EU GMP Annex 1 (draft)
2018

Revision process and key changes

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Introduction

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Scope of Annex 1

- Annex 1 - the manufacture of sterile products is subject to special requirements to minimise risks of microbiological, particulate and pyrogen contamination of sterile products.

- The Annex provides guidance as to how sterile products can be protected using the most effective systems and technology.
  - The guidance includes personnel training, equipment qualification, cleanroom design and environmental monitoring.

- Applies to manufacturing in Europe and exports into Europe.
Revision process #1

- Annex 1 of EU GMP has undergone no major revision since 2007 and has seen no change whatsoever to its contents since 2009.

- A signal that the draft was imminent was sent in January 2015 via a ‘Concept Paper’. This was proceeded by several ‘coming soon’ messages.

Revision Process #2

- FDA and PIC/S were part of the revision process.
- Aim for a new version to be issued later in 2018.
- The draft was followed by a consultation period, which ends on March 20, 2018.
- Professional bodies were able to input and many did— including Pharmig.
Main changes #1

- The resulting product has expanded considerably in length:
  - Increasing from around 15 pages to 50.
  - In addition there are now 269 different clauses (up from around 100 in the current version, and many of these expanded upon).
  - Some 100 clauses contain no link with an existing clause.
  - It is also notable that 14 clauses from the previous revision that are not present in any form in the update and that just 40 clauses are unchanged from the original version.

- Included among the new sections are:
  - Single use technologies;
  - Aseptic operator qualification;
  - The application of Quality Risk
  - Disinfectant qualification for cleanroom surfaces;
  - Process water systems, including the manufacture of Water-for-Injections;
  - Other utilities and closed manufacturing systems.
Main changes #2

Four broad areas of change:

- The global acceptance and implementation of ICH Q9 (Quality Risk Management) and Q10 (Pharmaceutical Quality System). The new draft contains many references to Quality Risk Management (QRM).

- To reflect advances in sterile manufacturing technology, especially with RABS and isolators, and with rapid microbiological methods.

- Some ambiguity with the current version and these needed correction or clarification.

- Annex 1 is often used beyond sterile manufacturing, including aspects of non-sterile manufacturing. The scope of the new draft has been modified to reflect this.
Contamination control strategy

- Requirement for a holistic contamination control strategy.
  - Set out in the first substantive part of the Annex titled ‘Principle’ (section 2).
  - A document to reflect the site-wide strategy for minimising contamination control.
  - Areas to be included:
    - design of the plant and process;
    - utilities;
    - materials control;
    - vendor approval;
    - control of outsourced activities, such as sterilisation;
    - process validation;
    - preventative maintenances;
    - cleaning and disinfection.
Pharmaceutical Quality System

The first main section of the draft refers to the Pharmaceutical Quality System.

With reference to specific aspects for sterile products manufacture:

- The proactive use of risk management.
- Regular review of risk assessments.
- Rationales in place to address different categories of risk arising from risk assessments.
- Employing staff with sufficient expertise to undertake risk assessments.
- Use of effective root cause and CAPA.
- Those tasked with releasing products must be fully conversant with risks and quality issues.
Cleanroom design #1

- **Potential** intent to mandate HEPA grade filtration in all classified areas (including Grade D).
  - The text is a little ambiguous.
- Requirement for each manufacturer to define 'in operation' and 'at rest' conditions for all cleanrooms or suites of cleanrooms.
  - Because facilities differ.
  - Suggested that clean up procedures, rest periods and any other variable conditions be defined.
- Laminar vs UDAF.
Cleanroom design #2

- Ambiguity around ‘Grade A’.
  - Annex makes reference to “Grade A conditions” for aseptic processing and to “Grade A air supply” for oversealing.
  - A new reference appears to “Grade A environment”.
  - Use of the term “Grade A /B”.
  - With unidirectional air there is an extension, with clause 5.12, from this being a requirement of Grade A environments to include Grade B in relation to the cleanroom used to house a RABS.
    - Challenging to some facilities?
- Reference to a specific temperature range for Grade B cleanrooms has been dropped and the scope widened to all cleanroom grades.
Cleanroom design #3

There is a reference in the draft to changing areas, stating that there should be separate changing rooms for entry and exit.

Is this required for all grade areas e.g. Grade C and D?
Cleanroom classification

- With cleanroom classification, classification according to ISO 14644-1 is mandated.
- Grade D – ISO class 8 equivalency stated for the first time.
- In keeping with the revisions to ISO 14644, the requirement to monitor for particles of a cut-off size of ≥5.0 µm has been removed.
  - The exclusion of ≥5.0 µm applies to classification only; the continued monitoring of these particles remains a requirement for monitoring of aseptic processing.
- The Annex discusses additional requirements for cleanroom classification (beyond ISO requirements) in critical areas.
  - Extra locations based on risk and examples such as stopper bowls inside filling machines are referenced.
- Particle counter tubing lengths mentioned.
Cleaning and disinfection #1

- The references to disinfection have been expanded.
- The need to rotate between two different disinfectants remains.
  - One of these should be a sporicidal agent is a change.
  - Reference made to disinfectant qualification.
  - This needs to be carried out within each facility because of the different types of surfaces.
- Need to assess the bioburden of non-sterile disinfectants.
Cleaning and disinfection #2

With cleaning, the draft text appears to infer that cleaning needs to be undertaken prior to each use of disinfectant.

In fact cleaning before every disinfection is not necessary, especially in higher grade areas where there is very little soiling.

With disinfection, the confusing reference to ‘resistant strains’ remains. Here the phrase "development of resistant strains “is often misinterpreted as development of acquired resistance (a theory which has largely been discredited).
RABS / Isolators

- Containment devices receive a number of references within the Annex:
  - RABS (which are described as passive, open or closed) and isolators.
  - The use is encouraged: “RABS, isolators or closed systems, should be considered in order to reduce the need for interventions into the grade A environment and minimize the risk of contamination”.
  - With all forms of RABS, the Annex requires that studies should be performed to demonstrate the absence of air ingress.

- With isolators, there is reference to the importance of selecting the correct isolator gloves; those with good mechanical and chemical resistance, and for testing gloves for leakage prior to each production batch.

- With both RABS and isolators there is the requirement that all items transferred in be decontaminated by a disinfection or sterilisation process.
Aseptic Processing #1

- New clarification that, within Grade A, monitoring must be performed for all of setup and critical operations.

- Sample frequency and size must be such that all excursions are captured.

- With sample sizes these do not necessarily need to meet full classification volumes.
Aseptic Processing #2

- For Grade A environments, monitoring needs to be continuous and with this respect the Annex remains unaltered.

- New: the requirement for continuous monitoring for Grade B areas, which has been added to section 8.
  
  - The new Annex now requires “a similar system” to Grade A continuous monitoring in Grade B areas.
  
  - The system should operate at a frequency and sample size to detect changes in contamination levels and system deterioration, including the triggering of alarms.
Aseptic Processing #3

- With controlling access to cleanrooms there is reference made to the importance of on-going checks completed outside of the cleanroom.
  - Use of inspection windows or use of a closed-circuit camera system.
- A further restriction applies to Microbiology staff who handle microbial cultures, suggesting some level of internal control.
The control of operation time is discussed in several places.

Time is referred to with:

- Pre-fill time should be assessed as part of media fills.
- A time limit required for aseptic assembly
- Maximum exposure time of sterilized containers and closures prior to closure. This infers oversealing times need to be set.
- For items sterilized “in house” (such as by autoclaving), these need to be stored in Grade A or B, using appropriately sealed packaging and a maximum hold period must be established.
Environmental monitoring plays a major part in the revised Annex.

With environmental monitoring, the use of swabs for the monitoring of machine surfaces is notably missing.

Swabs are the optimal method for swabbing Grade A surfaces like filling needles.
Sterile filtration

- Sterile filtration is a critical step for aseptically filled products and a key measure is an assessment of the product bioburden prior to filtration.
- The Annex makes no reference to the European CPMP guidance for 10 CFU/100mL, and instead makes a comment about a requirement to link bioburden limits to filter efficiency, which seems out of step with most approaches.
- The Annex also clarifies the need for conducting pre-use post-sterilization integrity testing (filter integrity test performed immediately before use).
- This is an issue that has begun to be raised by European Medicines Agency inspectors ahead of the draft Annex appearing.
Some guidance as to the knowledge and skills required for cleanroom operators, with reference to the need to understand hygiene, cleanroom practices, contamination control, aseptic techniques, and potential safety implications to the patient of a loss of product sterility together with the basic elements of microbiology.
Gowning

With gowning and change practices there are greater controls for the first stage changing process:
- Handwashing.
- Outdoor clothing is removed and that some type of garment is worn.

Other garment changes include the requirement for a sterile garment integrity check and with, for aseptic processing, a complete eye covering to be worn (goggles).
Personnel Sampling

- The text contains far greater detail on personnel monitoring.
- But this is sometimes ambiguous: “This monitoring should take place immediately after completion of a critical intervention and upon each exit from the cleanroom”.
- This level of monitoring, if required after every critical intervention, would also require the changing of garments, and consequent increase in the number of personnel.
Media simulation trials

- Tighter guidance is provided for aseptic processing simulations (media filling trials) with the acceptance criteria now set to zero.
- Recommendation that three media fills are conducted following the completion of an investigation into an incident.
With training and aseptic qualifications, the following text is ambiguous: “Only trained personnel who have passed the gowning assessment and have participated in a successful aseptic process simulation (APS) test, during which they performed their normal duties, should be authorized to enter any grade A/B area, in which aseptic operations will be conducted, or are being conducted, whilst unsupervised.”

Furthermore, the line “in which aseptic operations will be conducted” implies that environmental monitoring samplers, cleaners and engineers would need to be supervised when they enter the cleanroom unless they participated in an APS.

Excessive?
Other cleanrooms

- Requirements for Grade C and D routine monitoring detailed.
  - The Annex recommends that risk management techniques are required to justify locations (for both classification and for on-going monitoring) and that the number of samples for routine monitoring be assessed through risk assessment.
  - The use of classification and previous monitoring data, where available, should form part of the assessment.
  - Monitoring need not be continuous.
Sterilisation #1

- The sections on sterilization have been expanded, with different sterilization processes given subsections.
- A general comment about sterilizer qualification is made concerning temperature assessment. This is that temperature probes need to be checked against a second independent temperature probe located at the same position.
- For moist heat sterilization, the important validation parameters are spelt out, namely: equilibration time, exposure time, correlation of pressure and temperature and maximum temperature.
- Other sterilization technologies discussed are dry heat sterilization, sterilization by irradiation, and sterilization using ethylene oxide.
Sterilisation #2

- There is one section that reads confusingly in relation to moist heat sterilisation: “The position of the temperature probes used for controlling and/or recording should have been determined during the validation (which should include heat distribution and penetration studies), and, where applicable, also checked against a second independent temperature probe located at the same position.”
  - This is unclear.
- The following sentence is also unclear: “Chemical or biological indicators may also be used, but should not take the place of physical measurements.”
  - This could be seen as referring to either or both qualification and routine operations.
- With sterilization device validation, where the text states: “Determining the representative sizes of container/closure combinations to be used for validation. Bracketing or a matrix approach can be considered for initial validation of the same container/closure configuration.”
  - Here the word “initial” should be removed.
Visual Inspection

- Visual inspection is a subject that has not been covered in any great detail by the Annex before.
- Each facility is required to have a list of critical deficiencies – such as particle, hairs and turbidity – and to subject operators to regular assessment.
- The assessment should be under practical conditions, with control of inspection time, line speed, and component size. To capture operator fatigue the test should be executed at the end of the shift.
Container Integrity

- There are several references made to container integrity.
  - Containers sealed under vacuum should be tested for maintenance of vacuum after an appropriate, pre-determined period and during shelf life (which relates to a stability studies).
  - Container closure integrity testing needs to consider the impact of transportation, a further reference to Good Distribution Practices.
Water Systems #1

Reference to water systems is a new part of the text. The focus is with water-for-Injections.

There is one section that reads confusing in relation to water, the part which discusses methods other than distillation; however, this only refers to reverse osmosis.
Water Systems #2

- The proposal regarding sampling of water every time it is used is impractical.

- This is what validation is meant to show. Moreover, sampling regimes should be based on risk assessment.
Microbial Ingress

- With the section of the draft which refers to microbial ingress studies.
  - It is unclear why there is now the requirement to conduct these studies to determine how high a stopper detector needs to be.
  - This requirement can be better determined by the crimping capability on the line, since at a certain stopper height there is no guarantee of not squashing the stopper resulting in an imperfect seal under the crimp.
Rapid microbiological methods

Rapid methods are mentioned for the first time in the draft (in section 9 for environmental monitoring and section 10 for end-product testing, such as sterility testing).
Data integrity

- There are a number of references in respect to ‘Data’ i.e. Trend data, Qualification Data, Environmental Data etc., throughout the Annex.

- Surprisingly Annex 1 makes no mention of ‘Record, Data Integrity’ that is fundamental in respect to paper, electronic systems and practices.
General Issues

There are several general instances of unclear terminology. For example:

- The use of the word “cleanrooms”, without specifying what the grade of the area.
- The use of the phrase "critical area" does not align with the definition in the glossary which seems to apply to areas where products are exposed, such Grade A.
- Too many uses of “Grade A/B”.
- Reference to the term “action limits” in the main text and “action levels” used in the glossary.
The new Annex signals a shift in regulatory thinking for the manufacture of sterile products calling for tighter controls, more thoughtful environmental monitoring and nudging pharmaceutical manufacturers towards introducing new technologies.
References

Current Annex 1:

Draft Annex 1:
Summary

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Thank you

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