Manufacture of Sterile Medicines – The Countdown to Annex 1

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GMP FORUM 2024

2015
Concept Paper

1

PIC/S – EMA Concept paper
Modernise, ICH Q9 & 10, Address ambiguities

2017
Consultation 1

2

3-month public consultation
6300+ comments received

2020
Consultation 2

3

3-month public consultation
2000+ comments received

2022
Publication

4

Published September 2022
Entered into force August 2023 (ROW)

2025
TGA Adoption

5

TGA plan to adopt PE009-17 in Q1 2025
Consultation underway

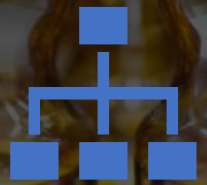
Managing the implementation of Annex 1

Initiation

Gap analysis

Milestones and timelines

Risks and roadblocks



Planning

Change management, what, how, when

Scope of changes

Estimate resources

Execution

Monitor implementation of project

Communication across organisation

Training

Monitoring & Control

Track performance against goals

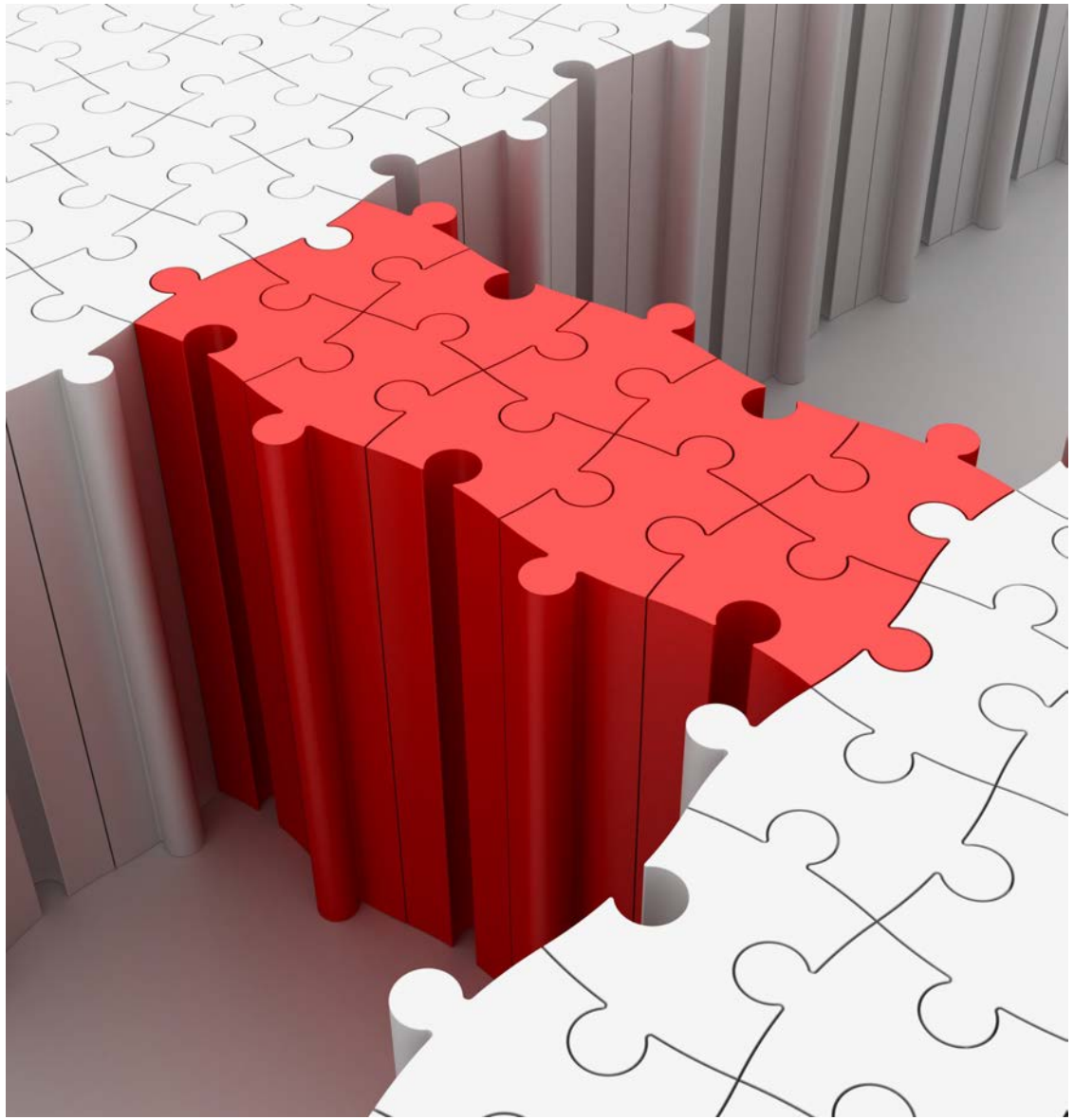
Monitor quality of deliverables

Closure

Post-implementation effectiveness review

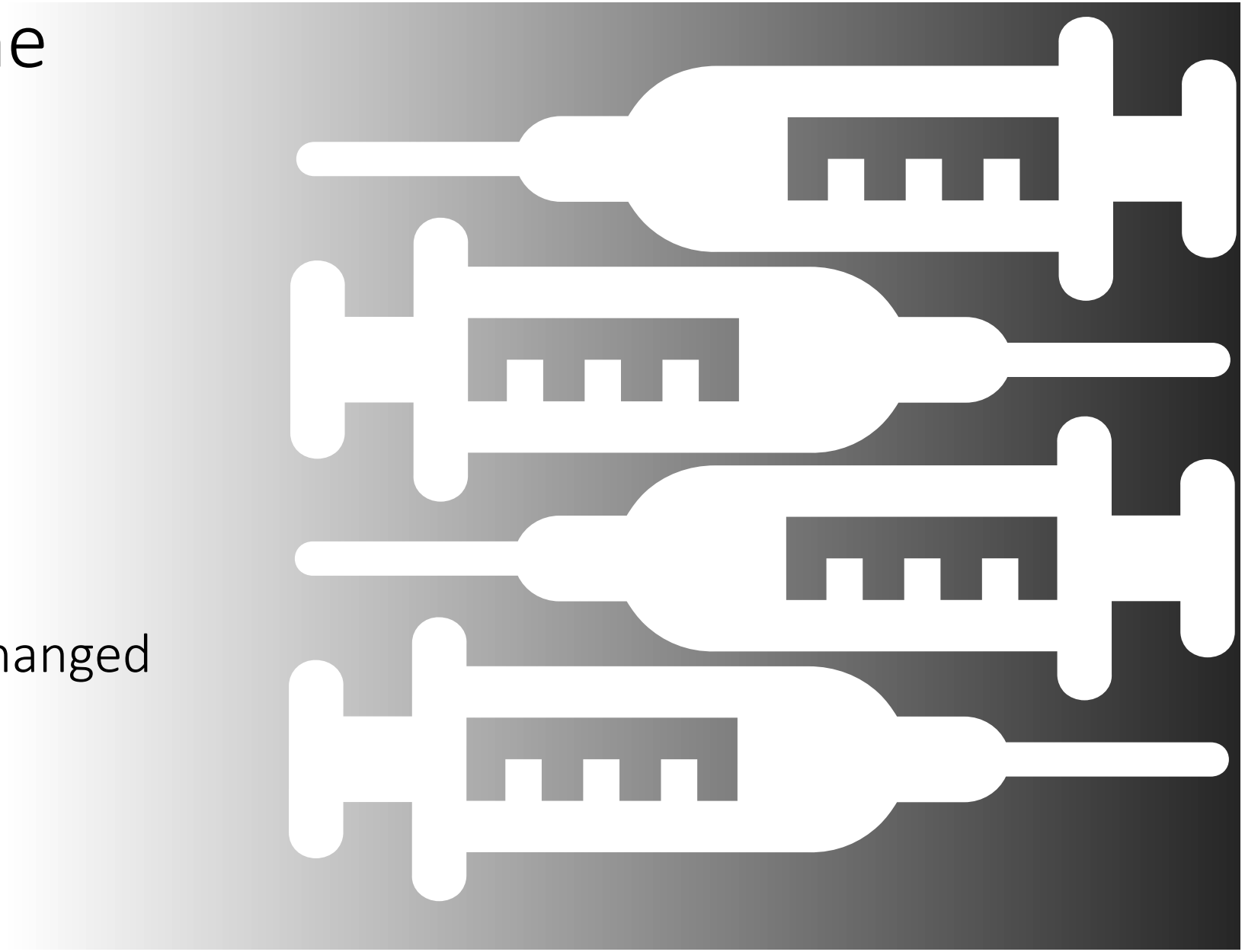
Your gap-analysis

- Read the Annex 1 document
  - Line-by-line evaluation
  - Identify changed and reworded clauses
  - Identify ‘new’ requirements
- Map your existing process
  - Identify current process flow and controls
  - Identify existing process documentation and procedures
- Cross-check
  - Identify and record where Ax1 requirements are met.
  - Identify gaps and roadblocks
  - Identify CAPA and action plan/timelines
    - Document any interim risk-mitigating actions
- Project-manage remedial actions

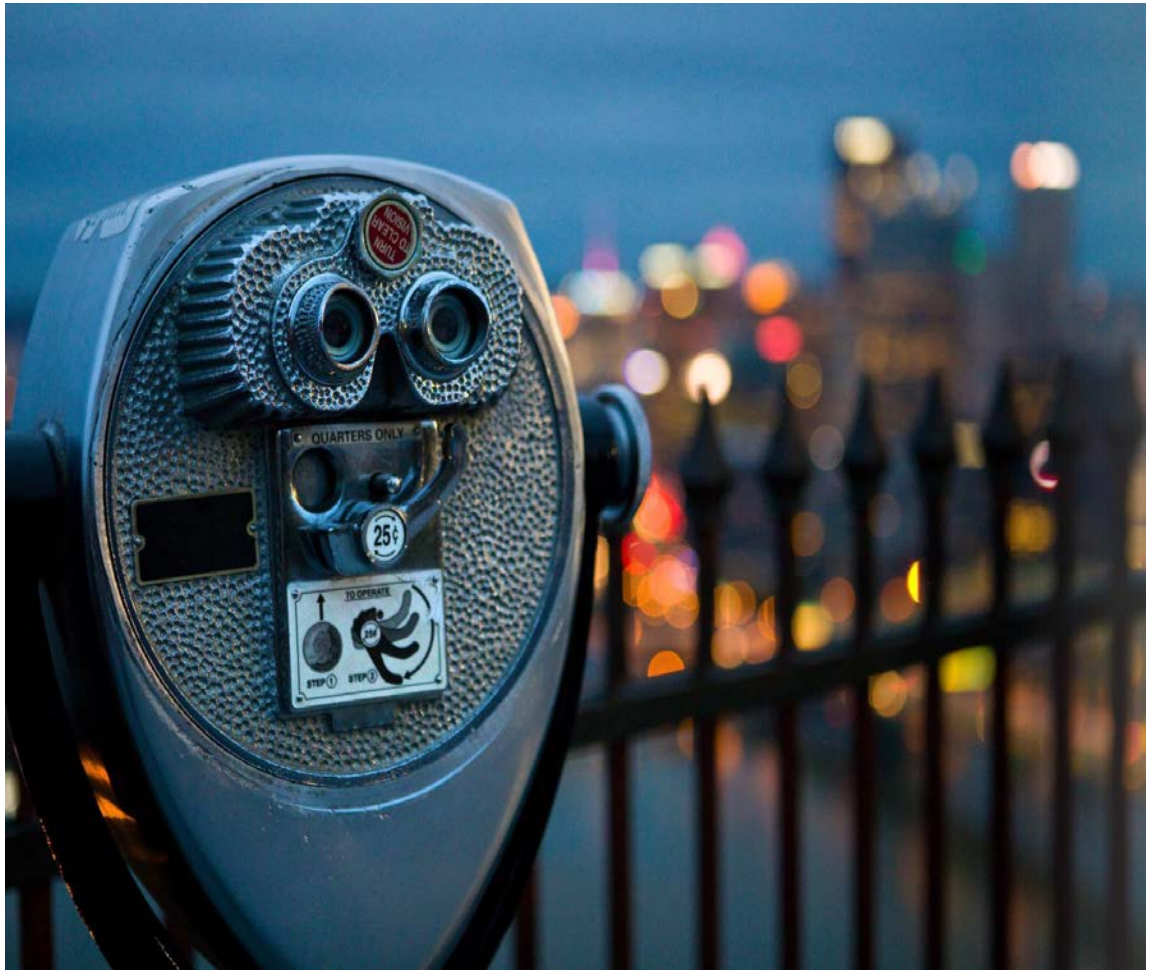


Understanding the main changes

- What has changed
- What this means
- Why these clauses changed



Part 1 - Scope



QRM applies to this document in its entirety and will not, normally, be referred to in specific paragraphs.

…some of the principles and guidance…may be used to support the manufacture of other products that are not intended to be sterile…

Where a manufacturer elects to apply guidance herein to non-sterile products, …clearly document which principles have been applied and …compliance with those principles should be demonstrated.

Part 2 - Principle

2.1i The use of appropriate technologies (e.g. Restricted Access Barriers Systems (RABS), isolators, robotic systems, rapid/alternative methods and continuous monitoring systems) should be considered to increase the protection of the product…and assist in the rapid detection of potential contaminants in the environment and the product.

Images courtesy of SKAN AG

2.1ii Personnel should have adequate qualifications and experience, training and behaviour

2.1iii Processes and monitoring systems for sterile product manufacture should be designed, commissioned, qualified, monitored and regularly reviewed by personnel with appropriate process, engineering and microbiological knowledge.

2.2 In the first instance, QRM priorities should include appropriate design of the facility, equipment and processes, followed by the implementation of well-designed procedures, and finally application of monitoring systems as the element that demonstrates that the design and procedures have been correctly implemented and continue to perform in line with expectations. Monitoring or testing alone does not give assurance of sterility.

A: There are fish, I just wasn’t lucky today

B: There are fish, I just used the wrong equipment/method

C: There are no fish in the water

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.

2.6 …ongoing and periodic review…

Part 3 - PQS (ICH Q10)

3.1 …the manufacturer's PQS should encompass and address the specific requirements of sterile product manufacture and ensure that all activities are effectively controlled so that the risk of microbial, particulate and endotoxin/pyrogen contamination is minimized in sterile products.

3.1v Senior management should effectively oversee the state of control throughout the facility and product lifecycle. Risk management outcome should be reviewed regularly as part of the on-going quality management, during change, in the event of a significant emerging problem, and during the periodic product quality review.

Part 4 - Premises

4.4 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)…

…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.

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4.11 The transfer of materials, equipment, and components into the grade A or B areas should be carried out via a unidirectional process…Where sterilisation upon transfer of the items is not possible, a procedure…should be validated and implemented, (e.g. using an effective transfer disinfection process, rapid transfer systems for isolators or, for gaseous or liquid materials, a bacteria-retentive filter).

Images courtesy of SKAN AG

4.12ii Only materials and equipment that have been included on an approved list and assessed during validation of the transfer process, should be transferred into the grade A or grade B areas via an airlock or pass-through hatches… Any unapproved items that require transfer should be pre-approved as an exception.

Part 4 - Premises

Airflow patterns within cleanrooms and zones should be visualised to demonstrate that there is no ingress from lower grade to higher grade areas and that air does not travel from less clean areas (such as the floor) or over operators or equipment that may transfer contamination to the higher-grade areas…Airflow pattern studies should be performed both at rest and in operation

4.16 …Air pressure differences identified as critical should be continuously monitored and recorded. …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.

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4.21 The materials used for glove systems (for both isolators and RABS) should be demonstrated to have appropriate mechanical and chemical resistance. The frequency of glove replacement should be defined within the CCS.

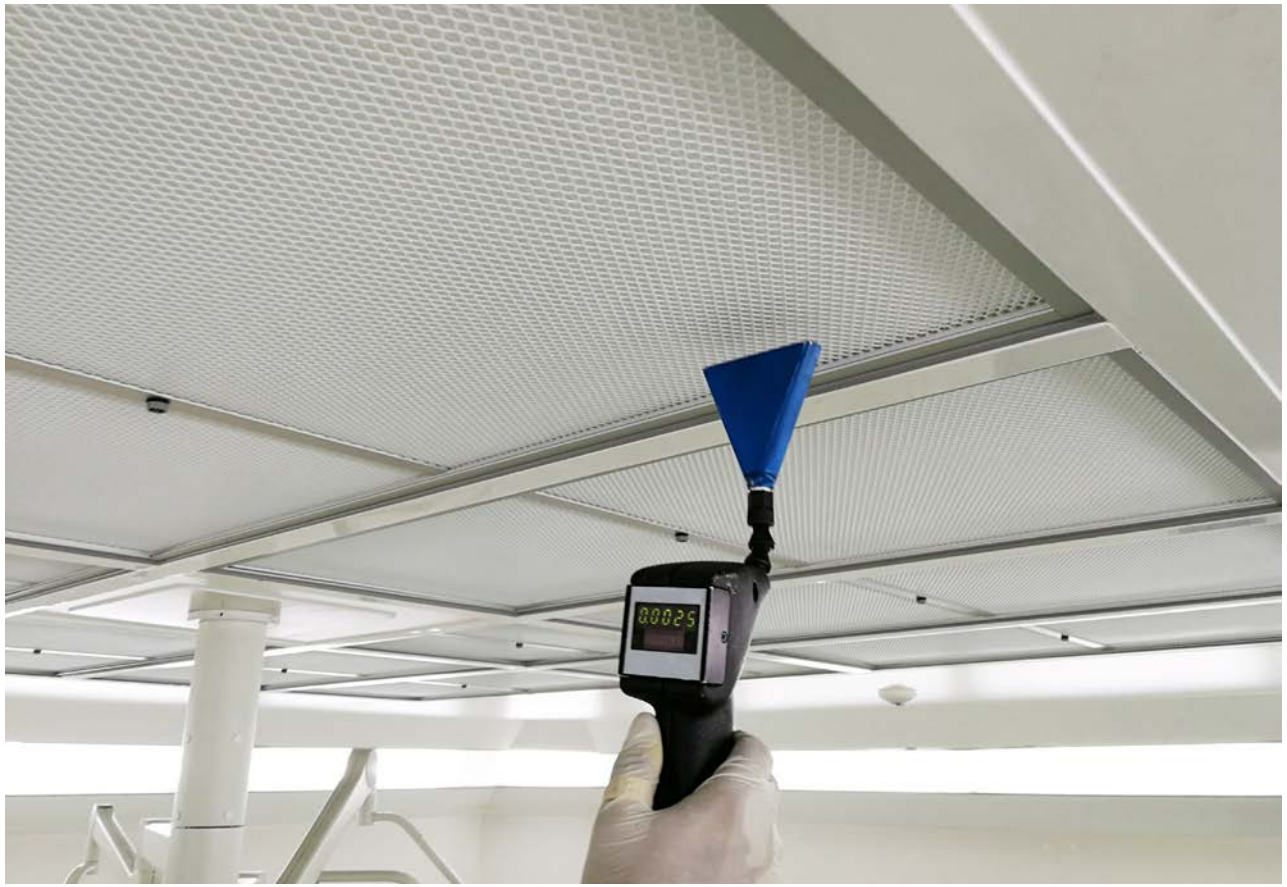
i. Isolators:

Generally glove integrity testing should be performed at a minimum frequency of the beginning and end of each batch or campaign.

Glove integrity monitoring should include a visual inspection associated with each use and following any manipulation that may affect the integrity of the system.

ii. RABS:

Gloves should be visually examined with each use, and integrity testing should be performed at periodic intervals.



4.27 For cleanroom classification, the total of particles equal to or greater than 0.5 and 5 µm should be measured.

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

Part 4/5 – Premises & Equipment

4.33 The disinfection of cleanrooms is particularly important. They should be cleaned and disinfected thoroughly in accordance with a written programme. For disinfection to be effective, prior cleaning to remove surface contamination should be performed.

4.34 The disinfection process should be validated.

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5.4 The cleaning process should be validated to be able to:

i. remove any residue or debris that would detrimentally impact the effectiveness of the disinfecting agent used,

ii. minimize chemical, microbial and particulate contamination of the product during the process and prior to disinfection.

Part 5 - Equipment

5.5 For aseptic processes, direct and indirect product contact parts should be sterilised.

- Direct product contact parts are those that the product passes through, such as filling needles or pumps.
- Indirect product contact parts are equipment parts that do not contact the product, but may come into contact with other sterilised surfaces, the sterility of which is critical to the overall product sterility (e.g. sterilised items such as stopper bowls and guides, and sterilised components).

Images courtesy of SKAN AG

Part 7 - Personnel

7.9 Electronic devices used in cleanrooms, e.g. mobile phones and tablets, that are supplied by the manufacturer solely for use in the cleanrooms, may be acceptable if suitably designed to permit cleaning and disinfection commensurate with the grade in which they are used. The use and disinfection of such equipment should be included in the CCS.

7.11 Garments should be visually checked for cleanliness and integrity immediately prior to and after gowning. Gown integrity should also be checked upon exit…Reusable garments (including eye coverings) should be replaced … at a set frequency that is determined during qualification studies ...qualification… should consider any necessary garment testing requirements, including damage to garments that may not be identified by visual inspection alone.

7.18 Activities in clean areas…should be kept to a minimum, especially when aseptic operations are in progress. Movement of personnel should be slow, controlled and methodical … Operators performing aseptic operations should adhere to aseptic technique … prevent changes in air currents that may introduce air of lower quality into the critical zone.

Movement adjacent to the critical zone should be restricted and the obstruction of the path of the unidirectional (first air) airflow should be avoided … airflow visualisation studies … considered as part of training...

Part 8 - Production and Specific Technologies

8.15 Aseptic manipulations (including non-intrinsic sterile connection devices) should be minimized through the use of engineering design solutions such as preassembled and sterilised equipment. Whenever feasible, product contact piping and equipment should be pre-assembled, and sterilised in place.

8.16 There should be an authorized list of allowed and qualified interventions, both inherent and corrective, that may occur during production … Interventions should be carefully designed to ensure that the risk of contamination of the environment, process and product is effectively minimized.

Engineering solutions should be used whenever possible to minimize incursion by operators during the intervention.

Images courtesy of SKAN AG

8.22 Where final containers are closed by fusion, e.g. Blow-Fill-Seal (BFS), Form-Fill-Seal (FFS), Small and Large Volume Parenteral (SVP & LVP) bags, glass or plastic ampoules, the critical parameters and variables that affect seal integrity should be evaluated, determined, effectively controlled and monitored during operations.

8.86 Routine process controls should be implemented to ensure adherence to validated filtration parameters. Results of critical process parameters should be included in the batch record…

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)

Images courtesy of Sartorius Australia

Part 9 – Environment & process monitoring

9.1 …the reliability of each of the elements … (viable, non-viable and APS) when taken in isolation is limited and should not be considered individually to be an indicator of asepsis. When considered together, the results help confirm the reliability of the design, validation and operation of the system that they are monitoring.

9.3 …information from these systems should be used for routine batch certification/release … periodic assessment during process review or investigation.

9.11 Monitoring procedures should define the approach to trending.

Trends should include, but are not limited to:

i. increasing numbers of excursions from action limits or alert levels;

ii. consecutive excursions from alert levels;

iii. regular but isolated excursion from action limits that may have a common cause, (e.g. single excursions that always follow planned preventative maintenance);

iv. changes in microbial flora type and numbers and predominance of specific organisms. Particular attention should be given to organisms recovered that may indicate a loss of control, deterioration in cleanliness or organisms that may be difficult to control such as spore-forming microorganisms and moulds.

9.20 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.

9.24 Continuous viable air monitoring in grade A (e.g. air sampling or settle plates) should be undertaken for the full duration of critical processing, including equipment (aseptic set-up) assembly and critical processing.

9.30 … for grade A, any growth should result in an investigation.

9.31 Microorganisms detected in the grade A and grade B areas should be identified to species level and the potential impact of such microorganisms on product quality (for each batch implicated) and overall state of control should be evaluated.

9.36 In developing the APS plan, consideration should be given to the following:

i. Identification of worst case conditions…justify the variables selected.

iv. The volume filled per container…

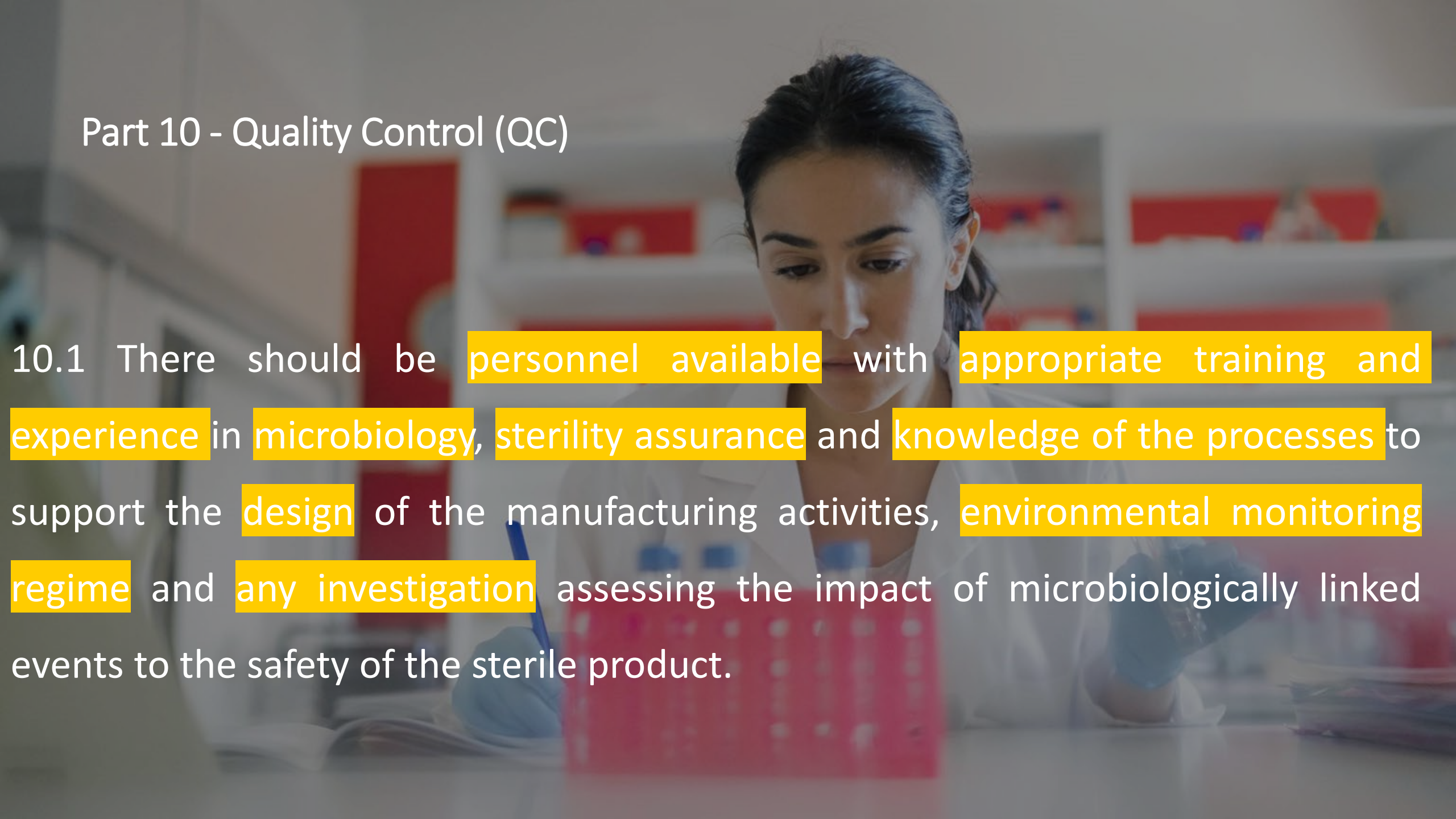
v. The requirement for substitution of any inert gas…

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

vii. The method of detection of microbial contamination should be scientifically justified to ensure that contamination is reliably detected.

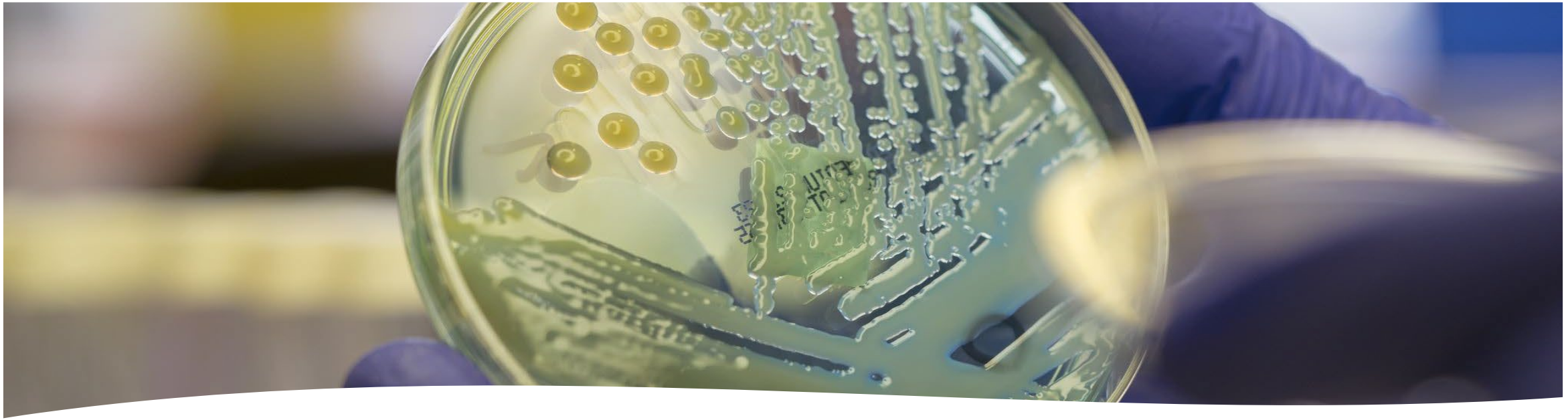
viii. The process simulation should be of sufficient duration to challenge the process, the operators that perform interventions, shift changes and the capability of the processing environment to provide appropriate conditions for the manufacture of a sterile product.

xiii. The performance of "end of production or campaign APS" may be used as additional assurance or investigative purposes; however, their use … justified in the CCS and should not replace routine APS.



Part 10 - Quality Control (QC)

10.1 There should be personnel available with appropriate training and experience in microbiology, sterility assurance and knowledge of the processes to support the design of the manufacturing activities, environmental monitoring regime and any investigation assessing the impact of microbiologically linked events to the safety of the sterile product.



10.4 Any organisms found during bioburden testing should be identified and their impact on the effectiveness of the sterilising process determined.

10.10 Environmental monitoring and trend data should be reviewed as part of product batch certification.

Summary

- TGA working towards Annex 1 adoption by Q1 2025
- Get prepared:
  - Familiarisation
  - Gap analysis
  - Remediation plan
  - QRM
- International guidance
- Critical to maintain patient safety

Questions?

Scan this QR code with your device to submit a question

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