Regulatory View on Annex 1

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Regulatory View on Annex 1

Scope

- Reminder of history
- Reg updates
- Annex 1 General
- Annex 1 Isolator specifics
- Questions

Remider of history

Reminder of history

- The original version was revised in 1996, 2003, 2005, 2007 and 2009 however there has not been a complete review of the document since it was originally issued
- Since the original issuance and the revisions there have been changes in technologies and significant changes in GMP consequent to the adoption of the ICH Q9 and Q10 guidelines.

Reminder of history

- Concept paper 2014
- Various consultations
- Publication 25 Aug 2022
- Effective 25 Aug 2023 (except lyo)
- Variation across PIC/S depending on the legal situation

Reminder of history

- Combined working group (PIC/S and EMA and later WHO) with a task of assessing the requirements of revision:
  - Complete re-write

Reminder of history

- PIC/S, EMA and WHO
- Revision by the working group (16 representative)
- Reviewed by all of the above
- EMA - 27 NCAs
- PIC/S - 54 Regulators (Vet and Human)
- WHO - A lot of the rest of the world, In total:
  - Europe
  - North America (Canada and **USA**)
  - Some of Asia (PMDA, TFDA)
  - Some of South America (Brazil, Mexico)
  - Africa and India

Who is it for?

- Large batch fill finish manufacturers
- Small batch fill finish manufacturers
- Automated filling
- Hand filling
- Sterile API
- Classical small molecule
- Large molecule

Who is it for?

- Shelf life of years
- Short shelf life of hours (or even minutes)
- Multiple technologies (BFS, Powder, liquids, lyo …….)
- Large established pharma
- Developing Pharma companies
- Academic institutes
- Hospitals
- Virtual operations

Regulatory updates

Regulatory updates

Swiss medic technical interpretation 31 October 2023

- Does apply to ATMPs!
- Transfer of items into the isolator
- Discusses Robotics to standardise processes
- Talks about the decontamination process
- RE-iterates PUPSIT is a base expectation (but does allow for some exceptions

Regulatory updates

Anecdotal updates

- Discussion as to whether no touch transfer is acceptable
- Some regulators stating all no processes and filings need to be in Isolators!?

Annex 1 General requirements

Annex 1 General

Key points:

- Need to keep people away from the product (mentioned in multiple places

- 2.1 The manufacture of sterile products is subject to special requirements in order to minimize risks of microbial, particulate and endotoxin/pyrogen contamination. The following key areas should be considered:

- i. Facility, equipment and process should be appropriately designed, qualified and/or validated and where applicable, subjected to ongoing verification according to the relevant sections of the Good Manufacturing Practices (GMP) guidelines. 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 from potential extraneous sources of endotoxin/pyrogen, particulate and microbial contamination such as personnel, materials and the surrounding environment, and assist in the rapid detection of potential contaminants in the environment and the product.

Annex 1 General

Key points:

- Need to keep people away from the product (mentioned in multiple places

- "4.3 Restricted Access Barrier Systems (RABS) or isolators are beneficial in assuring required conditions and minimizing 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."

Annex 1 General

Key points:

- Needs the correct knowledge

- iii. 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.

Annex 1 General

Key points:

- Needs the correct knowledge
- For isolators:
- VHP principles – key parameters (humidity temperature etc.)
- Mode of operation vapourised, fogged or ionised
- Occluded surface (what is an occluded surface)
- How do you validate and what does that mean (3 or 1 BI, reduced cycles?)

Annex 1 General

Key points:

- Needs the correct knowledge
- For isolators:
- What is the process?
    - Set up
    - Material transfer
    - Filling
    - Cleaning

Annex 1 General

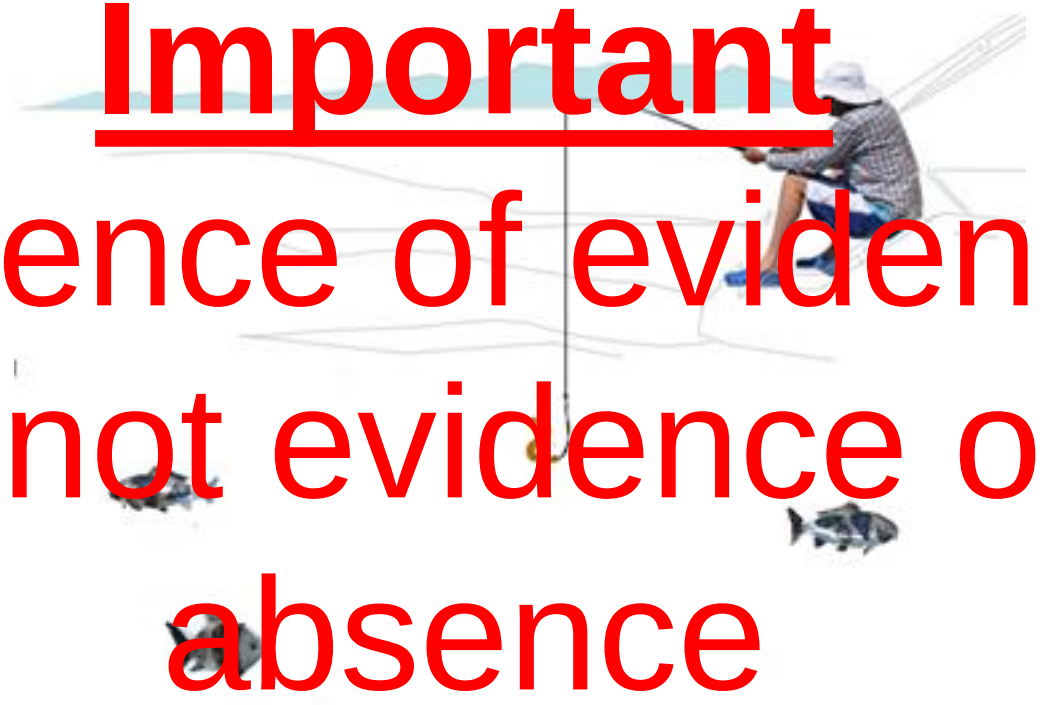
Key points:

Micro (EM)

- Needs to be based on risk assessment (linked to process knowledge and CCS)
- Limit for grade A (less than 1 (no averaging))
- Need to set limits ofr Grade D and also have alert limits
- Can use other methods as long as we can correlate to the existing methods e.g. Fluorescent events versus CFU
- Micro cannot be used to support bad processes

Important

Absence of evidence is not evidence of absence



Annex 1 General

Key points:

Micro (APS)

- Needs to be based on risk assessment (linked to process knowledge and CCS)
- Need to understand all interventions (even in an isolator you need to protect first air)
- Limit 1 recovery is a failure

Annex 1 General

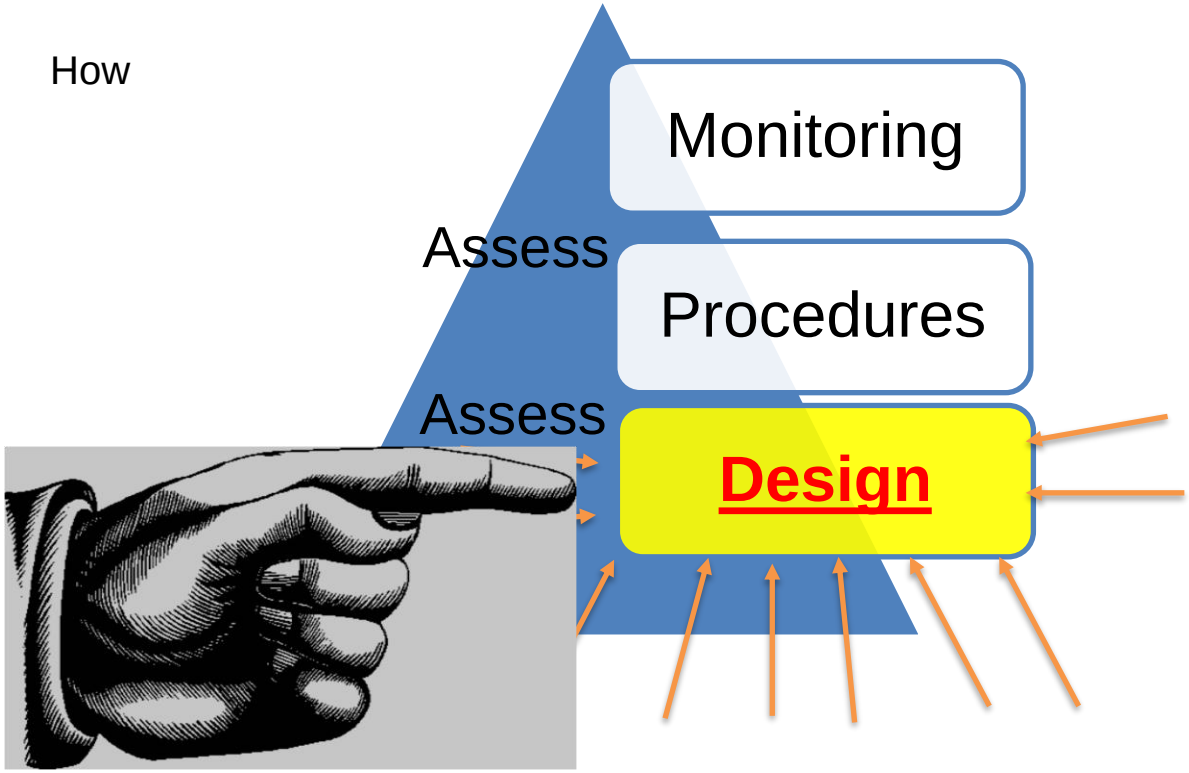
Key points:

QRM

- Links to CCS

CCS/QRM

How



Annex 1 isolator specific requirements

Annex 1 Isolator specific requirements

Key points:

- Barrier technologies (4.18 to 4.22)
- Decontamination needs to be automated (cleaning and sporicidal agent)
- Gloves appropriately extended and fingers separated
- Glove leak tested
- Background – open isolators minimum grade C closed minimum of grade D

Annex 1 Isolator specific requirements

Key points:

- i. Closed isolator systems exclude external contamination of the isolator's interior by accomplishing material transfer via aseptic connection to auxiliary equipment, rather than use of openings to the surrounding environment. Closed systems remain sealed throughout operations.
- ii. Open isolator systems are designed to allow for the continuous or semi-continuous ingress and/or egress of materials during operations through one or more openings. Openings are engineered (e.g. using continuous overpressure) to exclude the entry of external contaminant into the isolator.

Thank you for your time
Any questions?

Source:
BMGF,
via WHO