無菌藥廠污染管制策略(CCS)的考量要點 - Contamination Control Strategy (CCS)之 法規要求

王怡力

2021.10.26(南區)
2021.11.04(北區)

Introduction

- The term **"Contamination Control Strategy (CCS)"** was introduced in the recent changes of the European Union (EU) draft Annex 1 version 12.
  - Draft Annex 1 proposes a similar definition of CCS to the control strategy definition in the ICH Q10-Quality system.
    - ✓A planned set of controls for microorganisms, pyrogens and particulates, derived from current product and process understanding that assures process performance and product quality.
    - ✓The controls can include parameters and attributes related to active substance, excipient and drug product materials and components, facility and equipment operating conditions, in process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

ICH Q9- Quality Risk management

Is it a new and specific documentation requirement for Annex 1?

Introduction

The principle of contamination control or prevention of microbiological, particulates, or pyrogens contamination **is not new** and is significantly discussed in the regulatory and industrial guidelines.

Most manufacturers have documents that discuss contamination control program per process. However, they **may not** have a holistic or a single document summarizing all the critical control points to assess the effectiveness of all the controls and monitoring measures employed to manage risks associated with contamination across a facility or in the final product.

CCS is an holistic, systematic set of control mechanisms which act together to provide a high degree of assurance of elimination of contamination in finished product.

CCS in draft Annex 1 version 12

2. Principle

3. Pharmaceutical Quality System (PQS)

4. Premises

5. Equipment

6. Utilities

7. Personnel

8. Production and specific technologies

- Aseptic preparation and processing
- Filter sterilization of products which cannot be sterilized in their final container
- Lyophilization
- Single use systems (SUS)

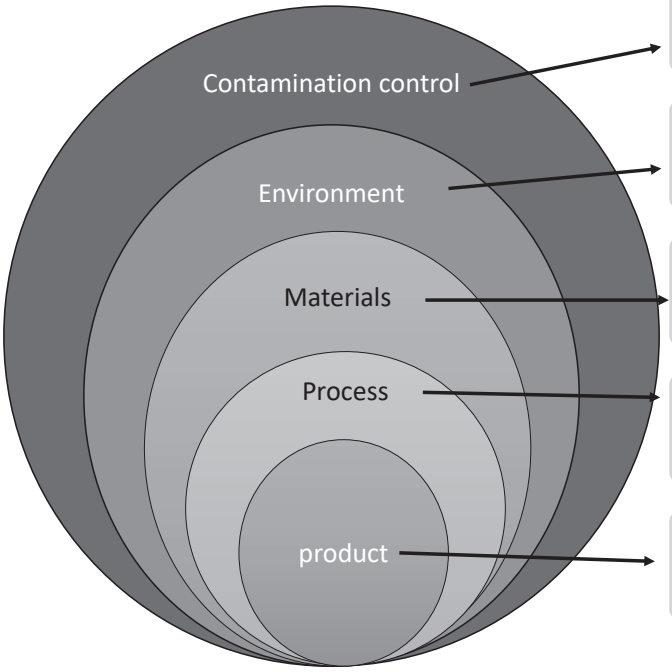
9. Viable and non-viable environmental & process monitoring

10. Quality Control (QC)

The key purpose of a CCS is allow assessment of the strategies implemented.

- ✓ Not just collation of risk assessments, validations, procedures and other information.
- ✓ Requires ongoing effectiveness evaluation and correction.

What's involved?



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

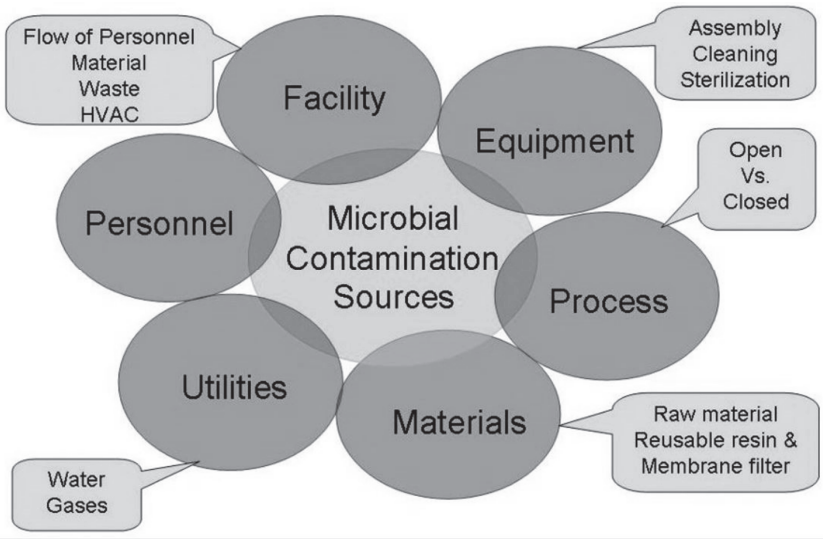
Personnel, facilities, utilities, HVAC

Raw materials, media/buffers, testing materials

Process controls, equipment & technology, cleaning, training, monitoring & trending

Product testing

What's involved?



Case Studies of Microbial Contamination in Biologic Product Manufacturing
Kalavati Suvarna, Ph.D. ,Anastasia Lolas Patricia Hughes, Ph.D Richard L Friedman

2. Principle

- 2.3 Quality Assurance is particularly important, and manufacture of sterile products must strictly follow carefully established and validated methods of manufacture and control. A Contamination Control Strategy (CCS) should be implemented across the facility in order to define all critical control points and assess the effectiveness of all the controls (design, procedural, technical and organisational) and monitoring measures employed to manage risks associated with contamination. The CCS should be actively updated and should drive continuous improvement of the manufacturing and control methods.
- 2.4 Contamination control and steps taken to minimize the risk of contamination from microbial and particulate sources are a series of successively linked events and measures. These are typically assessed, controlled and monitored individually but their collective effectiveness should be considered altogether.

2. Principle

- 2.5 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). Elements to be considered within a documented CCS should include (but are not limited to):

i. Design of both the plant and processes.

ii. Premises and equipment.

iv. Personnel.

v. Utilities.

vi. Raw material controls – including in-process controls.

vii. Product containers and closures.

viii. Vendor approval – such as key component suppliers, sterilization of components and single use systems (SUS), and services.

ix. For outsourced services, such as sterilization, sufficient evidence should be provided to the contract giver to ensure the process is operating correctly.

x. Process risk assessment.

xi. Process validation.

xii. Preventative maintenance – maintaining equipment, utilities and premises (planned and unplanned maintenance) to a standard that will not add significant risk of contamination.

xiii. Cleaning and disinfection.

xiv. Monitoring systems - including an assessment of the feasibility of the introduction of

scientifically sound, modern methods that optimize the detection of environmental contamination.

xv. Prevention – trending, investigation, corrective and preventive actions (CAPA), root cause determination and the need for more comprehensive investigational tools.

2. Principle

- 2.6 The CCS should consider all aspects of contamination control and its life cycle with ongoing and periodic review resulting in updates within the quality system as appropriate.
- 2.7 The manufacturer should take all steps and precautions necessary to assure the sterility of the products manufactured within its facilities. Sole reliance for sterility or other quality aspects should not be placed on any terminal process or finished product test.

3. Pharmaceutical Quality System (PQS)

- 3.1 The manufacture of sterile products is a complex activity that requires specific controls and measures to ensure the quality of products manufactured. Accordingly, the manufacturer's PQS should encompass and address the specific requirements of sterile product manufacture and ensure that all activities are effectively controlled so that microbial, particulate and pyrogen contamination is minimized in sterile products. In addition to the PQS requirements detailed in Chapter 1 of the GMPs, the PQS for sterile product manufacture should also ensure that:

i. An effective risk management system is integrated into all areas of the product life cycle with the aim to minimize microbial contamination and to ensure the quality of sterile products manufactured.

ii. The manufacturer has sufficient knowledge and expertise in relation to the products manufactured and the equipment, engineering and manufacturing methods employed that have an impact on product quality.

iii. Root cause analysis of procedural, process or equipment failure is performed in such a way that the risk to product is correctly understood and suitable corrective and preventative actions (CAPA) are implemented.

iv. Risk management is applied in the development and maintenance of the CCS, to identify, assess, reduce/eliminate (where applicable) and control contamination risks. Risk management should be documented and should include the rationale for decisions taken in relation to risk reduction and acceptance of residual risk.

v. The risk management outcome should be reviewed regularly as part of on-going quality management, during change control and during the periodic product quality review.

Each key aspect of the CCS:

Facility design

- Easy to clean, GMP compliant physical design
- Materials of construction
- HVAC

Separation of staff from open or critical stages in the process

Physical barriers

Process Design

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

Effective supporting procedures

- Gowning
- Aseptic technique and handling
- Cleanroom behaviors

Each key aspect of the CCS:

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

Each key aspect of the CCS:

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

4. Premises

- 4.1 The manufacture of sterile products should be carried out in appropriate cleanrooms, entry to which should be through changing rooms that act as airlocks for personnel and airlocks for equipment and materials. Cleanrooms should be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency. Controls and monitoring should be scientifically justified and capable of evaluating the state of environmental conditions for cleanrooms, airlocks and pass-throughs used for material and equipment transfer.
- 4.2 The various operations of component preparation, product preparation and filling should be carried out with appropriate technical and operational separation measures within the cleanroom or facility to prevent mix up and contamination.
- 4.3 Restricted Access Barrier Systems (RABS) and isolators are beneficial in assuring the required conditions and minimizing the microbial contamination associated with direct human interventions in the critical zone. Their use should be considered in the CCS. Any alternative approaches to the use of RABS or isolators should be justified.

4. Premises

- 4.12 Airlocks should be designed and used to provide physical separation and to minimize microbial and particulate contamination of the different areas, and should be present for material and personnel moving between different grades. Wherever possible, airlocks used for personnel movement should be separated from those used for material movement. Where this is not practical, time-based separation of movement (personnel /material) by procedure should be considered. Airlocks should be flushed effectively with filtered air to ensure that the grade of the cleanroom is maintained. The final stage of the airlock should, in the “at rest” state, be of the same cleanliness grade (viable and nonviable) as the cleanroom into which it leads. The use of separate changing rooms for entering and leaving Grade B cleanrooms is desirable. Where this is not practical, time-based separation of activities (ingress/egress) by procedure should be considered. Where the CCS indicates that the risk of cross-contamination is high, separate changing rooms for entering and leaving production areas should be considered. Airlocks should be designed as follow:

4. Premises

i. Personnel airlocks: Areas of increasing cleanliness used for entry of personnel (e.g. from Grade D to Grade C to Grade B). In general hand washing facilities should be provided only in the first stage of the changing room and not be present in changing rooms directly accessing Grade B cleanrooms.

ii. Material airlocks: used for materials and equipment transfer. Only materials and equipment that have been included on an approved list, developed during validation of the transfer process, should be allowed to be transferred into the Grade A zone or Grade B cleanroom via an airlock or pass-through hatch. Equipment and materials (intended for use in the Grade A zone) should be protected when transiting through the Grade B cleanroom. Any unapproved items that require transfer should be pre-approved as an exception. Appropriate risk assessment and mitigation measures should be applied and recorded as per the manufacturer's CCS and should include a specific disinfection and monitoring programme approved by quality assurance.

- Pass-through hatches should be designed to protect the higher grade environment, for example by effective flushing with an active filtered air supply.
- The movement of material or equipment from lower grade or unclassified area to higher grade clean areas should be subject to cleaning and disinfection commensurate with the risk and in line with the CCS.

4. Premises

- 4.16 Indicators of pressure differences should be fitted between cleanrooms and/or isolators. Set points and the criticality of pressure differentials should be documented within the CCS. Pressure differentials identified as critical should be continuously monitored and recorded. A warning system should be in place to instantly indicate and warn operators of any failure in the air supply or reduction of pressure differentials (below set limits for those identified as critical). The warning signal should not be overridden without assessment and a procedure should be available to outline the steps to be taken when a warning signal is given. Where alarm delays are set, these should be assessed and justified within the CCS. Other pressure differentials should be monitored and recorded at regular intervals.
- 4.22 The background environment of a closed isolator should correspond to a minimum of Grade D. The disinfection/decontamination programme should be included as a key consideration when performing the risk assessment for the CCS of an isolator. Where additional process risks are identified, a higher grade of background should be considered. The decision as to the supporting background environment should be documented in the CCS.

110TPDA04012-A

4. Premises

- 4.23 The materials used for glove systems (for both RABS and isolators), as well as other parts of an isolator, should be demonstrated to have good mechanical and chemical resistance. Integrity testing of the barrier systems, and leak testing of the glove system and the isolator should be performed using a methodology demonstrated to be suitable for the task and criticality. The testing should be performed at defined periods, at a minimum at the beginning and end of each batch, and should include a visual inspection following any intervention that may affect the integrity of the system. For single unit batch sizes, integrity may be verified based on other criteria, such as the beginning and end of each manufacturing session. RABS gloves used in Grade A zone should be sterilized before installation and sterilized (or effectively decontaminated by a validated method which achieves the same objective) prior to each manufacturing campaign. The frequency of glove replacement should be defined within the CCS.

4. Premises

- 4.32 The speed of air supplied by unidirectional airflow systems should be clearly justified in the qualification protocol including the location for air speed measurement. Air speed should be designed, measured and maintained to ensure that appropriate unidirectional air movement provides protection of the product and open components at the working height (e.g. where high risk operations and product and/or components are exposed). Unidirectional airflow systems should provide a homogeneous air speed in a range of 0.36 – 0.54 m/s (guidance value) at the working position, unless otherwise scientifically justified in the CCS. Airflow visualization studies should correlate with the air speed measurement.
- 4.34 The requalification of cleanrooms and clean air equipment should be carried out periodically following defined procedures.

5 Equipment

- 5.1 A written, detailed description of the equipment design should be available (including process and instrumentation diagrams as appropriate). This should form part of the initial qualification package and be kept up to date as part of the ongoing review of the CCS.

6. Utilities

- 6.1 The nature and extent of controls applied to utility systems should be commensurate with the risk to product quality associated with the utility. The impact should be determined via a risk assessment documented as part of the CCS.
- 6.2 In general higher risk utilities are those that:

i. Directly contact product e.g. water for washing and rinsing, gases and steam for sterilization.

ii. Contact materials that will ultimately become part of the product.

iii. Contact surfaces that come into contact with the product.

iv. Otherwise directly impact the product.

6. Utilities

- 6.13 Regular ongoing chemical and microbial monitoring of water systems should be performed. Alert levels should be based on the qualification or a review of ongoing monitoring data that will identify an adverse trend in system performance. Sampling programs should reflect the requirements of the CCS and include:

i. All points of use, at a specified interval, to ensure that representative water samples are obtained for analysis on a regular basis.

ii. Potential worst case sampling locations.

iii. A sample from the point at the end of the distribution loop each day that the water is used.

- 6.23 For both vacuum and cooling systems there should be periodic cleaning/disinfection as determined in the CCS.

7. Personnel

- 7.10 Wristwatches, make-up, jewellery, other personal items such as mobile phones and any other non-essential items should not be allowed in clean areas. Electronic devices used in cleanrooms, e.g. mobile phones and tablets, that are supplied by the company solely for use in the cleanrooms, may be acceptable if suitable designed to permit cleaning and disinfection commensurate with the Grade in which they are used. The cleaning and disinfection of such equipment should be included in the CCS.
- 7.14 The c

i. Grade … be covered. A single or headgear … with high neck and from the rest … ould be worn. They suit. A ste… ticulate matter

drop… be covered. A general plastic glo… oes or overshoes Trouser-le… e taken to avoid any into th… area.

fibres or pa… s when performing Garments should … as defined by the to gown without co… g the outer surface of the garment. CCS.

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

8. Production and specific technologies - Aseptic preparation and processing

- 8.7 Aseptic preparation and processing is the handling of sterile product, containers and/or devices in a controlled environment in which the air supply, materials and personnel are regulated to prevent microbial, pyrogenic and particulate contamination.
- 8.8 The aseptic process should be clearly defined. The risks associated with the aseptic process, and any associated requirements, should be identified, assessed and appropriately controlled. The site's CCS should clearly define the acceptance criteria for these controls, requirements for monitoring and the review of their effectiveness. Methods and procedures to control these risks should be described and implemented. Accepted residual risks should be formally documented.
- 8.9 Precautions to minimize microbial, pyrogenic and particulate contamination should be taken, as per the site's CCS, during the preparation of the aseptic environment, during all processing stages (including the stages before and after bulk product sterilization), and until the product is sealed in its final container. The presence of materials liable to generate particulates and fibres should be minimized in cleanrooms.

8. Production and specific technologies

- Filter sterilization of products which cannot be sterilized in their final container

- 8.81 If the product cannot be sterilized in the final container, solutions or liquids should be sterilized by filtration through a sterile sterilizing grade filter (with a nominal pore size of 0.22 μm (or less) that has been appropriately validated to obtain a sterile filtrate) and subsequently aseptically filled into a previously sterilized container. The selection of the filter used should ensure that it is compatible with the product and as described in the marketing authorization (refer to paragraph 8.125).
- 8.82 Suitable bioburden reduction prefilters and/or sterilizing grade filters may be used at multiple points during the manufacturing process to ensure a low and controlled bioburden of the liquid prior to the primary sterilizing grade filter. Due to the potential additional risks of a sterile filtration process, as compared with other sterilization processes, a second filtration through a sterile sterilizing grade filter, immediately prior to filling, should be considered as part of an overall CCS.

110TPDA04012-A

8. Production and specific technologies

- Filter sterilization of products which cannot be sterilized in their final container

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

i. Assess and document the risks associated with the duration of filter use for the sterile filtration process for a given fluid.

ii. Conduct and document effective validation and qualification studies to demonstrate that the duration of filter use for a given sterile filtration process and for a given fluid does not compromise performance of the sterilizing filter or filtrate quality.

iii. Document the maximum validated duration of use for the filter and implement controls to ensure that filters are not used beyond the validated maximum duration. Records of these controls should be maintained.

iv. Implement controls to ensure that filters contaminated with fluid or cleaning agent residues, or considered defective in any other way, are removed from use.

8. Production and specific technologies

- Filter sterilization of products which cannot be sterilized in their final container

- 8.101 The controls identified during qualification should be in alignment with the site's CCS. Aspects to be considered include but are not limited to:

i. Determination of the boundaries of the critical zone.

ii. Environmental control and monitoring, both of the machine and the background in which it is placed.

iii. Integrity testing of the product filling lines.

iv. Integrity testing of the cooling system.

v. Duration of the batch or filling campaign.

vi. Control of polymer starting material (including resin pellets).

vii. Cleaning-in-place and sterilization-in-place of equipment in direct contact to the formulation (product filling lines); sterilization-in-place of sterile air pathways.

8. Production and specific technologies

- Filter sterilization of products which cannot be sterilized in their final container

- 8.107 External particulate and microbial contamination of the polymer should be prevented by appropriate design, control, and maintenance of the polymer storage, sampling and distribution systems. The capability of the extrusion system to provide appropriate sterility assurance for the moulded container should be fully understood and validated. The sampling frequency, the bioburden and, where applicable, endotoxins levels of the raw polymer should be defined and controlled within the CCS.

8. Production and specific technologies
-Lyophilization

- 8.110 Lyophilization is a critical process step and all activities that can affect the sterility of the product or material need to be regarded as extensions of the aseptic processing of the sterilized product. The lyophilization equipment and its processes should be designed to ensure that product or material sterility is maintained during lyophilization by preventing microbial and particulate contamination between the filling of products for lyophilization, and completion of lyophilization process. All control measures in place should be determined by the site's CCS.
- 8.112 Lyophilizers that are manually loaded or unloaded should normally be sterilized before each load. For lyophilizers loaded by automated closed systems or located within systems that exclude operator intervention, the frequency of sterilization should be justified and documented as part of the CCS.
- 8.119 Appropriate measures should be in place to ensure the integrity of components used in aseptic connections. The means by which this is achieved should be determined and captured in the CCS. Appropriate system integrity tests should be considered when there is a risk of compromising product sterility. Supplier assessment should include the collation of data in relation to potential failure modes that may lead to a loss of system sterility.

8. Production and specific technologies
-Single use systems (SUS)

- 8.121 SUS are those technologies used in manufacture of sterile products which are used as an alternative to reusable equipment. SUS can be individual components or made up of multiple components such as bags, filters, tubing, connectors, valves, storage bottles and sensors.
- 8.122 There are some specific risks associated with SUS which should be assessed as part of the CCS. These risks include but are not limited to:

i. The interaction between the product and product contact surface (such as adsorption, or the formation of leachables and extractables).

ii. The fragile nature of the system compared to fixed reusable systems.

iii. The increase in the number and complexity of manual operations (including inspection and handling of the system) and connections made.

iv. The complexity of the assembly.

v. The performance of the pre-use integrity test for sterilizing grade filters (refer to paragraph 8.88)

vi. The risk of holes and leakage.

vii. The potential for compromising the system at the point of opening the outer packaging.

viii. The risk of particulate contamination.

9 Viable and non-viable environmental & process monitoring

- 9.1 The site's environmental and process monitoring program forms part of the overall CCS and is used to monitor the controls designed to minimize the risk of microbial and particulate contamination. It should be noted that the reliability of each of the elements of the monitoring system (viable, nonviable and APS) when taken in isolation is limited and should not be considered individually to be an indicator of asepsis. When considered together, their reliability is dependent on the design, validation and operation of the system that they are monitoring.
- 9.4 Risk assessments should be performed in order to establish a comprehensive environmental monitoring program, i.e. sampling locations, frequency of monitoring, monitoring method used and incubation conditions (e.g. time, temperature(s), aerobic and/or anaerobic conditions). These risk assessments should be conducted based on detailed knowledge of; the process inputs and final product, the facility, equipment, specific processes, the operations involved, historical monitoring data, monitoring data obtained during qualification and knowledge of typical microbial flora isolated from the environment. Consideration of other information such as air visualization studies should also be included. These risk assessments should be reviewed regularly in order to confirm the effectiveness of the site's environmental monitoring program. The monitoring program should be considered in the overall context of the trend analysis and the CCS for the site.

9 Viable and non-viable environmental & process monitoring

- 9.14 Non-viable particulate monitoring systems should be established to obtain data for assessing potential contamination risks and to ensure the maintenance of the environment for sterile operations in a qualified state.
- 9.15 The limits for environmental monitoring of airborne particulate concentrations for each graded area are given in Table 6.
- 9.20 In the case where contaminants are present due to the processes involved and would potentially damage the particle counter or present a hazard (e.g. live organisms, powdery products and radiation hazards), the frequency and strategy employed should be such as to assure the environmental classification both prior to and post exposure to the risk. An increase in viable particle monitoring should be considered to ensure comprehensive monitoring of the process. Additionally, monitoring should be performed during simulated operations. Such operations should be performed at appropriate intervals. The approach should be defined in the CCS.

9 Viable and non-viable environmental & process monitoring

- 9.24 Where aseptic operations are performed, microbial monitoring should be frequent using a combination of methods such as settle plates, volumetric air sampling, glove, gown and surface sampling (e.g. swabs and contact plates). The method of sampling used should be justified within the CCS and should be demonstrated not to have a detrimental impact on Grade A and B airflow patterns.
- 9.33 Microbial monitoring of personnel in the Grade A zone and Grade B area should be performed to assess their aseptic behaviour. Where filling operations are manual in nature e.g. hand filling, the process in its entirety may be considered as one critical intervention. In these cases, the frequency of microbial monitoring of gowning should be based on scientific principles and justified as part of the CCS. Where monitoring is routinely performed by manufacturing personnel, consideration should be given to periodic monitoring under the supervision of the quality unit.

9 Viable and non-viable environmental & process monitoring

- 9.38 In developing the process simulation test plan, consideration should be given to the following:

i. Identification of worst case conditions covering the relevant variables, such as container size and line speed, and their impact on the process. The outcome of the assessment should justify the variables selected.

ii. Determining the representative sizes of container/closure combinations to be used for validation. Bracketing or matrix approach may be considered for validation of the same container/closure configuration for different products where process equivalence is scientifically justified.

iii. The volume filled per container, which should be sufficient to ensure that the media contacts all equipment and component surfaces that may directly contaminate the sterile product. The volume used should provide sufficient headspace to support potential microbial growth and ensure that turbidity can be detected during inspection.

iv. Maximum permitted holding times for sterile product and associated sterile components and equipment exposed during the aseptic process.

v. The method of detection of microbial contamination should be scientifically justified to ensure that any contamination is detectable.

vi. The selected nutrient media should be capable of growing a designated group of reference microorganisms as described by the relevant pharmacopeia and suitably representative local isolates and supporting recovery of low numbers of these microorganisms.

vii. The requirement for substitution of any inert gas used in the routine aseptic manufacturing process by air unless anaerobic simulation is intended. In these situations, inclusion ofoccasional anaerobic simulations as part of the overall validation strategy should be considered (refer to paragraph 9.35 point iii).

viii. The process simulation should be of sufficient duration to challenge the process, the operators that perform interventions, shift changes and the capability of the processing environment to provide appropriate conditions for the manufacture of a sterile product.

ix. Where the manufacturer operates different shifts then the APS should be designed to capture specific factors (e.g. for those manufacturing during a night or extended shift, fatigue should be considered).

x. Simulating normal aseptic manufacturing interruptions where the process is idle (e.g. shift changeovers, recharging dispensing vessels, introduction of additional equipment, etc.).

xi. Ensuring that environmental monitoring is conducted as required for routine production, and throughout the entire duration of the process simulation.

xii. Where campaign manufacturing occurs, such as in the use of Barrier Technologies or manufacture of sterile active substances, consideration should be given to designing and performing the process simulation so that it simulates the risks associated with both the beginning and the end of the campaign and demonstrating that the campaign duration does not pose any risk. The performance of "end of production or campaign APS" may be used as additional assurance or investigative purposes; however, their use should be justified in the CCS and should not replace routine APS. If used, it should be demonstrated that any residual product does not negatively impact the recovery of any potential microbial contamination.

10 Quality Control (QC)

- 10.1 It is important that there are personnel with appropriate training and experience in microbiology and knowledge of the process to support the design of the manufacturing process, environmental monitoring regime and any investigation assessing the impact of microbiologically linked events to the safety of the sterile product.
- 10.2 Specifications for raw materials, components and products should include requirements for microbial quality when the need for this has been indicated by monitoring and/or by the CCS.
- 10.7 For some products it may not be possible to perform a sterility test prior to release because the shelf life of the product is too short to allow completion of a sterility test. In these cases, the CCS should clearly capture the identified risks, the additional considerations of design of the process and additional monitoring required to mitigate the identified risks.

The CCS main goals

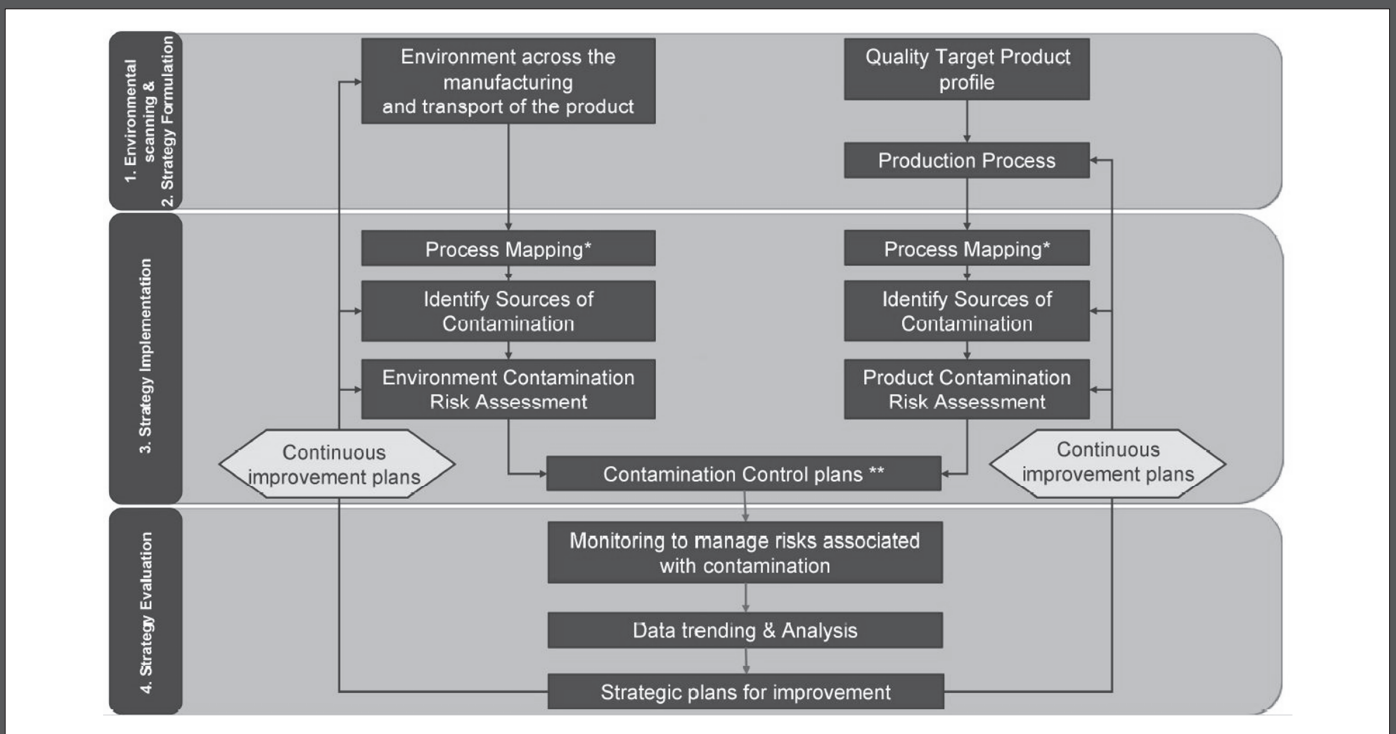
- ❑ **Identify** the set of controls required to detect and prevent microbial, pyrogen, and particulate contamination across the facility and in the final product.
- ❑ **Assess** the collective effectiveness of all the controls and monitoring measures employed to prevent the risk of contamination across the facility (e.g., utilities, cleaning and disinfection, process validation, facility design, etc.) and in the final product.
- ❑ **Improve** the quality system with continuous improvement plans based on the analysis and trending of data gathered through the monitoring measures employed.
- ❑ Assess the evolution of the contamination control performance **over time**.

- the CCS development and its documentation require robust technical, process, and contamination control expertise.

The implementation of a CCS consists of four steps

1. **Environmental scanning:** In this article, environmental or environment refers to all the design, procedural, technical, and organizational elements needed to manufacture the product (e.g., facility design, cleaning and disinfection, utilities, equipment, sterilization, depyrogenation, aseptic manipulation, etc.). Scanning refers to a process of collecting, scrutinizing, and providing information to formulate the strategy.
2. **Strategy formulation** is the process of deciding the best course of action for accomplishing the desired results.
3. **Strategy implementation** implies making the strategy work as intended by implementing the organizational activities, procedures, controls, monitoring, resources, and decision-making tools, and more.
4. **Strategy evaluation** measures the performance of the processes and confirms the strategy put in place to achieve the desired results.

The content of the CCS could be documented following the four steps listed earlier.



Conclusion

- Manufacturers can formulate their contamination control strategy based on the quality target product profile or critical quality attributes, the facility, and the processes used to manufacture and transport the product.
- The strategy implementation involves executing the strategic plan and managing the implementation by priority over time.
- The strategy evaluation uses the historical performance and data trend analysis to shed light on the efficiency and effectiveness of the contamination control strategy.
- The strategy evaluation allows the manufacturer to identify a new strategic plan to support improvement goals or new measures and controls to achieve the desired result, minimizing the contamination risk.

See it.
Say it.
Sorted!

Thanks for your attention!

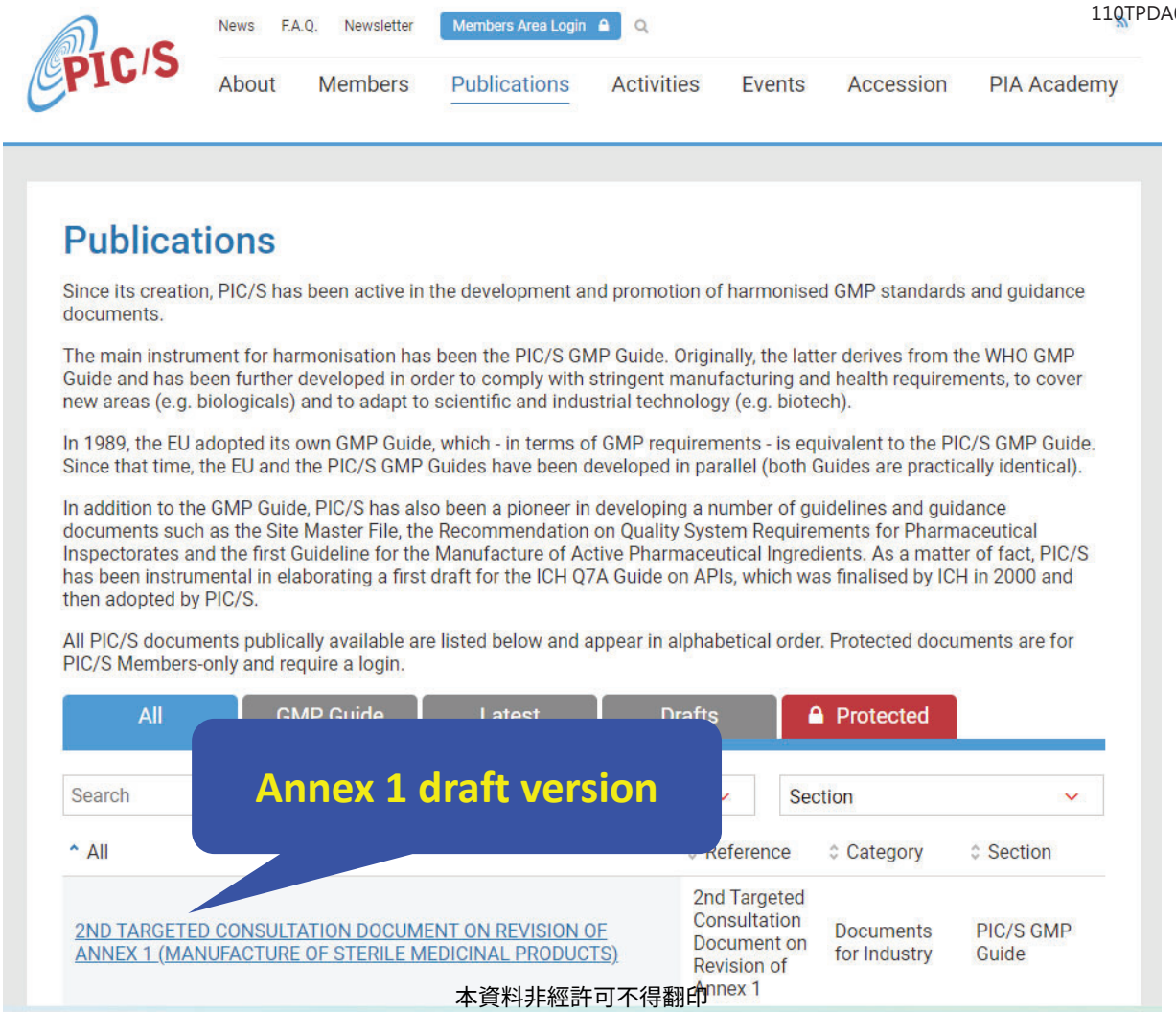
Reference

- European Union (EU) draft Annex 1 version 12
- PDA Journal of Pharmaceutical Science and technology: Contamination Control Strategy: Implementation Roadmap
- PDA: contamination control in healthcare product manufactoring
- Establishing a Contamination Control Strategy for Aseptic Processing (Tim Sandle, PHD)
- Case Studies of Microbial Contamination in Biologic Product Manufacturing (Kalavati Suvarna, Ph.D. ,Anastasia Lolas Patricia Hughes, Ph.D Richard L Friedman)

無菌藥廠污染管制策略(CCS)的考量要點(2)

Contamination Control strategy (CCS)之擬定探討

洪鼎超



Annex 1 : Manufacture of Sterile Products

Document map

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

Contamination Control Strategy (CCS) Annex 1 draft version 2020

What is Contamination Control Strategy (CCS)?

Contamination?

Definition:

Contamination – The undesired introduction of impurities of a chemical or microbiological nature or of foreign matter, into or on to a starting material or intermediate during production, sampling, packaging, repacking, storage and transport.

Decontamination – The overall process of removal or reduction of any contaminants (chemical, waste, residue or microorganisms) from an area, object, or person. The method of decontamination used (e.g. cleaning, disinfection, sterilization) should be chosen and validated to achieve a level of cleanliness appropriate to the intended use of the item decontaminated.

Contaminant – An impurity or any substance or material that causes contamination or spoilage.

1 Scope

The manufacture of sterile products covers a wide range of sterile product types (active substance, sterile excipient, primary packaging material and finished dosage form), packed sizes (single unit to multiple units), processes (from highly automated systems to manual processes) and technologies (e.g. biotechnology, classical small molecule manufacturing and closed systems). This Annex provides general guidance that should be used for the manufacture of all sterile products using the principles of Quality Risk Management (QRM), to ensure that **microbial**, **particulate** and **pyrogen** contamination is prevented in the final product.

Contamination Control Strategy (CCS) Annex 1 draft version 2020

What is CCS ?

110TPDA04012-B

Contamination Control Strategy (CCS) Annex 1 draft version 2020

2.3 Quality Assurance is particularly important, and manufacture of sterile products must strictly follow carefully established and validated methods of manufacture and control.

A Contamination Control Strategy (CCS) **should be implemented across the facility** in order to **define all critical control points** and **assess the effectiveness of all the controls** (design, procedural, technical and 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**.

~ Implemented across the facility~
~ Risk assessment & control/monitoring strategy ~
~ actively updated & continuous improvement ~

How to develop CCS and implement CCS?

2.5 **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).

~ Technical and process knowledge~

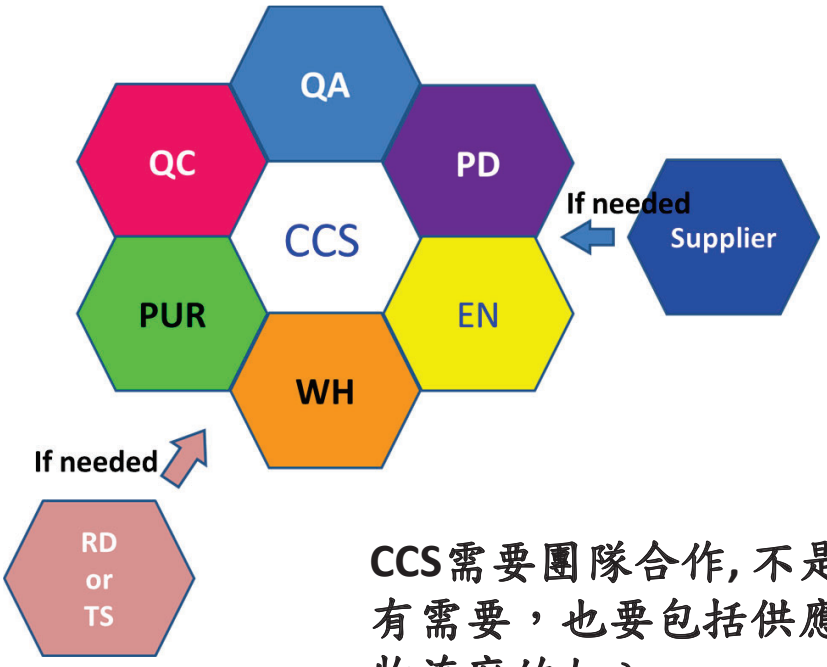
Contamination Control Strategy (CCS) Annex 1 draft version 2020

2.5 **Elements** to be considered within such a documented CCS should include (but are not be limited to):

i) Design of both the plant and process.
ii) Equipment and facilities.
iii) Personnel.
iv) Utilities.
v) Raw Material Controls–including in-process controls.
vi) Product containers and closures.
vii) Vendor approval
viii) Outsourced services
ix) Process risk assessment.
x) Process validation.
xi) Preventative maintenance
xii) Cleaning and disinfection
xiii) Monitoring systems
xiv) Prevention
xv) Continuous improvement based on information from the above.

Contamination Control Strategy (CCS) Annex 1 draft version 2020

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



CCS需要團隊合作,不是只有廠內,若有需要，也要包括供應商,委製廠,物流廠的加入。

Contamination Control Strategy (CCS) Annex 1 draft version 2020

2.6 The CCS should consider all aspects of contamination control and its life cycle with ongoing and periodic review resulting in updates within the quality system as appropriate.

~ ongoing and periodic review & update~

110TPDA04012-B

Contamination Control Strategy (CCS) Annex 1 draft version 2020

Not only CCS but also PQS

Contamination Control Strategy (CCS) Annex 1 draft version 2020

3.1 In addition to the Pharmaceutical Quality System (PQS) requirements detailed in Chapter 1 of the GMPs, the PQS for sterile product manufacture should also ensure that:

1. There is an effective risk management system integrated into the product life cycle.

2. The manufacturer has sufficient knowledge and expertise for (1) products manufactured, (2) equipment, (3) engineering, (4) manufacturing methods that have an impact on product quality.

3. Root cause analysis and suitable CAPA system.

Contamination Control Strategy (CCS) Annex 1 draft version 2020

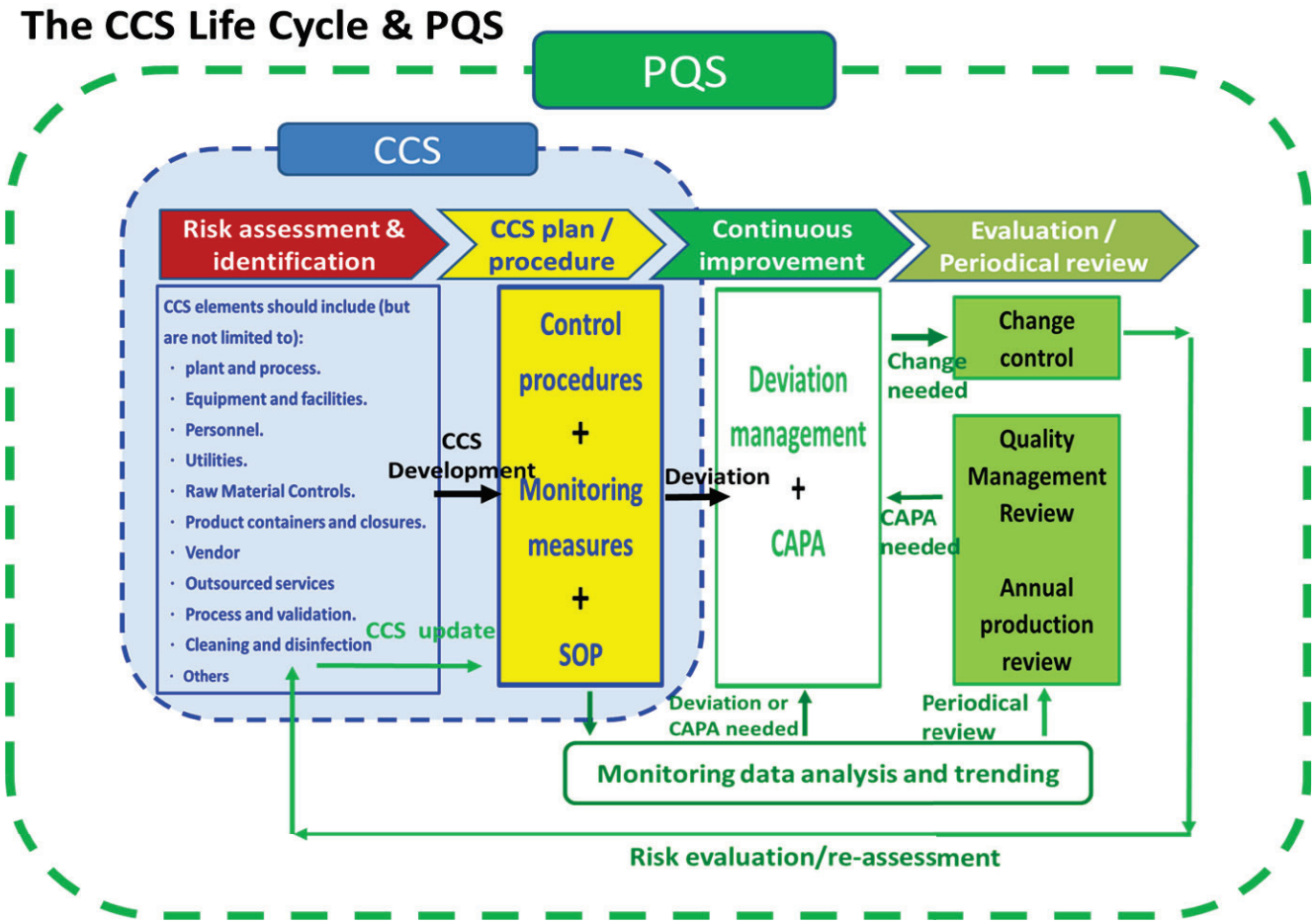
4. Risk management is applied in the development and maintenance of the CCS, to (1) identify, (2)assess, (3)reduce/eliminate (where applicable) and (4) control the contamination risks.

5. Risk management outcome should be reviewed during (1) on-going quality management, (2) change control, (3) periodic product quality review.

6. Processes associated with the (1)finishing, (2)transport, (3)stored and maintained of sterile products.

7. Product release

Contamination Control Strategy (CCS) Annex 1 draft version 2020



110TPDA04012-B

Contamination Control Strategy (CCS) Annex 1 draft version 2020

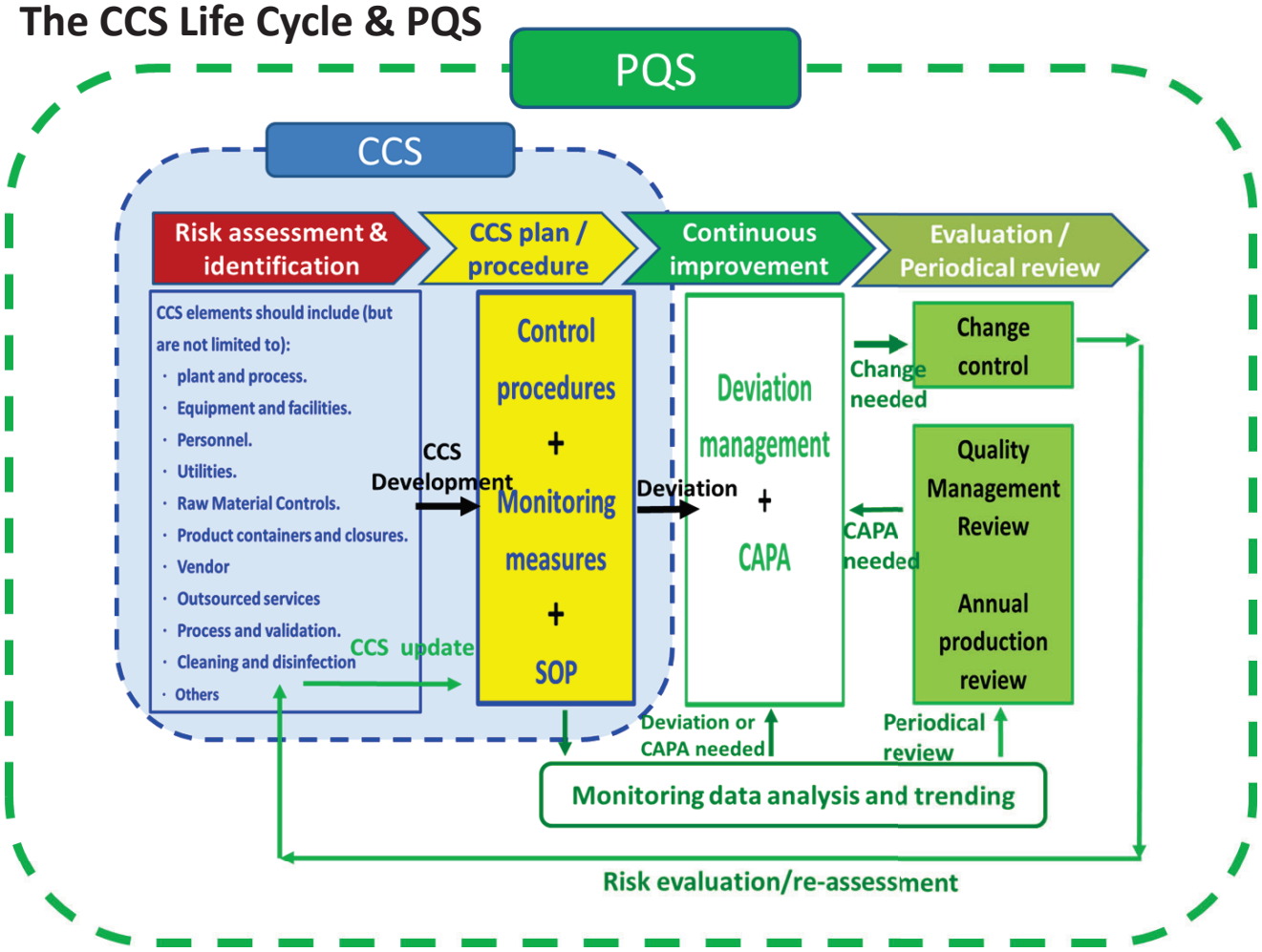
Question

How to develop CCS ?

Contamination Control Strategy (CCS) Annex 1 draft version 2020

4 Key steps for CCS

The CCS Life Cycle & PQS



Question

What are the targets for risk assessment?

CCS

~ Implemented across the facility~

Contamination Control Strategy (CCS) Annex 1 draft version 2020

2.5 **Elements** to be considered within such a documented CCS should include (but are not be limited to):

i) Design of both the plant and process.
ii) Equipment and facilities.
iii) Personnel.
iv) Utilities.
v) Raw Material Controls–including in-process controls.
vi) Product containers and closures.
vii) Vendor approval
viii) Outsourced services
ix) Process risk assessment.
x) Process validation.
xi) Preventative maintenance
xii) Cleaning and disinfection
xiii) Monitoring systems
xiv) Prevention
xv) Continuous improvement based on information from the above.

Risk assessment/identification for process ---- Process Mapping

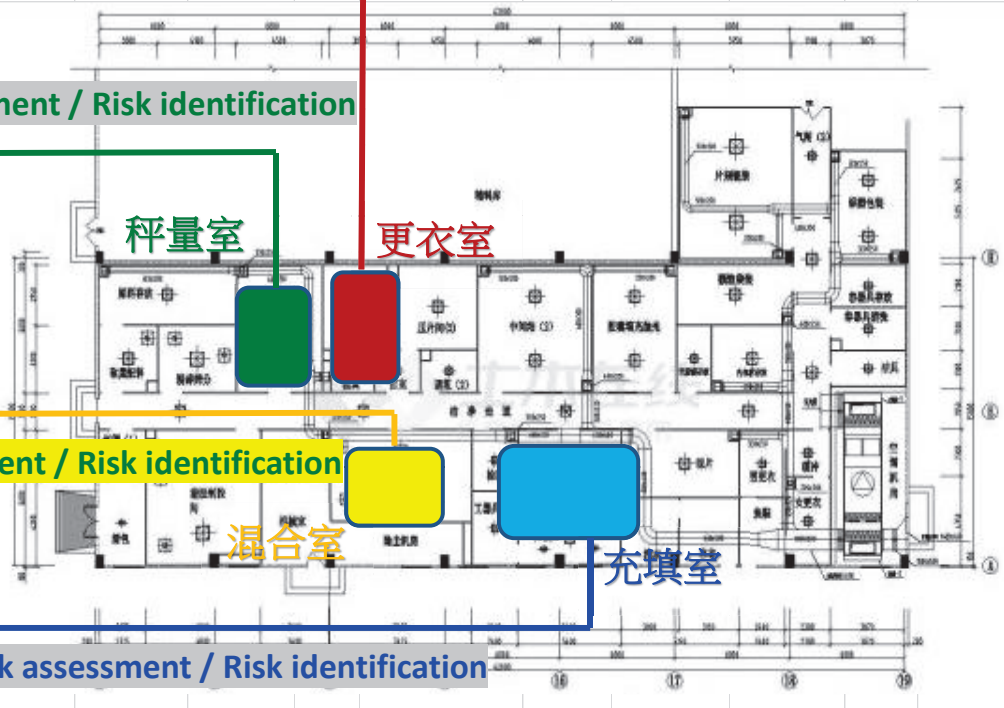
編號	流程/區域	失效模式	造成原因	嚴重性 Severity1	發生頻率 Occurance1	可偵測性 Detection1	RPN1	Risk Mitigation/ CAPA	嚴重性 Severity2	發生頻率 Occurance2	可偵測性 Detection2	RPN2	是否可接受改善後之風險
1	更衣												
	更衣												
	更衣												
	更衣												
2	秤量												
	秤量												
	秤量												
	秤量												
	秤量												
3	混合												
	混合												
	混合												
	混合												
	混合												
	混合												
	混合												
4	充填												
	充填												
	充填												
	充填												
	充填												
	充填												
	充填												

Risk assessment / Risk identification

Risk assessment / Risk identification

Risk assessment / Risk identification

Risk assessment / Risk identification



Risk assessment/identification for process ---- Process Mapping

編號	流程/區域	失效模式	造成原因	嚴重性 Severity1	發生頻率 Occurance1	可偵測性 Detection1	RPN1	Risk Mitigation/ CAPA	嚴重性 Severity2	發生頻率 Occurance2	可偵測性 Detection2	RPN2	是否可接受改善後之風險
1	更衣	mix-up	作業人員未仔細核對MBR	10	3	1	30	Double check與人員教育訓練	10	1	1	10	Y
	更衣	Retention	清潔不夠確實	10	6	5	300	加強人員清潔之訓練,執行清潔驗證	10	1	1	10	Y
	更衣	Airbone Trans.	秤量時所產生的粉塵	10	7	5	350	手套箱(密閉系統)	1	7	1	7	Y
2	秤量	Mech. Trans.	秤量時所產生的粉塵	10	7	5	350	手套箱(密閉系統)執行清潔驗證	1	7	2	14	Y
	秤量	mix-up	作業人員未仔細核對MBR	10	3	1	30	Double check與人員教育訓練	10	1	1	10	Y
	秤量	Mech. Trans.	運送過程之原料傾倒或溢出	10	3	1	30	加強人員教育訓練,依SOP規範洩漏處理程序執行	4	1	1	4	Y
	秤量	Airbone Trans.	秤量時所產生的粉塵	10	7	5	350	手套箱(密閉系統)	1	7	1	7	Y
3	混合	Mech. Trans.	秤量時所產生的粉塵	10	7	5	350	手套箱(密閉系統)執行清潔驗證	1	7	2	14	N
	混合	mix-up	作業人員未仔細核對MBR	10	7	5	350	Double check與人員教育訓練	4	1	1	4	Y
	混合	Retention	清潔不夠確實	10	3	1	30	加強人員清潔之訓練,執行清潔驗證	1	7	1	7	Y
	混合	Mech. Trans.	秤量時所產生的粉塵	10	7	5	350	Double check與人員教育訓練	4	1	1	4	Y
	混合	mix-up	作業人員未仔細核對MBR	10	7	5	350	加強人員清潔之訓練,執行清潔驗證	1	7	1	7	Y
4	充填	Retention	清潔不夠確實	10	3	1	30	加強人員教育訓練,依SOP規範洩漏處理程序執行	1	7	2	14	Y
	充填	Mech. Trans.	運送過程之原料傾倒或溢出	10	3	1	30	手套箱(密閉系統)	10	1	1	10	N
	充填	Airbone Trans.	秤量時所產生的粉塵	10	7	5	350	Double check與人員教育訓練	4	1	1	4	Y
	充填	Mech. Trans.	秤量時所產生的粉塵	10	7	5	350	Double check與人員教育訓練	1	7	1	7	Y
	充填	mix-up (無法正確充填產品)	作業人員未仔細核對MBR	10	3	1	30	加強人員清潔之訓練,執行清潔驗證	1	7	2	14	Y
	充填	Retention	清潔不夠確實	10	3	1	30	加強人員教育訓練,依SOP規範洩漏處理程序執行	10	1	1	10	Y

Contamination Control Strategy (CCS) Annex 1 draft version 2020

Question

What are the methods/tools for the risk assessment?

Risk assessment / Risk identification

- Risk Management Methods and Tools:
  - Fish bone diagram
  - FMEA
  - HACCP
  - Others…
- Internal audit, Gemba walk
- Consultant audit
- External audit: Health authority audit, customer audit
- Others

Example of CCS development

Contamination Control Strategy (CCS) Annex 1 draft version 2020

2.5 **Elements** to be considered within such a documented CCS should include (but are not be limited to):

i) Design of both the plant and process.
ii) Equipment and facilities.
iii) Personnel.
iv) Utilities.
v) Raw Material Controls–including in-process controls.
vi) Product containers and closures.
vii) Vendor approval
viii) Outsourced services
ix) Process risk assessment.
x) Process validation.
xi) Preventative maintenance
xii) Cleaning and disinfection
xiii) Monitoring systems
xiv) Prevention
xv) Continuous improvement based on information from the above.

Example:
Risk assessment & Risk identification for Sampling/Weighing procedure

Contamination Control Strategy (CCS) Annex 1 draft version 2020

Risk assessment & identification → CCS plan / procedure → Continuous improvement → Evaluation / Periodical review

1. Risk assessment / Risk identification
- Establish the project team: QA, QC, EN, PD, PUR….
- Understand the requirement of the related GMP regulation
- Risk management activities

2. CCS plan /procedures development

3. Root cause investigation and CAPA for deviation

4. Update CCS plan

Contamination Control Strategy (CCS) Annex 1 draft version 2020

Risk assessment & identification | CCS plan / procedures | Continuous improvement | Periodical review /evaluation

1. Risk assessment / Risk identification
- Establish the project team: QA, QC, EN, PD, PUR….
- Understand the requirement of the related GMP regulation
- Risk management activities

2. CCS plan /procedures development

3. Root cause investigation and CAPA for deviation

4. Update CCS plan

Contamination Control Strategy (CCS) Annex 1 draft version 2020

Risk assessment & identification | CCS plan / procedures | Continuous improvement | Periodical review /evaluation

Example:
Risk assessment & Risk identification for Sampling/Weighing procedure.

Establish the project team --- Warehouse, QC, QA?

Contamination Control Strategy (CCS) Annex 1 draft version 2020

Risk assessment & identification → CCS plan / procedures → Continuous improvement → Periodical review /evaluation

Understand the requirement of the related GMP regulation

西藥藥品優良製造規範
（第一部、附則）

PIC/S：Guide to Practice for Medicinal Products
（Part I、Annexes）
PE009-14 (1 July 2018)
© PIC/S July 2018

尋找contamination

Annex 1 draft version 2020

Annex 1 : Manufacture of Sterile Products

Document map

尋找 CCS --- 43項

Section Number	
1. Scope	Includes additional areas (other than sterile products) where the general principles of the annex can be applied.
2. Principle	General principles as applied to the manufacture of sterile products.
3. Pharmaceutical Quality System (PQS)	Highlights the specific requirements of the PQS when applied to sterile products.
4. Premises	General guidance regarding the specific needs for premises design and also guidance on the qualification of premises including the use of Barrier Technology.
5. Equipment	General guidance on the design and operation of equipment.
6. Utilities	Guidance with regards to the special requirements of utilities such as water, gas and vacuum.
7. Personnel	Guidance on the requirements for specific training, knowledge and skills. Also gives guidance to the qualification of personnel.

110TPDA04012-B

Contamination Control Strategy (CCS) Annex 1 draft version 2020

Risk assessment & identification → CCS plan / procedures → Continuous improvement → Periodical review /evaluation

Understand the requirement of the related GMP regulation

例: PIC/S 總則第二章 人事 --- 人員訓練

2.12 對於在一有污染即產生危害之區域，例如在潔淨區域或在處理高活性、毒性、傳染性或致敏性物質之區域中工作的人員，應給予特別的訓練。

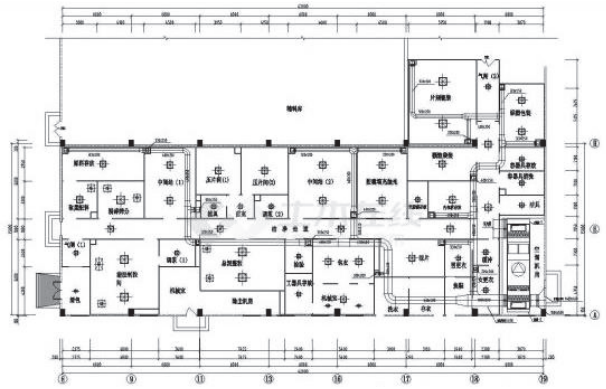
Contamination Control Strategy (CCS) Annex 1 draft version 2020

Risk assessment & identification → CCS plan / procedures → Continuous improvement → Periodical review /evaluation

Understand the requirement of the related GMP regulation

例: 第三章 廠房設施與設備---廠房設施及設備的設計原則

廠房設施及設備的定位、設計、建造、調適及維護皆應適合於其所要執行的作業。其配置與設計應將產生錯誤的風險降到最低並容許有效的清潔及維護保養，以避免交叉污染、聚積粉塵或污垢，總之，應以避免對產品品質有任何不利影響為目標。



新廠房--- Risk assessment & Quality by design

既有廠房--- Risk assessment & Risk control / CAPA

35

110TPDA04012-B

Contamination Control Strategy (CCS) Annex 1 draft version 2020

Risk assessment & identification → CCS plan / procedures → Continuous improvement → Periodical review /evaluation

Understand the requirement of the related GMP regulation

3.22 原料通常應有隔離的抽樣區域。在儲存區內執行抽樣者，應以可防止污染或交叉污染的方式執行之。

3.37 洗滌及清潔設備應加以選擇與使用，使其不會成為污染的來源。

3.38 設備應以適當的方式安裝，以防止任何錯誤或污染的風險。

36

Contamination Control Strategy (CCS) Annex 1 draft version 2020

Risk assessment & identification | CCS plan / procedures | Continuous improvement | Periodical review /evaluation

- Risk Management Methods and Tools:

e.g. FMEA (Failure Mode & Effect Analysis) 失敗模式效應分析

Contamination Control Strategy (CCS) Annex 1 draft version 2020

Risk assessment & identification | CCS plan / procedures | Continuous improvement | Periodical review /evaluation

PIC/S GMP 附則 20 品質風險管理 --- I.2 失敗模式效應分析（Failure Mode Effects Analysis (FMEA)）

FMEA (參見IEC 60812) 係就**程序**及其對結果及/或產品性能之可能的效應，提供潛在失敗模式的評估。失敗模式一旦建立，風險減低便可用以排除、圍堵、減少或控制該潛在失敗。FMEA倚賴對**產品**及**製程**的瞭解。FMEA在方法上將複雜程序的分析分解成可管理的步驟。對於總結失敗之重要模式、引起這些失敗的因素及這些失敗之可能效應，這是一個強而有力的工具。

失敗模式效應分析 （Failure Mode Effects Analysis (FMEA)）

失敗模式的評估

以排除、圍堵、減少或控制該失敗模式

編號	流程/區域	失效模式	造成原因	嚴重性 Severity1	發生頻率 Occurance1	可偵測性 Detection1	RPN1	Risk Mitigation/ CAPA	嚴重性 Severity2	發生頻率 Occurance2	可偵測性 Detection2	RPN2	是否可接受改善後之風險
1	更衣	mix-up	作業人員未仔細核對MBR	10	3	1	30	ouble check與人員教育訓	10	1	1	10	Y
	更衣	Retention	清潔不夠確實	10	6	5	300	加強人員清潔之訓練, 清潔驗證	10	1	1	10	Y
	更衣	Airbone Trans.	秤量時所產生的粉塵	10	7	5	350	套(密閉系統)	1	7	1	7	Y
2	秤量	Mech. Trans.	秤量時所產生的粉塵	10	7	5	350	套(密閉系統) 清潔驗證	1	7	2	14	Y
	秤量	mix-up	作業人員未仔細核對MBR	10	3	1	30	ouble check與人員教育訓	10	1	1	10	Y
	秤量	Mech. Trans.	運送過程之原料傾倒或溢出	10	3	1	30	加強人員教育訓練, SOP規範洩漏處理程序執	4	1	1	4	Y
	秤量	Airbone Trans.	秤量時所產生的粉塵	10	7	5	350	套(密閉系統)	1	7	1	7	Y
3	混合	Mech. Trans.	秤量時所產生的粉塵	10	7	5	350	套(密閉系統) 清潔驗證	1	7	2	14	N
	混合	mix-up	作業人員未仔細核對MBR	10	7	5	350	ouble check與人員教育訓	4	1	1	4	Y
	混合	Retention	清潔不夠確實	10	3	1	30	加強人員清潔之訓練, 清潔驗證	1	7	1	7	Y
	混合	Mech. Trans.	秤量時所產生的粉塵	10	7	5	350	ouble check與人員教育訓	4	1	1	4	Y
	混合	mix-up	作業人員未仔細核對MBR	10	7	5	350	加強人員清潔之訓練, 清潔驗證	1	7	1	7	Y
4	充填	Retention	清潔不夠確實	10	3	1	30	加強人員教育訓練, SOP規範洩漏處理程序執	1	7	2	14	Y
	充填	Mech. Trans.	運送過程之原料傾倒或溢出	10	3	1	30	套(密閉系統)	10	1	1	10	N
	充填	Airbone Trans.	秤量時所產生的粉塵	10	7	5	350	ouble check與人員教育訓	4	1	1	4	Y
	充填	Mech. Trans.	秤量時所產生的粉塵	10	7	5	350	ouble check與人員教育訓	1	7	1	7	Y
	充填	mix-up (無法正確充填產品)	作業人員未仔細核對MBR	10	3	1	30	加強人員清潔之訓練, 清潔驗證	1	7	2	14	Y
	充填	Retention	清潔不夠確實	10	3	1	30	加強人員教育訓練, 依SOP規範洩漏處理程序執行	10	1	1	10	Y

Contamination Control Strategy (CCS) Annex 1 draft version 2020

Risk assessment & identification → CCS plan / procedures → Continuous improvement → Periodical review /evaluation

Example:

Risk assessment & Risk identification for Sampling/ Weighing procedure

Risk identification of Sampling/Weighing procedure

Man (people)
Machine (equipment)
Material
Method
Environment

Contamination Control Strategy (CCS) Annex 1 draft version 2020

Risk assessment & identification → CCS plan / procedures → Continuous improvement → Periodical review /evaluation

	Area/ Process	Failure Mode	造成原因 Potential Cause
01	秤量室/秤量作業	人: 人員操作不當，造成污染	• 人員訓練不足, • 未依SOP執行, • SOP制訂不適當 • 人員衣著設計不佳
02	秤量室/秤量作業	法: 取樣過程或取樣方法不佳，造成污染	• 取樣的程序不當或未有相關SOP。 • 取樣出來後的樣品又倒回原料藥桶中 • 取樣工具清潔不確實 • 取樣工具材質
03	秤量室/秤量作業	環: 取樣環境不適當，潔淨度不夠	• 未有專用的取樣區/取樣室 • 環境潔淨度不夠,級區等級不足

Contamination Control Strategy (CCS) Annex 1 draft version 2020

Risk assessment & identification → CCS plan / procedures → Continuous improvement → Periodical review /evaluation

FMEA 失敗模式與效應分析之範例

	Area/ Process	Failure Mode	造成原因 Potential Cause	嚴重性 Severity	發生頻率 Occurance	可偵測性 Detection	RPN	Risk Mitigation	嚴重性 Severity	發生頻率 Occurance	可偵測性 Detection	RPN
01	秤量室/秤量作業	人: 人員操作不當，造成污染	• 人員訓練不足, • 未依SOP執行, • SOP制訂不適當 • 人員衣著設計不佳									
02	秤量室/秤量作業	法: 取樣過程或取樣方法不佳，造成污染	• 取樣的程序不當或未有相關SOP。 • 取樣出來後的樣品又倒回原料藥桶中 • 取樣工具清潔不確實 • 取樣工具材質									
03	秤量室/秤量作業	環: 取樣環境不適當，潔淨度不夠	• 未有專用的取樣區/取樣室 • 環境潔淨度不夠,級區等級不足									

範例: Risk Priority Number (RPN)＝嚴重性 S (S, Severity) × 發生率 (O, Occurrence) x 偵測率 (D, Detectability)

分級	嚴重性Severity
5	災難性的 污染已影響產品品質，並傷害到病人或員工，產品亦需回收。
4	嚴重 污染已影響產品品質，且造成客訴及退貨，對病人或員工造成傷害可能性高。
3	重大 會產生污染並影響產品品質，該情形會導致客訴，但對病人或員工造成傷害可能性低。
2	輕微 很有可能會導致污染，產品品質亦可能受影響。
1	可忽略的 可能會導致污染，但不影響產品品質

分級	發生率Occurrence
5	每批發生
4	每3批發生一次or每月發生
3	每10批發生一次 or 每6個月發生一次
2	每15批發生一次 or 每年發生一次
1	每30批發生一次 or 每3年發生一次

分級	偵測率Detectability
5	失效的狀況幾乎不可能被偵測，偵測機率不到10%
4	失效的狀況極不容易被偵測到，偵測機率為10%-30%
3	失效的狀況有適度的機會可被偵測到，偵測機率為30%-50%
2	失效的狀況有非常高的機會可被偵測到，偵測機率為50%-80%
1	失效的狀況幾乎可完全被偵測到，偵測機率為80%-100%

Contamination Control Strategy (CCS) Annex 1 draft version 2020

Risk assessment & identification → CCS plan / procedures → Continuous improvement → Periodical review /evaluation

FMEA 失敗模式與效應分析之範例

	Area/ Process	Failure Mode	造成原因 Potential Cause	嚴重性 Severity
01	秤量室/秤量作業	人: 人員操作不當，造成污染	• 人員訓練不足, • 未依SOP執行, • SOP制訂不適當 • 人員衣著設計不佳	5
02	秤量室/秤量作業	法: 取樣過程或取樣方法不佳，造成污染	• 取樣的程序不當或未有相關SOP。 • 取樣出來後的樣品又倒回原料藥桶中 • 取樣工具清潔不確實 • 取樣工具材質	5
03	秤量室/秤量作業	環: 取樣環境不適當，潔淨度不夠	• 未有專用的取樣區/取樣室 • 環境潔淨度不夠,級區等級不足	5

分級	嚴重性Severity
5	災難性的 污染已影響產品品質，並傷害到病人或員工，產品亦需回收。
4	嚴重 污染已影響產品品質，且造成客訴及退貨，對病人或員工造成傷害可能性高。
3	重大 會產生污染並影響產品品質，該情形會導致客訴，但對病人或員工造成傷害可能性低。
2	輕微 很有可能會導致污染，產品品質亦可能受影響。
1	可忽略的 可能會導致污染，但不影響產品品質

Contamination Control Strategy (CCS) Annex 1 draft version 2020

Risk assessment & identification → CCS plan / procedures → Continuous improvement → Periodical review /evaluation

FMEA 失敗模式與效應分析之範例

	Area/ Process	Failure Mode	造成原因 Potential Cause	嚴重性 Severity	發生頻率 Occurance
01	秤量室/秤量作業	人：人員操作不當，造成污染	• 人員訓練不足， • 未依SOP執行， • SOP制訂不適當 • 人員衣著設計不佳	5	3
02	秤量室/秤量作業	法：取樣過程或取樣方法不佳，造成污染	• 取樣的程序不當或未有相關SOP。 • 取樣出來後的樣品又倒回原料藥桶中 • 取樣工具清潔不確實 • 取樣工具材質	5	3
03	秤量室/秤量作業	環：取樣環境不適當，潔淨度不夠	• 未有專用的取樣區/取樣室 • 環境潔淨度不夠，級區等級不足	5	4

分級	發生率Occurrence
5	每批發生
4	每3批發生一次or每月發生
3	每10批發生一次or 每6個月發生一次
2	每15批發生一次or 每年發生一次
1	每30批發生一次or 每3年發生一次

110TPDA04012-B

Contamination Control Strategy (CCS) Annex 1 draft version 2020

Risk assessment & identification → CCS plan / procedures → Continuous improvement → Periodical review /evaluation

FMEA 失敗模式與效應分析之範例

	Area/ Process	Failure Mode	造成原因 Potential Cause	嚴重性 Severity	發生頻率 Occurance	可偵測性 Detection
01	秤量室/秤量作業	人：人員操作不當，造成污染	• 人員訓練不足， • 未依SOP執行， • SOP制訂不適當 • 人員衣著設計不佳	5	3	2
02	秤量室/秤量作業	法：取樣過程或取樣方法不佳，造成污染	• 取樣的程序不當或未有相關SOP。 • 取樣出來後的樣品又倒回原料藥桶中 • 取樣工具清潔不確實 • 取樣工具材質	5	3	4
03	秤量室/秤量作業	環：取樣環境不適當，潔淨度不夠	• 未有專用的取樣區/取樣室 • 環境潔淨度不夠，級區等級不足	5	4	4

分級	偵測率Detectability
5	失效的狀況幾乎不可能被偵測，偵測機率不到10%
4	失效的狀況極不容易被偵測到，偵測機率為10%-30%
3	失效的狀況有適度的機會可被偵測到，偵測機率為30%-50%
2	失效的狀況有非常高的機會可被偵測到，偵測機率為50%-80%
1	失效的狀況幾乎可完全被偵測到，偵測機率為80%-100%

Contamination Control Strategy (CCS) Annex 1 draft version 2020

Risk assessment & identification → CCS plan / procedures → Continuous improvement → Periodical review /evaluation

FMEA 失敗模式與效應分析之範例

	Area/ Process	Failure Mode	造成原因 Potential Cause	嚴重性 Severity	發生頻率 Occurance	可偵測性 Detection	RPN	Risk Mitigation
01	秤量室/秤量作業	人：人員操作不當，造成污染	• 人員訓練不足， • 未依SOP執行， • SOP制訂不適當 • 人員衣著設計不佳	5	3	2	30	
02	秤量室/秤量作業	法：取樣過程或取樣方法不佳，造成污染	• 取樣的程序不當或未有相關SOP。 • 取樣出來後的樣品又倒回原料藥桶中 • 取樣工具清潔不確實 • 取樣工具材質	5	3	4	60	
03	秤量室/秤量作業	環：取樣環境不適當，潔淨度不夠	• 未有專用的取樣區/取樣室 • 環境潔淨度不夠，級區等級不足	5	4	4	80	

110TPDA04012-B

Contamination Control Strategy (CCS) Annex 1 draft version 2020

Risk assessment & identification → CCS plan / procedures → Continuous improvement → Periodical review /evaluation

FMEA 失敗模式與效應分析之範例

	Area/ Process	Failure Mode	造成原因 Potential Cause	嚴重性 Severity	發生頻率 Occurance	可偵測性 Detection	RPN	Risk Mitigation
01	秤量室/秤量作業	人：人員操作不當，造成污染	• 人員訓練不足， • 未依SOP執行， • SOP制訂不適當 • 人員衣著設計不佳	5	3	2	30	• 制/修訂取樣SOP，並執行人員教育訓練。 • 適當的衣著及更衣程序。
02	秤量室/秤量作業	法：取樣過程或取樣方法不佳，造成污染	• 取樣的程序不當或未有相關SOP。 • 取樣出來後的樣品又倒回原料藥桶中 • 取樣工具清潔不確實 • 取樣工具材質	5	3	4	60	• 制/修訂取樣SOP，並執行人員教育訓練。 • 取樣出來後的樣品不倒回原料藥桶中 • 加強人員清潔之取樣工具訓練， • 執行清潔驗證
03	秤量室/秤量作業	環：取樣環境不適當，潔淨度不夠	• 未有專用的取樣區/取樣室 • 環境潔淨度不夠，級區等級不足	5	4	4	80	• 專用的取樣區/取樣室 • 提升取樣環境為D級區，若風險高則為C級區，並裝設BMS

Contamination Control Strategy (CCS) Annex 1 draft version 2020

Risk assessment & identification → **CCS plan / procedure** → Continuous improvement → Periodical review /evaluation

1. Risk assessment / Risk identification
- Establish the project team: QA, QC, EN, PD, PUR….
- Understand the requirement of the related GMP regulation
- Risk management activities

2. CCS plan /procedures development

3. Root cause investigation and CAPA for deviation

4. Update CCS plan

110TPDA04012-B

Contamination Control Strategy (CCS) Annex 1 draft version 2020

Risk assessment & identification → **CCS plan / procedure** → Continuous improvement → Periodical review /evaluation

	Area/ Process	Failure Mode	造成原因 Potential Cause	嚴重性 Severity	發生頻率 Occurance	可偵測性 Detection	RPN	Risk Mitigation	嚴重性 Severity	發生頻率 Occurance	可偵測性 Detection	RPN	是否可接受改善後之風險
01	秤量室/秤量作業	人: 人員操作不當,造成污染	• 人員訓練不足, • 未依SOP執行, • SOP制訂不適當 • 人員衣著設計不佳	5	3	2	30	• 制/修訂取樣SOP，並執行人員教育訓練。 • 適當的衣著及更衣程序。	5	1	2	10	Y
02	秤量室/秤量作業	法: 取樣過程或取樣方法不佳，造成污染	• 取樣的程序不當或未有相關SOP。 • 取樣出來後的樣品又倒回原料藥桶中 • 取樣工具清潔不確實 • 取樣工具材質	5	3	4	60	• 制/修訂取樣SOP，並執行人員教育訓練。 • 取樣出來後的樣品不倒回原料藥桶中 • 加強人員清潔之取樣工具訓練, • 執行清潔驗證	5	1	4	20	Y
03	秤量	環: 取樣環境不適當，潔淨度不夠	• 未有專用的取樣區/取樣室 • 環境潔淨度不夠,級區等級不足	5	4	4	80	• 專用的取樣區/取樣室 • 提升取樣環境為D級區，若風險高則為C級區,並裝設BMS	5	2	2	20	Y

Contamination Control Strategy (CCS) Annex 1 draft version 2020

Risk assessment & identification → **CCS plan / procedure** → Continuous improvement → Periodical review /evaluation

範例: 秤量室CCS development

Risk Mitigation Plan:

制/修訂取樣SOP，並執行人員教育訓練。
取樣出來後的樣品不倒回原料藥桶中
加強人員清潔之取樣工具訓練
執行清潔驗證
專用的取樣區/取樣室
提升取樣環境為D級區，若風險高則為C級區,並裝設監控系統BMS

秤量室的CCS

51

110TPDA04012-B

Contamination Control Strategy (CCS) Annex 1 draft version 2020

Risk assessment & identification → **CCS plan / procedure** → Continuous improvement → Periodical review /evaluation

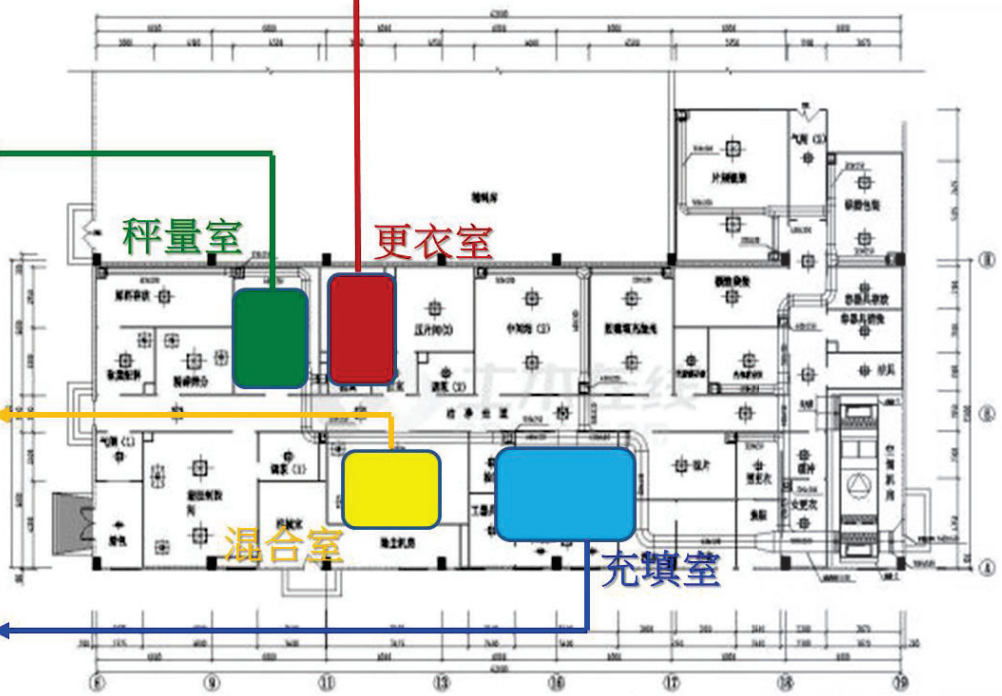
CCS Plan --- process mapping

更衣室 CCS

秤量室CCS

混合室CCS

充填室CCS



52

Contamination Control Strategy (CCS) Annex 1 draft version 2020

Risk assessment & identification → CCS plan / procedures → **Continuous improvement** → **Evaluation / Periodical review**

1. Risk assessment / Risk identification
- Establish the project team: QA, QC, EN, PD, PUR….
- Understand the requirement of the related GMP regulation
- Risk management activities

2. CCS plan /procedures development

3. Root cause investigation and CAPA for deviation

4. Update CCS plan

Contamination Control Strategy (CCS) Annex 1 draft version 2020

Risk assessment & identification → CCS plan / procedures → **Continuous improvement** → **Evaluation / Periodical review**

Evaluation/ Periodical review:
例如:
Deviation --- 秤量過程發現有微生物污染。

Contamination Control Strategy (CCS) Annex 1 draft version 2020

Risk assessment & identification | CCS plan / procedures | **Continuous improvement** | **Evaluation / Periodical review**

範例討論:

Root cause investigation ---

可以使用人、機、料、法、環原則進行根本原因調查。

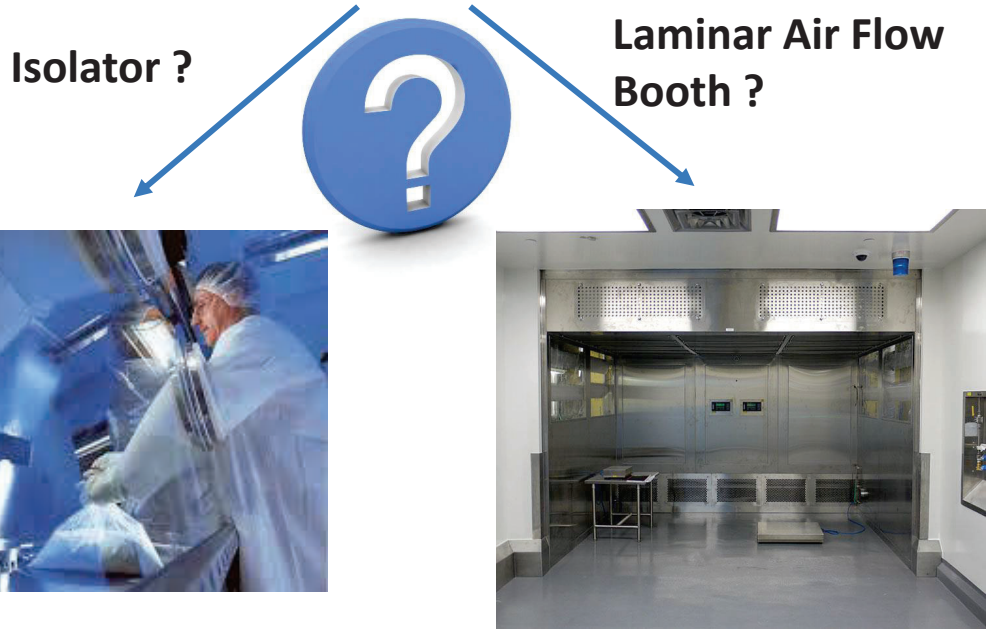
調查結果發現，執行Sampling/ Weighing時，係由合格人員依規定的穿著，以專用的乾淨器具，依SOP的規範在秤量台上進行Sampling/ Weighing。

D級區之空調系統也都定期維護。惟，發現當日之環控數據的微生物數值有接近行動值的情形，推測是由於環境潔淨度所影響。

根本原因: 環境清淨度(C級區)不夠。

55

CAPA: 提升環境清淨度



56

Contamination Control Strategy (CCS) Annex 1 draft version 2020

Risk assessment & identification | CCS plan / procedures | **Continuous improvement** | **Evaluation / Periodical review**

範例討論:

CAPA plan ---

1.依SOP執行環境的清潔與消毒。

2.提升硬體設備，使用Isolator 的技術。→ change control

Contamination Control Strategy (CCS) Annex 1 draft version 2020

Risk assessment & identification | CCS plan / procedures | **Continuous improvement** | **Evaluation / Periodical review**

範例討論:

Change control --- 新增Isolator的使用

評估: Impact assessment

- 廠房設施設備
- 原物料
- 製程/產品
- 文件/SOP
- 人員

Update 秤量室的CCS

Contamination Control Strategy (CCS) Annex 1 draft version 2020

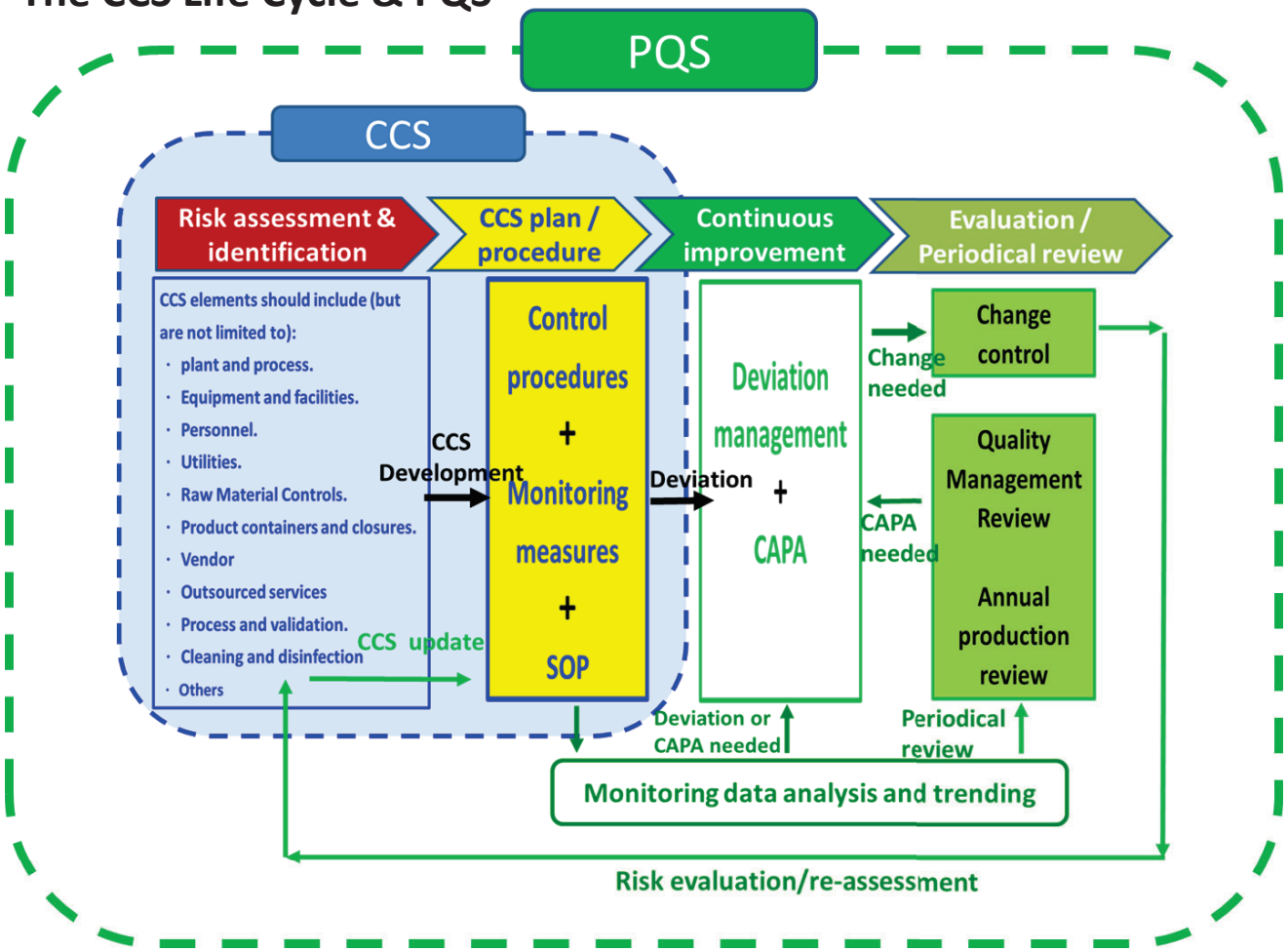
Risk assessment & identification → CCS plan / procedures → Continuous improvement → Evaluation / Periodical review

	Area/ Process	Failure Mode	造成原因 Potential Cause	嚴重性 Severity	發生頻率 Occurance	可偵測性 Detection	RPN	Risk Mitigation	嚴重性 Severity	發生頻率 Occurance	可偵測性 Detection	RPN	是否可接受改善後之風險
01	秤量室/秤量作業	人: 人員操作不當，造成污染	• 人員訓練不足, • 未依SOP執行, • SOP制訂不適當 • 人員衣著設計不佳	5	3	2	30	• 制/修訂取樣SOP，並執行人員教育訓練。 • 適當的衣著及更衣程序。	5	1	2	10	Y
02	秤量室/秤量作業	法: 取樣過程或取樣方法不佳，造成污染	• 取樣的程序不當或未有相關SOP。 • 取樣出來後的樣品又倒回原料藥桶中 • 取樣工具清潔不確實 • 取樣工具材質	5	3	4	60	• 制/修訂取樣SOP，並執行人員教育訓練。 • 取樣出來後的樣品不倒回原料藥桶中 • 加強人員清潔之取樣工具訓練, • 執行清潔驗證	5	1	4	20	Y
03	秤量室/秤量作業	環: 取樣環境不適當，潔淨度不夠	• 未有專用的取樣區/取樣室 • 環境潔淨度不夠,級區等級不足	5	4	4		• 專用的取樣				20	Y
03項的CAPA	秤量室/秤量作業	機器 /設備: 未有保護取樣過程免受污染的設備	• 單靠空調系統的提供潔淨度與壓差的取樣環境仍不足.	5	3	2	30	• Isolator的使用	5	1	2	10	Y

Update 秤量室的CCS

59

The CCS Life Cycle & PQS



60

Thank you for your attention

意見調查表
及
課後測試

請學員務必填寫，並保留最後畫面供確認後領取「上課證明及藥師學分證明」，謝謝您的配合！