Regulatory View on Annex 1

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Regulatory View on Annex 1

Scope

- History and background
- Key changes
- Questions

History and background

History and Background

- 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.

History and Background

- In 2012 The German Authorities (ZLG) issued a concept statement to the EMA's IWG proposing revision of the Annex and a subsequent request was made to PIC/S for support in updating
- 2014 PIC/S Working group was set up and started work in August.
- September 2014 a draft concept paper was re-issued to IWG (by the MHRA) supporting the update.

Process of revision

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

Process of revision

- Combined working group with a task of assessing the requirements of revision:
  - Understand Industry concerns
  - Understand Regulatory concerns

Process of revision

- Draft Concept paper proposed at EMA IWG September.
- Following regulatory comments and PIC/S input issued for public consultation on 5th February 2015
- Deadline for comments was 31st March 2015

- Annex 1 updated
- There were a few comments and some interest!

Annex 1 process

- Draft first published 20th December 2017
- Published by EMA/WHO and PIC/S
- Consultation period closed 20th March 2018
- Public consultation comments and reviewed (6215 comments received)
- New draft version (4 years) later (but multiple iterations)
- Focussed public consultation 2021
- Issued 25 August 2022 (1 year implementation August 2023)
- Except section regarding lyophiliser sterilisation!!!!!!!

Who is it for?

- 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

Key changes

New structure:

Title
1 Scope
2 Principles
3 PQS
4 Premises
5 Equipment
6 Utilities
7 Personnel
8 Production and Specific technologies
9 Non Viable and Viable Environmental and process Monitoring
10 Quality Control
11 Glossary

Section updates

1 Scope

New section to link to other annexes and chapters (but not mandated)

2 Principles

Re enforce the **existing** requirements of EU GMP

- EU Directive 2003/94 Article 5
- EU Directive 2001/83 Article 23
- Chapter 3
- Chapter 5 (5.10)

3 PQS

- Re-enforcing the process of quality risk management.
- Re-enforcing the process of Root Cause Analysis and product impact assessment

4 Premises & 5 Equipment

- Again re-enforcing the need to keep the operators away from the product using current technology
- Airlocks/pass throughs
- LABS, RABs and Isolators
- Cleanroom qualification
  - ISO 14644
  - 5.0 µm

Annex 1

6 Utilities

- General services such as compressed air
- WFI by RO
- Biofilms
- Possibility that this could then be moved to a separate section of the GMPS

7 Personnel

- Goggles/full face enclosure
- Socks
- Training/knowledge

8 Production and Specific technologies

- BFS, etc.
- Lyophilisation
- CCI
- PUPSIT

9 Non Viable and V[illegible]ring

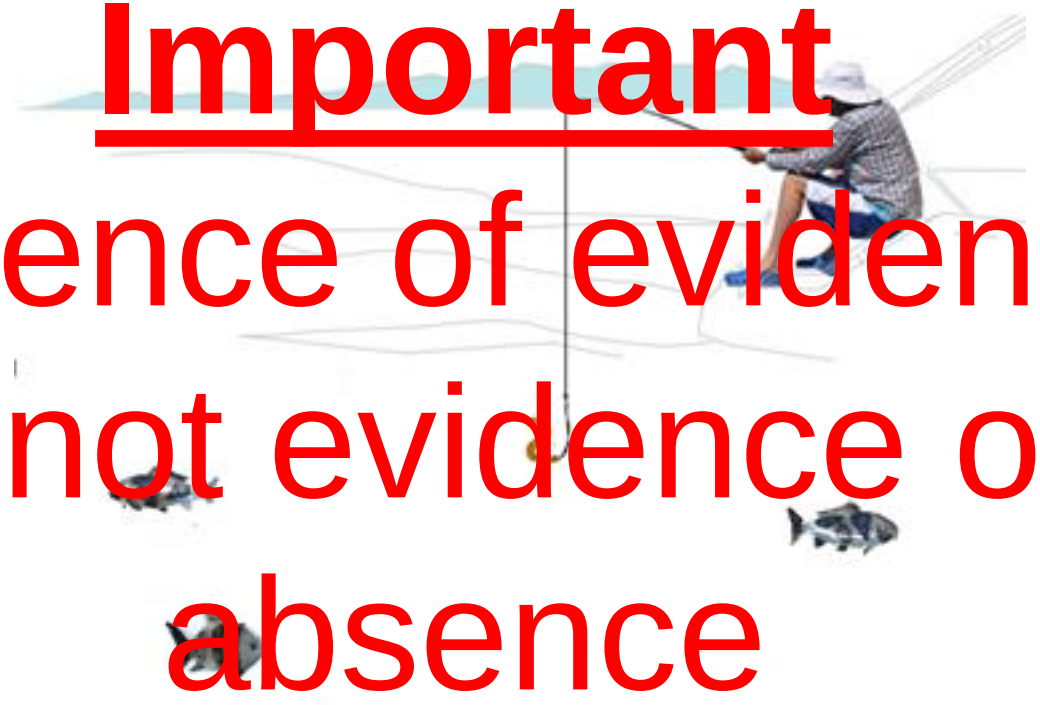
- Keep all m[illegible] one [illegible]ce
- To include
  - NVP
  - Aseptic [illegible]
  - All viable

9 Non Viable and Viable Environmental and process Monitoring

- Re-enforce the development of the “system” by risk assessment
- Setting of limits and evaluation of trend data
- Rapid microbial methods

Important

Absence of evidence is not evidence of absence



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11 Quality Control

12 Glossary

- Key principles
- Introduction of QRM
  - Recognise that we do not know what is in the future
- Conversely cannot be too prescriptive!
  - Has to fit to the lowest acceptable common denominator
- Clarify existing requirements (that may not be detailed currently)
- **<u>But no step change in stringency</u>**
  - Potential to cause stock shortage

Key changes:

- 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. The intent of the Annex is to provide guidance for the manufacture of sterile products.

Key changes:

- However, some of the principles and guidance, such as contamination control strategy, design of premises, cleanroom classification, qualification, validation, monitoring and personnel gowning, may be used to support the manufacture of other products that are not intended to be sterile such as certain liquids, creams, ointments and low bioburden biological intermediates, but where the control and reduction of microbial, particulate and endotoxin/pyrogen contamination is considered important. Where a manufacturer elects to apply guidance herein to non-sterile products, the manufacturer should clearly document which principles have been applied and acknowledge that compliance with those principles should be demonstrated.

Key changes:

Principles

- 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.

Key changes:

Principles

2.2 Processes, equipment, facilities and manufacturing activities should be managed in accordance with QRM principles to provide a proactive means of identifying, scientifically evaluating and controlling potential risks to quality. Where alternative approaches are used, these should be supported by appropriate rationale, risk assessment and mitigation, and should meet the intent of this Annex. 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.

Key changes:

- 2.4 Contamination control and steps taken to minimize the risk of contamination from microbial, endotoxin/pyrogen and particle sources includes a series of interrelated events and measures. These are typically assessed, controlled and monitored individually but their collective effectiveness should be considered together.

- 2.5 The development of the CCS requires detailed technical and process knowledge. Potential sources of contamination are attributable to microbial and cellular debris (e.g. pyrogen, endotoxin) as well as particulate (e.g. glass and other visible and sub-visible particles). Elements to be considered within a CCS should include (but are not limited to):

Key changes:

- 2.7 The manufacturer should take all steps and precautions necessary to assure the sterility of the products manufactured within its facilities. Sole reliance for sterility or other quality aspects should not be placed on any terminal process or finished product test.

Key changes in summary

- Based on QRM, design is paramount to risk reduction
- Need to have a documented contamination control strategy.

Note: not just a list of RPNs, need to be linked ot the process e.g. via process maps

Key changes:

- 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 update

Key changes:

- i. Isolators: a. The background environment for open isolators should generally correspond to a minimum of grade C. The background for closed isolators should correspond to a minimum of grade D. The decision on the background classification should be based on risk assessment and justified in the CCS.

Annex 1 update

Key changes:

- 5.3 As far as practicable, equipment, fittings and services should be designed and installed so that operations, maintenance, and repairs can be performed outside the cleanroom. If maintenance has to be performed in the cleanroom, and the required standards of cleanliness and/or asepsis cannot be maintained, then precautions such as restricting access to the work area to specified personnel, generation of clearly defined work protocols and maintenance procedures should be considered. Additional cleaning, disinfection and environmental monitoring should also be considered. If sterilisation of equipment is required, it should be carried out, wherever possible, after complete reassembly.

ISPE Annex 1 update

Key changes:

- Smoke studies:
- Linked to velocities
- Must include review of process
- *Classification*
- *5.0 um (for grade A not required?)*

Annex 1 update

Key changes:

- Integrity of fused containers, especially LVP.
- Sterilisation – Autoclaves links to EN285 requirements equilibration times and steam quality testing (non condensable gasses, dryness and superheat)

Annex 1 update

- Key changes:

Section 10:

- 10.6 The sterility test should be performed under aseptic conditions. Samples taken for sterility testing should be representative of the whole of the batch but should in particular include samples taken from parts of the batch considered to be most at risk of contamination, for example:

i. For products which have been filled aseptically, samples should include containers filled at the beginning and end of the batch. Additional samples, e.g. taken after critical interventions should be considered based on risk.

ii. For products which have been heat sterilised in their final containers, samples taken should be representative of the worst case locations (e.g. the potentially coolest or slowest to heat part of each load).

iii. For products which have been lyophilized, samples taken from different lyophilization loads.

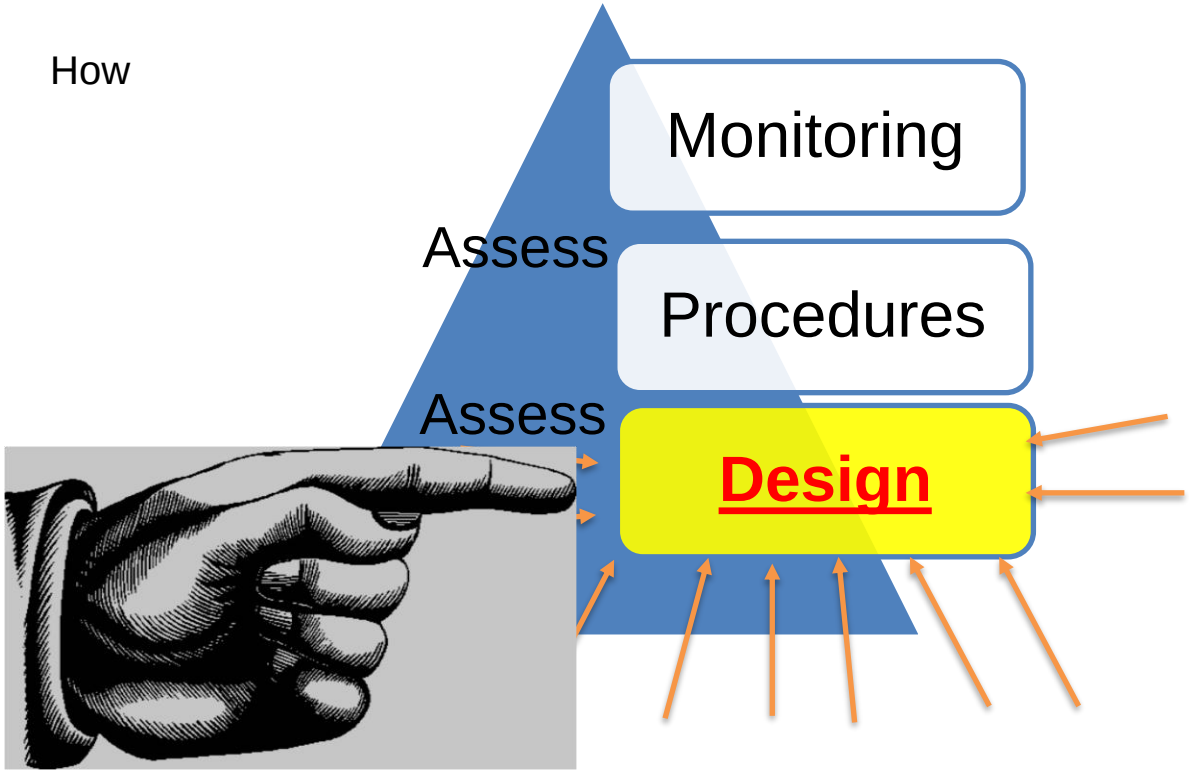
Annex 1 update

Key changes:

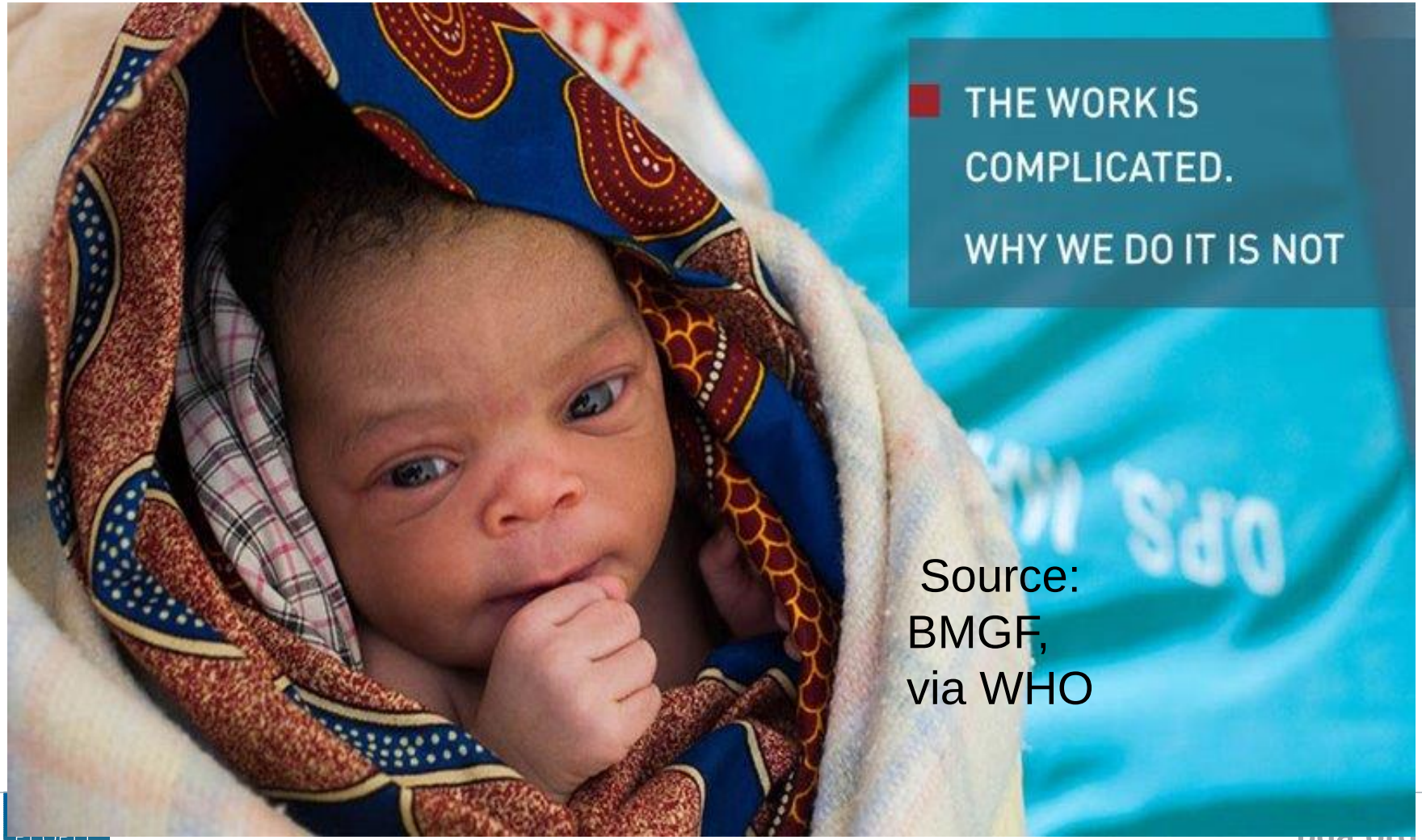
Section 10:

- 10.8 Any process (e.g. Vaporized Hydrogen Peroxide, Ultra Violet) used to decontaminate the external surfaces of sterility samples prior to testing should not negatively impact the sensitivity of the test method or the reliability of the sample

CCS/QRM



- Key changes in summary



Source:
BMGF,
via WHO

Thank you for your time
Any questions?