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

edqm

European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

COUNCIL OF EUROPE

CONSEIL DE L'EUROPE

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

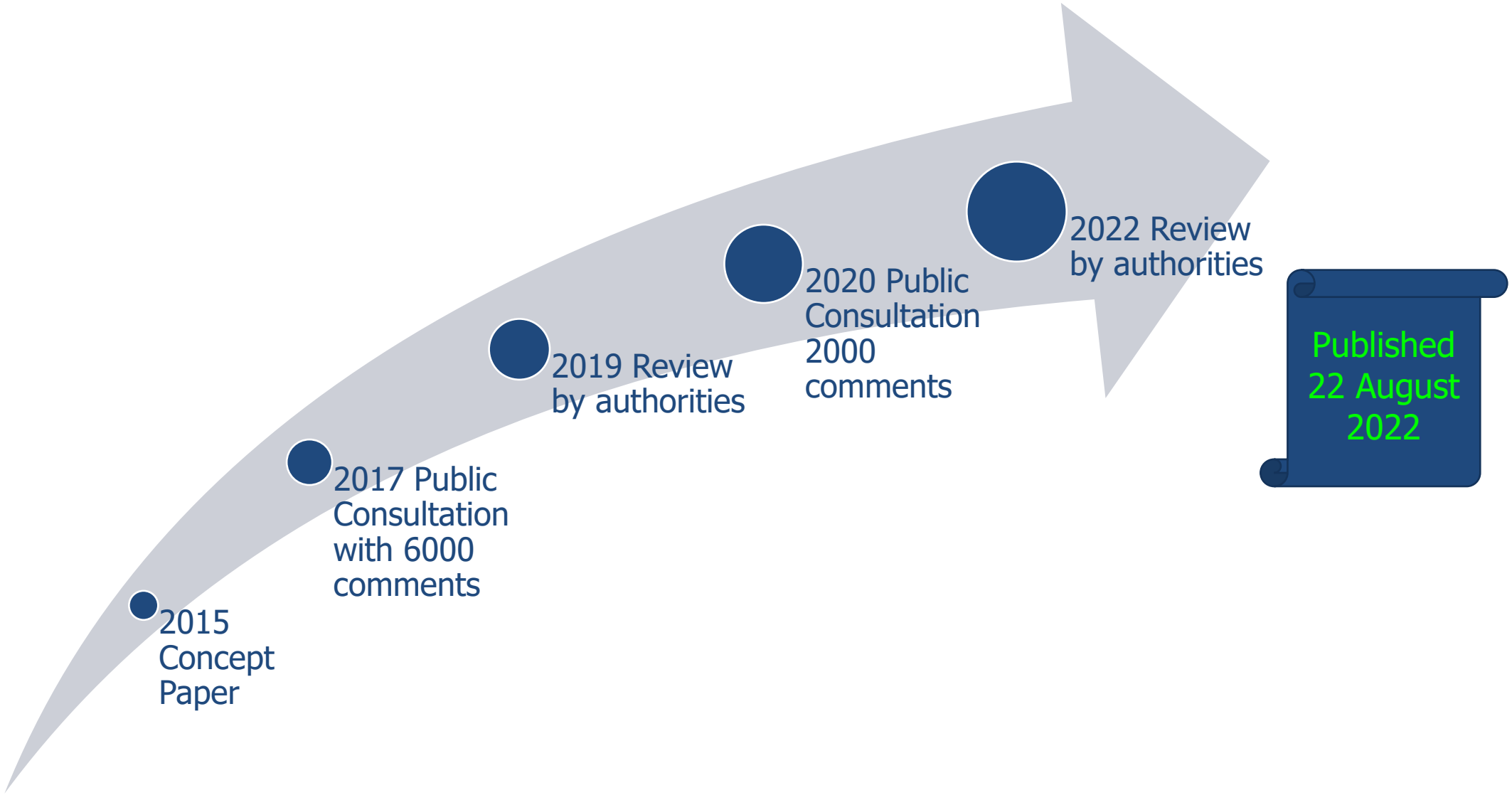
22nd June 2023

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 → 1996, 2003, 2007, 2009: minor revisions → 2015: Concept Paper on the full scale Revision → 25 August 2023 (2024, Point 8.123)

Annex 1 Revision timeline



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)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

PIC/S
PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO- OPERATION SCHEME

2 February 2015
EMA/INS/GMP/735037/2014
GMP/GDP Inspectors Working Group (GMP/GDP IWG)

8 January 2015
PS/W 1/2015

Concept paper on the revision of annex 1 of the guidelines on good manufacturing practice – manufacture of sterile medicinal products

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

Ph. Eur.
WFI monograph

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

PRODUCTION section

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.

System design, operation, maintenance

GMP

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 August 2017
EMA/INS/GMP/443117/2017
GMP/GDP Inspectors Working Group

Questions and answers on production of water for injections by non-distillation methods – reverse osmosis and biofilms and control strategies

Final

7

Scope extension:

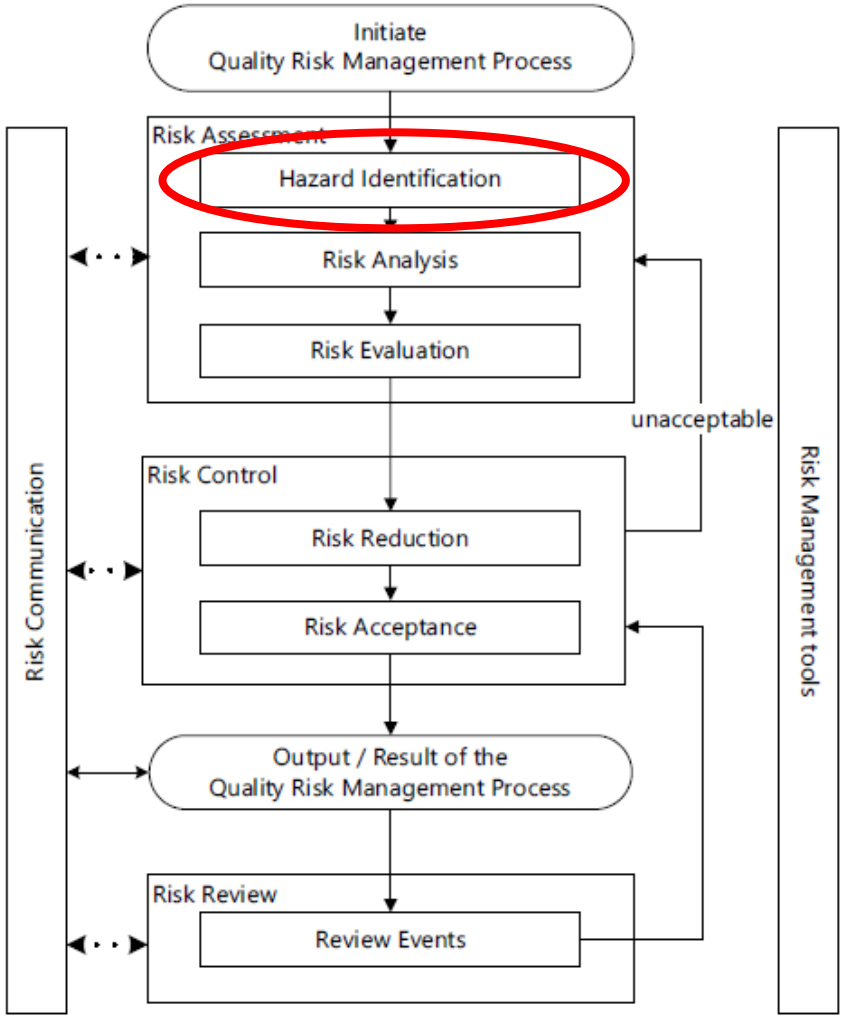
Quality Risk Management (QRM)

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, …

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

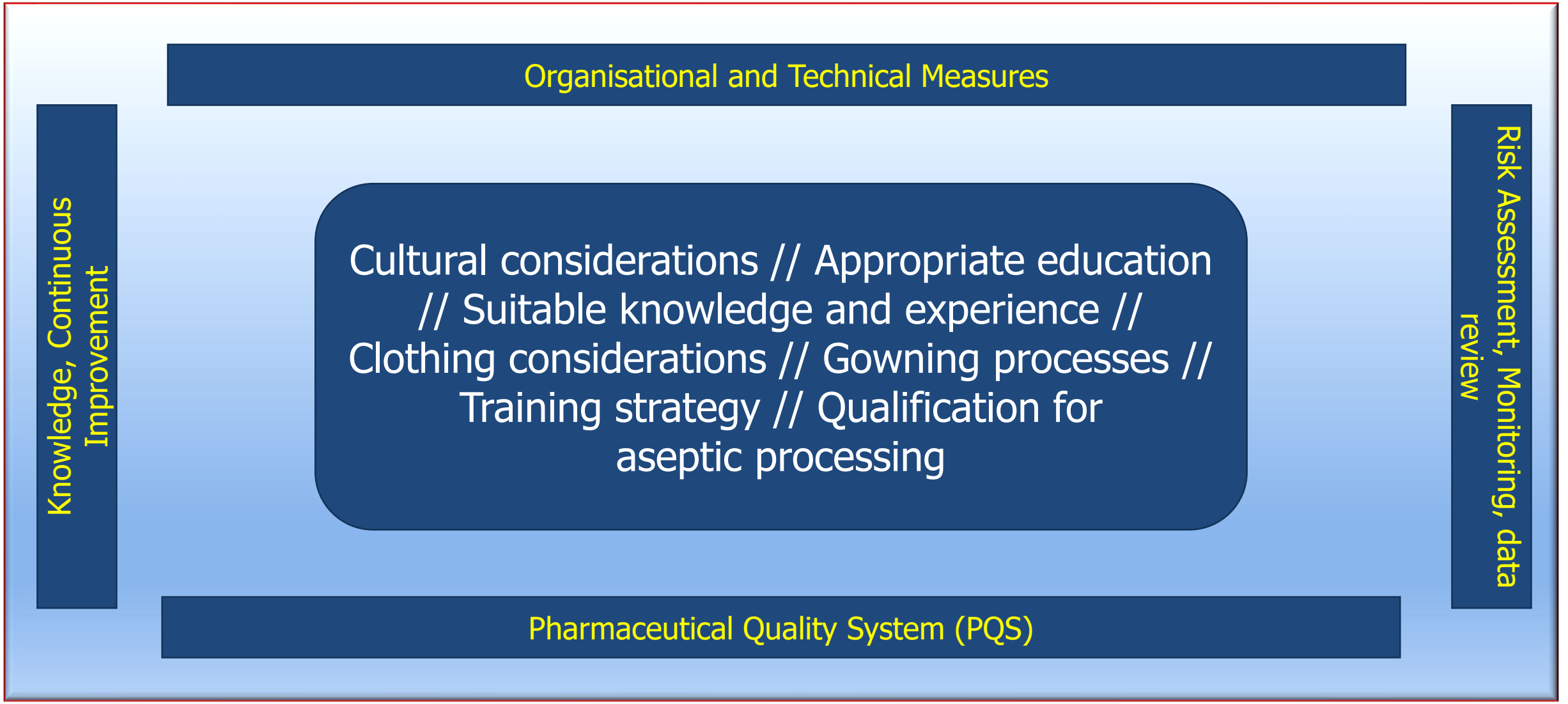
- Subjectivity
- Product Availability Risks
- Formality
- Risk-Based Decision-Making
- Risk Review

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.

CCS: What's new?

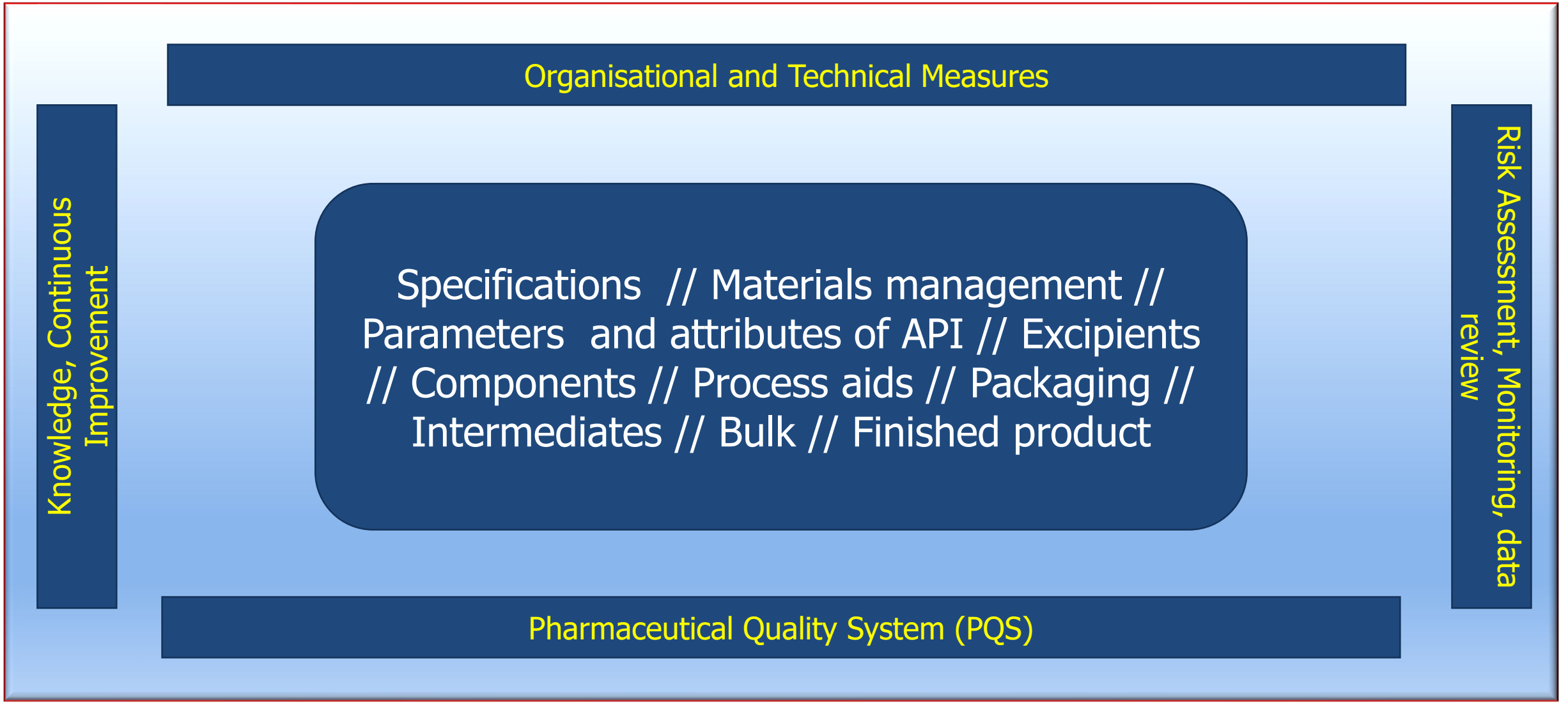
CCS: Personnel



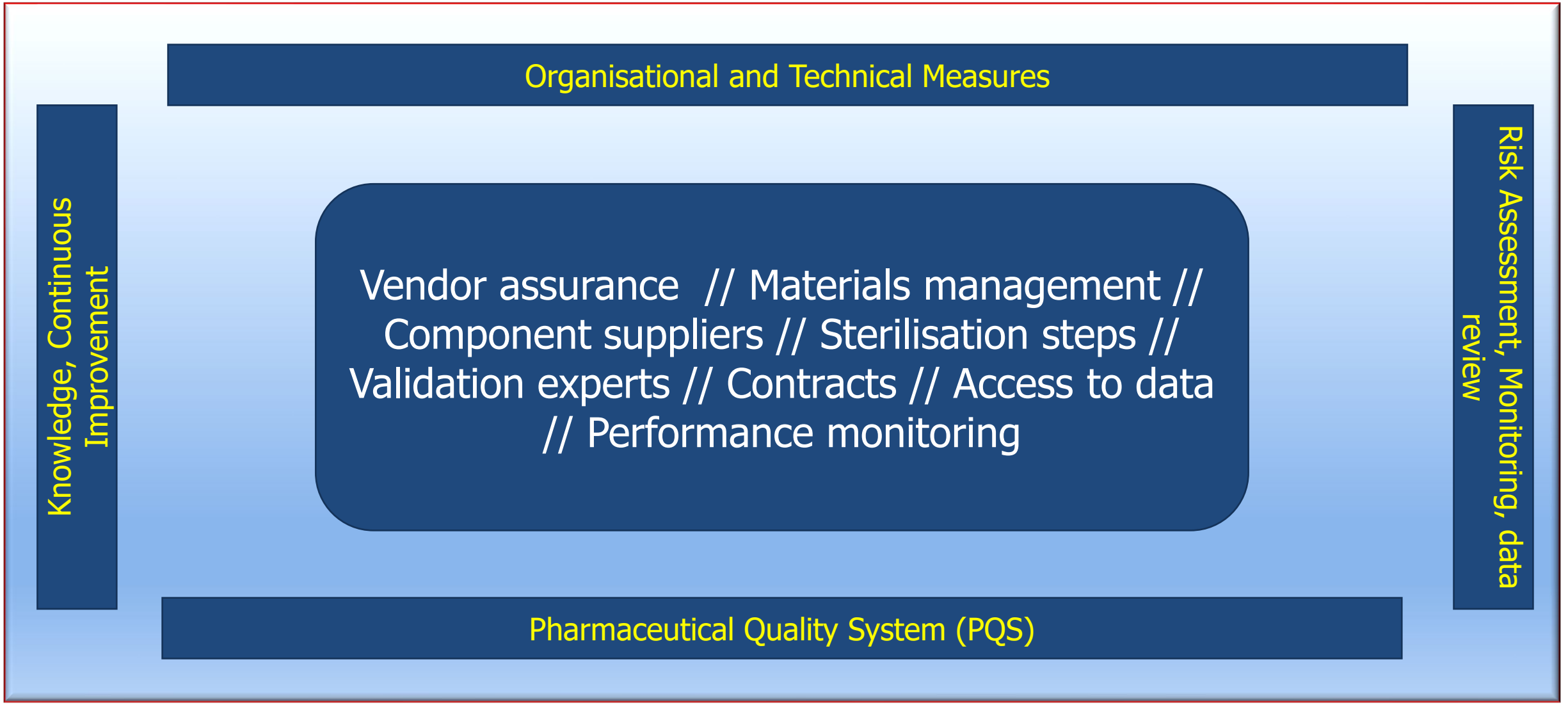
CCS: Premises, Equipment, Utilities

CCS: Production and Process

CCS: Materials and Quality Control



CCS: Outsourced Activities



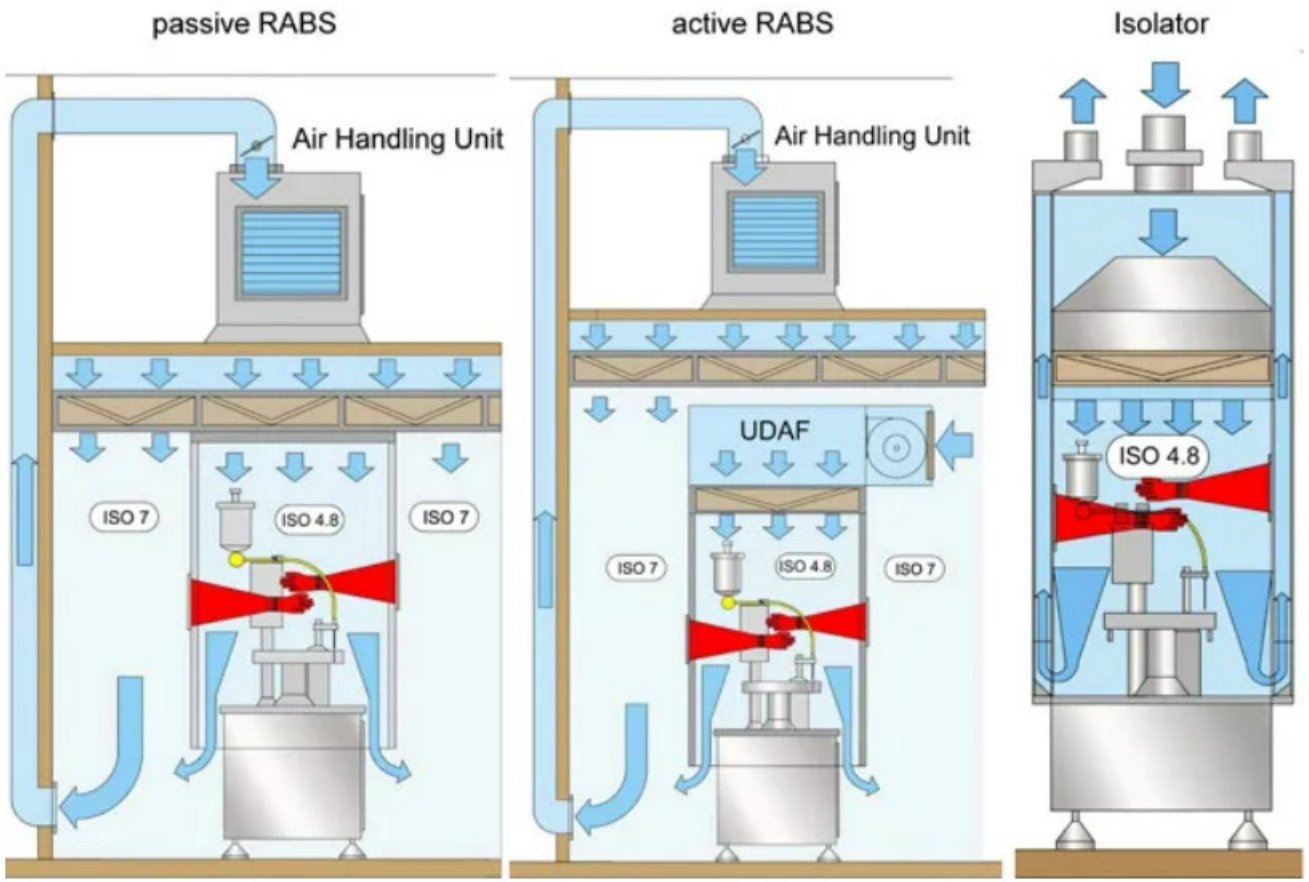
Just one example…

"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

Barrier Technologies



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

Barrier Technologies

More flexibility because of higher sterility assurance levels

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

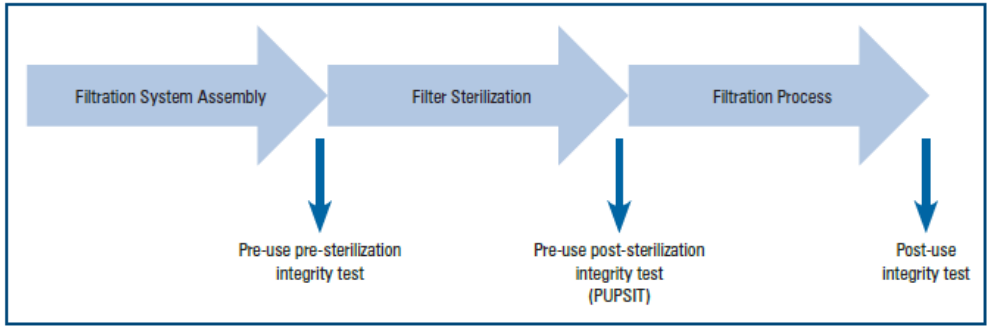
Background Environment	- Open isolators a minimum of grade C; closed isolators grade D based on RA considering
	  - bio-decontamination programme
	  - the extent of automation
	  - the impact of glove manipulations that may potentially compromise 'first air' protection of critical process points
	  - 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.
		- 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.

Barrier Technologies

	Isolators	RABS
Glove Systems: Material of appropriate mechanical and chemical resistance	- 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. - 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. - Glove integrity monitoring should include a visual inspection associated with each use and following any manipulation that may affect the integrity of the system.	- 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. - If exposed to the background environment during operation, disinfection using an approved methodology following each exposure should be completed. - Gloves should be visually examined with each use, and integrity testing should be performed at periodic intervals.
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). - Gloves should be appropriately extended with fingers separated to ensure contact with the agent.	- 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.

Pre-Use Post Sterilisation Integrity Testing: PUPSIT

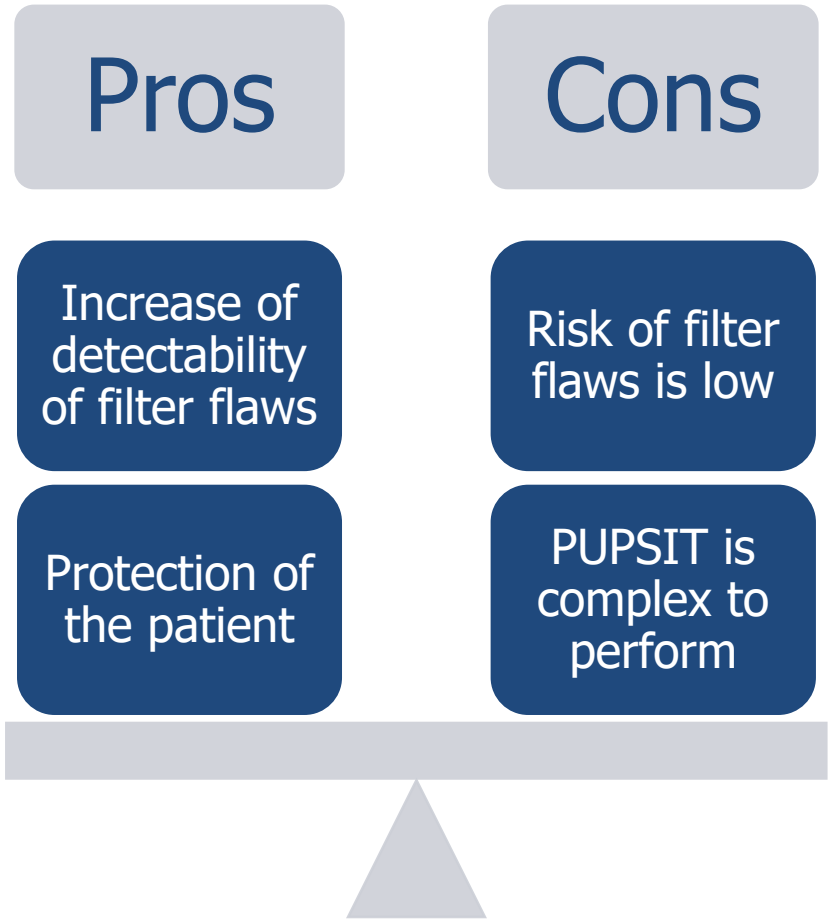
- 8.87 The integrity of the sterilised filter assembly should be verified by integrity testing before use (pre-use post sterilisation integrity test or PUPSIT), to check for damage and loss of integrity caused by the filter preparation prior to use. A sterilising grade filter that is used to sterilise 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 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 my be blocked/clogged and remains therefore undetected during post-use integrity testing



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**