衛生福利部食品藥物管理署委辦計畫

「精進無菌製劑製造品質達國際標準之研究」

再生醫療及核酸藥物製劑GMP訓練活動（1）

日期：民國 114 年 5 月 21 日

主辦單位：衛生福利部食品藥物管理署

承辦單位：TPDA 社團法人中華無菌製劑協會

講 師 資 料

陳永宜 副總經理 / 祥翊製藥股份有限公司

時 間 表

時 間	內 容	講 師
13:00-13:30	報 到	
13:30-13:40	長 官 致 詞	TFDA 監管組代表
13:40-15:00	➢ **污染管制策略(CCS)法規介紹** ■**CCS 之法規要求** ■**CCS 之管理層面重點考量**	**陳永宜 副 總**
15:00-15:20	休 息	
15:20-16:40	➢ **污染管制策略(CCS)範例說明** ■**製藥廠常用品質風險管理工具** ■**案例分享**	**陳永宜 副 總**
16:40-17:00	交流討論 / 課後評估	

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Contamination Control Strategy (CCS)之法規要求

Prepared by : Whitney Chen(陳永宜)

Date: May 21,2025

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What is a Contamination Control Strategy?

The term "Contamination Control Strategy (CCS)" was introduced in the recent changes of the European Union (EU) Annex 1.

The Annex 1 glossary defines a holistic CCS as:

- 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 replacing equipment components.
- 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。

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What is a Contamination Control Strategy?

- Documented Contamination Control Strategy
- Relies on good knowledge management (ICH Q10)
- Risk based approach (ICH Q9)/TR 54
- Annex 1 requires an effective contamination control strategy (CCS)
- TR 90
- Holistic Review
- A cyclic process

Within the General Manufacturing area the following aspects of the design, operation and maintenance of the facilities and equipment were deficient:

- Mixing room #1 and #2 operated at **positive pressure** and airflow to the main access corridor and contrary to the principle of containment; while mixing room #3 (M06), in contrast, operated at **negative pressure** and airflow to the main access corridor.
- The risks associated with inconsistencies in pressure differentials and the directions of airflow were compounded by the presence and operation of the **interconnecting doors between mixing rooms #1, #2 and #3**, in that these doors allowed the unrestricted movement of equipment, materials, personnel and (intermediate) product between these rooms during formulation.
- The wash room, packing room #2, the dispensary and mixing room #3 operated at negative pressure to the main access corridor, and consequentially were **"sinks"** to mixing rooms #1 & #2, and Packaging rooms #1 & #3.
- The equipment **washroom** was congested and used for **storage of 'cleaned' equipment** .

Lack of Appropriate Controls - Issues

Re-usable equipment for CYTOTOXIC was stated to be dedicated, however the inspector observed that:

- Although the filling needles and carboy siphon tubes were marked, these filling needles and carboy siphon tubes were **stored mixed up with needles and siphon tubes for other products**.
- Although the Equipment Preparation List for CYTOTOXIC stated "use CYTOTOXIC dedicated equipment" the records available **did not demonstrate that CYTOTOXIC dedicated equipment was used**, and the system in place did not clearly demonstrate that CYTOTOXIC dedicated equipment was controlled in a manner to ensure that the dedicated equipment was not used for the manufacture of other products;
- The flasks used for the collection of CYTOTOXIC flush and priming solutions **were not dedicated** to CYTOTOXIC.

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Scope – Annex 1

- 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.
- 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。

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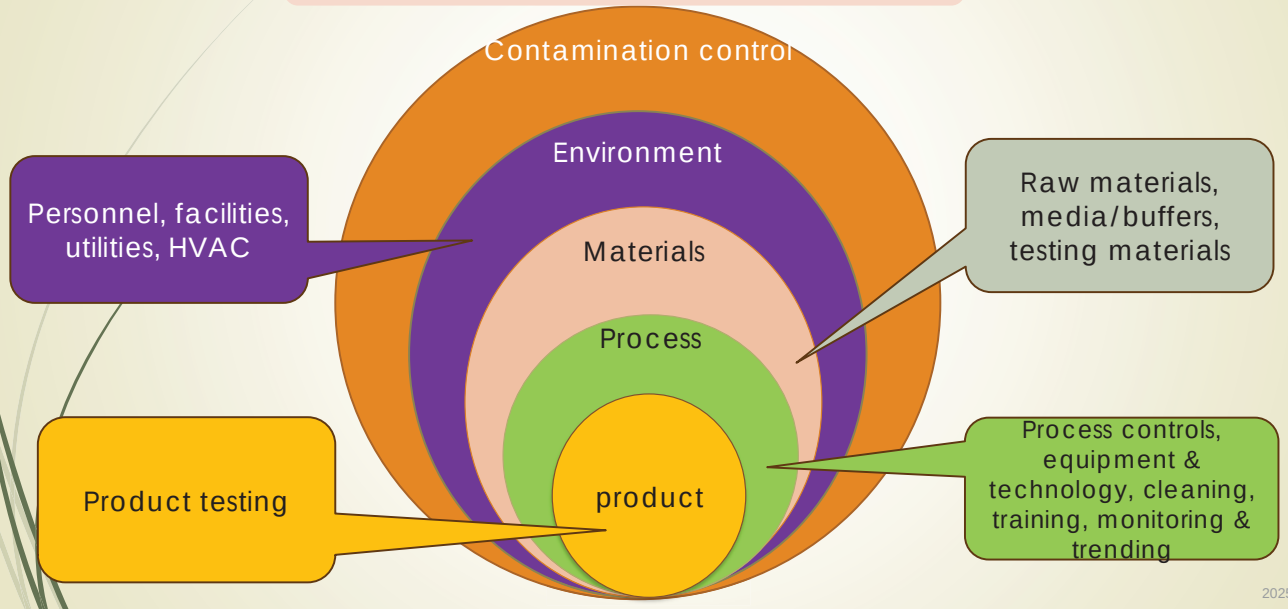
Holistic program that encompasses concepts within the context of the entire manufacturing facility and process.



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CCS in Annex 1

1. Scope 範圍
2. Principle原則
3. Pharmaceutical Quality System (PQS)
   製藥品質系統
4. Premises廠房設施
5. Equipment設備
6. Utilities公用設施
7. Personnel組織與人事
8. Production and specific technologies
   生產及特定技術
   - Aseptic preparation and processing
   - Aseptic and terminal sterilization processes.
   - Lyophilization
   - Form-Fill-Seal
9. Environmental and process monitoring
   環境與製程監測
10. Quality Control (QC)品質管制

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2. Principle原則

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:

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
ii. 人員應具有充分的資格及經驗、訓練及行為
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。
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。

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。

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2. Principle原則

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。

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。

2.5 CCS 的建立需要詳細的技術及製程知識

i. 工廠及流程的設計，包括相關文件；
ii. 廠房設施及設備；
iii. 組織與人事；
iv. 公用設施；
v. 原料管制—包括製程中管制；
vi. 產品容器及封蓋；
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；
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；
ix. 製程風險管理；
x. 製程確效；
xi. 滅菌製程的確效；
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；
xiii. 清潔及消毒
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；
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
xvi. 基於上述資訊的持續改進。

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3. 製藥品質系統（Pharmaceutical Quality System, PQS）

- 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。無菌產品製造的 PQS 還應確保：

  - 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。
  - 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。
  - 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）。
  - 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。
  - 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。
  - 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。
  - 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。

- 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。

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3. 製藥品質系統（Pharmaceutical Quality System, PQS）

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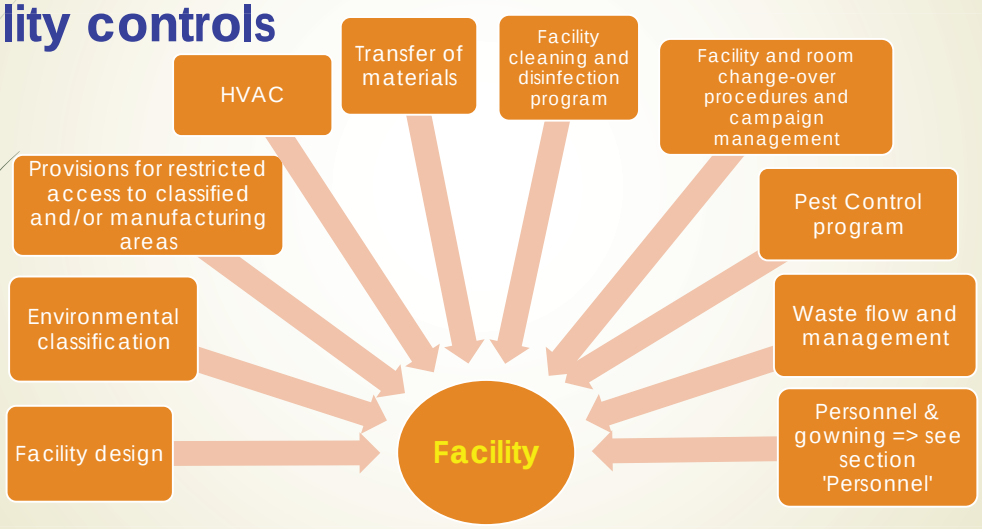
4.廠房設施 (Premises)

- **Facility controls**



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CCS關鍵考量:

Facility design

- Easy to clean, GMP compliant physical design: Containment
- Materials of construction
- HVAC/Airborne Transfer :Pressure regimen
- Material /Personnel movement

屏障技術: 隔離裝置Isolator/RABs

Process Design

- Aseptic considerations, pre-sterilization handling
- Validated sterilization and depyrogenation processes

Effective supporting procedures

- Gowning(De-contaimination)
- Aseptic technique and handling
- Cleanroom behaviors

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CCS關鍵考量:

Personnel Training

- Qalification for aseptic operation
- Gowning qualification
- Effective production task training

Education, not training!

Technology/Equipment

- Single use product contact equipment
- Barrier systems/isolators
- Automation, including CIP/SIP

Environmental Monitoring

- Monitoring program
- Effective data analysis and appropriate alerts
- Acquired knowledge/understanding of facility risks

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CCS關鍵考量:

Cleaning & Disinfection

- Agents used? Rotations? Effectiveness?
- Types of clean and relevant frequencies
- Validation for disinfection and cleaning

Media Fills

- Appropriate for all product types (worst cases?)
- Well defined interventions
- Data analysis and frequency of events

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5 設備 (Equipment)

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。

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.

- 設備驗證:URS/FS/DS/DQ/IOPQ
- 清潔程序應經確效/消毒劑的有效性產生不利影響的殘留物或碎屑，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。
- 設備監測及維護保養計劃

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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

一般來說，有較高風險的公用設施如下：

- 水系統Water systems : PW/WFI
- 蒸汽作為直接滅菌劑Steam used as a direct sterilising agent: Steam/Clean Steam
- 氣體及真空系統Gases and vacuum systems
- 加熱、冷卻及液壓系統Heating and cooling and hydraulic systems

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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。

7.9 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。

7.10 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。

7.14 潔淨室著衣應在適當潔淨等級的更衣室內進行，以確保防護服可以被維持。廠外衣著包括襪子在內(個人內衣除外），不應帶往B級及C級區域的更衣室中。廠服及廠襪不應對更衣區或製程有

Mask test results	
Contaminant source	CFU per minute
Breathe	0-4
Speak	1-28
Sing	1-128
Cough咳嗽	1-1000
Sneeze打噴嚏	12-3400

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8 生產及特定技術 (Production and Specific Technologies)無菌製備及操作 –

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。

8.8 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。

8.9 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）。

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8 生產及特定技術 (Production and Specific Technologies) 無菌製備及操作 –

8.16 應有核准清單，列出在生產過程中可能發生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。

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：

i. 設備、組件及容器的清潔、乾燥及滅菌之間的保持時間；
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；
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）；
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；
v. 已滅菌產品在充填前的保持時間
vi. 無菌操作時間
vii. 充填時間。

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8 生產及特定技術(Production and Specific Technologies)
- 對無法在最終容器中滅菌的產品進行過濾滅菌

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）。

8.80 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。

8.82 過濾系統的設計應：

i. 允許在經過確效的製程參數範圍內操作；
ii. 保持濾液的無菌性；
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
iv. 需要時，允許執行清潔程序；
v. 允許進行必要的滅菌程序，包括原位滅菌。
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。

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8 生產及特定技術(Production and Specific Technologies)

-對無法在最終容器中滅菌的產品進行過濾滅菌

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。

8.95 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：

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；

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；

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

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。

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8 生產及特定技術(Production and Specific Technologies)

成型-充填-密封（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。

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。

8.100 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：

i. 確定關鍵區域的界線

ii. 環境管制及監測，包括機器及它所在的背景

iii. 人員著裝要求，

iv. 產品充填線及過濾系統的完整性測試（相關時）

v. 批次或充填活動的持續時間

vi. 包裝膜的管制，包括對包裝膜去污染或滅菌的任何要求，

vii. 必要時對設備進行原位清潔及原位滅菌，

viii. 機器操作、設定及警報管理（相關時）。

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8 生產及特定技術(Production and Specific Technologies)

吹製-充填-密封(Blow-Fill-Seal - BFS)

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。

8.109 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

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。

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8 生產及特定技術(Production and Specific Technologies)

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。

8.123 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。

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：

i. 應規定凍乾機內的裝載型式並予文件化。

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）。

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。

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。

v. 如果在打開凍乾機艙室之前產品屬於未完成封塞狀態，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。

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。

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8 生產及特定技術(Production and Specific Technologies)

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。

8.128 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）。

8.129 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。

8.130 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）。

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8 生產及特定技術(Production and Specific Technologies)

一次性使用系統 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。

8.132 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：

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），
ii. 相較於固定的可重複使用系統之脆弱本質
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
iv. 組裝的複雜性，
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），
vi. 存在孔洞及洩漏的風險
vii. 打開外包裝時可能危及系統
viii. 微粒污染的風險

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

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。

9.2 該計畫通常由以下要項組成：

i. 環境監測—總微粒

ii. 環境及人員監測—微生物

iii. 溫度、相對濕度及其他特定性質；

iv. APS（僅限於無菌製造之產品）

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。

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9 環境與製程監測(Environmental & 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：

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。

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。

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。

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。

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

環境監測—總微粒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。

9.15 每一級區環境監測之浮游微粒濃度限量見表5。(表5：各級區被允許動/靜態之總微粒監測的最大濃度。)

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。

9.20 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。

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

環境及人員監測—微生物

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。

9.25 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。

9.26 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。

9.31 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。

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

無菌製程模擬（APS-Aseptic process simulation）（培養基充填）

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。

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

無菌製程模擬（APS-Aseptic process simulation）（培養基充填）

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：

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。

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。

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。

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。

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。

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 。

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，(Holding time)
- 重現過濾與凍乾之間的最長期間，以及 (Duration time)
- 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。

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

無菌製程模擬（APS-Aseptic process simulation）（培養基充填）

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。

9.39 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。

9.40 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。

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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。

10.2 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。

10.7 某些產品可能由於架儲期太短，以致無法在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。

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。

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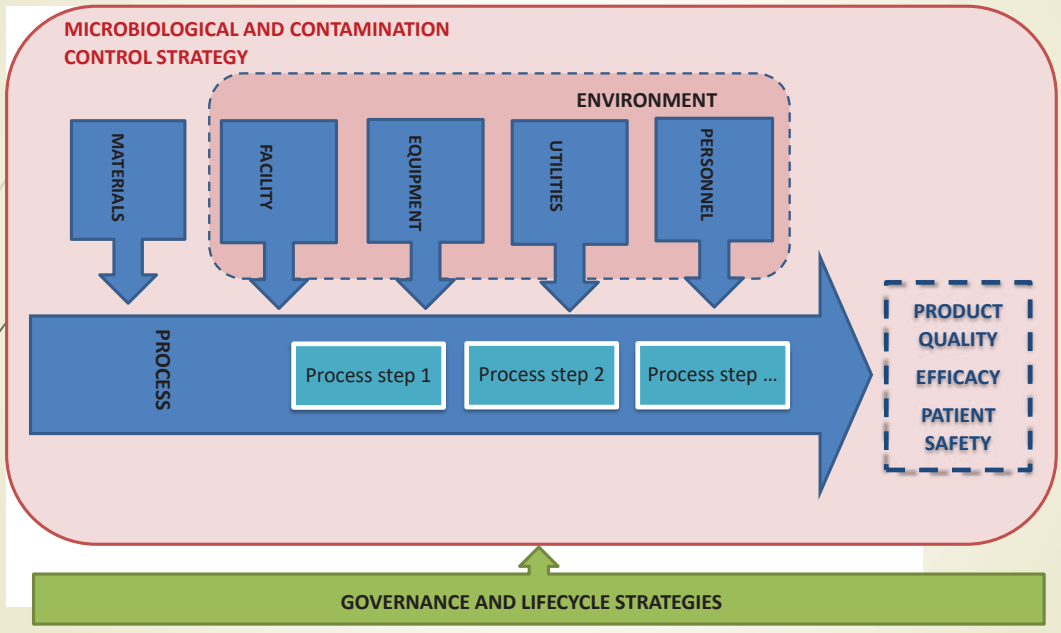

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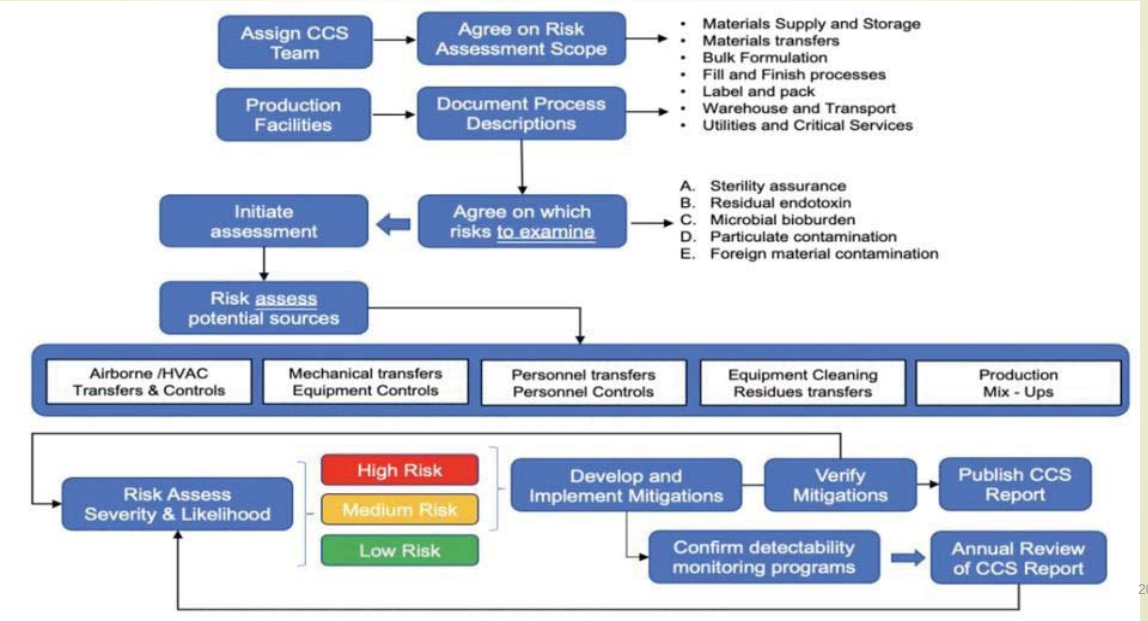
Organising for CCS - What is a CCS Plan?



2025/5/9

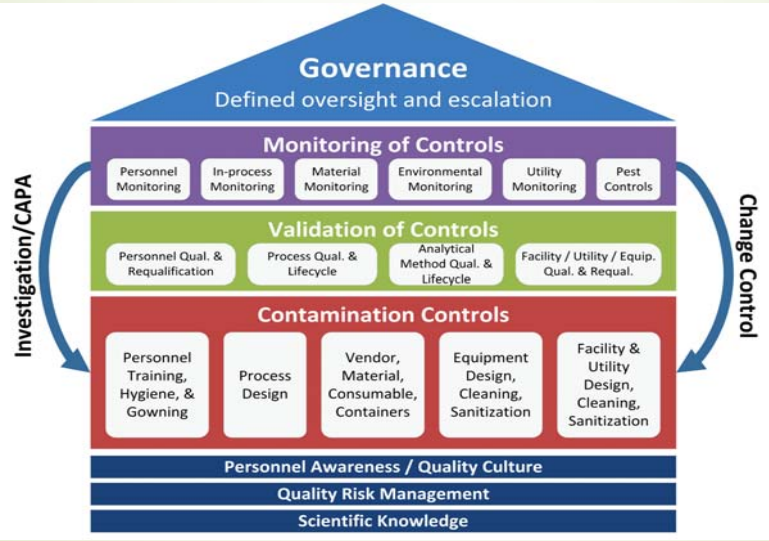
CCS 之各個管理層面重點考量

Prepared by : Whitney Chen(陳永宜)

Date: May 21,2025

This technical report outlines how to implement an effective CCS using a holistic approach, highlights a selection of best practices, and identifies outdated practices and mindsets.

如何使用整體方法實施有效的CCS，重點介紹一些最佳實踐，並確定過時的做法和思維方式



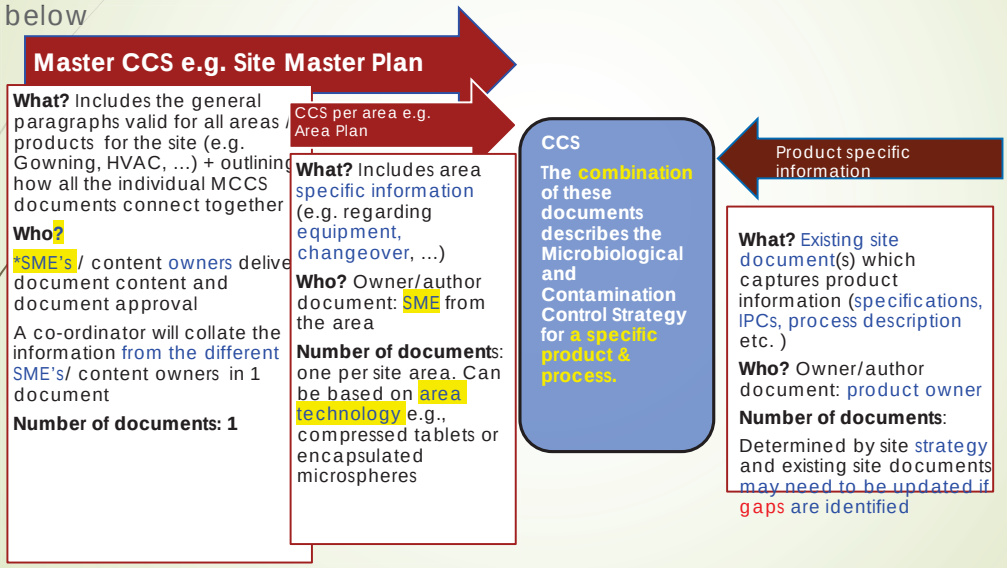
Roles and Responsibilities

- Each company needs to define who's responsible for CCS
- Development
- Review
- The Quality Authority must approve the CCS

Preparing the CCS is a cross functional effort. Consider developing a project plan to define who, what and how the CCS will come together.

Potential Approach to Document CCS

- At **larger sites** with **multiple manufacturing areas**, where **different types of products are made**, **multiple CCS**, each focused on a separate area of the site, product, or process, may be issued. The overall organisation of documents could be represented by the graphic below



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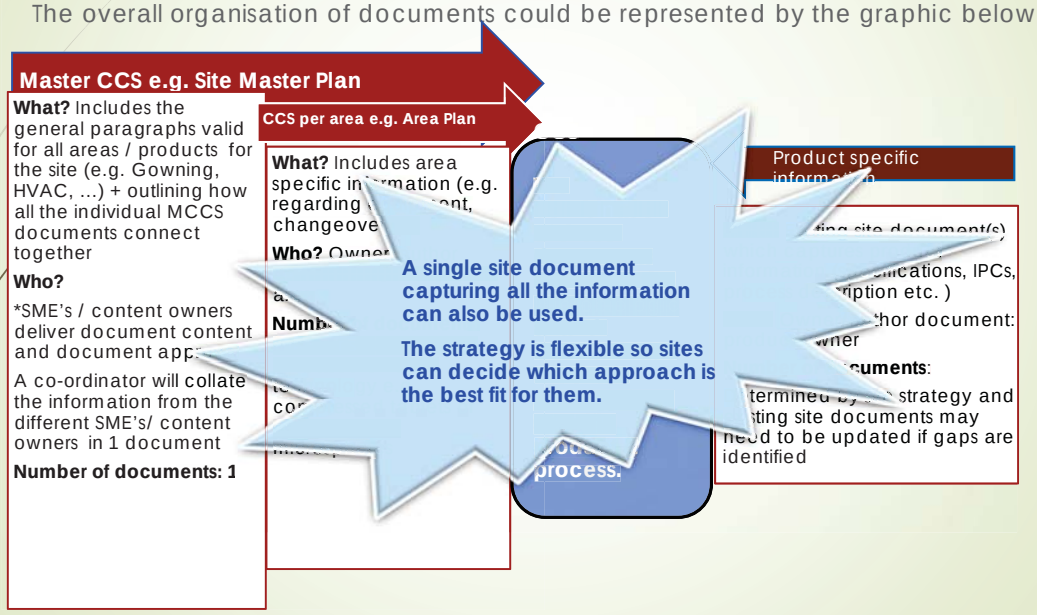

Potential Approach to Document CCS

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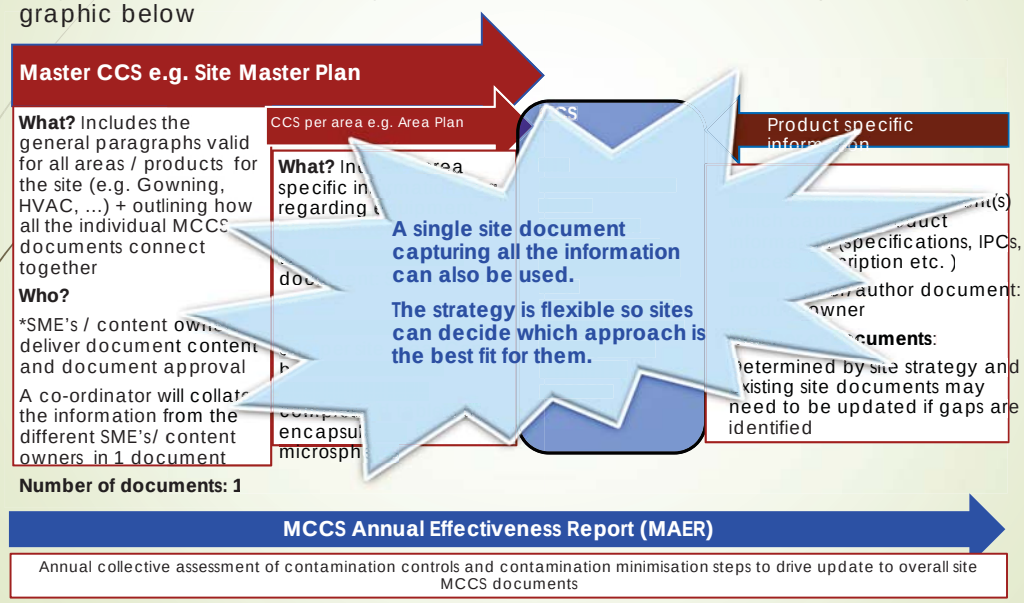
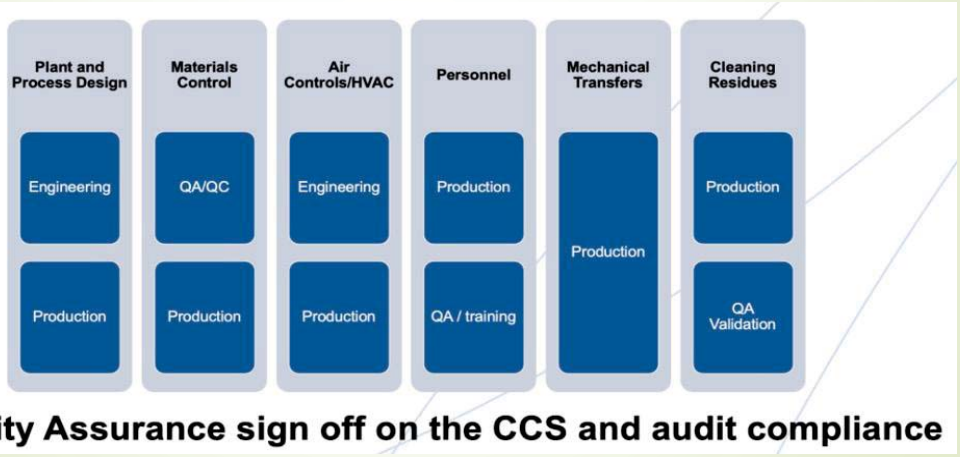


Ownership & Development

- Multiple functions
- Coordination and overall plan – Validation/Production, QA Approval
- Sites to determine

Establish the project team: QA, QC, EN, PD, PUR…



Detailed Content of the CCS

Overall CCS Contents

- PURPOSE AND OBJECTIVES
- SCOPE
- ROLES AND RESPONSIBILITIES
- GOVERNANCE AND LIFECYCLE STRATEGIES IMPACTING MICROBIOLOGICAL AND CONTAMINATION CONTROL STRATEGIES
- MICROBIOLOGICAL AND CONTAMINATION CONTROL STRATEGY
- CONCLUSION
- REFERENCES
- DOCUMENT HISTORY

Governance and Life Cycle Strategies impacting CCS

- QUALITY OVERSIGHT
- PREVENTIVE MAINTENANCE MANAGEMENT
- CALIBRATION MANAGEMENT (CM)
- VALIDATION LIFE CYCLE MANAGEMENT AND PERIODIC REVIEW
  - QUALIFICATION OF MICROBIOLOGICAL ANALYTICAL AND MONITORING METHODS
- SUPPLIER MANAGEMENT
- MANAGEMENT OF OUTSOURCED ACTIVITIES AND PURCHASED MATERIALS
- SITE SELF AUDIT
- RESPONSE PROCESSES
  - DEVIATION MANAGEMENT
  - CAPA (CORRECTIVE AND PREVENTIVE ACTIONS) MANAGEMENT
  - CHANGE MANAGEMENT
- QUALITY RISK MANAGEMENT
- ANNUAL REVIEW PROCESS OF MCCS AND CONTINUOUS IMPROVEMENT

Detailed Content of the CCS (cont.)

- PURPOSE AND OBJECTIVES
- SCOPE
- ROLES AND RESPONSIBILITIES
- GOVERNANCE AND LIFECYCLE STRATEGIES IMPACTING MICROBIOLOGICAL AND CONTAMINATION CONTROL STRATEGIES
- MICROBIOLOGICAL AND CONTAMINATION CONTROL STRATEGY
- CONCLUSION
- REFERENCES
- DOCUMENT HISTORY

FACILITY
- FACILITY DESIGN
- ENVIRONMENTAL CLASSIFICATION (FACILITY ZONING) if applicable
- PROVISIONS FOR RESTRICTED ACCESS TO CLASSIFIED AND/OR MANUFACTURING AREAS
- HVAC
- FACILITY CLEANING AND DISINFECTION PROGRAM
- FACILITY AND ROOM CHANGE-OVER PROCEDURES AND CAMPAIGN MANAGEMENT
  TRANSFER OF MATERIALS
- PEST CONTROL PROGRAM
- WASTE FLOW AND MANAGEMENT

EQUIPMENT
- EQUIPMENT DESIGN
- USE OF SINGLE USE SYSTEMS
- EQUIPMENT CLEANING PROGRAM
- EQUIPMENT DECONTAMINATION /

PERSONNEL
GOWNING PRACTICE
TRAINING AND QUALIFICATION

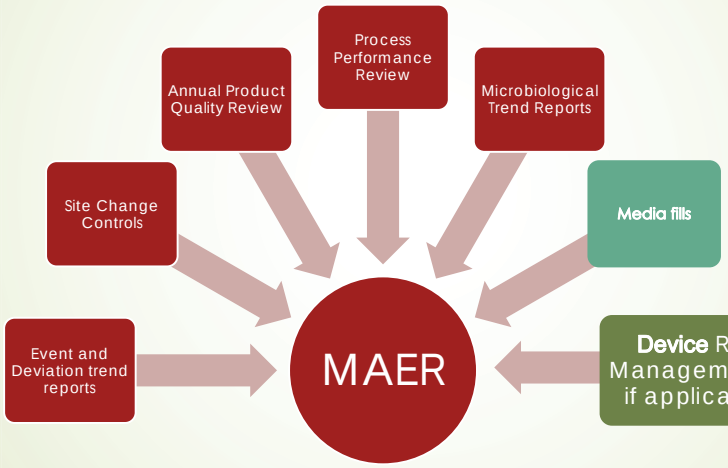
UTILITIES
- WATER SYSTEMS
- CLEAN STEAM SYSTEMS
- GAS SYSTEMS

MATERIALS
- HANDLING OF INCOMING GOODS
- MICROBIOLOGICAL QUALITY CONTROL (RAW MATERIALS, COMPONENTS

REJECTION AND DISPOSAL OF MATERIALS

PROCESS AND PRODUCT
- PROCESS UNIT OPERATION INTEGRITY
- CONTAINER CLOSURE INTEGRITY

(M)CCS Annual Effectiveness Report (MAER)



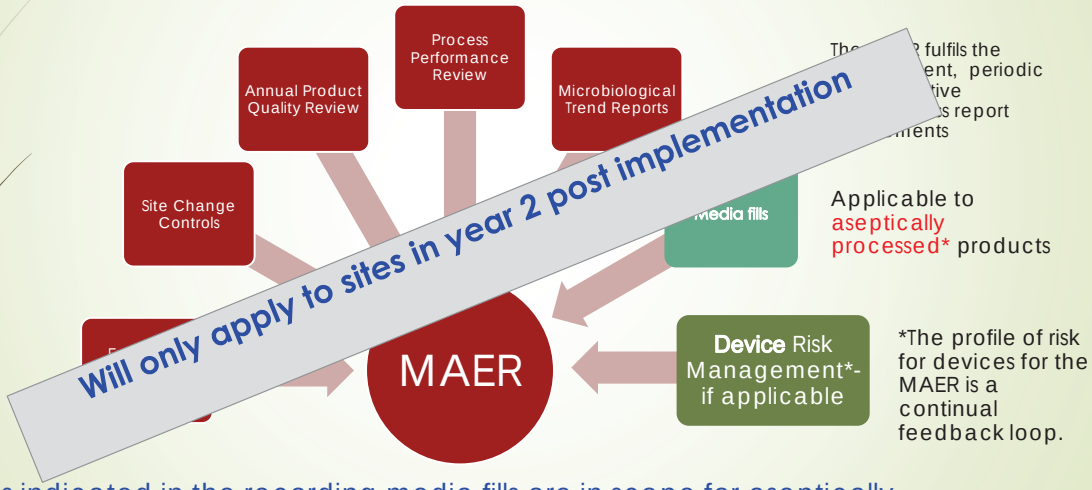
The MAER fulfils the improvement, periodic and collective effectiveness report requirements

Applicable to aseptically processed* products

*The profile of risk for devices for the MAER is a continual feedback loop.

* As indicated in the recording media fills are in scope for aseptically processed products

(M)CCS Annual Effectiveness Report (MAER)



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Contents of PQS CCS Forms 1 & 2

- PQS forms 1 & 2 include sections
  - Scope
  - Roles and responsibilities
  - Definitions and acronyms
  - Governance and lifecycle strategies

Contents of PQS MCCS Forms (cont.)

Each control described needs to address *'the why'*

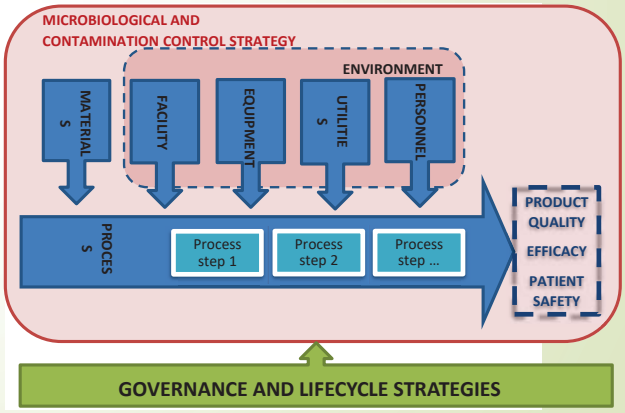
Design

- The CCS describes how microbiological control is ensured and how contamination risk is minimized.
- The references and the rationales are documented in the CCS.

Effectiveness

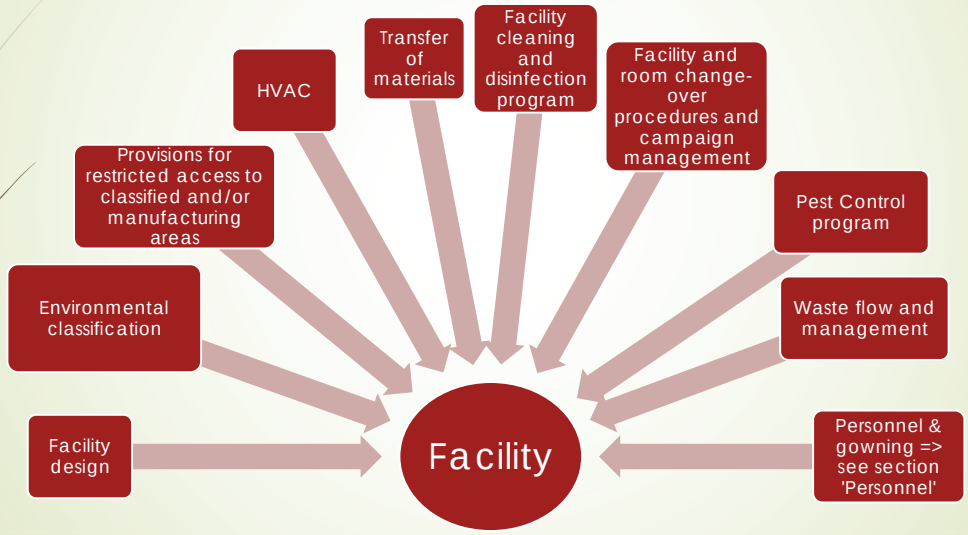
- How is the effectiveness of a control demonstrated?

Initial validation and periodic requalification
Ongoing monitoring and evaluation of trending data



Detailed CCS Form Contents (cont.)

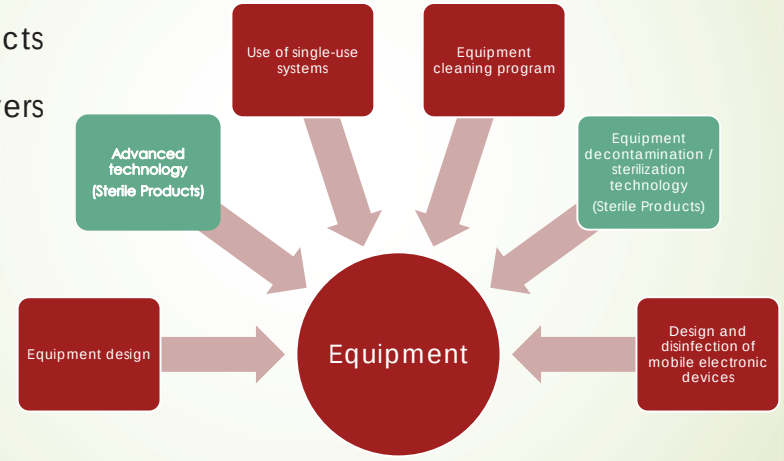
Facility controls



Detailed CCS Form Contents (cont.)

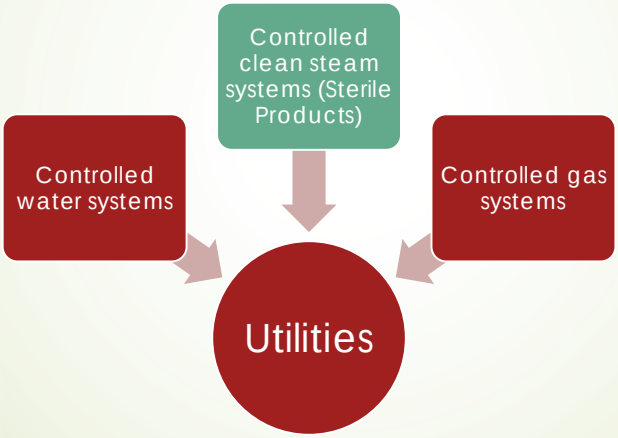
Equipment controls

- For Sterile Products advanced technology covers
  - RABS
  - Isolators
  - Automation
  - Robotics



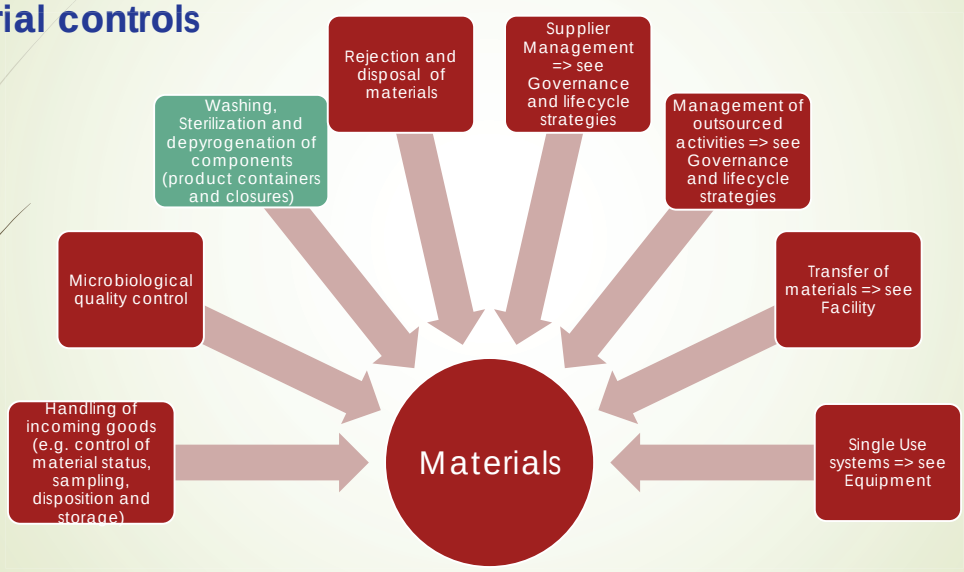
Detailed CCS Form Contents (cont.)

Utility controls



Detailed MCCS Form Contents (cont.)

Material controls



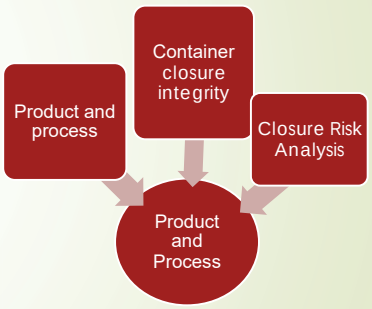
Detailed CCS Form Contents (cont.)

Design of Product and Process controls covers

- Dispensing
- QC Material Sampling
- Formulation
- Sterilising filtration (PUPSIT & redundant filtration & vent filters)
- Filling operations
- Hold times
- Terminal Sterilisation – if used
- Lyophilisation – if used
  - Lyo sterilisation
  - Product transfers to and from the lyo
- Blow Fill Seal and form fill seal – if used
- Process changeovers and campaigns
- In-process and finished product storage conditions
- Re processing and rework
- Medical device product monitoring – if applicable

Effectiveness of Product and Process Controls covers

- Process validation Formulation
- Filtration strategy, validation & vent filter reuse
- Media Fill program
- In process controls, filter integrity program, system controls and alarms
- Sample and analysis plans
- Microbiological control level management
- Ultrafiltration / diafiltration / chromatography rationales / controls and monitoring programs.



- **Additional elements**
  - Biotech specific topics – arising from FDA feedback for Biotech DS filing reviews

(Biotech / Biological Products)

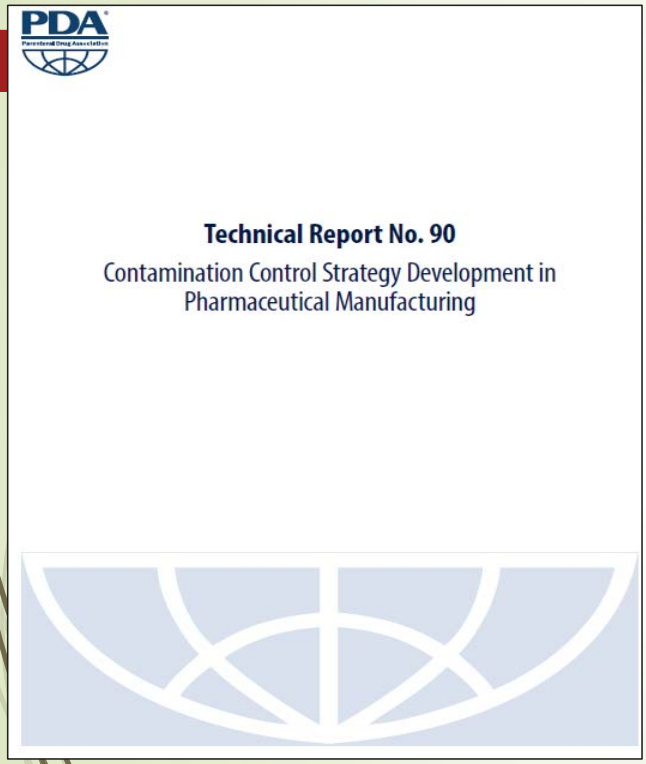
Timing of CCS Development and Periodic Review

- Product Microbiological Control Strategies are developed during product and process development.
  - *Product microbiological control strategy: a practice (chemical, physical or procedural) that **acts to ensure that microbiological risk is kept within defined limits for a specific product** 採取行動，確保將特定產品的微生物風險保持在規定的限度內*
- The CCS is revisited and updated as appropriate during **product Technology Transfer** must be in place for routine commercial manufacturing at individual facilities CCS會根據需要進行重新審查和更新，以便在各個工廠進行常規商業生產
  - ***Technology Transfer**: the process transferring the manufacture of a product, with associated knowledge and expertise, between development and commercial manufacturing, or within or between manufacturing sites. The transfer could involve the complete product manufacturing process, including packaging and testing, or parts thereof*
  - **Given CCSs are GMP requirements, it is recommended that they are in place to support pre-approval inspections for new products at sites.**
- **The MCCS** is subject to change control and change controls must be **evaluated for the impact of the change** on the MCCS
- MCCS Annual Effectiveness Report (MAER): An **assessment** of the effectiveness of the collective microbiological and contamination control strategies.

What is a Contamination Control Strategy?

- Documented Contamination Control Strategy
- Relies on good knowledge management (ICH Q10)
- Risk based approach (ICH Q9)
- Annex 1 requires an effective contamination control strategy (CCS)
- **TR 90 Contamination Control Strategy Development in Pharmaceutical Manufacturing**
- Holistic Review
- A cyclic process

Technical Report No. 90



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FIGURES AND TABLES INDEX

CCS

Many GMP practices are part of a company's contamination control strategy (CCS) including, for example, how processes and facilities are designed (including cleaning and disinfection), how raw materials and consumables are selected and managed, and how personnel are trained and developed. The CCS is also intended to drive **continuous improvement and/or remediation**. The success of any one CCS element is intrinsically linked to the others, and the success of the CCS depends upon how well the individual elements work together to reduce the contamination hazards for a specific process

CCS的成功取決於如何各個要素共同合作作業，以減少特定製/過程的污染危害

All drug manufacturers have a CCS that includes a multitude of GMP practices documented across numerous operational procedures and programs. The rationales for those practices are often captured in risk assessments, validations, and technical documents.所有藥品製造商都有一個CCS，其中包括記錄在案的眾多 GMP 實踐許多操作程式和程式。這些做法的基本原理經常被捕捉到在風險評估、驗證和技術文檔中

A CCS record creates an umbrella document that brings the relevant information together so it can be understood and evaluated holistically. All CCS documents should summarize the contamination control practices, along with the underlying rationales, and reference the supportive procedures and reports. CCS 記錄創建一個總括文檔，將相關信息彙集在一起，以便可以全面理解和評估。所有CCS檔都應總結污染控制實踐及其基本原理，並參考支援性程序和報告。

CCS

This technical report outlines how to implement an effective CCS using a holistic approach, highlights a selection of best practices, and identifies outdated practices and mindsets.

如何使用整體方法實施有效的CCS，重點介紹一些最佳實踐，並確定過時的做法和思維方式

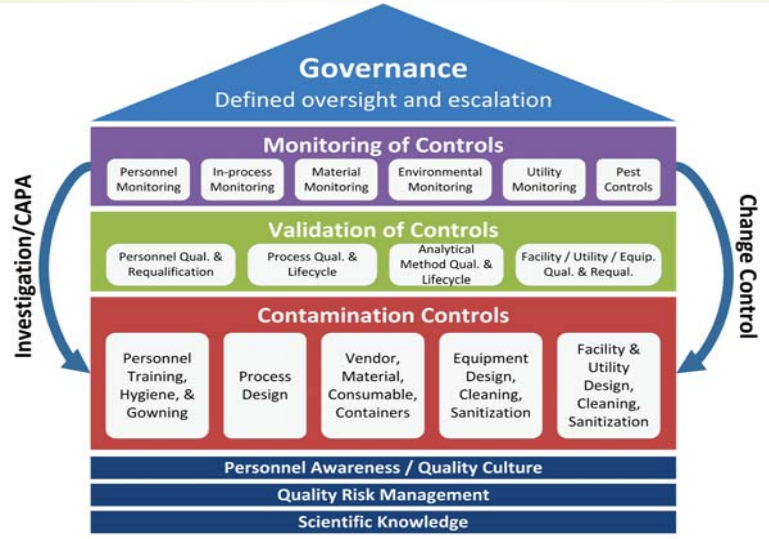


Figure 3.0-1 Elements of a Contamination Control Strategy (courtesy of Sanofi)

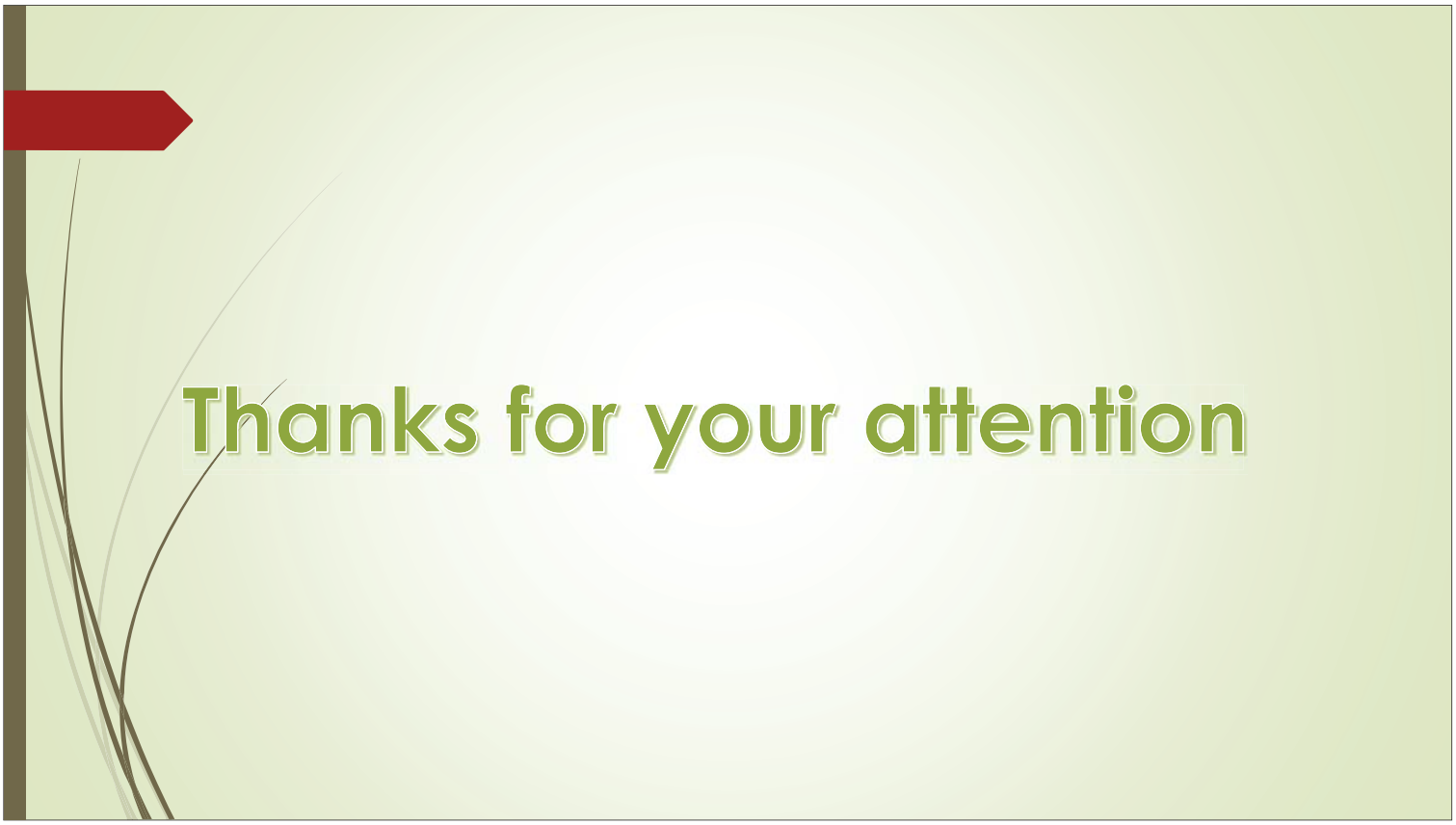
CCS Governance and Effectiveness Review

The CCS should include a governance structure to oversee the effectiveness of the contamination controls and to escalate control issues. The person(s) or body governing the CCS should have:

- Appropriate microbiology and process expertise to understand the meaningfulness of the data outputs , for example, quality control in-process and product-release testing, EM, and utility monitoring
- Clear responsibility to perform regular assessments of the contamination controls related to process, product, personnel, and facility/utility and to drive proactive improvement
- Authority to respond to potentially adverse trends or events, both proactively and reactively
- Clear pathways for escalation to the top site management

The CCS lifecycle begins during the design of the facility and process. Further, the CCS should be considered during quality-by-design activities and formally documented as a prerequisite to GMP manufacturing.

The CCS should also be reviewed periodically (preferably reviewed annually) for effectiveness to ensure it remains current with the process and aligned with industry standards, specifically the potential need to adopt new, more effective technologies



QRM for CCS

Prepared by : Whitney Chen(陳永宜)

Date: May 21,2025

Document Purpose

A documented strategy should:

1. Prescribe a path for the prevention of product contamination and cross-contamination
2. Explain, with reference to industry standards and existing company procedures, how the risks of contamination and cross-contamination are understood, controlled and monitored
3. Elaborate on the connection between the contamination control strategy and other elements of the Pharmaceutical Quality System
4. Set a program for the review and improvement of the strategy to confirm that it is sufficient and appropriate for protecting the overall quality of products

- Explain the reason for the document
- Provide industry definitions

Purpose & Scope: The Challenge of Definitions (ICH, PIC/S & ISO)

Contamination: The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or product during production, sampling, packaging or repackaging, storage or transport. (ICH Q7)

Cross-contamination: Contamination of a material or product with another material or product. (ICH Q7; PIC/S Glossary)

Control Strategy: A planned set of controls derived from current product and process understanding that ensure process performance and product quality. The controls can include parameters and attributes related to drug substance 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. (ICH Q10)

Purpose & Scope: The Challenge of Definitions (ICH, PIC/S & ISO)

Decontamination: Procedure that eliminates or reduces microbial or toxic agents to a safe level with respect to transmission of infection or other adverse effects. (ISO 15190:2003 3.7)

Disinfection: Removal, destruction or de-activation of microorganisms on objects or surfaces. (ISO 13408-1:2008 3.18)

Sanitation: All actions dealing with cleaning or maintaining hygienic conditions in an establishment, ranging from cleaning and/or sanitising of specific equipment to periodic cleaning activities throughout the establishment (including building, structural, and grounds cleaning activities)

Sanitisation: Operation used to reduce undesirable micro-organisms on inert contamination surfaces depending on the objectives set

Sterilisation: Validated process used to render a product free of all forms of viable microorganisms. (ISO 22442-3:2007 3.10)

Cleaning Validation: Cleaning validation is documented evidence that an approved cleaning procedure will reproducibly remove the previous product or cleaning agents used in the equipment below the scientifically set maximum allowable carryover level. (PIC/S Glossary)

Cleaning Verification: The gathering of evidence through chemical analysis after each batch/campaign to show that the residues of the previous product or cleaning agents have been reduced below the scientifically set maximum allowable carryover level. (PIC/S Glossary)

Campaign manufacture: The manufacture of a series of batches of the same product in sequence in a given period of time followed by strict adherence to accepted control measures before transfer to another product. The products are not run at the same time but may be run on the same equipment. (PIC/S Annex 2)

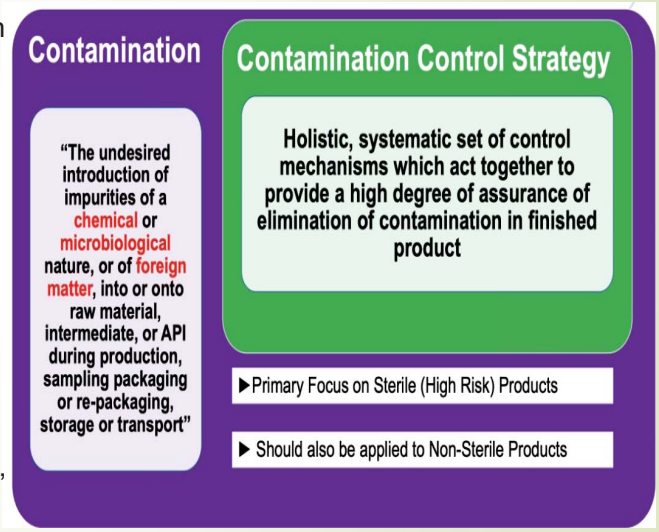
Learning Objectives

1. Consider if you have a Contamination Control Strategy? How to establish this document?
2. Is it in a single overview document? Easy to understand?
3. Have a look at what risk we have and provide as examples?

Regulatory expectations

• Annex 1 “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 organizational) and monitoring measures employed to manage risks associated with contamination. The CCS should be actively updated and should drive continuous improvement of the manufacturing and control methods.” **CCS 應積極更新並應驅動製造和控制方法的持續改進。**

• PICs cGMP **Basic Tenant** = Commensurate to risk (Premises/Facilities , Dust & Waste Control, Production Equipment, Rationale for uncontrolled releases of aerosols, operator clothing contaminates, QRM – potency , toxicological evaluation to assess cross-contamination risks, separation strategies, cleaning programs, supervision, training…etc.)



The Pillars of Success

As illustrated in **Figure 1**, a holistic CCS for a sterile pharmaceutical dosage form has three inter-related pillars for success.

Prevention – Prevention is the most effective means to control contamination. Prevention of contaminants reaching the critical processing areas should be the goal of the CCS. Complete prevention may not always be practical or feasible; however, it should remain a target of continuous improvement in every site. The prevention strategy should include the establishment of a well-defined, organized program starting with a sound understanding of the sterile product manufacturing process, objective risk assessments focusing on process variables and sources of contamination, setting achievable acceptance criteria and metrics, means to monitor performance and a plan to adjust the strategy as needed.

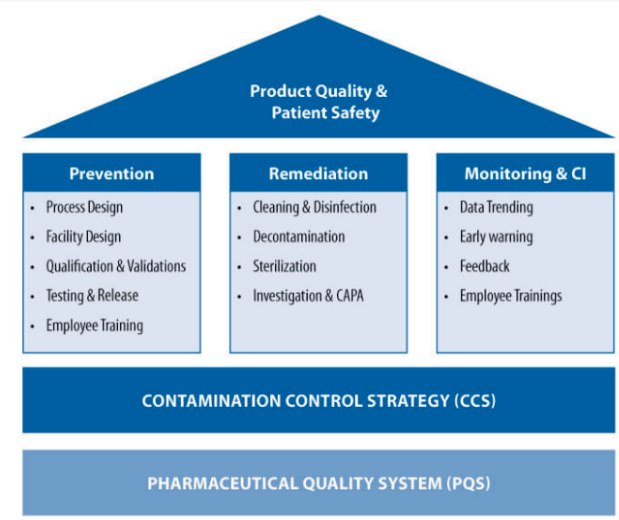
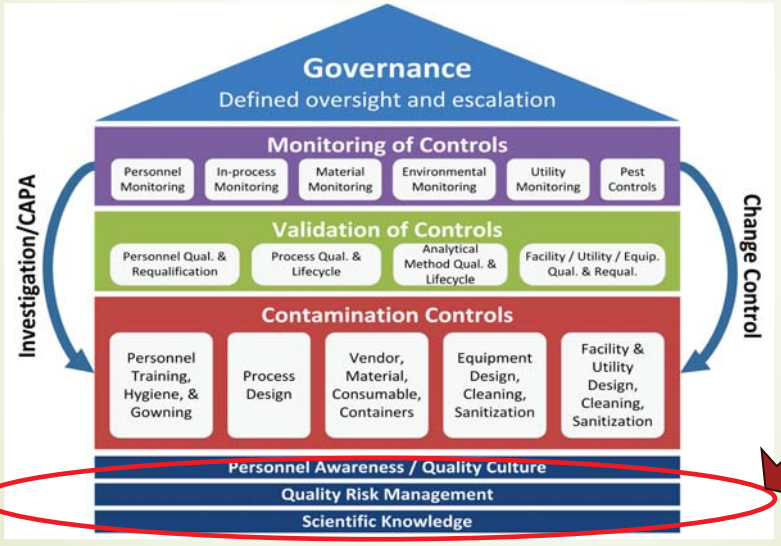


Figure 1 Important Pillars for Success of CCS

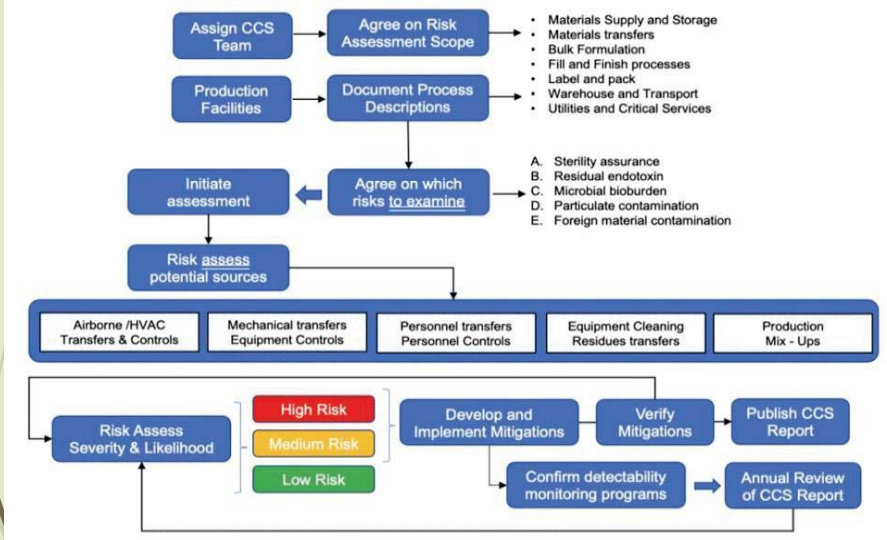
This technical report outlines how to implement an effective CCS using a holistic approach, highlights a selection of best practices, and identifies outdated practices and mindsets.

如何使用整體方法實施有效的CCS，重點介紹一些最佳實踐，並確定過時的做法和思維方式



Product knowledge: Process understanding

Organizing for CCS – Start from QRM



- An example of a roadmap on how to consider set up of a CCS
- Risks A to E are usually examined
- Then look at the various sources
- Assess Risks
  - Patient risk can be different depending on dose form
  - CPPs process & environment
  - Likelihood/probability of contaminates being present
  - Analysis of monitoring & control programs
  - Deploy Controls in Operating procedures & into Quality Control plans
- Develop mitigations & Verify mitigations
- Publish CCS
- Annual Review

Quality Risk Management (QRM) and Quality by Design (QbD) are both innately connected to knowledge of the process. Figure 1 outlines the stages to perform a complete risk assessment of a process.

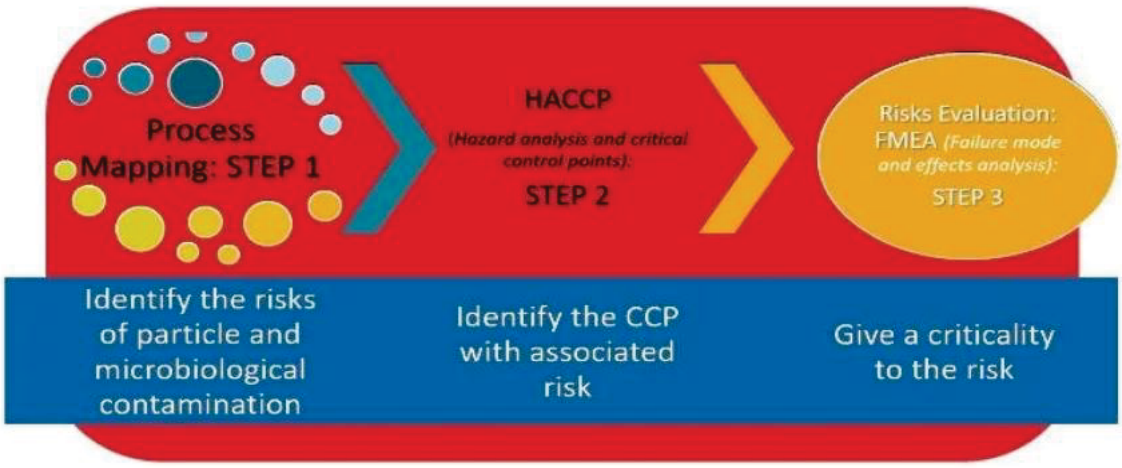


Figure 1. *The steps to understanding your process. Image Credit: Particle Measuring Systems*

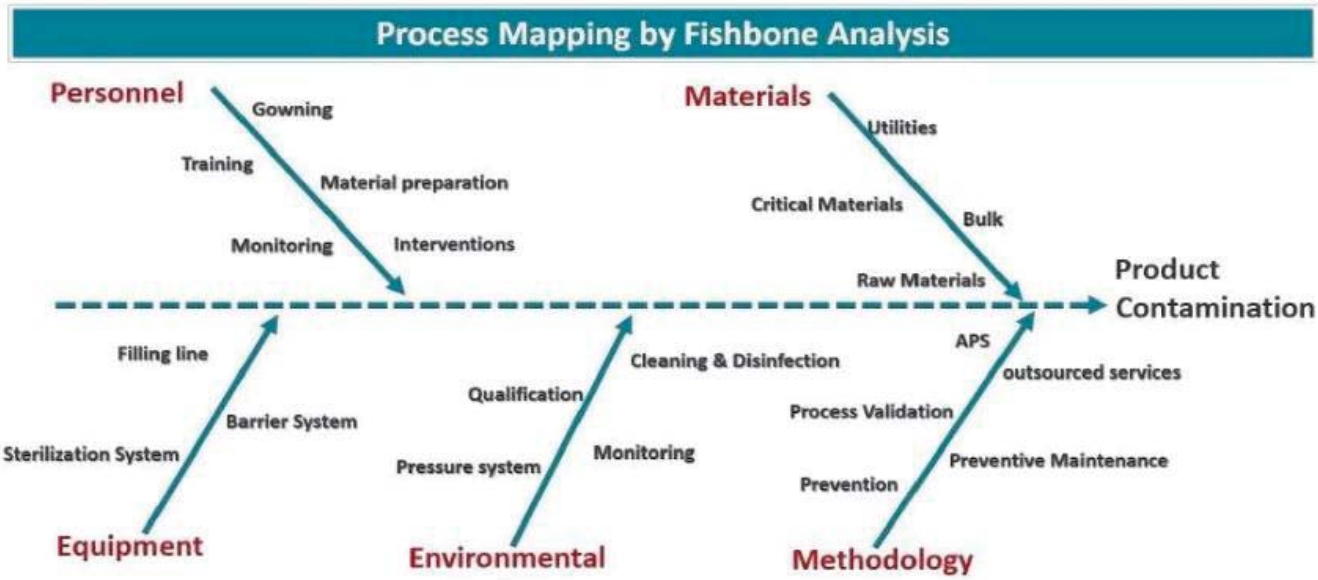
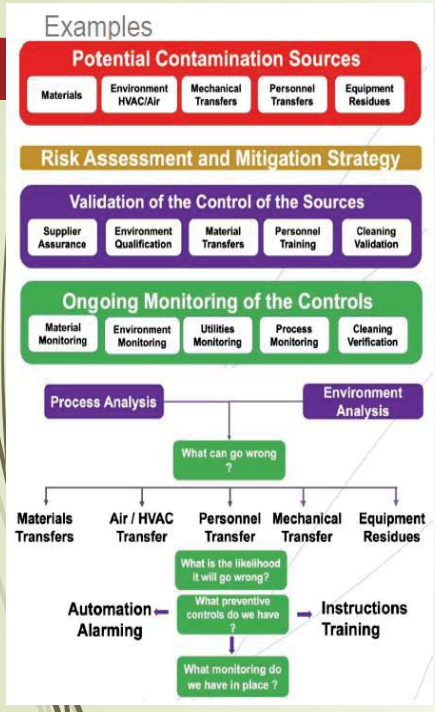


Figure 2. *Fishbone diagram showcasing all sources of possible particle contamination. Image Credit: Particle Measuring Systems*

S

- CCS for each product with rationale for the CS elements
- Microbial, endotoxin, particle risks (FMEA) for each process
- Periodic review or Major change may trigger a re-review of the CCS
- Determine what the CAPAs will be based on findings
- Inclusion of CCS in Site Master File

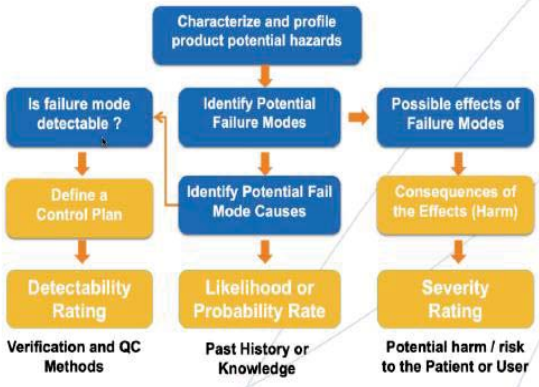


Preliminary Hazard Analysis (PHA) – Process Driven Analysis

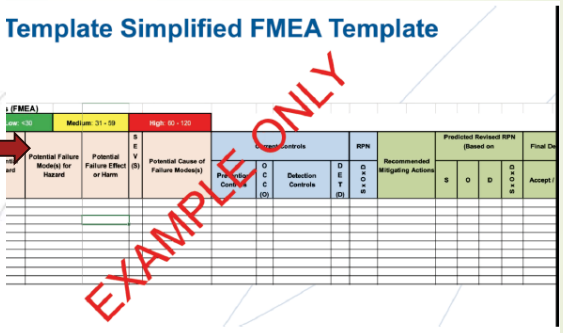
PHA is a tool of analysis based on applying prior experience or knowledge of a hazard or failure to identify future hazards, hazardous situations and events that might cause harm, as well as to estimate their probability of occurrence for a given activity, facility, product or system.

#	Potential Failure Mode(s) for Contamination	Potential Risk or Harm	Patient Severity / Consequences	Severity Score	Likelihood Assessment	Likelihood Score	Ranking Score	Proposed Mitigations/Controls	Revised Score (with mitigation) Sev.	Lik'hd	Score
3. Sub-assembly – Device Component											
3.1	Residues: The component making equipment uses foil for fabrication. The foil is not pre-cleaned and may contain residues of particulates or factory grease	Post washing solvent reside remains	Marginal as device uses sub-cutaneous delivery	4	Likely without additional controls	8	32	1. Develop a procedure for washing/drying			
3.2		Post washing and drying particulate residues remain	Marginal as device uses sub-cutaneous delivery	4	Likely without additional controls	8	32	2. Validate the washing and drying step			
3.3		Post washing the grease residue is not fully removed	Marginal as device uses sub-cutaneous delivery	4	Likely without additional controls	8	32	3.Implement sampling inspection plan			
4. sub-assembly - Moulding											
4.1	HVAC / Air	None identified	None identified	1	None identified	1	1	1.Develop a procedure for moulding ans IPQC			
4.2	Personnel	None identified	None identified	1	None identified	1	1	2. Validate the moulding step			
4.3	Mechanical / Equipment	Residual particles remain on the assembled part	Device and product has many residual particles - could impact delivery or patient.	7	Likely without additional controls – undetected by 100% inspection	8	56	3. Implement sampling inspection plan for moulded component			

How is an "FMEA Risk Analysis" done ?



Template Simplified FMEA Template



Examples

HACCP is a technique to identify specific hazards (contaminants) and preventative control measures to minimise risk of manufacturing defective products.

Hazard Analysis and **Critical Control Point**

Identifying Potential Hazards/Contaminants

Identify Ways to Prevent Them

Example (OSD) Layout for HACCP – CCS Plan

Process Step	Process Name	Hazard Description	Materials	Air	Mechanical	Personnel	Equipment	Other	Risk Level (H,M,L)	CCP ?	Validation ?	Corrective Action	Monitoring	Documents
1	Starting Materials	Impurities							L			Qualify Supplier	QC Test Impurities	
		Microbial contamination							M	CP		Qualify Supplier	3rd Lot test + Cof A	
		Pesticides							L			Qualify Supplier	Annual + Cof A	
2	Dispensary	Dust escapes to the plant							M	CP		Contain booth / validate air	Record air pressures	
		Cross Contamination - previous							H	CCP	Yes	Cleaning Validation	Cleaning Logs/Audit	
		Personnel contamination										Train, Gown,Sanitise	Cleaning Logs/Audit	
3	Sieving	Cross Contamination - previous							M	CP		Cleaning validation	Cleaning Logs/Audit	
		Loose metal particles							M	CP		Dedicated sieves + PM	Cleaning Logs/Audit	
		Dust escape to the plant							H	CCP		Local dust control - neg press	PM and maintain. Log	
4	Wet Granulation	Contaminated water							L		Yes	Validate water system	Sample Water	
		Metal scrapings							M	CP		PM program	Visual check pre use	
		Dust escape to the plant							L			Air Containment	Monitor pressures	
5	Fluid Bed Dryer	Dirty inlet air - microbes							M	CP	Yes	Local dust control - neg press	PM and maintain. Log	
		Cross Contamination - socks							M	CP		Dedicated socks	Verify colours	
		Cross Contamination - previous							H	CCP		Cleaning Validation	Cleaning Logs/Audit	
6	Milling	Metal particles							M	CP		PM over mill and chops	Inspect mill pre- use	
		Cross Contamination - previous							L			Cleaning Validation	Inspect mill pre- use	
		Dust escapes to the plant							M	CP		Local Dust Collection/Contain	Monitor room press.	
	Blending	Cross Contamination - previous							M	CP	Yes	Cleaning Validation	Cleaning Logs/Audit	
		Metal particles							L			PM over blender	Inspect blend pre- use	
		Dust escape to the plant							M	CP		Room Containment	Monitor room press.	
8	Tabletting	Dust escape to the plant							M	CP	Yes	Local Dust Collection/Contain	Monitor room press.	
		Cross Contam - tools, dies/punches							L			Cleaning and Inspection	Inspect pre use	
		Microbial contamination							L			Store equipment dry	Period Monitor EM	
9	Coating	Microbial contam- coat solution							M	CP	Yes	Low bioburden water	Monitor water	
		Metal particles							L			PM program	Inspect pre use	
		Personnel Contam - microbes							L			Train, Gloved hnads,Sanitise	Audit and Train	
10	Packaging	Blister plastics							L		Yes	Supplier Assurance	QC Test foreign partd	
		Glass fragments							H	CCP		PM on line - line clearance	Record defects	

Contamination Control Strategy Development: Manufacturing Process

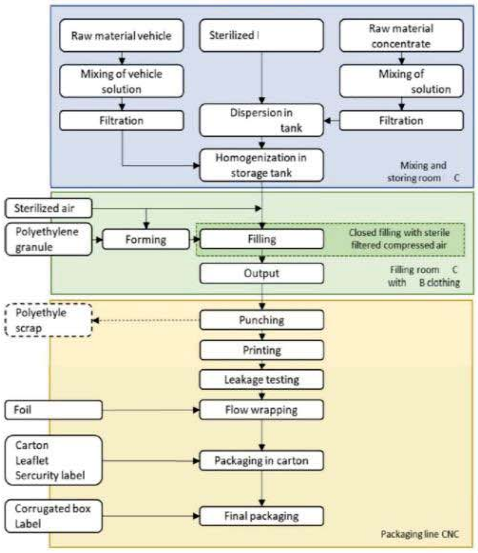
Summary : Include name of the product(s) and the associated manufacturing facility and brief summary of collective control measures.

Introduction: contamination that is to be controlled (e.g. microbiological, particulate, cross contamination).

Process Maps should be included in the CCS to make clear the boundaries where CCS apply.

Product Microbial Characterisation

Conclusion



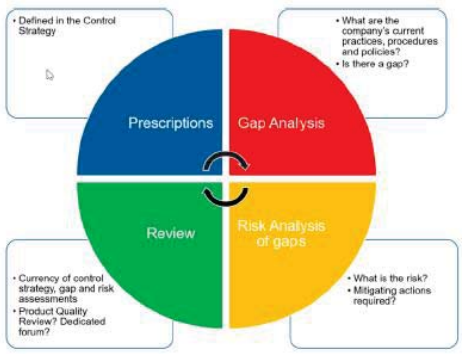
Worked Example of FMEA for Filling Process

Function Process Step	Failure Mode	Hazard	Harm	Risk statement	Quality Compliance Impact (S)	Likelihood (L)	RPN (S*L)	Mitigations	CAPA ref no	(CAPA) Due date	Post RPN (S*L)	Residual risk accepted (Yes/no)	Justification risk acceptance
Media fills	Risk for a contaminated system if cleaning and sterilisation is not performed correctly	Contaminated product-contact surfaces	Non-sterile product	Contaminated product-contact surfaces due to insufficient cleaning/sterilization after performed media fill causes non-sterile product	5	1	5	Validated CIP and SIP processes	N/A	N/A	N/A	Yes	Mitigations in place are sufficient for the risk
Clean room	Contamination of cleanroom when filling tower is withdrawn in between batches to adjust filling needles, clean the dye (performed in CNC) and then taken into grade C again	Contamination of cleanroom	Cleanroom requirements are not met	Contamination of clean room when filling tower is withdrawn in between batches to adjust filling needles, clean the dye (performed in CNC) and then taken into grade C again leading to cleanroom requirements are not met	3	2	6	SOP descibes how to perform this. Outside of tower disinfected. Trained operators.	N/A	N/A	N/A	Yes	Mitigations in place are sufficient for the risk
	Pressure dips in room during withdrawn of filling tower	Failure of pressure requirements	Cleanroom requirements are not met	Pressure dips in room during withdrawn of filling tower causes failure of pressure requirements leading to cleanroom requirements are not met	3	3	9	Smoke visualizations performed show that no inflow of CNC air occurs. Continuous monitoring of pressure (EMS system). Alarms in place. SOP describes how to handle pressure dips. Suggestion to perform a more detailed risk assessment to justify this risk.	CAPA suggested				

Recommended Elements to be included in a contamination control strategy document

a) Design of both the plant and process.
b) Equipment and facilities.
c) Personnel.
d) Utilities.
e) Raw Materials Control – including in-process controls.
f) Product containers and closures.
g) Vendor approval – such as key component suppliers, sterilization of components and single use systems, and services.
h) For outsourced services, such as sterilization, sufficient evidence should be provided to the contract giver to ensure the process is operating correctly.
i) Process risk assessment.
j) Process validation.
k) Preventative maintenance – maintaining equipment and premises (planned and unplanned maintenance) to a standard that will not add significant risk of contamination.
l) Cleaning and disinfection.
m) Monitoring systems - including an assessment of the feasibility of the introduction of scientifically sound, modern methods that optimize the detection of environmental contamination.
n) Prevention – Trending, investigations, corrective and preventive actions (CAPA), root cause determination and the need for more robust investigational tools.
o) Continuous improvement based on information from the above systems.

Gap Analysis/Risk Analysis & Review

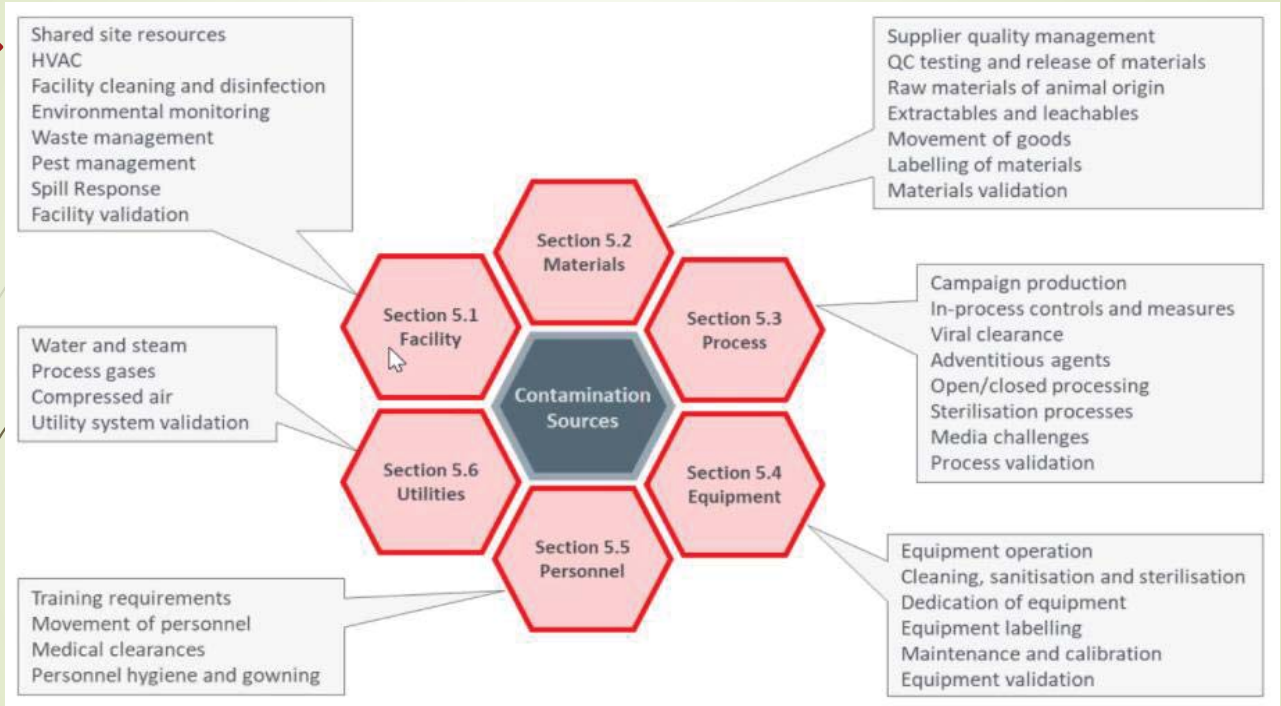


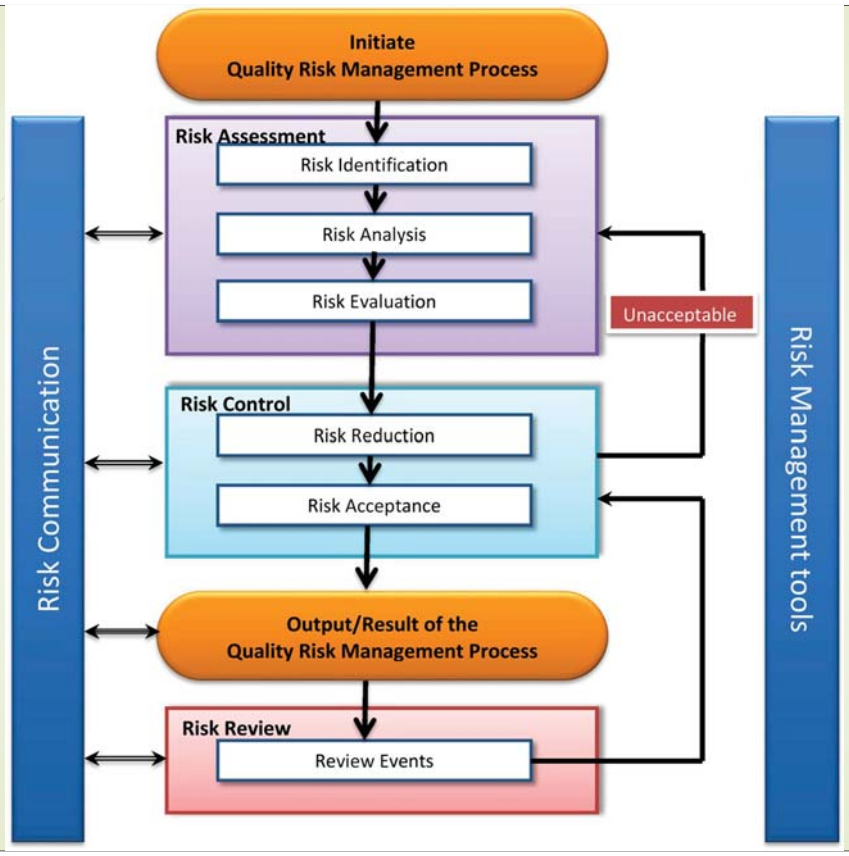
•This is all defined within a site strategy.
•Assess gap against each sub vector (ie materials, process, equipment…etc)
•Lots of work to do prescriptions and gap analysis however after that it flows.

Learnings
•CCS is a complement to and reliant upon the major elements of the PQS

o**Risk Assessment** processes for the identification & appraisal of contamination risks and the implementation of mitigation controls
o**Validation Programs** to demonstrate the suitability of facilities, equipment and processes
o**Change Control** for the evaluation, prior to implementation of changes to facilities, equipment and processes that might impact product quality
o**Deviation** and **Corrective and Preventative Action (CAPA)** programs to identify, assess and resolve issues
•Applications

•Return on Investment





Key Areas	Key Elements	Detailed CCS Elements		Annex 1 rev12 draft reference	Identified potential gap or documentation improvement needs versus Annex 1 draft expectations	Key supporting Site Strategies, Rationales, Risk assessments *Include Reference, title and if possible hyperlink to the document*	Key Site Procedures *Include Reference, title and hyperlink to the document*
Contamination Control Definition and management	**Key Overarching Strategies (SVMP, PQS, risk management, etc...)**	**Requirements for the risk based approach applied for the Contamination Control Strategy (during development, during project and construction phases, during qualification and validation, during production)**		Glossary for definition Chapter 2 & 3 for scope Points 8.8 and 8.9 for risk management documentation			
Facilities, equipment, utilities and infrastructure Design, Qualification, Maintenance and Control	**Facilities**	**Facilities Design**	Facility design requirements (plant layout, air filtration, material of construction, cleanability, airlock design, logical and chronological activities flows)	4.1, 4.2, 4.3, 4.5, 4.8, 4.7, 4.8, 4.9 4.10, 4.11, 4.12, 4.13, 4.17 6.6 9.21	4.1 explain how controls and monitoring are " *scientifically justified and capable of evaluating the zone of environmental conditions for cleanrooms, airlocks and pass throughs used for material and equipment transfer*" 4.3 Barriers should be considered in the CCS. " *Any alternative approaches to the use of RABS ans Isolators should be justified* " Develop the current material transfer and airlocks sections using wording of 4.10, 4.11, 4.12, 4.13		
			HVAC system design requirements (Air Filtration, HEPA Filters, Pressure cascades, Temperature, RH, locations of air inlets & outlets, ducts cleanability, air exchanges rates, alarms settings and controls ...)	4.13, 4.14, 4.15, 4.16 4.35	Develop an adequate section to cover 4.16 "*Setpoints and the criticality of pressure differentials should be documented within the CCS* " / "*where alarm delays are set, these should be assessed and justified within the CCS* "		
			Area Classification / Grade cascading	4.1, 4.4, 4.12, 4.13, 4.20 8.14	No potential gap		
			Physical segregation of activities (dedicated facility/area, use of closed systems, other containment systems, ...) / Barriers	4.2, 4.3, 4.4 4.18, 4.19, 4.20, 4.21, 4.22, 4.23 8.10, 8.14, 8.15, 8.16	4.3 Use of barriers should be considered in the CCS : any alternative approaches to the *use of RABS or isolators should be justified*		
			Localized Unidirectional Air Flow application/protection, dust control systems	4.2, 4.25 6.6	No potential gap		
		Classification & Qualification of facilities / Barriers	Qualification Program and control (APPT, Air velocity...)	4.15, 4.23, 4.26, 4.27, 4.28, 4.29, 4.30, 4.31, 4.32, 4.33, 4.34	4.30 & 4.33 develop the current section to explain how current strategy fulfills the requirement for the sampling locations and their positioning during classification " *critical processing locations should be based on a documented risks assessment and knowledge of the process and operations* " and during qualification "*the number of sampling locations should be based on a documented risk assessment, including the results of the classification, air visualisation and knowledge of the process and operations* "		
		Facility Cleaning and Disinfection	Cleaning Programs (agents selection, frequency, materials...) / Practices	4.22, 4.36, 4.37	No potential gap		
			Sanitisation agents validation (including verification against local flora)	4.24, 4.37, 4.38	No potential gap		
		Pest Control	Pest control Program / Traps location maps		No potential gap		
		Preventive and Corrective Maintenance	Program for facilities (including Fit and Finish program)	5.3, 5.8	No potential gap		
			Periodic HEPA filters integrity testing	4.14	No potential gap		
			Maintenance practices for product protection	5.8	No potential gap		
			Return to service after maintenance	5.6, 5.7	No potential gap		
		Waste Management	Waste flow and segregation		No potential gap		
	Equipment	**Equipment Design**	Equipment design requirements/capability / cleanability	9.1, 9.2, 9.3, 9.8 5.9 8.34	5.9 Include in the CCS the more precise requirement for particles counters maximum tubing length and minimum bend radius		
			Operational practices (out of place or in place cleaning of pieces of equipment, draining, drying, steaming, sterilisation, ...)	5.6	No potential gap		
			Equipment integrity and storage conditions after cleaning and sterilization (system integrity , storage under positive pressure prior to use...)	4.11 8.45, 8.46, 8.47, 8.48	No potential gap		
		Preventive and Corrective Maintenance	Maintenance Program for equipment	5.6	No potential gap		
			Maintenance practices for product protection	5.8	No potential gap		
			Return to service after maintenance	5.6, 5.7	No potential gap		
		Qualification and Validation of Equipment	Cleaning / Sterilization of all Equipment (e.g. tanks, filtration systems, filler parts, isolator decontamination etc) - Validation Program	5.4, 5.5	5.5 "*Indirect Contact parts should be sterilized* "		
	Utilities	**Utilities Design (Water systems, Clean steam, Compressed gases)**	Utilities generation and distribution systems design (materials of construction, loops, recirculation conditions, heat exchangers design, process control limits, on-line control systems, sanitization capabilities, ...), Quality level and applications	6.1, 6.2, 6.3, 6.4, 6.5, 6.6 6.7, 6.8, 6.9, 6.10, 6.11 6.16, 6.17 6.18, 6.19	6.19 add to existing chapter for gases that " *any transfer pipework or tubing that is located after the final sterilising filter* " is sterilised		
		Sanitization	Sanitization Program (method, frequency...)	6.10, 6.12	No potential gap		
		Preventive and Corrective Maintenance	Maintenance Program for utilities	6.11	No potential gap		
			Maintenance practices for product protection	6.12, 6.20 6.22, 6.23	6.22, 6.23 Create adequate section to document the contamination control of heating, cooling and hydraulic systems		
			Return to service after maintenance	6.12	No potential gap		
		Qualification and Validation of Utilities	Utilities Qualification Strategy and control	6.13 6.15	6.15 ill explain how current risk based strategy (including the frequency) fulfills the requirement "*a sample from the point at the end of the distribution loop each day that the water is used* "		

13.0 Appendix I: Case Study 1

This appendix provides the first of two case studies that reflect the principles discussed in *Technical Report No. 54-5: QRM for the Design, Qualification, and Operation of Manufacturing Systems.*

Case Study 1 provides an example of the process for establishing a quality risk management (QRM) and risk control strategy to upgrade a company's existing facility (applicable to either large or small molecule products). Case Study 2 provides an example of a system risk assessment (SRA) approach when adding a new buffer preparation and hold tank to an existing purification area.

13.1 Background

Global Company A, comprising drug substance and drug product plants, wants to upgrade one of its drug product plants; the plant is approximately 20 years old and has not had any major technology upgrades over its years of operation. Manufacturing/filling rooms were designed to be in a Grade B environment, and equipment was placed in Grade A laminar flow units with attached plastic strip barriers. The plant has depreciated over the years and has been used beyond its originally intended functional life.

The latest regulatory inspection resulted in several major regulatory observations related to the age of the facility and the technology in use as well as personnel flow and potential for cross-contamination.

Company A wishes to be a premier provider of sterile and aseptic filling operations and has secured funding to undertake facility renovations and improvements to process manufacturing equipment. The goals for the plant are:

- Secure and retain the right to operate by remaining compliant with regulatory requirements.
- Ensure product quality by minimizing the risk of contamination during production.
- Be able to be appropriately flexible with facility and equipment design to maximize throughput for multiple products through efficient cleaning, decontamination, and single use technology.
- Provide a competitive cost of goods and make a reasonable return on investment.
- Increase plant capacity while maintaining adequate product supply.

A preliminary evaluation of the plant by a team consisting of management decision-makers from manufacturing, quality, engineering, finance, and regulatory determined that the current facility lay-out and product/personnel/process flow is not ideal, and its intended use no longer aligns with the Company A's future vision to increase capacity and remain compliant with regulatory requirements.

Two options—one for a greenfield facility and the other for a facility upgrade—were presented to senior leadership. Based on the information for cost effectiveness and risk mitigation, a decision was made to adapt the aging plant by upgrading the open processing filling lines to isolators. In addition, the decision addressed the return on investment goal and other business model aspects not presented in this case study. This decision was documented in the project charter.

Based on the operations as described above, the team assessed all process functions, determined the below systems to require modification, and included them in the project scope **(Table 13.1.1-1).**

Table 13.1.1-1 Systems Requiring Modification

System	Current State	Future State	Risk Mitigation Rationale
Filler	Conventional with curtains; parts sterilized in autoclave and aseptically assembled	New filler in isolator with SIP	Reduce risk of microbial contamination
Stopper processor	Stoppers washed and autoclaved separately and transferred into clean room	Use rapid transfer port (RTP) transfer to deliver stoppers into isolator	Reduce risk of microbial contamination
Capper	Connected to fill line but located in adjacent clean room	Integrated with the filling line isolator with Grade A quality air	Reduce risk of contamination
Cleaning process for the filler	Parts manually cleaned	Automated CIP System	Reduce risk of microbial and cross-contamination
Sterilization process for the filler	Parts autoclaved	Automated SIP System	Reduce risk of microbial and cross-contamination
Clean steam system	Generation meets current URS	Distribution system needs modification for SIP and requires an increase in capacity	Enabling SIP

13.1.3 Project Execution Plan

Scope: Since the project execution plan (PEP) defines how to execute the project, certain risk decisions were made and risk to project success identified and mitigated. The team used the PEP to ensure that the project had a suitable execution approach.

Team: The team was composed of personnel from the following departments:

- Quality
- Engineering
- Operations
- Project Management

13.1.4 Tool Selection

Based on the risk question, the team needed a qualitative tool that would allow them to look at high-level risks. The team selected a simple risk estimation matrix **(Table 13.1.4-1).** An excerpt of the deliverable is shown below.

Table 13.1.4-1 Risk Estimation Matrix

Risk Estimation Matrix		Occurrence			
		2	4	6	8
Consequence/Impact	8	16	32	48	64
	6	12	24	36	48
	4	8	16	24	32
	2	4	8	12	16
	High: Most critical risks must be addressed on a high priority basis. The project team should prepare for immediate action so as to eliminate the risk completely. In addition to evaluating risk elimination, substitution strategies can be evaluated.				
	Medium: These risks should be sorted out early in the project and evaluated for reduction or elimination. Such risks do not typically require extensive resources; rather, they can be handled with smart thinking and logical planning.				
	Low: Acceptable. Risks do not pose any significant problem. However, if some reasonable steps can help in fighting these risks, such steps should be taken to improve overall performance of the project.				

Based on the severity of the damage **(Table 13.1.4-2),** the consequences or impact of a risk could be ranked again and classified into one of the four categories **(Table 13.1.4-3).**

Table 13.1.4-2 Example of Probability of Occurrence

Score	Category	Criteria
8	Definite	A risk that is almost certain to occur during project execution.
6	Frequent	Risks that are highly likely to occur.
4	Seldom	Risks that have a low probability of occurrence but still cannot be ruled out completely.
2	Unlikely	Rare and exceptional risks which have a less than 10% chance of occurrence.

Table 13.1.4-3 Example of Consequences or Impact

Score	Category	Criteria
8	Catastrophic	These are the risks that can derail the project completely unproductive and must be a top priority during risk management.
6	Critical	Risks with significantly large consequences that can lead to a great amount of loss.
4	Moderate	Risks that do not impose a great threat yet are capable of causing sizable damage.
2	Negligible	Risks that will cause a near negligible amount of damage to the overall progress of the project.

As the project proceeded, new risks were identified and added to this table **(Table 13.1.4-4).** In this respect, the risk assessment became a "living" document through the project lifecycle and was continually assessed and the identified risks mitigated throughout the risk review. The status was tracked by the project manager on a monthly basis through a project dashboard.

Table 13.1.4-4 "Living" Risk Assessment

Type of Risk	Nature of Risk	Impact Resulting in Project Delays	Probability/ Impact	Risk Category	Risk Response	Risk Owner
Personnel	No in-house knowledge of isolator technology	Improperly designed isolator filling line	8/6	48	Contract external resources with skills required	Technology Operations (Process Engineering)
Timeliness	Long-lead equipment installation	Project delays result in lapses in qualification quality	4/6	24	Ensure vendor is reliable and will deliver on time to meet schedule	Project Engineering and Procurement
Equipment	Unproven nature of new or novel equipment	Start-up challenges	4/4	16	Include engineering studies in schedule to acquire understanding of the equipment	Technology Operations and Process Engineering
Constructability	Electrical city permits not approved	Redesign required	6/4	24	Review design with permit office prior to design completion	Engineering and Project manager

PDA
Parenteral Drug Association

Technical Report No. 54-5

Quality Risk Management for the Design, Qualification, and Operation of Manufacturing Systems

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Attachment 3: Template for the Contamination Control Strategy Document (example)

About this CCS-document template and how to use and understand it

This template is meant to support the documentation of the CCS strategy. It is not an instruction how to develop and implement the CCS strategy, although – implicitly – essential steps for implementing a CCS can be deduced from this document.

Experience shows that – although a well-elaborated CCS may be implemented - yet, it can be a challenge to find / identify the document, where the specific information is laid down, stated, or defined! The compilation of the CCS elements in this document should be holistic and provide a good overview.

> Note: For larger companies, e.g., with an extensive product portfolio, it may be advisable to create appendices instead of listing all information in the CCS document.

Similar to a Site Master File, this CCS document needs to be kept current but not updated with, e.g., a new version of an SOP quoted in the document.

Although not explicitly required in Annex 1, the CCS document should be a controlled document approved by a Quality Unit. The template has a signature section on the front page.

The CCS document guides the reader to the respective Risk Assessments / Risk Analyses (RAs), reports, SOPs, and other relevant documents and should indicate what is said in these documents, but – to avoid mismatches and conflicting statements – not repeat or summarize in detail the contents of the underlying documents.

For Sections 1 – 16, it is suggested to use tables wherever possible; this document indicates a format in each section. Sub-sections have been added to provide room for further details: e.g., Section 5 "Utilities" includes sub-sections for "water," "steam," "gases" – if further sections are required, they may be added. If less sub-sections are needed for your specific situation, just delete them!

Some guiding hints regarding color coding and fonts:

Text in blue in this template is explanatory provides tips and suggestions. This text is not meant to remain in the company's CCS-Document.

Text quoted from Annex 1 is written in *Times New Roman* fonts and in Italics.

Text in black may be regarded as "suggested text," which can be adopted, adapted, modified, amended – as adequate.

Contamination Control Strategy

Document Approval

Name	Function	Responsible for Section(s)	Date / Signature
	QA	Approval of the CCS-document	

Different functions may be responsible for different sections of the document – There is no single CCS-SME

Table of Contents

A. Introduction

A.1 Objective

This document is based on Annex 1, which requires to develop of a Contamination Control Strategy based on the following principles (quoted from Annex 1):

"The development of the CCS requires thorough technical and process knowledge. Potential sources of contamination are attributable to microbial and cellular debris (e.g., pyrogen, endotoxins) as well as particulate matter (e.g., glass and other visible and sub-visible particulates)."

The elements to be considered are listed in Annex 1:

i. *Design of both the plant and processes, including the associated documentation.*
ii. *Premises and equipment.*
iii. *Personnel.*
iv. *Utilities.*
v. *Raw material controls – including in-process controls.*
vi. *Product containers and closures.*
vii. *Vendor approval includes key component suppliers, sterilization of components and single-use systems (SUS), and critical service providers.*
viii. *Management of outsourced activities and availability/transfer of critical information between parties, e.g. contract sterilisation services.*
ix. *Process risk assessment.*
x. *Process validation.*
xi. *Validation of sterilisation processes.*
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. *Cleaning and disinfection.*
xiv. *Monitoring systems – including an assessment of the feasibility of introducing scientifically sound, alternative methods that optimize the detection of environmental contamination.*
xv. *Prevention mechanisms – trend analysis, detailed, investigation, root cause determination, corrective and preventive actions (CAPA), and the need for comprehensive investigational tools.*
xvi. *Continuous improvement based on information derived from the above.*

Add more elements if applicable! – e.g., further conditions that need contamination control, summary and conclusion, attachments, document history

This CCS-Document summarizes how our company approached each of the elements and how we maintain the standard to ensure an adequate level of contamination control. This document considers quality risk assessment and the overall approach to managing microbiological, particulate, and cross-contamination of products manufactured in the sites. It makes to relevant documents, where details are defined and documented to avoid mismatches; this CCS document does not repeat details provided in other documents.

To facilitate reading and understanding of the document, the document follows some rules:

- In order to maintain clear reference to the Elements mentioned in Annex 1, the numbers of Sections B.1 – B.16 refer precisely to the numbers of the elements. As relevant, sub-sections may need to be added.
- If text is quoted from Annex 1, it is written in *italics*.
- Whenever there is clear guidance is provided in regulatory documents, design, processes, and procedures are based on this guidance (e.g., clean room grades and related particle and microbiological requirements). Thus, such details are not repeated.
- The principles of Quality Risk Management have been applied.
- Reference to documents (reports, instructing documents, SOPs, etc.) is provided in each section.

A.2 Definitions and Abbreviations

Term / Abbreviation	Definition / Long Version
CCS	Contamination Control Strategy: *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 the 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.*
CCS-document	This document compiles references to all documents related to the CCS as well as conclusions on how to ascertain and maintain contamination control.
The Elements	The elements mentioned in Annex 1 under i. – xvi., which refer to Sections B.1 – B.16 of this document.
PV	Process Validation
QRM	Quality Risk Management
RA	Risk Assessment / Risk Analysis
SMF	Site Master File
SV	Sterilisation Validation

Add further Definitions and Abbreviations as required

B. Documentation of the Contamination Control Strategy

B.1. Design of both the plant and processes including the associated documentation

Provide the name of the products and associated manufacturing facilities. Provide some information of the:

- product presentation (e.g., syringes, vials, cartridge)
- formulation or product-specific variants (e.g., volumes, strength)

B.1.1. The plant

B.1.1.1. General

The plant is designed to ensure the process steps are performed in the clean room Grades are required according to Annex 1.

Access to the clean room grades is via separate air-locks for personnel and material.

Layouts of the different areas may be inserted to show hygienic zones, personnel, and material flow. Reference to SMF could be extremely useful at this point.

B.1.1.2. Terminally Sterilized Products

Process Step	Clean room grade	High level Contamination control measures

B.1.1.3. Aseptically Manufactured Products

Process Step	Clean room grade	High level Contamination control measures

B.1.1.4. Low Bioburden Processes / Bioburden-Controlled Processes

Process Step	Clean room grade	High level Contamination control measures

B.1.2. The Processes

Describe the different processes– terminally sterilized products, aseptic manufacturing, low bioburden, bioburden controlled – a brief description to evaluate if the CCS is adequate.

B.1.2.1. Terminally Sterilized Products

Describe specific information about sterilization methods / processes.

Mention / list the products / types of products manufactured as terminally sterilized products

Product Name	Product Type	Container	
		Volume	Material

B.1.2.2. Aseptic Manufacturing

Mention / list the products / types of product manufactured under aseptic conditions

Product Name	Product Type	Container	
		Volume	Material

B.1.2.3. Low Bioburden Processes / Bioburden-Controlled Processes

Mention / list the products / types of product manufactured as low bioburden / bioburden controlled products

Product Name	Product Type	Container	
		Volume	Material

Product Name	Product Type	Container	
		Volume	Material

B.2. Premises and Equipment

Although not part of the elements listed in Annex 1, reference to Qualification (SOPs, Master Plan, etc.) may be made here.

B.2.1. Premises

Concerning Premises, refer to Section B.1.2.

B.2.2. Equipment

For major equipment in regard to contamination control, consider making reference to the SMF – or copy from SMF.

List major equipment related to contamination prevention such as autoclave and refer to the measure in place in the section of the CCS e.g. B11

B.3. Personnel

B.3.1. General

Personnel is trained in all areas of their responsibilities. More details about the areas and the applicable procedures are provided:

Type of Training	Reference Document	
	Title	No.
Induction training		
General GMP-training		
Hygienic behavior		
Personnel Qualification		

B.3.2. Gowning Requirements

Description	Reference Document	
	Title	No.
Gowning requirements for the different clean room grades are defined.		

B.3.3. Clean Room Clothing

Description	Reference Document	
	Title	No.
Material, quality, and design of clean room clothing is adequate for the respective clean room Grade		
Changing and replacement of clean room clothing		
Cleaning of clean room clothing		
Sterilization of clean room clothing		
Validation of the sterilization process		

B.3.4. Personnel Monitoring

Note: Section 14 in Annex 1 is about monitoring, thus, in this template, Personnel Monitoring is mentioned in Section 14.3. Personnel Monitoring may either be mentioned under Section B.4 "Personnel" or in Section B.14. – a matter of taste. But: cross-reference should be made.

Description	Reference Document	
	Title	No.
RAs, SOPs, evaluation	Refer to section B.14.	

In this section, add the information around aseptic media fill, aseptic intervention risk assessment, monitoring after intervention. Finally, give an explanation on the residual risk accepted.

B.4. Utilities

Consider making reference to SMF!

Briefly describe the method of preparation / distribution – refer to the monitoring Section.

Brief description of the contamination prevention program in place such as sanitization, decontamination, etc.

B.4.1. Water

B.4.1.1. Purified Water

Description	Reference Document	
	Title	No.
Risk Assessment		
Specification		
Preparation		
Distribution		
Monitoring	refer to Section B.14.	

B.4.1.2. WFI

Description	Reference Document	
	Title	No.
Specification		
Preparation		
Distribution		
Monitoring	refer to Section B.14.	

B.4.2. Steam

Description	Reference Document	
	Title	No.
Specification		
Preparation		
Distribution		
Monitoring	refer to Section B.14.	

B.4.3. Gases

B.4.3.1. Product-contact-compressed air (direct or indirect product contact)

Description	Reference Document	
	Title	No.
Specification		
Preparation		
Distribution		
Monitoring	refer to Section B.14.	

B.4.3.2. N_2

Description	Reference Document	
	Title	No.
Specification		
Storage		
Distribution		
Monitoring	refer to Section B.14.	

B.4.3.3. CO_2

Description	Reference Document	
	Title	No.
Specification		
Storage		
Distribution		
Monitoring	refer to Section B.14.	

B.4.3.4. O_2

Description	Reference Document	
	Title	No.
Specification		
Storage		
Distribution		
Monitoring	refer to Section B.14.	

B.4.3.5. Further Gases

Description	Reference Document	
	Title	No.
Specification		
Storage		
Distribution		
Monitoring	refer to Section B.14.	

B.5. Raw Material Controls – including in-process controls

Relevant aspects

- how starting materials are sampled and tested
- microbiological requirements and endotoxin limits are part of the raw material specification.

Raw Material (Starting Material) Controls Description	Reference Document	
	Title	No.
Test specifications for each starting material are prepared and approved; specifications follow the Marketing Authorization		
Incoming goods' testing		
Sampling		
QC-Testing		
Starting Material release procedure		

B.5.1. In-Process Controls

Relevant aspects

- the stages for contamination-control-related IPC-testing
- the limits
- link this section to the section B.1.1

Description	Reference Document	
	Title	No.
Stages at which IPC-tests are performed		
Bioburden limits for the respective stages		

B.6. Product Containers and Closures

Relevant aspects

- different products, their container and closures
- CCI tests
- Routine process for testing container closure integrity
- When containers are a SUS or other material refer to the extractible and leachable reports and include the monitoring on these containers to prevent contamination (e.g. particulate, integrity test).

Description	Reference Document	
	Title	No.
Container Type - Specification		
Closure Type - Specification		
Container System Qualification		
Container Closure Integrity Testing		
Routine tests for container closure integrity		
Extractables & Leachables (where applicable)		

B.7. Vendor approval – such as key component suppliers, sterilization of components and single-use systems (SUS), and critical service providers

B.7.1. General processes

Relevant aspects:

- SOP for vendor qualification (presumably the same SOP as for supplier qualification, which is relevant in Section B.8.) – consider combining Sections B.7. and B.8. or make cross-references!
- Routine vendor evaluation / auditing

Description	Reference Document	
	Title	No.
Vendor / supplier qualification process		
Vendor / supplier evaluation		

Description	Reference Document	
	Title	No.
Vendor / supplier auditing		

B.7.2. Detailed information regarding vendors

Component	Vendor	Reference Document	
		Title	No.
		Contract	
		Qualification document	
		Audit Report	
		Annual evaluation	
		Contract	
		Qualification document	
		Audit Report	
		Annual evaluation	
		Contract	
		Qualification document	
		Audit Report	
		Annual evaluation	

B.8. Management of outsourced activities and availability/transfer of critical information between parties, e.g. contract sterilisation services.

Note: This Section is quite similar to section B.7.

B.8.1. General processes

Refer to Section B.7.1.

B.8.2. Detailed information regarding suppliers

Service	Contract acceptor	Reference Document	
		Title	No.
		Contract	
		Qualification document	
		Audit Report	
		Annual evaluation	
		Process Validation	
		Contract	
		Qualification document	
		Audit Report	
		Annual evaluation	
		Process Validation	
		Contract	
		Qualification document	
		Audit Report	
		Annual evaluation	
		Process Validation	

B.9. Process Risk Assessment

The title "process risk assessment" is somehow narrowing the scope of the general requirement to base decisions on Quality Risk Management – suggestion to broaden the scope (but still keep the title for clear reference to Annex 1)

Relevant aspects:

- SOP(s)
- Registers
- Overview of existing RAs for manufacturing / cleaning / decontamination / depyrogenation

Description	Reference Document	
	Title	No.
The concept of QRM is implemented throughout the organization (SOP)		
A register of RAs is maintained by QA		
RAs for manufacturing processes:		
RAs for aseptic manufacturing processes:		
RAs for cleaning processes:		

Description	Reference Document	
	Title	No.
RAs for decontamination (incl. depyrogenation) processes:		

RAs for sterilisation processes are part of B.11.

B.10. Process Validation

Following the GMP-requirements, all manufacturing processes have been validated and re-validation takes place on a regular basis / processes are under continuous verification Processes are re-validated after Changes that require re-validation.

Process Validation is based on a QRM approach and the underlying RAs mentioned in Section B.9.

Note: The CCS does not refer to general cleaning validation but should focus on microbiological (incl. endotoxins) aspects.

Relevant aspects:

- Process Validation SOP
- PV-reports

Description	Reference Document	
	Title	No.
The concept of PV is described in SOP		
The concept of continuous process verification is described in SOP		
Aseptic process simulation is performed according to SOP		
PV-reports for manufacturing processes:		

Description	Reference Document	
	Title	No.
Aseptic process simulation reports (media fill reports)		
PV-reports for cleaning processes:		
PV-reports for decontamination processes:		
PV-reports for depyrogenation processes:		

B.11. Validation of sterilisation processes

Following the GMP-requirements, all sterilisation processes have been validated and re-validation takes place on a regular basis / processes are under continuous verification Processes are re-validated after Changes that require re-validation.

Validation of sterilisation processes is based on a QRM approach and the underlying RAs mentioned in Section B.9.

Note: The CCS does also refer to depyrogenation processes and their validation but this topic is covered in the previous chapter B.10.

Relevant aspects for the validation of sterilisation processes:

- Sterilisation Validation SOP or VMP
- SV-reports

Description	Reference Document	
	Title	No.
The concept of SV is described in SOP or VMP		
The concept of continuous process verification or re-validation of sterilization processes is described in SOP or VMP		
SV-reports for sterilization processes		

It is also an option to cover the validation of sterilization processes in Section 10 and make a cross-reference to Section 10 here, in Section 11. – Importance of sterilization processes may trigger the decision whether to handle Validation of sterilization processes in a separate Section or not.

B.12. Preventative maintenance – maintaining equipment, utilities, and premises (planned and unplanned maintenance) to a standard that will ensure there is no additional risk of contamination

Relevant aspects – presumably covered in SOP(s):

- The way to define maintenance requirements (e.g., vendor involvement, in-house-experience, involvement of external companies)
- QA involvement
- How are maintenance plans developed (servicing / inspection / replacement actions and for the system) - Are log-book-entries considered
- The basis for the development of the maintenance program (frequency for performing maintenance actions)
- Calibration
- Responsibility for system approval after maintenance
- Risk assessments

If CC aspects are addressed in the documents for preventive maintenance programs, an additionally reference to these documents may be useful.

B.13. Cleaning and Disinfection

Procedures are in place for cleaning and disinfection.

Note: "decontamination" is not mentioned in the enumeration in Annex 1; however, it appears feasible to cover these important aspects in this section.

List the procedures and make reference to the SOP numbers and – as applicable – validation reports (cross-references to Section B.10. should be considered)

B.13.1. Equipment

Equipment Type	Activity	Reference Document	
		Title	No.
	Cleaning		
	Disinfection		
	Decontamination		
	Cleaning		
	Disinfection		
	Decontamination		
	Cleaning		
	Disinfection		
	Decontamination		
	Cleaning		
	Disinfection		

Equipment Type	Activity	Reference Document	
		Title	No.
	Decontamination		
	Cleaning		
	Disinfection		
	Decontamination		
	Cleaning		
	Disinfection		
	Decontamination		

B.13.2. Clean Rooms / Clean Areas

Room No. / Area	Grade	Activity	Reference Document	
			Title	No.
	A	Cleaning		
		Disinfection		
		Decontamination		
	B	Cleaning		
		Disinfection		
		Decontamination		
	C	Cleaning		
		Disinfection		
		Decontamination		
	D	Cleaning		
		Disinfection		
		Decontamination		

B.13.3 Clean Room Clothing

Refer to Section B.3.3.

B.14. Monitoring Systems - including an assessment of the feasibility of the introduction of scientifically sound, alternative methods that optimize the detection of environmental contamination

Relevant aspects:

- Reference to Risk Assessments, which lead to the sampling points
- SOPs
- Reference the summary reports and how the description of how trending is done (SOP!) and conclusions are drawn.

B.14.1. General Procedures

Description	Reference Document	
	Title	No.
Instruction on how to develop sampling points / frequency / warning and action limits		
Instruction for the preparation of reports		
SOP on how to perform trending		

B.14.2. Monitoring of Systems

B.14.2.1. Water and Steam

Type	Activity	Reference Document	
		Title	No.
City Water optional!	RA		
	Monitoring SOP		
	Summary Report		
Purified Water	RA		
	Monitoring SOP		
	Summary Report		
Clean Steam	RA		
	Monitoring SOP		
	Summary Report		

B.14.2.2. Clean Rooms

Summarize and cross-reference with the relevant section of this document to describe the viable and non-viable monitoring and testing methods associated. Describe if the sampling is performed by internal or external personnel and the overall oversight by the quality department.

Describe the frequency, location, and type of sampling, including the definition of the alert and action limits. State the frequency of the historical EM data review and analysis.

Refer to the section discussing the filter integrity, the velocity of air supplied, smoke studies, pressure differential, temperature, relative humidity, etc.

Refer to the microbial media and incubation program used, air exposure of the media (e.g., settle plate) validated, etc.

Consider further differentiation into different areas and / or clean room grades

Type	Activity	Reference Document	
		Title	No.
Viable environmental monitoring	RA		
	Monitoring SOP		
	Summary Report		
Non-viable (physical) environmental monitoring	RA		
	Monitoring SOP		
	Summary Report		

B.14.2.3. Gases

Type	Activity	Reference Document	
		Title	No.
Product-contact-compressed air	RA		
	Monitoring SOP		
	Summary Report		
N_2	RA		
	Monitoring SOP		
	Summary Report		

Type	Activity	Reference Document	
		Title	No.
CO_2	RA		
	Monitoring SOP		
	Summary Report		
O_2	RA		
	Monitoring SOP		
	Summary Report		
Further	RA		
	Monitoring SOP		
	Summary Report		

B.14.2.4. Personnel

Note: see remark in Section B.3.4.

Area Grade	Activity	Reference Document	
		Title	No.
Grade B	RA		
	Monitoring SOP		
	Summary Report		
Grade C	RA		
	Monitoring SOP		
	Summary Report		
Grade D	RA		
	Monitoring SOP		
	Summary Report		

B.15. Prevention mechanisms – trend analysis, detailed investigation, root cause determination, corrective and preventive actions (CAPA), and the need for comprehensive investigational tools

Refer to the document that describe the requirement for an effective investigation, quality management systems, and the document that describes the deviations process and CAPA including document that track and trend reoccurrence and CAPA effectiveness.

State the procedure in place to address reoccurring deviation to ensure proper contamination control states.

Description	Reference Document	
	Title	No.
Incidents and deviations are managed via:		
Investigation of incidents and deviations (Root causes analyses) is described in SOP:		
Corrective and preventive actions (CAPAs) are managed according to:		

B.16. Continuous improvement based on information derived from the above

Summarize processes and procedures for continuous improvement and include the document subject to periodic updates

- preparation of reports (define frequency!), e.g., management reports or PQRs
- evaluation of incidents and deviations and related CAPAs
- trending analysis of EM, product quality review, etc.
- internal communication/escalation via regular or extraordinary meetings with defined participants.

B.17. Further relevant aspects – e.g., with regard to viral safety (where applicable)

C. Summary and Conclusion (including identified gaps and how to assess them)

Summarize the results and conclusions.

During the preparation of the document, you may have come across areas that need further improvement, assessment or for which no or insufficient regulations are available. Then, this may be recorded in this

section (or by adding sub-sections). Include the path forward (schedule, responsibilities) to rectify the deficits.

“Summary and Conclusions …. “ may also be at the beginning!

D. References

List the regulatory, literature, or industrial references used as feasible.

E. Attachments

As applicable

F. Document History

Attachment 4: Relevant/Helpful Guidelines and Documents:

Regulatory:

i) *European Commission, EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines, Chapter 3: Premises and Equipment, (2014)*
ii) *European Commission, EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines, Chapter 5: Production, (2014)*
iii) *European Commission, EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines, Part II: Basic Requirements for Active Substances used as Starting Materials, (2014)*
iv) *European Union, Guidelines of 19 March 2015 on the formalized risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use, Official Journal of the European Union, (2015/C 95/02), (2015)*
v) *European Commission, EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines, Annex 2: Manufacture of Biological active substances and Medicinal Products for Human Use, (2018)*
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Industry:

I. ECA Guidelines for the Evaluation and Investigation of Microbiological Deviations
- Chapter 1 - Deviation Handling of Microbiological Environmental Monitoring Excursions in Non-Sterile Pharmaceutical Manufacturing
- Chapter 2 - Lab Investigations – Endotoxin Out of Specification (OOS)/ Out of Trend (OOT)/ Atypical Results Investigations
- Chapter 3 - Guidance for Sterility Test Failures

II. ECA Standard Operating Procedure (SOP): Laboratory Data Management - Out of Specification (OOS) Results

III. ECA Laboratory Data Management Guidance: Out of Expectation (OOE) and Out of Trend (OOT) Results

IV. ECA Good Practice Guide on Validation

V. ECA Good Practice Guide "Visual Inspection of Medicinal Products for Parenteral Use - Version 3.2"

VI. Container Closure Integrity Testing of Medicinal Products for Parenteral Use - Position Paper - Version 2.0

VII. USP general chapter discussing contamination control: <1116>; <1072>; <1231>; <1229>; etc.