THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)
Indian Pharmaceutical Alliance

8th Global Pharmaceutical Quality Summit 2023

Session 7: Updated EU GMP Annex 1 Guidelines – Current Expectations

Dr Thomas Hecker, GMP Inspector,
Certification of Substances Department, EDQM
22nd June 2023
DISCLAIMER: The views and opinions expressed in this presentation are those of the author and do not necessarily represent official policy or position of the European Directorate for the Quality of Medicines & Healthcare
History

1989 - first issuance


2015: Concept Paper on the full scale Revision

25 August 2023 (2024, Point 8.123)
Annex 1 Revision timeline

- **2015 Concept Paper**
- **2017 Public Consultation with 6000 comments**
- **2019 Review by authorities**
- **2020 Public Consultation 2000 comments**
- **2022 Review by authorities**
- **Published 22 August 2022**
The 2015 Concept Paper:

Main reasons for revision:

• Changes in technology

• Changes in GMP following adoption of
  • ICH Q9 (Quality Risk Management)
  • ICH Q10 (Pharmaceutical Quality System)

Furthermore:

• Clarify areas of applicability utilising quality risk management principles for non-sterile finished products

• Correct the inaccuracies and offer more detail to remove ambiguity and to give clearer interpretation of GMP expectations

• Revision of European Pharmacopoeia Monograph: Water for Injections (0169)
Water for Injections by membrane techniques

- Quality standard
- Defines quality of WFI in terms of microbiological and physico-chemical requirements

Water for injections in bulk

PRODUCTION
Water for injections in bulk is obtained from water that complies with the regulations on water intended for human consumption laid down by the competent authority or from purified water. It is produced either:
- by distillation in an apparatus of which the parts in contact with the water are of neutral glass, quartz or a suitable metal and which is fitted with an effective device to prevent the entrainment of droplets; or
- by a purification process that is equivalent to distillation. Reverse osmosis, which may be single-pass or double-pass, coupled with other appropriate techniques such as electro-deionisation, ultrafiltration or nanofiltration, is suitable. Notice is given to the supervisory authority of the manufacturer before implementation.
Scope extension:

- Drug Products
- Drug Substances
- Excipients
- Packaging Material
Quality Risk Management (QRM)

QRM applies to this document in its entirety and will not, normally, be referred to in specific paragraphs. Where specific limits or frequencies or ranges are specified, these should be considered as a minimum requirement. They are stated due to historical regulatory experience of issues that have been identified and have impacted the safety of patients.

But:

QRM: 2.2, 9.30
Risk Management: 2.5, 3.1, 8.16, 8.106
Risk Assessment: 4.12, 4.20, 4.27, 4.28, 4.31, 4.32, 6.1, 8.16, 8.87, 8.92, 9.4, ...
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
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.
CCS: What’s new?
CCS: Personnel

Organisational and Technical Measures

Cultural considerations // Appropriate education // Suitable knowledge and experience // Clothing considerations // Gowning processes // Training strategy // Qualification for aseptic processing

Pharmaceutical Quality System (PQS)
CCS: Premises, Equipment, Utilities

Organisational and Technical Measures


Pharmaceutical Quality System (PQS)
Organisational and Technical Measures

Process design // Sterility Assurance //
In-process controls // Process risk assessments
// Process Validation // Intermediate
Specifications // PUPSIT // Operating
conditions // Cleaning and Disinfection //
Materials Management

Pharmaceutical Quality System (PQS)
CCS: Materials and Quality Control

Organisational and Technical Measures


Pharmaceutical Quality System (PQS)
CCS: Outsourced Activities

Organisational and Technical Measures

Knowledge, Continuous Improvement


Pharmaceutical Quality System (PQS)

Risk Assessment, Monitoring, data review
“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 Management
- Process Validation including sterilisation
- Cleaning / Disinfection
- Monitoring / Trend Analysis
- Preventative Maintenance
Barrier Technologies

© https://manoxblog.com/2019/06/05/restricted-access-barriers-vs-isolators-an-energy-consumption-comparison/
## Isolators

<table>
<thead>
<tr>
<th>Design</th>
<th>RABS</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Grade A conditions with first air protection in the critical zone and unidirectional airflow</td>
<td>- The design of RABS should ensure grade A conditions with unidirectional airflow and first air protection in the critical zone.</td>
</tr>
<tr>
<td>- Airflow may not be fully unidirectional in closed isolators where simple operations are conducted</td>
<td>- A positive airflow from the critical zone to the supporting background environment should be maintained.</td>
</tr>
<tr>
<td>- Negative pressure isolators should only be used when containment of the product is considered essential</td>
<td></td>
</tr>
</tbody>
</table>

## Background Environment

| - Open isolators a minimum of grade C; closed isolators grade D based on RA considering spontaneous decontamination programme | - The background environment for RABS used for aseptic processing should correspond to a minimum of grade B and airflow pattern studies should be performed to demonstrate the absence of air ingress during interventions, including door openings if applicable. |
| - the extent of automation | |
| - the impact of glove manipulations that may potentially compromise ‘first air’ protection of critical process points | |
| - the impact of potential loss of barrier/glove integrity | |
| - transfer mechanisms used and activities such as set-up or maintenance that may require the doors to be opened prior to the final bio-decontamination of the isolator. | |

More flexibility because of higher sterility assurance levels
## Barrier Technologies

<table>
<thead>
<tr>
<th>Glove Systems: Material of appropriate mechanical and chemical resistance</th>
<th>Isolators</th>
<th>RABS</th>
</tr>
</thead>
<tbody>
<tr>
<td>- For isolators, leak testing of the glove system should be performed using a methodology demonstrated to be suitable for the task and criticality. The testing should be performed at defined intervals.</td>
<td>- For isolators, leak testing of the glove system should be performed using a methodology demonstrated to be suitable for the task and criticality. The testing should be performed at defined intervals.</td>
<td>- For RABS, gloves used in the grade A area should be sterilised before installation and sterilised or effectively bio-decontaminated by a validated method prior to each manufacturing campaign.</td>
</tr>
<tr>
<td>- minimum frequency of the beginning and end of each batch or campaign. Additional glove integrity testing may be necessary depending on the validated campaign length.</td>
<td>- minimum frequency of the beginning and end of each batch or campaign. Additional glove integrity testing may be necessary depending on the validated campaign length.</td>
<td>- If exposed to the background environment during operation, disinfection using an approved methodology following each exposure should be completed.</td>
</tr>
<tr>
<td>- Glove integrity monitoring should include a visual inspection associated with each use and following any manipulation that may affect the integrity of the system.</td>
<td>- Glove integrity monitoring should include a visual inspection associated with each use and following any manipulation that may affect the integrity of the system.</td>
<td>- Gloves should be visually examined with each use, and integrity testing should be performed at periodic intervals.</td>
</tr>
</tbody>
</table>

| Decontamination Methods | - The bio-decontamination process of the interior should be automated, validated and controlled within defined cycle parameters and should include a sporicidal agent in a suitable form (e.g. gaseous or vaporized form). | - The sporicidal disinfection should include the routine application of a sporicidal agent using a method that has been validated and demonstrated to robustly include all areas of the interior surfaces and ensure a suitable environment for aseptic processing. |
| - Gloves should be appropriately extended with fingers separated to ensure contact with the agent. | - Gloves should be appropriately extended with fingers separated to ensure contact with the agent. | - Gloves should be appropriately extended with fingers separated to ensure contact with the agent. |
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 validation. ...

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 ...
Pre-Use Post Sterilisation Integrity Testing: PUPSIT

- Introduced because of potential flaws of a sterilising filter that may be blocked/clogged and remains therefore undetected during post-use integrity testing

**Pros**
- Increase of detectability of filter flaws
- Protection of the patient

**Cons**
- Risk of filter flaws is low
- PUPSIT is complex to perform
Other major improvements:

- Additional guidance for consideration of premises and cleanroom design - maintaining control of contamination and separation of non-essential processes from critical production steps
- Additional guidance regarding the expectations for cleaning and disinfection of cleanrooms
- The limits for microbial contamination have changed with regard to Grade A limits: <1 CFU to “no growth”.
  
  no micro-organisms are expected to be recovered from a Grade A environment
- Both EM and PM are expected to be incorporated in the overall aseptic manufacturing process based on risk and completed at regular intervals. ; new requirement for sampling of personnel upon each exit of the Grade B cleanroom.
- The use of rapid or automated monitoring systems is encouraged in the new Annex 1 to expedite detection of microbial contamination, i.e. increase detectability or reduce time of detection: 
  Demonstrate at least equivalency (better superiority) to the conventional methodology through validation.
- Additional Guidance on utilities, e.g. WFI
Acknowledgments

- Abdelaali Sarakha (ANSM, France)
- Mihaela Buda (EDQM)
- Tracy Moore (former MHRA)
Thank you for your attention

Stay connected with the EDQM

EDQM Newsletter: https://go.edqm.eu/Newsletter
LinkedIn: https://www.linkedin.com/company/edqm/
Twitter: @edqm_news
Facebook: @EDQMCouncilofEurope