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Sterile substance CEP webinar
-
EU GMP Annex 1 - sterile APIs

Dr Thomas HECKER

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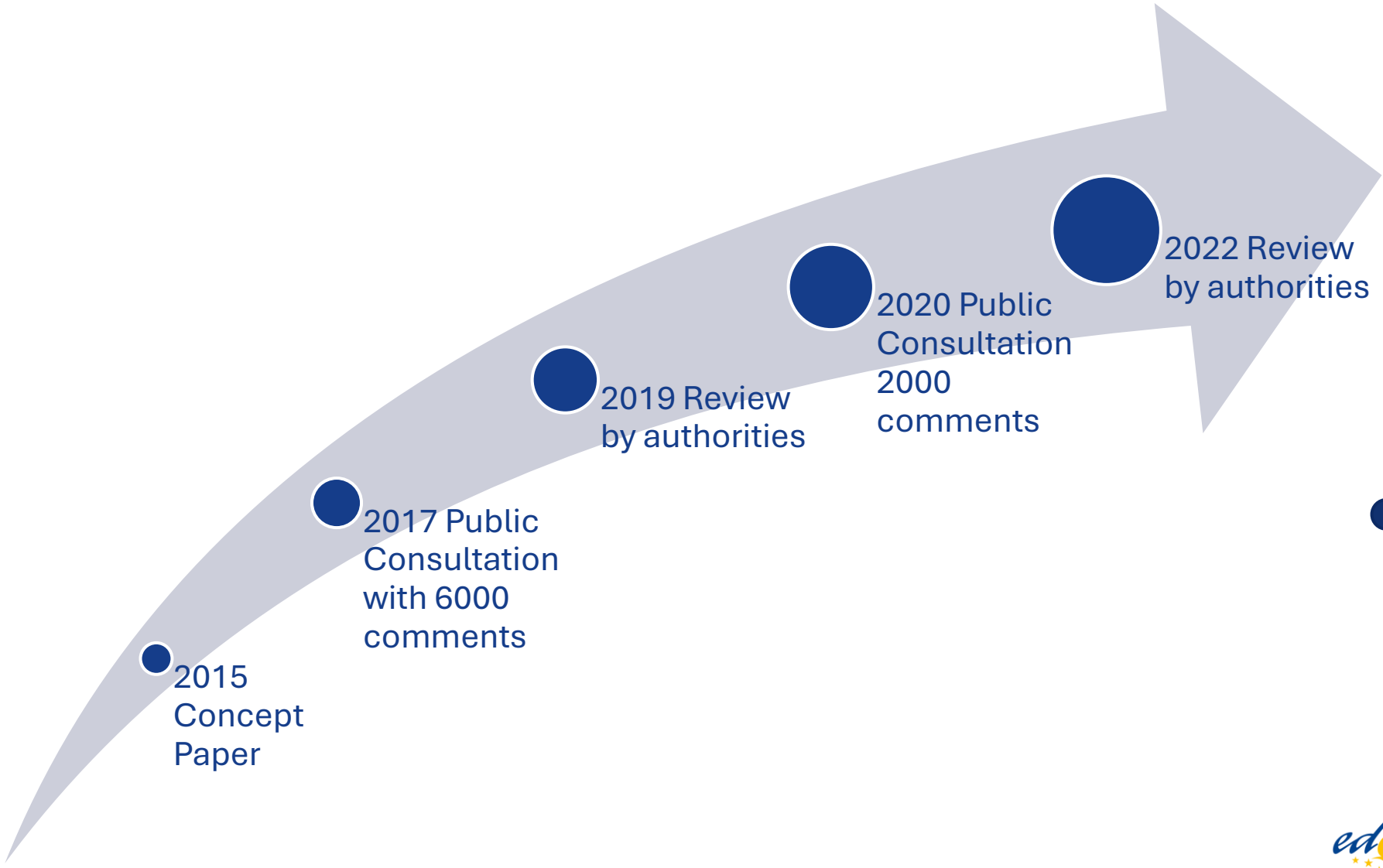
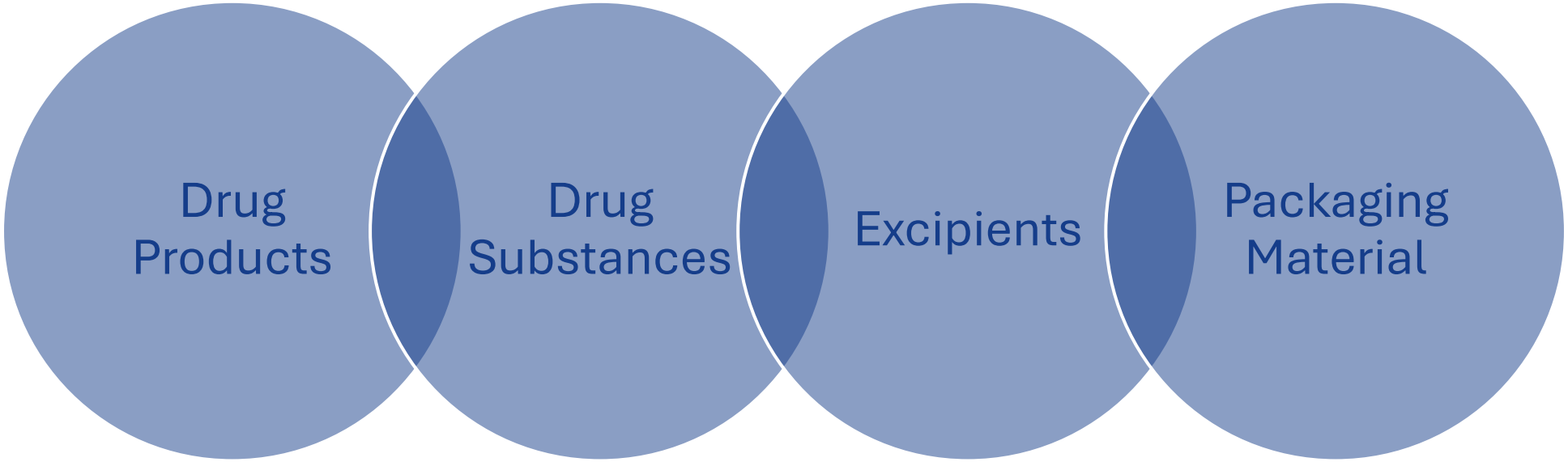
Annex 1 Revision timeline



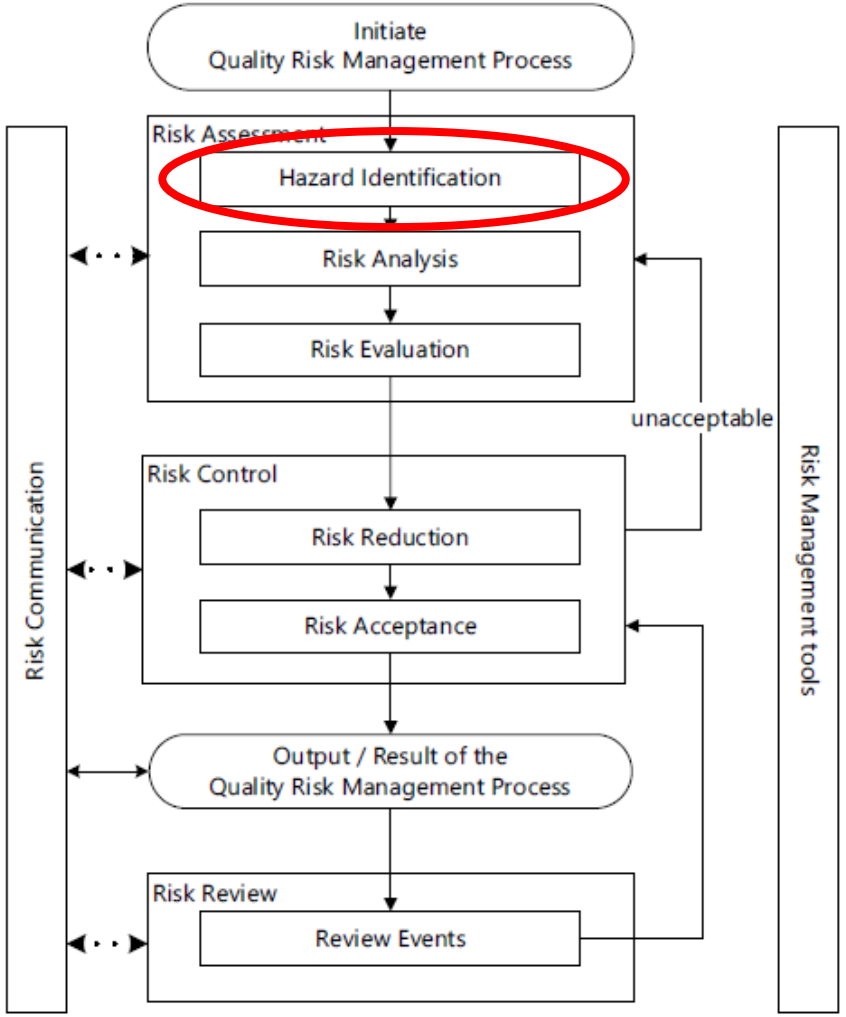
Scope extension:



1 Scope

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

Quality Risk Management (QRM)



ICH Q9 Revision Concept Paper in relation to Hazard Identification:

"This change will align with the expectation to identify hazards relevant to patients when evaluating risks; moreover, it may improve how hazards are perceived and assessed"

ICH Q9(R1): Other Topics in the Scope of the Revision

- Subjectivity
- Product Availability Risks
- Formality
- Risk-Based Decision-Making
- Risk Review

Contamination Control Strategy (CCS)

2.3 A Contamination Control Strategy (CCS) should be implemented across the facility in order to define all critical control points and assess the effectiveness of all the controls (design, procedural, technical and organisational) and monitoring measures employed to manage risks to medicinal product quality and safety. The combined strategy of the CCS should establish robust assurance of contamination prevention. The CCS should be actively reviewed and, where appropriate, updated and should drive continual improvement of the manufacturing and control methods. Its effectiveness should form part of the periodic management review. Where existing control systems are in place and are appropriately managed, these may not require replacement but should be referenced in the CCS and the associated interactions between systems should be understood.

Just one example…

"Five monitoring locations were identified in class B corridor C223; however the firm had failed to consider surface monitoring of those door handles that were at high risk because of their design. The only door handle surface monitoring identified was for the door handle of room C222, although its design allowed operators to easily open the door using their elbows."

Just one example…

- Design: Processes & Plant
- Premises & Equipment
- Personnel
- Raw Material Control
- Vendor/Manufacturer Approval
- Product Containers & Closures
- Outsourced Activities / transfer of information
- Process Risk Managment
- Process Validation including sterilisation
- Cleaning / Disinfection
- Monitoring / Trend Analysis
- Preventative Maintenance

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Further examples of EM failures

D17 → "The following observations with regard to the risk assessment executed to identify the environmental monitoring (EM) positions as well as the EM itself were made:

a. The exact positions for the surface monitoring are not indicated on facility/equipment (although it is done for settle plates).

b. With regard to the contact plates:

i. Location ID 06 and its justification referred to the monitoring of the outer surface of EQUIPMENT-02, whilst the firm stated that the monitoring takes place on the mezzanine level at the media supply (e.g. WFI)

ii. Although a surface monitoring of EQUIPMENT -01 (Loc ID 05) was identified for contact plates, no surface monitoring of EQUIPMENT -02 takes place.

iii. The justification for Location ID-18 was not sound, because the location indicated at the drawing [redacted] referred to the wall that is barely accessible and/or near the usual men movement and therefore less prone to microbiological contamination.

iv. The firm did not identify the two Human-Machine-Interfaces (PLCs) connected to the EQUIPMENT as high risk for potential microbial contamination and therefore they were not part of the environmental monitoring scheme.

c. The surface swab sampling of the crystalliser room included only three locations: ID-01 bottom surface of crystalliser as well as ID-02 and ID-03 that were attributed to the EQUIPMENT-01 and EQUIPMENT-02. No considerations were made to include frequently touched surfaces, such as the rails to the mezzanine level or the opening valves of the EQUIPMENTs (sampling procedure) into the EM.

API sterilisation

Filter sterilisation of products which cannot be sterilised in their final container

8.79 If the product cannot be sterilised in its final container, solutions or liquids should be sterilised by filtration through a sterile sterilising grade filter (with a nominal pore size of a maximum of 0.22 µm that has been appropriately validated to obtain a sterile filtrate) and subsequently aseptically filled into a previously sterilised container. The selection of the filter used should ensure that it is

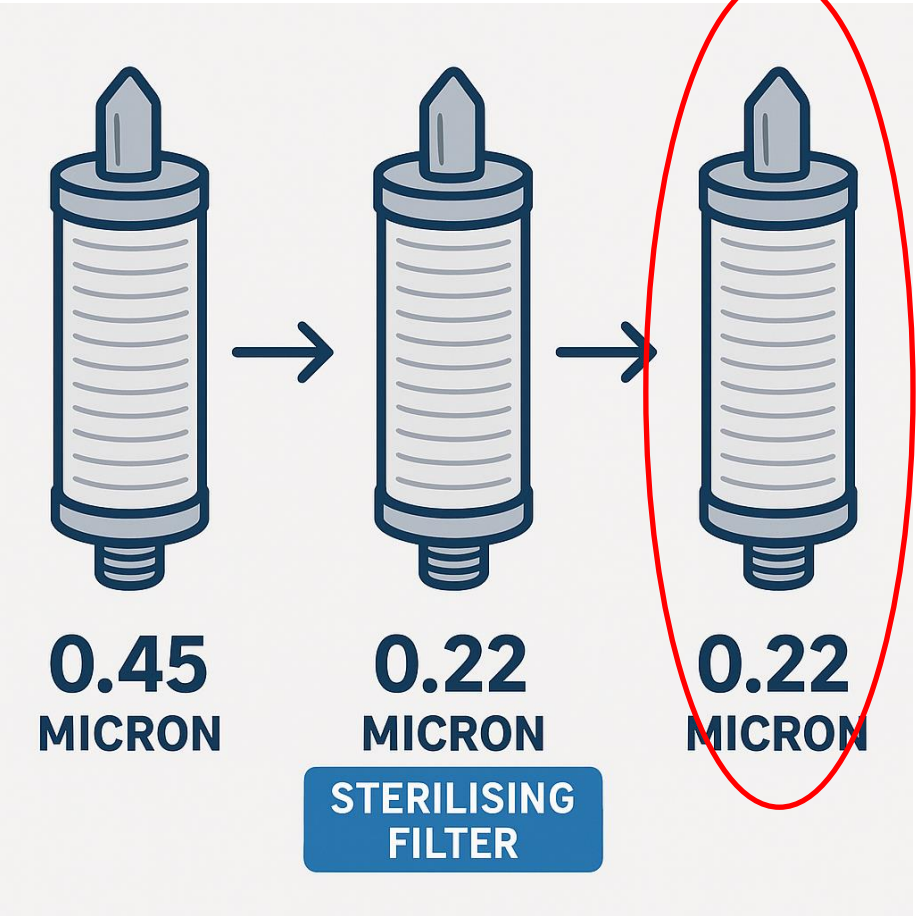
API sterilisation

Grade A: The critical zone for high-risk operations (e.g. aseptic processing line, filling zone, stopper bowl, open primary packaging or for making aseptic connections under the protection of first air). Normally, such conditions are provided by a localised airflow protection, such as unidirectional airflow workstations within RABS or isolators. The maintenance of unidirectional airflow should be demonstrated and qualified across the whole of the grade A area. Direct intervention (e.g. without the protection of barrier and glove port technology) into the grade A area by operators should be minimized by premises, equipment, process and procedural design.

Grade B: For aseptic preparation and filling, this is the background cleanroom for grade A (where it is not an isolator). Air pressure differences should be continuously monitored. Cleanrooms of lower grade than grade B can be considered where isolator technology is used (see paragraph 4.20).

Aseptic API sterilisation: process simplified

API sterilisation



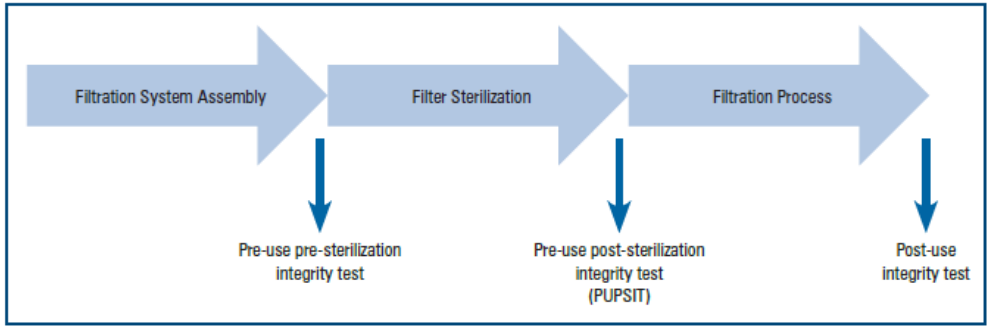
8.80: Due to the potential additional risks*) of a sterile filtration process, as compared with other sterilisation processes, an additional filtration through a sterile sterilising grade filter, as close to the point of fill as possible, should be considered as part of an overall CCS.

*)e.g.

- Filter damaged during sterilisation prior to use
- Initial non-integrity - not detectable

Pre-Use Post Sterilisation Integrity Testing: PUPSIT

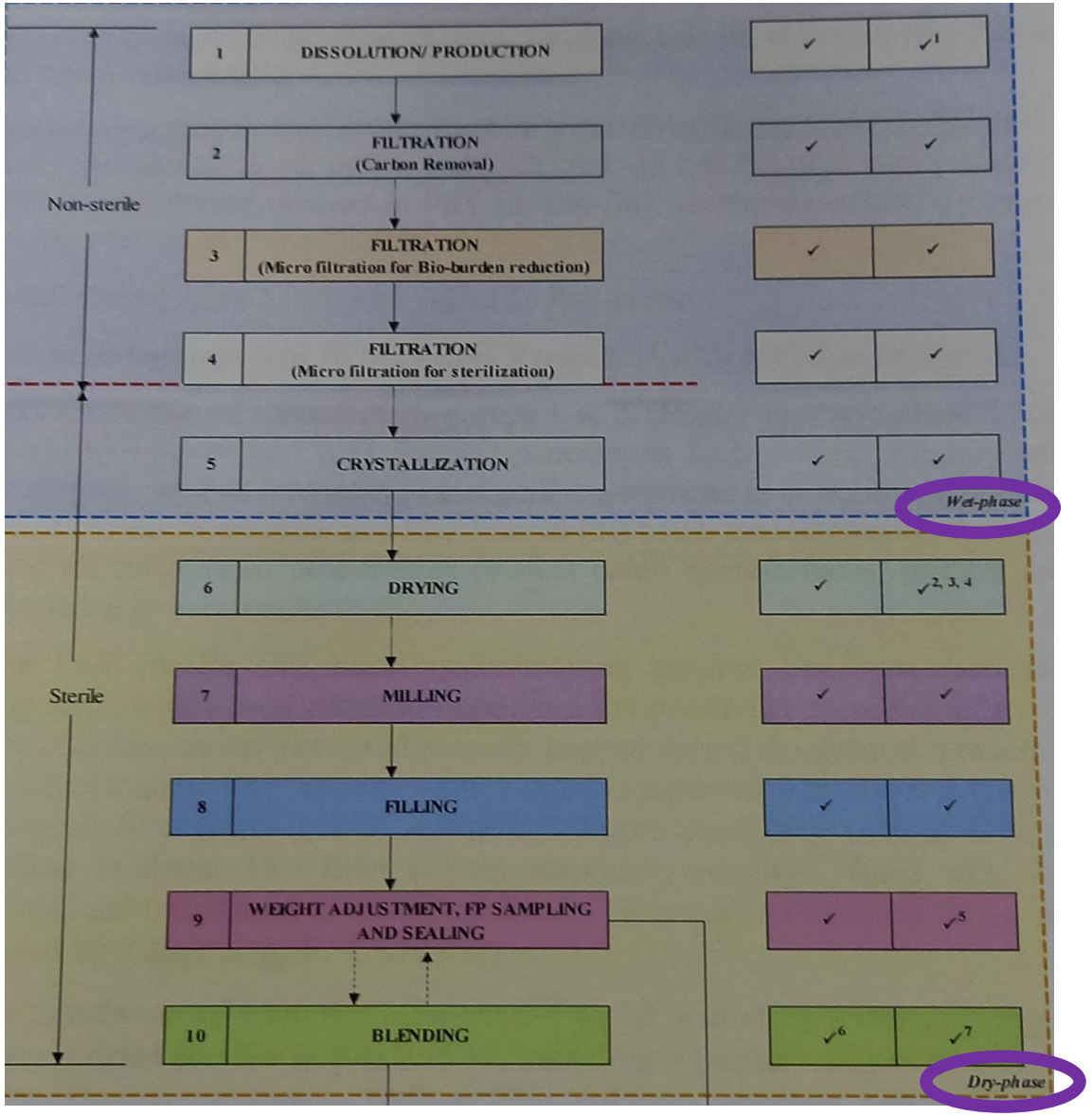
- 8.87 The integrity of the sterilised filter assembly should be verified by integrity testing before use (pre-use post sterilisation integrity test or PUPSIT), to check for damage and loss of integrity caused by the filter preparation prior to use. A sterilising grade filter that is used to sterilise a fluid should be subject to a non-destructive integrity test post-use prior to removal of the filter from its housing. The integrity test process should be validated and test results should correlate to the microbial retention capability of the filter established during valida



- … It is recognized that PUPSIT may not always be possible after sterilisation due to process constraints (e.g. the filtration of very small volumes of solution). In these cases, an alternative approach may be taken providing that a thorough risk assessment has been performed and compliance is achieved by the implementation of appropriate controls to mitigate any risk of a non-integral filtration system. Points to consider in such a risk assessment should include but are not limited to …

Aseptic Process Simulation (APS)

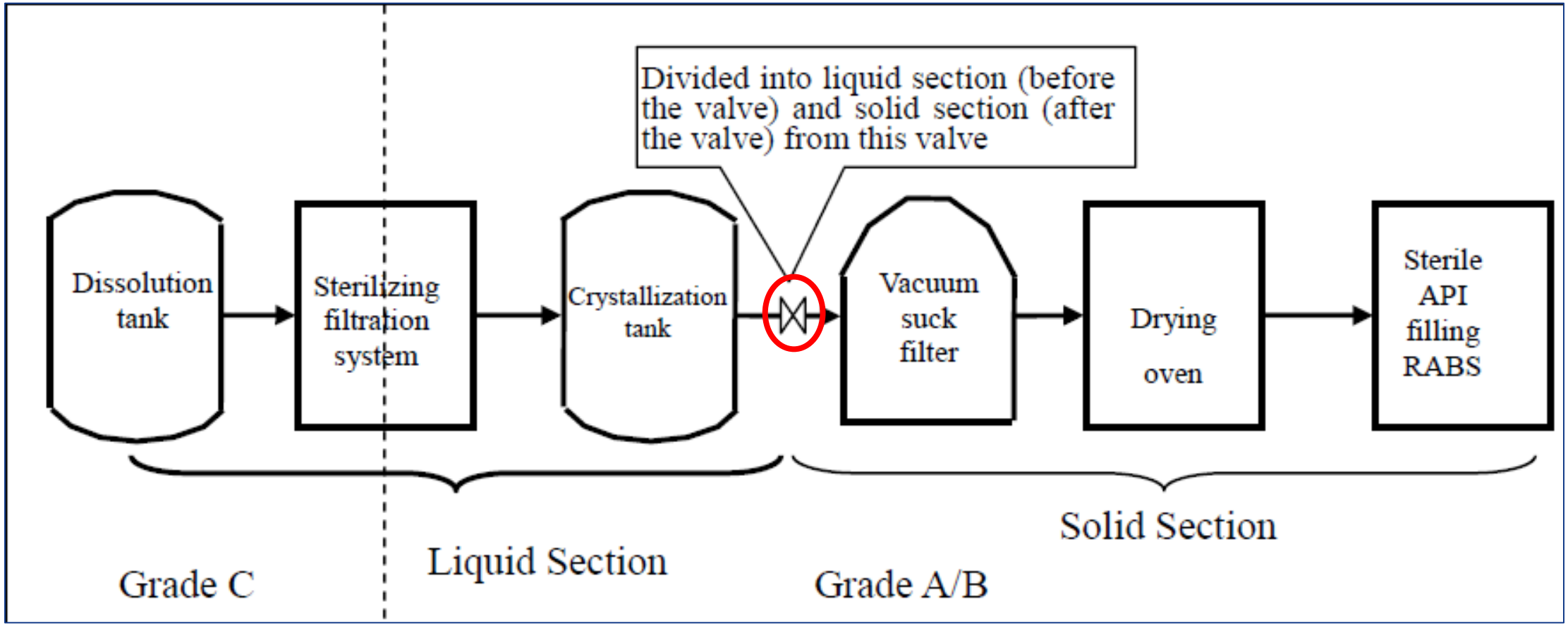
9.36-vi:
The selected nutrient media should be capable of growing a designated group of reference microorganisms as described by the relevant pharmacopeia and suitably representative local isolates.



Wet phase:
e.g. tryptic soy broth

Dry phase:
e.g. sterile lactose

Aseptic Process Simulation (APS)



Aseptic Process Simulation (APS)

b. The APS was executed in two steps: the liquid and the solid phase. According to the firm's instructions (SOP on APS and Process flow chart of [redacted], eff date 29 May 2023), the APS solution is to be obtained after having passed the crystalliser and before entering the ANF. Since in the regular manufacturing processes the slurry is transferred from the Crystalliser into the Agitated Nutsche Filter Dryer, the liquid phase of the APS was considered as incomplete. ¶

Aseptic Process Simulation (APS)

D1. [MAJOR] The Aseptic Process Simulation was found deficient in that:

a) The firm violated the requirement of EU GMP Annex 1 section 9.33 that states “APS should imitate as closely as possible the routine aseptic manufacturing process” as well as their own SOP (section 4.5) evidenced as follows: The firm used liquid lactose solution to determine the effectiveness of the aseptic process of a solid phase product that starts with the drying of the API in the filtration/washing/dryer. The firm failed to provide a sound justification demonstrating equivalency of the APS.

b) The firm deviated from the simulation of the adding of seed crystals insofar, as the seed crystal containers were not filled with a solid phase using the routine process and equipment at the O-RABs, but filled with liquid lactose next to the crystalliser reactor under LAF protection.

Further examples of GMP failures

[**Critical**]·The·company·failed·to·implement·core·principles·of·EU·GMP·Annex·1·"Manufacture·of·Sterile·Medicinal·Products".·Consequently,·the·sterility·of·the·Active·Pharmaceutical·Ingredients·(API)·manufactured·in·[redacted],·cannot·be·guaranteed,·posing·a·risk·to·human·and/or·veterinary·health.·This·was·evidenced·as·follows.¶

a.→With·regard·to·the·design·of·the·facility:¶

b.→The·firm·failed·to·identify·applicable·requirements,·risks·and·risk·mitigation·measures·with·regard·to·revised·Annex·1.·The·executed·QA·Review·and·the·related·Failure·Modes,·Effects,·and·Criticality·Analysis·FMECA·of·the·revised·EU·GMP·Annex·1,·performed·between·18·June·2024·to·03·July·2024,·showed·the·following·shortcomings:¶

c.→With·regard·to·the·Grade·A/B·manufacturing·zones·in·[redacted],·several·shortcomings·related·to·maintenance·were·seen,·as·follows:¶

rust.·¶

d.→With·regard·to·the·Grade·C·manufacturing·area·of·[redacted],·multiple·maintenance·issues·were·found·during·the·tour·of·the·facility,·such·as:¶

equipment on 08 January 2020 did not address

e.→With·regard·to·the·aseptic·manufacturing·operations:¶

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