態”及“靜態”的狀況。</p>
<p>For the manufacture of sterile medicinal products 4 grades can be distinguished.</p>	<p>對於無菌藥品的製造，可區分成四個等級。</p>
<p><u>Grade A:</u> The local zone for high risk operations, e.g. filling zone, stopper bowls, open ampoules and vials, making aseptic connections. Normally such conditions are provided by a laminar air flow work station. Laminar air flow systems should provide an homogeneous air speed of 0.36 – 0.54 m/s (guidance value) at the working position in open clean room applications. The maintenance of laminarity should be demonstrated and validated. A uni-directional air flow and lower velocities may be used in closed isolators and glove boxes.</p>	<p><u>A 級：</u> 高風險作業的局部區域，例如，充填區、橡皮塞貯盆、開口安瓿及小瓶、執行無菌連接。通常，此種條件由層流工作站/檯提供。在使用開放潔淨室 (open clean room application) 的工作位置，層流空氣流動系統應提供每秒 0.36 至 0.54 公尺 (指引值) 的均勻空氣流速。層流性 (laminarity) 的維持應予證明 (1.3)，並予確效。單向性空氣流 (uni-directional air flow) 及較低速率得使用在密閉的隔離裝置及手套箱 (glove boxes)。</p>

<u>Grade B:</u> For aseptic preparation and filling, this is the background environment for grade A zone.	<u>B 級：</u> 對於無菌製備及充填，這是 A 級區域的背景環境。
<u>Grade C and D:</u> Clean areas for carrying out less critical stages in the manufacture of sterile products.	<u>C 級與 D 級：</u> 在無菌產品的製造中，執行較非關鍵性階段的潔淨區。

The airborne particulate classification for these grades is given in the following table.

Grade	At rest ^(b)		In operation ^(b)	
	Maximum permitted number of particles/m ³ equal to or above ^(a)			
	0.5 μm ^(d)	5 μm	0.5 μm ^(d)	5 μm
A	3,500	1 ^(e)	3,500	1 ^(e)
B ^(c)	3,500	1 ^(e)	350,000	2,000
C ^(c)	350,000	2,000	3,500,000	20,000
D ^(c)	3,500,000	20,000	not defined ^(f)	not defined ^(f)

這些等級之浮游微粒的分類如下表：

等 級	靜態 ^(b)		動態 ^(b)	
	每立方公尺等於或大於下述粒徑之微粒的最大容許量 ^(a)			
	0.5 μm ^(d)	5 μm	0.5 μm ^(d)	5 μm
A	3,500	1 ^(e)	3,500	1 ^(e)
B ^(c)	3,500	1 ^(e)	350,000	2,000
C ^(c)	350,000	2,000	3,500,000	20,000
D ^(c)	3,500,000	20,000	未界定 ^(f)	未界定 ^(f)

註 (Notes) :

(a) Particle measurement based on the use of a discrete airborne particle counter to measure the concentration of particles at designated sizes equal to or greater than the threshold stated. A continuous measurement system should be used for monitoring the concentration of particles in the grade A zone, and is recommended for the surrounding grade B areas. For routine testing the total sample volume should not be less than 1 m ³ for grade A and B areas and preferably also in grade C areas.	(a) 以離散浮游粒子計數儀 (discrete airborne particle counter) 之使用為基礎的粒子測量法，測量等於或大於規定門檻之指定大小的粒子濃度。連續的量測系統應使用於監測 A 級區中的粒子濃度，並建議使用於其周圍的 B 級區。為例行的測試，對 A 級與 B 級區的總樣品容量不得少於 1 立方公尺，對 C 級區，最好也是這個容量。
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<p>(b) The particulate conditions given in the table for the “at rest” state should be achieved after a short “clean up” period of 15-20 minutes (guidance value) in an unmanned state after completion of operations. The particulate conditions for grade A “in operation” given in the table should be maintained in the zone immediately surrounding the product whenever the product or open container is exposed to the environment. It is accepted that it may not always be possible to demonstrate conformity with particulate standards at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself.</p>	<p>(b) 對於“靜態”，應在作業完成後，在無人狀態，於15-20分鐘（指引值？）之短暫的“清除”期間後，達到表中所列的微粒條件。每當產品或開口容器暴露於該環境時，應在緊鄰圍繞產品的區域維持表中對於“動態”A級區所列的微粒條件。由於來自產品本身之微粒或小液滴的產生，在充填作業中，可能在充填點不能一直呈現符合微粒標準。這是可接受的。</p>
<p>(c) In order to reach the B, C and D air grades, the number of air changes should be related to the size of the room and the equipment and personnel present in the room. The air system should be provided with appropriate terminal filters such as HEPA for grades A, B and C.</p>	<p>(c) 為達到B、C及D級空氣等級，空氣交換的次數應與潔淨室的大小及潔淨室中所存在的設備與人員相對應。空氣系統應裝備適當的終端濾器，例如為A、B及C級裝備HEPA濾器。</p>
<p>(d) The guidance given for the maximum permitted number of particles in the “at rest” and “in operation” conditions correspond approximately to the cleanliness classes in the EN/ISO 14644-1 at a particle size of 0.5 μm.</p>	<p>(d) 指引所定“靜態”及“動態”條件下之微粒最大容許數，大約相當於EN/ISO 14644-1中就0.5μm微粒大小所定的潔淨度等級。 註：EN/ISO 14644-1指BSI 1999年版的Cleanrooms and associated controlled environments. Classification of air cleanliness.（潔淨室及關聯的控制環境。空氣潔淨度的等級）</p>
<p>(e) These areas are expected to be completely free from particles of size greater than 5 μm. As it is impossible to demonstrate the absence of particles with any statistical significance, the limits are set to 1 particle / m³. During the clean room qualification it should be shown that the areas can be maintained within the defined limits.</p>	<p>(e) 這些區域是被期待完全無大於5μm的微粒。因為證明粒子之不存在並具有任何統計意義，是不可能的，所以，將其限量設定為每立方公尺1個。在潔淨室之驗證期間，應顯示該區域能維持在界定之限量內。</p>
<p>(f) The requirements and limits will depend on the nature of the operations carried out.</p>	<p>(f) 該要求及限量取決於從事之作業的性質。</p>

Examples of operations to be carried out in the various grades are given in the table below (see also para. 11 and 12)

Grade	Examples of operations for terminally sterilised products (see para. 11)
A	Filling of products, when unusually at risk
C	Preparation of solutions, when unusually at risk. Filling of products
D	Preparation of solutions and components for subsequent filling

Grade	Examples of operations for aseptic preparations (see para. 12)
A	Aseptic preparation and filling
C	Preparation of solutions to be filtered
D	Handling of components after washing

在各種不同等級從事之作業之實例，如下表所示（亦請參見第 11 及 12 節段）：

等級	最終滅菌產品的作業實例（請參見第 11 節）
A	當產品的充填處於異常風險時
C	當溶液的調製處於異常風險時。產品的充填
D	供後來的充填之溶液和組件的製備/準備

等級	無菌製備作業的實例（請參見第 12 節）
A	無菌製備與充填
C	要過濾之溶液的調製
D	洗滌後之組件的處理

4. The areas should be monitored during operation in order to control the particulate cleanliness of the various grades.	4. 為管制各種等級的微粒潔淨度，該區域應在作業期間加以監測。
5. Where aseptic operations are performed monitoring should be frequent using methods such as settle plates, volumetric air and surface sampling (e.g. swabs and contact plates). Sampling methods used in operation should not interfere with zone protection. Results from monitoring should be considered when reviewing batch documentation for finished product release. Surfaces and personnel should be monitored after critical operations.	5. 在從事無菌作業時，作業區應時常使用諸如落菌培養皿、容量測定空氣取樣及表面取樣(例如擦拭法與培養皿接觸法)等方法監測。使用在作業狀態中的取樣方法不得干擾區域的保護措施。當審查最終產品之放行的批次文件時，監測結果應列入考慮。在關鍵作業後應監測表面及人員。
Additional microbiological monitoring is also required outside production operations, e.g. after validation of systems, cleaning and sanitation.	在生產作業外之作業亦需附加之微生物學的監測，例如在系統確效、清潔與滅菌處理後。

6. Appropriate alert and action limits should be set for the results of particulate and microbiological monitoring. If these limits are exceeded, operating procedures should prescribe corrective action.	6. 微粒及微生物監測的結果，應設定適當的警戒與行動限量。作業程序應規定超出這些限量時之改正的行動。
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Recommended limits for microbiological monitoring of clean areas in operation:

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

Notes: (a) These are average values

(b) Individual settle plates may be exposed for less than 4 hours.

動態潔淨區之微生物監測的建議限量

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

註：(a) 這些都是平均值。

(b) 個別的落菌培養皿暴露時間得少於4小時。

隔離裝置技術 (ISOLATOR TECHNOLOGY)

<p>7. The utilisation of isolator technology to minimise human interventions in processing areas may result in a significant decrease in the risk of microbiological contamination of aseptically manufactured products from the environment. There are many possible designs of isolators and transfer devices. The isolator and the background environment should be designed so that the required air quality for the respective zones can be realised. Isolators are constructed of various materials more or less prone to puncture and leakage. Transfer devices may vary from a single door to double door designs to fully sealed systems incorporating sterilisation mechanisms.</p>	<p>7. 使用隔離裝置技術以將加工區域之人為的介入降到最低，可能獲致顯著減少來自環境對無菌製造的產品之微生物污染風險的結果。隔離裝置及轉送裝置有許多可能的設計。隔離裝置及其背景環境應如此設計，使個別區域所需之空氣品質得以實現。隔離裝置由不同的材料所建造，或多或少有穿孔或漏裂的傾向。轉送裝置可以從單門到雙門，再到結合滅菌機制在一起的完全密閉系統等不同的設計。</p>
<p>The transfer of materials into and out of the unit is one of the greatest potential sources of contamination. In general the area inside the isolator is the local zone for high risk manipulations, although it is recognised that laminar air flow may not exist in the working zone of all such devices. The air classification required for the background environment depends on the design of the isolator and its application. It should be controlled and for aseptic processing be at least grade D.</p>	<p>原物料之轉入及轉出隔離裝置是其污染的最大潛在來源之一。雖然承認，層流空氣可能不會存在於一切此種裝置的作業區中，但隔離裝置的內部區域通常是高風險作業的局部區域。背景環境所需之空氣等級取決於隔離裝置的設計及其應用。這應加以管制，且為無菌操作應至少是D級。</p>
<p>8. Isolators should be introduced only after appropriate validation. Validation should take into account all critical factors of isolator technology, for example the quality of the air inside and outside (background) the isolator, sanitation of the isolator, the transfer process and isolator integrity.</p>	<p>8. 隔離裝置只有在適當確效後始得導入。確效應考慮隔離裝置技術之全部關鍵性因素，例如，隔離裝置內部與外部（背景環境）的空氣品質、隔離裝置的滅菌處理、轉送過程及隔離裝置的完整性等。</p>
<p>9. monitoring should be carried out routinely and include frequent leak testing of the isolator and glove/sleeve system.</p>	<p>9. 監測應例行執行，且應包含隔離裝置及手套/袖套系統之頻繁洩漏試驗。</p>

成型/充填/密封技術 (BLOW/FILL/SEAL TECHNOLOGY)

10. Blow/fill/seal units are purpose built machines in which, in one continuous operation, containers are formed from a thermoplastic granulate, filled and then sealed, all by the one automatic machine. Blow/fill/seal equipment used for aseptic production which is fitted with an effective grade A air shower may be installed in at least a grade C environment, provided that grade A/B clothing is used. The environment should comply with the viable and non-viable limits at-rest and the viable limit only when in operation. Blow/fill/seal equipment used for the production of products for terminal sterilisation should be installed in at least a grade D environment.

10. 成型/充填/密封是一套以連續作業為目的建造之設備，其容器是從熱塑性塑膠粒成型，充填然後再予密封。該作業完全由一部自動化機器進行。連接一個有效的 A 級氣浴裝置之供無菌生產使用的成型/充填/密封設備，其配有 A/B 級衣著者，得安裝在至少 C 級的環境中。該環境在靜態時，應符合微生物及浮游微粒的限量；在動態時只要符合微生物的限量。最終滅菌產品之生產使用的成型/充填/密封設備應安裝在至少 D 級的環境中。

Because of this special technology particular attention should be paid to at least the following: equipment design and qualification, validation and reproducibility of cleaning-in-place and sterilisation-in-place, background clean room environment in which the equipment is located, operator training and clothing, and interventions in the critical zone of the equipment including any aseptic assembly prior to the commencement of filling.

由於這是特別的技術，所以，至少要特別注意下列事項：設備設計與驗證、就地清潔與就地滅菌的確效及再現性、設備座落之背景的潔淨室環境、操作者的訓練與衣著，以及在設備之關鍵區的介入，包括在充填開始前之任何無菌組裝在內。

最終滅菌的產品 (TERMINALLY STERILISED PRODUCTS)

11. Preparation of components and most products should be done in at least a grade D environment in order to give low risk of microbial and particulate contamination, suitable for filtration and sterilisation. Where there is unusual risk to the product because of microbial contamination, for example, because the product actively supports microbial growth or must be held for a long period before sterilisation or is necessarily processed not mainly in closed vessels, preparation should be done in a grade C environment.

11. 組件與大多數產品的製備應在至少 D 級環境中執行，以提供適合於過濾與滅菌之微生物與微粒污染的低風險。因為微生物污染，而對於該產品有異常風險者，例如因為該產品能滋養微生物生長、或應在滅菌前長期間保存、或主要非在密閉容器中加工，其製備應在 C 級環境中執行。

<p>Filling of products for terminal sterilisation should be done in at least a grade C environment.</p>	<p>最終滅菌產品的充填，應在至少 C 級環境中為之。</p>
<p>Where the product is at unusual risk of contamination from the environment, for example because the filling operation is slow or the containers are wide-necked or are necessarily exposed for more than a few seconds before sealing, the filling should be done in a grade A zone with at least a grade C background. Preparation and filling of ointments, creams, suspensions and emulsions should generally be done in a grade C environment before terminal sterilisation.</p>	<p>產品處於來自環境的污染之異常風險者，例如因為充填作業緩慢、或容器為廣口、或在密封前必需暴露數秒鐘以上的時間，其充填應在具有至少 C 級背景之 A 級區中為之。於最終滅菌前，軟膏劑、乳膏劑、懸液劑與乳劑之製備與充填，通常應在 C 級環境中為之。</p>
<p>無菌製備 (ASEPTIC PREPARATION)</p>	
<p>12. Components after washing should be handled in at least a grade D environment. Handling of sterile starting materials and components, unless subjected to sterilisation or filtration through a micro-organism-retaining filter later in the process, should be done in a grade A environment with grade B background.</p>	<p>12. 洗滌後的組件，應在至少 D 級環境中處理。無菌原料與組件的處理，除非要經過滅菌，或要在製程中的後段經由微生物滯留濾器過濾，否則，就應在具有 B 級背景之 A 級環境中執行。</p>
<p>Preparation of solutions which are to be sterile filtered during the process should be done in a grade C environment; if not filtered, the preparation of materials and products should be done in a grade A environment with a grade B background.</p>	<p>在製程中要無菌過濾之溶液的製備，應在 C 級環境中為之；不要過濾者，原物料與產品的製備，應在具有 B 級背景之 A 級環境中為之。</p>
<p>Handling and filling of aseptically prepared products should be done in a grade A environment with a grade B background.</p>	<p>無菌製備之產品的處理及充填應在具有 B 級背景之 A 級環境中為之。</p>
<p>Transfer of partially closed containers, as used in freeze drying, should, prior to the completion of stoppering, be done either in a grade A environment with grade B background or in sealed transfer trays in a grade B environment.</p>	<p>部份封閉之容器的轉送，如使用在冷凍乾燥時，在完成封塞前，應在具有 B 級背景之 A 級環境中，或在 B 級環境之密閉的轉送盤中執行。</p>
<p>Preparation and filling of sterile ointments, creams, suspensions and emulsions should be done in a grade A environment, with a grade B background, when the product is exposed and is not subsequently filtered.</p>	<p>製程中暴露之無菌軟膏劑、乳膏劑、懸液劑及乳劑不經後續過濾者，其製備與充填應在具有 B 級背景之 A 級環境中執行。</p>

人員 (PERSONNEL)	
13. Only the minimum number of personnel required should be present in clean areas; this is particularly important during aseptic processing. Inspections and controls should be conducted outside the clean areas as far as possible.	13. 只有需要之最少數的人員可在潔淨區的現場；這在無菌作業期間特別重要。檢查與管制應儘可能在潔淨區外執行。
14. All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive regular training in disciplines relevant to the correct manufacture of sterile products, including reference to hygiene and to the basic elements of microbiology. When outside staff who have not received such training (e.g. building or maintenance contractors) need to be brought in, particular care should be taken over their instruction and supervision.	14. 在潔淨區中工作的全部人員(包含負責清潔及維修保養之人員)，應接受有關無菌產品之正確製造的定期訓練，包含衛生及微生物學的基本原理在內。有必要將未接受過此種訓練的外部人員(例如建築物或維修保養的承包商)帶進無菌區時，應特別注意對其指導及監督。
15. Staff who have been engaged in the processing of animal tissue materials or of cultures of micro-organisms other than those used in the current manufacturing process should not enter sterile-product areas unless rigorous and clearly defined entry procedures have been followed.	15. 已經從事於非目前製造過程使用的動物組織材料或微生物培養物之工作人員，不得進入無菌產品區，除非已遵守嚴格且清楚界定的進入程序。
16. High standards of personnel hygiene and cleanliness are essential. Personnel involved in the manufacture of sterile preparations should be instructed to report any condition which may cause the shedding of abnormal numbers or types of contaminants; periodic health checks for such conditions are desirable. Actions to be taken about personnel who could be introducing undue microbiological hazard should be decided by a designated competent person.	16. 高標準的人員衛生與潔淨度是必要的。應指示參與無菌製劑製造的人員，提報可能引起異常數目或類型之污染物脫落的任何狀況；對這種狀況定期的健康檢查是必要的。要對可能導入不適當微生物之危險的人員採取之行動，應由指派的權責人員決定。
17. Changing and washing should follow a written procedure designed to minimize contamination of clean area clothing or carry-through of contaminants to the clean areas.	17. 衣服之更換與洗滌應依循指定之書載程序，以將潔淨區衣著的污染或帶入潔淨區之污染物降至最低。

<p>18. Wristwatches, make-up and jewellery should not be worn in clean areas.</p>	<p>18. 在潔淨區中不得配戴手錶、珠寶及使用化粧品。</p>
<p>19. 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.</p>	<p>19. 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。</p>
<p>The description of clothing required for each grade is given below:</p>	<p>每一等級的區域要求之衣著，其說明如下：</p>
<p><u>Grade D:</u> Hair and, where relevant, beard should be covered. A general protective suit and appropriate shoes or overshoes should be worn. appropriate measures should be taken to avoid any contamination coming from outside the clean area.</p>	<p><u>D 級：</u> 人員的頭髮，以及鬍鬚如有蓄留，應予覆蓋。一般的保護套裝及適當的鞋子或鞋套應予穿著。為避免任何來自潔淨區外的污染，應採取適當的措施。</p>
<p><u>Grade C:</u> Hair and, where relevant, beard and moustache should be covered. A single or two-piece trouser suit, gathered at the wrists and with high neck and appropriate shoes or overshoes should be worn. They should shed virtually no fibres or particulate matter.</p>	<p><u>C 級：</u> 人員的頭髮，以及鬍鬚如有蓄留，應予覆蓋。在腕部收緊及高領的單件式或兩件式褲套裝及適當的鞋子或鞋套應予穿著。實際上應無纖維或微粒異物之脫落。</p>
<p><u>Grade A/B:</u> Headgear should totally enclose hair and, where relevant, beard and moustache; it should be tucked into the neck of the suit; a face mask should be worn to prevent the shedding of droplets. Appropriate sterilised, non-powdered rubber or plastic gloves and sterilised or disinfected footwear should be worn. Trouser-bottoms should be tucked inside the footwear and garment sleeves into the gloves. The protective clothing should shed virtually no fibres or particulate matter and retain particles shed by the body.</p>	<p><u>A/B 級：</u> 頭罩應完全包裹頭髮，以及如有蓄留之鬍鬚和八字鬚；頭罩應塞入套裝的領子內；應戴面罩，以防止小液滴的散逸。應穿戴適當滅菌過的、未沾粉末的橡皮或塑膠手套及滅菌過的或消毒過的鞋子；褲管底端應塞入鞋子裏，衣服袖子應塞入手套內。防護衣實際上應不會脫落纖維或微粒異物，並擋住由身體脫落的粒子。</p>

<p>20. Outdoor clothing should not be brought into changing rooms leading to grade B and C rooms. For every worker in a grade A/B area, clean sterile (sterilised or adequately sanitised) protective garments should be provided at each work session, or at least once a day if monitoring results justify this. Gloves should be regularly disinfected during operations. Masks and gloves should be changed at least at every working session.</p>	<p>20. 廠外衣服不得帶入通到 B 級及 C 級區之更衣室中。應在每個工作時段，或在監測結果證明其為正當時，至少每天一次，對在 A/B 級區之每一位工作人員提供潔淨無菌(經過滅菌或適當消毒)的防護裝。在作業期間，手套應定期消毒。面罩與手套至少在每一工作時段應予更換。</p>
<p>21. Clean area clothing should be cleaned and handled in such a way that it does not gather additional contaminants which can later be shed. These operations should follow written procedures. Separate laundry facilities for such clothing are desirable. Inappropriate treatment of clothing will damage fibres and may increase the risk of shedding of particles.</p>	<p>21. 潔淨區的衣服應以使其不致積聚後來會脫落之其他污染物的方式清潔及處理。這些作業應依循書載程序。對於此類衣服，最好有其單獨的洗衣設備。衣服之不適當的處理會損傷其纖維，從而可能增加微粒脫落的風險。</p>
<p>廠房 (PREMISES)</p>	
<p>22. In clean areas, all exposed surfaces should be smooth, impervious and unbroken in order to minimise the shedding or accumulation of particles or micro-organisms and to permit the repeated application of cleaning agents, and disinfectants where used.</p>	<p>22. 為使微粒或微生物的釋出或積聚降到最低，並容許重覆使用採用之清洗劑及消毒劑，在潔淨區內，一切暴露的表面均應平滑、不滲透且未破裂。</p>
<p>23. To reduce accumulation of dust and to facilitate cleaning there should be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment. Doors should be designed to avoid those uncleanable recesses; sliding doors may be undesirable for this reason.</p>	<p>23. 為減少灰塵的積聚及便利清潔，應沒有無法清潔的凹處及最少的突出壁架、儲架、杯架及設備。門之設計應避免無法清潔的凹處；因此，滑動門可能是不合適的。</p>
<p>24. False ceilings should be sealed to prevent contamination from the space above them.</p>	<p>24. 夾層天花板應予密封，以防止來自其上方空間的污染。</p>
<p>25. Pipes and ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces which are difficult to clean.</p>	<p>25. 管線與管道以及其他共用設施，應安裝成使其不會產生凹處、未密封的開口以及難以清潔的表面。</p>

<p>26. Sinks and drains should be prohibited in grade A/B areas used for aseptic manufacture. In other areas air breaks should be fitted between the machine or sink and the drains. Floor drains in lower grade clean rooms should be fitted with traps or water seals to prevent back-flow.</p>	<p>26. A/B 級區之無菌製造場所，應禁用水槽與排水設施。在其他區域，應在機器或水槽及排水設施間裝配空氣阻斷裝置。在潔淨度等級較低的潔淨室內，其地板的排水設施應裝配捕集器或水封，以防止逆流。</p>
<p>27. Changing rooms should be designed as airlocks and used to provide physical separation of the different stages of changing and so minimise microbial and particulate contamination of protective clothing. They should be flushed effectively with filtered air. The final stage of the changing room should, in the at-rest state, be the same grade as the area into which it leads. The use of separate changing rooms for entering and leaving clean areas is sometimes desirable. In general hand washing facilities should be provided only in the first stage of the changing rooms.</p>	<p>27. 更衣室應設計成氣鎖室，並用來提供不同更衣階段之實體的隔離，藉以將防護裝之微生物與微粒污染減到最少。更衣室應以過濾的空氣有效地沖洗。更衣室的最後階段，在靜態時，其潔淨度應與將進入之潔淨區的潔淨度等級相同。為進入與離開潔淨區，使用各自的更衣室有時是必要的。原則上，洗手設備應只在更衣室的第一個階段提供之。</p>
<p>28. Both airlock doors should not be opened simultaneously. An interlocking system or a visual and/or audible warning system should be operated to prevent the opening of more than one door at a time.</p>	<p>28. 氣鎖室兩邊的門不得同時開啟，應啟動互鎖系統或是視覺及/或聽覺的警報系統，以防止在同一時間有一個以上的門同時開啟。</p>
<p>29. A filtered air supply should maintain a positive pressure and an air flow relative to surrounding areas of a lower grade under all operational conditions and should flush the area effectively. Adjacent rooms of different grades should have a pressure differential of 10-15 pascals (guidance values). Particular attention should be paid to the protection of the zone of greatest risk, that is, the immediate environment to which a product and cleaned components which contact the product are exposed. The various recommendations regarding air supplies and pressure differentials may need to be modified where it becomes necessary to contain some materials, e.g. pathogenic, highly toxic, radioactive or live viral or bacterial materials or products. Decontamination of facilities and treatment of air leaving a clean area may be necessary for some operations.</p>	<p>29. 在全部的作業條件下，相對於較低潔淨度等級的周圍區域，過濾過的空氣應維持其正壓及空氣的流動，且應有效地沖洗該潔淨區。不同等級之毗鄰潔淨室應有 10-15 pa (1.0-1.5 mm 水柱) 的壓差 (指引值?)。最大風險區域的保護應予特別注意。該區域就是產品及接觸產品之潔淨組件所暴露之直接環境。在需要圍堵某些物質，例如：致病性、高毒性、放射性或活病毒或活細菌的原物料或產品的情況時，關於其空氣供應及壓差的各種建議可能需要修改。對於某些作業，設施的去污染與離開潔淨室之空氣的處理可能是必需的。</p>

<p>30. It should be demonstrated that air-flow patterns do not present a contamination risk, e.g. care should be taken to ensure that air flows do not distribute particles from a particle-generating person, operation or machine to a zone of higher product risk.</p>	<p>30. 應證明空氣流動的型態不會呈現污染的風險，例如，應小心確保空氣流動不會把來自於產生微粒之人員、作業或機器的微粒散佈到較高產品風險的區域。</p>
<p>31. A warning system should be provided to indicate failure in the air supply. Indicators of pressure differences should be fitted between areas where these differences are important. These pressure differences should be recorded regularly or otherwise documented.</p>	<p>31. 應提供警報系統，以顯示空氣供應上的失靈。在壓差重要的區域間，應安裝壓差計。這些壓差應定期記錄，或用其他的方法予以文件化。</p>
<p>設備 (EQUIPMENT)</p>	
<p>32. 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).</p>	<p>32. 輸送帶不得通過介於 A 級或 B 級區與較低空氣潔淨度之作業區間的隔板/隔牆，除非該輸送帶本身是持續地滅菌的（例如：在一個滅菌的隧道中）。</p>
<p>33. As far as practicable, equipment, fittings and services should be designed and installed so that operations, maintenance and repairs can be carried out outside the clean area. If sterilisation is required, it should be carried out after complete reassembly wherever possible.</p>	<p>33. 只要可行，設備、配件及支援設施應如此設計與安裝，以使其作業、維護保養及修理能在潔淨區外執行。需要滅菌者，應儘可能在完成再度組裝後執行。</p>
<p>34. When equipment maintenance has been carried out within the clean area, the area should be cleaned, disinfected and/or sterilised where appropriate, before processing recommences if the required standards of cleanliness and/or asepsis have not been maintained during the work.</p>	<p>34. 倘曾在潔淨區內維護保養設備，且在該維修工作期間未維持要求之潔淨度及/或無菌性的標準者，於製造作業再開始前，該區域應予清潔、消毒及/或滅菌(合適時)。</p>
<p>35. Water treatment plants and distribution systems should be designed, constructed and maintained so as to ensure a reliable source of water of an appropriate quality. They should not be operated beyond their designed capacity. Water for injections should be produced, stored and distributed in a manner which prevents microbial growth, for example by constant circulation at a temperature above 70°C.</p>	<p>35. 水處理設施及輸送系統，應如此設計、建造與維護保養，以確保適當品質之可靠水源。該系統不得超出其設計能力運轉。注射用水應以阻止微生物生長的方式生產、儲存及輸送，例如在 70°C 以上恆定循環。</p>

<p>36. All equipment such as sterilisers, air handling and filtration systems, air vent and gas filters, water treatment, generation, storage and distribution systems should be subject to validation and planned maintenance; their return to use should be approved.</p>	<p>36. 一切設備，例如：滅菌器、空氣處理及過濾系統、空氣排氣口以及氣體過濾器、水處理、水製造、儲存與輸送系統，均應受確效及有計畫的維護保養；其回復使用應經認可。</p>
<p>衛生 (SANITATION)</p>	
<p>37. The sanitation of clean areas is particularly important. They should be cleaned thoroughly in accordance with a written programme. Where disinfectants are used, more than one type should be employed. monitoring should be undertaken regularly in order to detect the development of resistant strains.</p>	<p>37. 潔淨區的衛生特別重要。這應依書載程序徹底清潔。使用消毒劑者，應採用一種以上的消毒劑。為了檢測阻抗性菌株的產生，應進行定期監測。</p>
<p>38. Disinfectants and detergents should be monitored for microbial contamination; dilutions should be kept in previously cleaned containers and should only be stored for defined periods unless sterilised. Disinfectants and detergents used in Grades A and B areas should be sterile prior to use.</p>	<p>38. 消毒劑與清潔劑應監測其微生物的污染；稀釋液應保存在預先洗淨的容器中，且除非經過滅菌，應只在界定的期間內儲存之。使用在 A 級與 B 級區的消毒劑與清潔劑，在使用前應是無菌的。</p>
<p>39. Fumigation of clean areas may be useful for reducing microbiological contamination in inaccessible places.</p>	<p>39. 潔淨區的燻蒸對於降低不容易接近之處所的微生物污染，可能是有用的。</p>
<p>加工作業 (PROCESSING)</p>	
<p>40. Precautions to minimise contamination should be taken during all processing stages including the stages before sterilisation.</p>	<p>40. 在一切加工作業階段中，包含滅菌前的階段在內，應採取預防措施，以將污染降到最低。</p>
<p>41. Preparations of microbiological origin should not be made or filled in areas used for the processing of other medicinal products; however, vaccines of dead organisms or of bacterial extracts may be filled, after inactivation, in the same premises as other sterile medicinal products.</p>	<p>41. 微生物學起源的製劑，不得在使用於其他藥品之加工作業區域中製備或充填；不過，死的生物體或細菌萃取物的疫苗，在去活化後，可以在使用於其他無菌藥品之相同的廠房設施中充填。</p>

<p>42. Validation of aseptic processing should include a process simulation test using a nutrient medium (media fill). Selection of the nutrient medium should be made based on dosage form of the product and selectivity, clarity, concentration and suitability for sterilisation of the nutrient medium.</p>	<p>42. 無菌作業的確效，應包含使用營養培養基之製程模擬試驗（培養基充填）。營養培養基的選擇應基於產品的劑型及營養培養基滅菌之選擇性、澄明度、濃度及適合性執行。</p>
<p>The process simulation test should imitate as closely as possible the routine aseptic manufacturing process and include all the critical subsequent manufacturing steps. It should also take into account various interventions known to occur during normal production as well as worst case situations. Process simulation tests should be performed as initial validation with three consecutive satisfactory simulation tests per shift and repeated at defined intervals and after any significant modification to the HVAC system, equipment, process and number of shifts. Normally process simulation tests should be repeated twice a year per shift and process. The number of containers used for media fills should be sufficient to enable a valid evaluation.</p>	<p>製程模擬試驗應儘可能模仿例行的無菌製造過程，並包含一切關鍵的後續製造步驟。這並應考慮，已知在正常生產中以及在最差狀況發生的各種介入。在初始確效，製程模擬試驗應對每一個作業輪班，執行三次連續滿意的模擬試驗；並在界定的時間間隔，以及在對 HVAC 系統、設備、製程與輪班次數有任何重大變更後，再予執行。通常，製程模擬試驗應對每一個輪班與製程每年重複兩次。使用於培養基充填的容器數目應足可達成有效的評估。</p>
<p>For small batches, the number of containers for media fills should at least equal the size of the product batch. The target should be zero growth but a contamination rate of less than 0.1% with 95% confidence limit is acceptable. The manufacturer should establish alert and action limits. Any contamination should be investigated.²</p>	<p>對於小批次的生產，其充填培養基的容器數目應至少等於該產品批次的批量。目標值應為零生長。但具有 95%信賴區間之小於 0.1%的污染率是可以接受的。藥廠應建立警戒及行動限量。任何污染都應加以調查²。</p>
<p>² For further details on the validation of aseptic processing, please refer to the PIC/S Recommendation on the Validation of Aseptic Processing (PI 007)</p>	<p>² 關於無菌操作的確效之進一步細節，請參考 PIC/S 關於無菌操作之確效的建議(PI 007)。</p>
<p>43. Care should be taken that any validation does not compromise the processes.</p>	<p>43. 應注意到任何確效都不得損及製程。</p>

<p>44. Water sources, water treatment equipment and treated water should be monitored regularly for chemical and biological contamination and, as appropriate, for endotoxins. Records should be maintained of the results of the monitoring and of any action taken.</p>	<p>44. 水源、水處理設備及經過處理的水均應定期監測其化學上的及生物學上的污染，以及內毒素(當合適時)，該監測的結果及採取的任何行動之紀錄均應予保存。</p>
<p>45. Activities in clean areas and especially when aseptic operations are in progress should be kept to a minimum and movement of personnel should be controlled and methodical, to avoid excessive shedding of particles and organisms due to over-vigorous activity. The ambient temperature and humidity should not be uncomfortably high because of the nature of the garments worn.</p>	<p>45. 在潔淨區中，尤其是當無菌作業正在進行時，應保持最小的作業活動，且人員的移動應加以管制並使其井然有序，以避免由於過度激烈的作業活動引起微粒及微生物的過分散落。週遭的溫度與濕度不應高到因所穿戴衣服的材質而覺得不舒適。</p>
<p>46. Microbiological contamination of starting materials should be minimal. Specifications should include requirements for microbiological quality when the need for this has been indicated by monitoring.</p>	<p>46. 原料的微生物污染應為最低。經由監測顯示需要微生物學上之品質要求者，其規格應包含該要求。</p>
<p>47. Containers and materials liable to generate fibres should be minimised in clean areas.</p>	<p>47. 在潔淨區中，容易產生纖維的容器與原物料，應降到最低。</p>
<p>48. Where appropriate, measures should be taken to minimise the particulate contamination of the end product.</p>	<p>48. 合適時，應採取措施，將最終產品的微粒污染降到最低。</p>
<p>49. Components, containers and equipment should be handled after the final cleaning process in such a way that they are not recontaminated.</p>	<p>49. 組件、容器及設備應在最後清潔過程後，以使其不會再受污染的方式處理之。</p>
<p>50. The interval between the washing and drying and the sterilisation of components, containers and equipment as well as between their sterilization and use should be minimised and subject to a time-limit appropriate to the storage conditions.</p>	<p>50. 組件、容器及設備之洗滌與乾燥和滅菌間，以及其滅菌與使用間的時間間隔，應縮減到最短，且應受制於適合於其儲存條件的時間限度。</p>
<p>51. The time between the start of the preparation of a solution and its sterilisation or filtration through a micro-organism-retaining filter should be minimised. There should be a set maximum permissible time for each product that takes into account its composition and the prescribed method of storage.</p>	<p>51. 溶液製備的開始及其滅菌或經由微生物滯留濾器過濾間的時間間隔，應縮減到最短。對於每一產品應有考慮其組成及規定之儲存方法所設定的最長容許時間。</p>

<p>52. The bioburden should be monitored before sterilisation. There should be working limits on contamination immediately before sterilisation which are related to the efficiency of the method to be used. Where appropriate the absence of pyrogens should be monitored. All solutions, in particular large volume infusion fluids, should be passed through a micro-organism-retaining filter, if possible sited immediately before filling.</p>	<p>52. 在滅菌之前，應監測其負荷菌。應有緊接滅菌前之污染的作業限量。該限量與要採用的滅菌方法之效果有關。合適時，應監測無熱原的存在。一切溶液，尤其是大型輸注液應通過微生物滯留濾器過濾。如果可能，應緊接於充填之前。</p>
<p>53. Components, containers, equipment and any other article required in a clean area where aseptic work takes place should be sterilised and passed into the area through double-ended sterilisers sealed into the wall, or by a procedure which achieves the same objective of not introducing contamination. Noncombustible gases should be passed through micro-organism retentive filters.</p>	<p>53. 在潔淨區進行無菌作業所需要之組件、容器、設備及任何其他物品，應予滅菌，並通過密封在牆壁中的雙門滅菌器進入該潔淨區，或經由可達到不會導入污染之相同目的之程序進入。非可燃性氣體應通過微生物滯留濾器。</p>
<p>54. The efficacy of any new procedure should be validated, and the validation verified at scheduled intervals based on performance history or when any significant change is made in the process or equipment.</p>	<p>54. 任何新程序的效能都應予確效，且該確效應在以其性能表現史為基礎所定之時程間隔，或在製程或設備有任何重大變更時，加以確證之。</p>
<p>滅菌 (STERILISATION)</p>	
<p>55. All sterilisation processes should be validated. Particular attention should be given when the adopted sterilisation method is not described in the current edition of the European Pharmacopoeia, or when it is used for a product which is not a simple aqueous or oily solution. Where possible, heat sterilisation is the method of choice. In any case, the sterilisation process must be in accordance with the marketing and manufacturing authorizations.</p>	<p>55. 一切滅菌過程都應加以確效。當採用的滅菌方法不是現行藥典版本(歐洲藥典)規定的方法，或當該方法使用於非單純水性或油性溶液的產品時，應特別注意。可能時，加熱滅菌是首選的方法。在任何情況中，滅菌過程應符合上市與製造許可。</p>

<p>56. Before any sterilisation process is adopted its suitability for the product and its efficacy in achieving the desired sterilising conditions in all parts of each type of load to be processed should be demonstrated by physical measurements and by biological indicators where appropriate. The validity of the process should be verified at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment. Records should be kept of the results.</p>	<p>56. 任何滅菌過程在採用前，應就其對產品及其在每一種要滅菌處理之裝載型式的全部部位，達成所期的滅菌條件之效能的適當性，以物理量測或以生物指示劑(合適時)加以證明。該滅菌過程的有效性應在安排的時程間隔，至少每年一次，以及每當設備有重大修改時，加以確證。這些結果的紀錄應予保存。</p>
<p>57. For effective sterilisation the whole of the material must be subjected to the required treatment and the process should be designed to ensure that this is achieved.</p>	<p>57. 為有效滅菌，該物料的全部均應接受必要的處理，且該過程應加以設計，以確保達成有效滅菌。</p>
<p>58. Validated loading patterns should be established for all sterilisation processes.</p>	<p>58. 一切滅菌過程，均應建立經過確效的裝載型式。</p>
<p>59. Biological indicators should be considered as an additional method for monitoring the sterilisation. They should be stored and used according to the manufacturers instructions, and their quality checked by positive controls.</p>	<p>59. 生物指示劑作為監測滅菌的附加方法應予考慮。生物指示劑應依製造者的使用說明儲存及使用，且其品質應以陽性對照品核對之。</p>
<p>If biological indicators are used, strict precautions should be taken to avoid transferring microbial contamination from them.</p>	<p>如果使用生物指示劑時，應採取嚴格的預防措施，以避免來自於生物指示劑的微生物污染。</p>
<p>60. There should be a clear means of differentiating products which have not been sterilised from those which have. Each basket, tray or other carrier of products or components should be clearly labelled with the material name, its batch number and an indication of whether or not it has been sterilised. Indicators such as autoclave tape may be used, where appropriate, to indicate whether or not a batch (or sub-batch) has passed through a sterilisation process, but they do not give a reliable indication that the lot is, in fact, sterile.</p>	<p>60. 應有清楚區分未滅菌及已滅菌產品的方法。產品或組件的每個籃子、盤子或其他搬運架，均應清楚標示其名稱、批號及是否經過滅菌的標識。合適時，可以使用指示物，例如高壓蒸氣滅菌指示帶，標識一個批次（或次批次）是否已通過滅菌過程。但事實上這尚非提供該批次為無菌的可靠指標。</p>

61. Sterilisation records should be available for each sterilisation run. They should be approved as part of the batch release procedure.	61. 每一個滅菌操作應有其滅菌紀錄，應當作批次放行程序的一部份予以核准。
加熱滅菌法 (STERILISATION BY HEAT)	
62. Each heat sterilisation cycle should be recorded on a time/temperature chart with a suitably large scale or by other appropriate equipment with suitable accuracy and precision. The position of the temperature probes used for controlling and/or recording should have been determined during the validation and, where applicable, also checked against a second independent temperature probe located at the same position.	62. 每一個加熱滅菌週期應在具有適當刻度之時間/溫度的圖表上，或以具有適當準確度與精密度之其他適當設備記錄之。使用於控制及/或記錄之溫度探針的位置應在確效時即已決定；可行時，也用置放在相同位置之第二個獨立溫度探針核對之。
63. Chemical or biological indicators may also be used, but should not take the place of physical measurements.	63. 化學或生物指示劑雖也可使用，但不得取代物理量測。
64. Sufficient time must be allowed for the whole of the load to reach the required temperature before measurement of the sterilising time-period is commenced. This time must be determined for each type of load to be processed.	64. 在滅菌期間之量測開始前，應有足夠的時間容許裝載物的全部都達到要求的溫度。該時間應針對要處理之每一種裝載型式定之。
65. After the high temperature phase of a heat sterilisation cycle, precautions should be taken against contamination of a sterilised load during cooling. Any cooling fluid or gas in contact with the product should be sterilised, unless it can be shown that any leaking container would not be approved for use.	65. 在加熱滅菌週期的高溫階段後，應採取預防措施，防止經過滅菌的裝載物在冷卻中受到污染。與產品接觸之任何冷卻流體或氣體應已經過滅菌，除非能顯示任何洩漏的容器不會被核准使用。
濕熱滅菌法 (MOIST HEAT)	
66. Both temperature and pressure should be used to monitor the process. Control instrumentation should normally be independent of monitoring instrumentation and recording charts. Where automated	66. 溫度與壓力均應用來監測濕熱滅菌過程。通常，控制儀器裝置應與監測儀器裝置及其記錄圖表各自獨立。對這些應用使用之自動控制與監測系統應加以確效，以確保其符合關鍵過程的要求。系統及滅菌

<p>control and monitoring systems are used for these applications they should be validated to ensure that critical process requirements are met. System and cycle faults should be registered by the system and observed by the operator. The reading of the independent temperature indicator should be routinely checked against the chart recorder during the sterilisation period. For sterilisers fitted with a drain at the bottom of the chamber, it may also be necessary to record the temperature at this position, throughout the sterilisation period. There should be frequent leak tests on the chamber when a vacuum phase is part of the cycle.</p>	<p>週期的故障，應能為系統自動記錄並為操作者觀察到。在滅菌期間，獨立溫度指示器的讀數，應與圖表記錄器例行核對之。對滅菌艙底部裝有排水口的滅菌器，可能也需要在滅菌期間全期記錄該位置的溫度。真空階段是該滅菌週期之一部分者，對該艙應有經常的洩漏試驗。</p>
<p>67. The items to be sterilised, other than products in sealed containers, should be wrapped in a material which allows removal of air and penetration of steam but which prevents recontamination after sterilisation. All parts of the load should be in contact with the sterilising agent at the required temperature for the required time.</p>	<p>67. 除在密封容器中的產品外，要滅菌的物品，應以容許空氣之移除及蒸氣之穿透，而在滅菌後，能防止再污染的材料包裹之。裝載物的全部，在所要求的溫度並達到所要求的時間，皆應與滅菌劑接觸。</p>
<p>68. Care should be taken to ensure that steam used for sterilisation is of suitable quality and does not contain additives at a level which could cause contamination of product or equipment.</p>	<p>68. 應注意確保用於滅菌的蒸氣具有適當的品質，且不含會引起產品或設備污染之濃度的添加物。</p>
<p>乾熱滅菌法 (DRY HEAT)</p>	
<p>69. The process used should include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. Any air admitted should be passed through a HEPA filter. Where this process is also intended to remove pyrogens, challenge tests using endotoxins should be used as part of the validation.</p>	<p>69. 乾熱滅菌採用的製程，應含艙內空氣的循環及正壓的維持，以防止非無菌之空氣的進入。容許進入的任何空氣，應通過 HEPA 過濾器。在本製程亦要移除熱原時，使用內毒素的挑戰試驗應用為確效的一部分。</p>

輻射滅菌法 (STERILISATION BY RADIATION)

<p>70. Radiation sterilisation is used mainly for the sterilisation of heat sensitive materials and products. Many medicinal products and some packaging materials are radiation-sensitive, so this method is permissible only when the absence of deleterious effects on the product has been confirmed experimentally. Ultraviolet irradiation is not normally an acceptable method of sterilisation.</p>	<p>70. 輻射滅菌主要用於對熱敏感的原物料與產品的滅菌。許多藥品及一些包裝材料是對輻射線敏感的，因此，本方法僅在經由實驗確認其對於產品不具有害效應時，始可使用。紫外線照射通常不是一個可接受的滅菌方法。</p>
<p>71. During the sterilisation procedure the radiation dose should be measured. For this purpose, dosimetry indicators which are independent of dose rate should be used, giving a quantitative measurement of the dose received by the product itself. Dosimeters should be inserted in the load in sufficient number and close enough together to ensure that there is always a dosimeter in the irradiator. Where plastic dosimeters are used they should be used within the time-limit of their calibration. Dosimeter absorbances should be read within a short period after exposure to radiation.</p>	<p>71. 在輻射滅菌程序中，輻射劑量應予量測。為此目的，應使用與劑量率無關的劑量指示劑，以提供產品本身接受之劑量的定量性量測。在裝載物中應插入足夠數目與分布的劑量計，以確保在輻射照射器中一直有一個劑量計。使用塑膠劑量計者，應在其校正的時間限度內使用之。劑量計的吸光度應在暴露於輻射後的短時間內讀取之。</p>
<p>72. Biological indicators may be used as an additional control.</p>	<p>72. 生物指示劑可以當作附加的管制使用。</p>
<p>73. Validation procedures should ensure that the effects of variations in density of the packages are considered.</p>	<p>73. 確效程序應確保考慮到包裝/包件密度上之差異所造成的效應。</p>
<p>74. Materials handling procedures should prevent mix-up between irradiated and non-irradiated materials. Radiation-sensitive colour disks should also be used on each package to differentiate between packages which have been subjected to a irradiation and those which have not.</p>	<p>74. 原物料之處理程序，應防止經輻射滅菌與未經輻射滅菌之原物料間的混雜。輻射敏感性的變色圓片，也應使用在每一件包裝/包件上，以區分經輻射滅菌及未經輻射滅菌的包裝/包件。</p>
<p>75. The total radiation dose should be administered within a predetermined time span.</p>	<p>75. 總輻射劑量應在預定的照射時間內達到。</p>

環氧乙烷滅菌 (STERILISATION WITH ETHYLENE OXIDE)

<p>76. This method should only be used when no other method is practicable. During process validation it should be shown that there is no damaging effect on the product and that the conditions and time allowed for degassing are such as to reduce any residual gas and reaction products to defined acceptable limits for the type of product or material.</p>	<p>76. 本方法應只用在沒有其他方法可用的情形。在滅菌製程確效期間，應顯示對產品無有害的效應，及其除氣所容許的條件與時間可將任何殘留氣體及反應產物減低至為該類型產品或原物料界定之允許限量。</p>
<p>77. Direct contact between gas and microbial cells is essential; precautions should be taken to avoid the presence of organisms likely to be enclosed in material such as crystals or dried protein. The nature and quantity of packaging materials can significantly affect the process.</p>	<p>77. 氣體與微生物細胞間的直接接觸是必需的，應採取預防措施，以避免可能會包在像結晶或乾燥蛋白質這類物質之微生物的存在，包裝材料的性質與數量會顯著影響該滅菌過程。</p>
<p>78. Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process. The time required for this should be balanced against the opposing need to minimise the time before sterilisation.</p>	<p>78. 原物料在暴露於氣體之前，應使其與該製程要求之濕度與溫度達於均衡。達到該均衡所需的時間，應與其對立的需求相權衡，以將滅菌前的時間縮減到最短。</p>
<p>79. Each sterilisation cycle should be monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load. The information so obtained should form part of the batch record.</p>	<p>79. 每一個滅菌週期皆應以適當的生物指示劑試驗片監測之，並將適當數目之試驗片分佈在整個裝載。由此取得的資訊應構成該批次紀錄的一部分。</p>
<p>80. For each sterilisation cycle, records should be made of the time taken to complete the cycle, of the pressure, temperature and humidity within the chamber during the process and of the gas concentration and of the total amount of gas used. The pressure and temperature should be recorded throughout the cycle on a chart. The record(s) should form part of the batch record.</p>	<p>80. 為每一滅菌週期，應將完成該週期所用的時間，在滅菌期間艙內的壓力、溫度與濕度，以及所使用之氣體濃度和氣體總量做成記錄。在滅菌週期的全程，應將壓力與溫度記錄在一張圖表上。該等紀錄應構成該批次之紀錄的一部分。</p>

<p>81. After sterilisation, the load should be stored in a controlled manner under ventilated conditions to allow residual gas and reaction products to reduce to the defined level. This process should be validated.</p>	<p>81. 在滅菌後，裝載物應以管制的方式在通風的條件下儲存，以容許將殘留氣體及反應產物降低到界定的水準。此製程應予確效。</p>
<p>不適於在最終容器中滅菌之藥品的過濾 (FILTRATION OF MEDICINAL PRODUCTS WHICH CANNOT BE STERILISED IN THEIR FINAL CONTAINER)</p>	
<p>82. Filtration alone is not considered sufficient when sterilisation in the final container is possible. With regard to methods currently, steam sterilisation is to be preferred. If the product cannot be sterilised in the final container, solutions or liquids can be filtered through a sterile filter of nominal pore size of 0.22 micron (or less), or with at least equivalent micro-organism retaining properties, into a previously sterilised container. Such filters can remove most bacteria and moulds, but not all viruses or mycoplasma's. Consideration should be given to complementing the filtration process with some degree of heat treatment.</p>	<p>82. 可在最終容器中滅菌者，只使用過濾除菌不被認為是足夠的。在目前可用的方法中，蒸氣滅菌是較好的。產品不能在最終容器中滅菌者，溶液或液體得通過一個0.22微米（或更小）之孔徑的濾器，或以至少具有同等微生物滯留性質之濾器，濾入事先滅菌的容器中。此種濾器能移除大多數的細菌與黴菌，但不能移除全部的病毒或黴漿菌。應考慮以某種程度的熱處理補充該過濾製程。</p>
<p>83. Due to the potential additional risks of the filtration method as compared with other sterilisation processes, a second filtration via a further sterilised microorganism retaining filter, immediately prior to filling, may be advisable. The final sterile filtration should be carried out as close as possible to the filling point.</p>	<p>83. 由於過濾方法與其他滅菌製程比較時，有潛在的附加風險，所以，在緊接於充填前，透過一個進一步滅菌過的微生物滯留濾器為第二次過濾可能是明智的。最終的無菌過濾應儘可能接近於充填點為之。</p>
<p>84. Fibre shedding characteristics of filters should be minimal.</p>	<p>84. 濾器之纖維脫落的特性應為最少。</p>
<p>85. The integrity of the sterilised filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test. The time taken to filter a known volume of bulk solution and the pressure difference to be</p>	<p>85. 滅菌過之濾器的完整性在使用前應經證明，且應在使用後，立即以適當的方法，例如起泡點、擴散流或持壓試驗確認之。過濾一已知容量的大量溶液所需的時間，以及跨越要使用之濾器的壓差應在確效期間予以確定，且在例行製造中，有與之任何顯著之差異者，應予註記並調查。</p>

<p>used across the filter should be determined during validation and any significant differences during routine manufacturing from this should be noted and investigated. Results of these checks should be included in the batch record. The integrity of critical gas and air vent filters should be confirmed after use. The integrity of other filters should be confirmed at appropriate intervals.</p>	<p>這些檢查的結果應包含在該批次的紀錄中。重要氣體及空氣通氣口濾器的完整性應在使用後加以確認。其他濾器的完整性應在適當的時間間隔加以確認。</p>
<p>86. The same filter should not be used for more than one working day unless such use has been validated.</p>	<p>86. 同一濾器不得使用超過一個工作天，除非這樣使用已經經過確效。</p>
<p>87. The filter should not affect the product by removal of ingredients from it or by release of substances into it.</p>	<p>87. 濾器不得因從產品移除成分或因濾器組成份之釋入產品，而影響到產品。</p>
<p>無菌產品的完成 (FINISHING OF STERILE PRODUCTS)</p>	
<p>88. Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. glass or plastic ampoules should be subject to 100% integrity testing. Samples of other containers should be checked for integrity according to appropriate procedures.</p>	<p>88. 容器應以經適當確效的方法封閉。以熔封法封閉的容器，例如玻璃或塑膠的安瓿應接受百分之百之完整性試驗。其他容器樣品，應依適當的程序檢查其完整性。</p>
<p>89. Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period.</p>	<p>89. 在真空下密封的容器，應在適當的、預先設定的期間後，測試該真空度的維持。</p>
<p>90. Filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. When inspection is done visually, it should be done under suitable and controlled conditions of illumination and background. Operators doing the inspection should pass regular eye-sight checks, with spectacles if worn, and be allowed frequent breaks from inspection. Where other methods of inspection are used, the process should be validated and the performance of the equipment checked at intervals. Results should be recorded.</p>	<p>90. 已充填的容器應個別檢查其外來污染或其他瑕疵。以目視檢查者，應在適當且經控制的照明與背景條件下執行。執行該檢查的作業人員，應通過定期的視力健檢，其戴眼鏡者，應戴上眼鏡接受健檢，並在產品檢查中給予慣常的休息。使用其他檢查方法者，其過程應予確效，並在一定時間間隔檢查該設備的性能。其結果應予記錄。</p>

品質管制 (QUALITY CONTROL)	
91. The sterility test applied to the finished product should only be regarded as the last in a series of control measures by which sterility is assured. The test should be validated for the product(s) concerned.	91. 應用於最終產品的無菌試驗，應只認定為是一連串確保無菌性之控制措施的最後措施。該測試應就所涉產品加以確效。
92. In those cases where parametric release has been authorised, special attention should be paid to the validation and the monitoring of the entire manufacturing process.	92. 在參數放行業經核准的情形，應特別注意全部製造過程的確效與監測。
93. Samples taken for sterility testing should be representative of the whole of the batch, but should in particular include samples taken from parts of the batch considered to be most at risk of contamination, e.g.:	93. 為無菌試驗抽取的樣品，應為整個批次的代表性樣品，尤其應包含取自該批次中被認為最具污染風險之部分的樣品，例如：
a) for products which have been filled aseptically, samples should include containers filled at the beginning and end of the batch and after any significant intervention;	a) 為經無菌充填的產品，其樣品應包含在該批次之開始與結束時及在任何重大介入後充填的容器。
b) for products which have been heat sterilised in their final containers, consideration should be given to taking samples from the potentially coolest part of the load.	b) 對於已經在其最終容器中加熱滅菌的產品，應考慮取自裝載中可能最冷部分的樣品。