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Annex 1 Overview

On 25 August 2022, the European Commission published the long-awaited revised updated version of Annex 1 of EU Good Manufacture Practices (GMP) focusing on the manufacture of sterile medicinal products and requiring the manufacturers to have a systematic Contamination Control Strategy (CCS) to eliminate contamination of final products by micro-organism, particulate or endotoxin/pyrogen.

The new Annex 1 update will come into action by 25 August 2023, except for the lyophilizers point (section 8.123) which is postponed until 25 August 2024.

The last update on EU GMP Annex 1 was in 2008, and as a result new requirements are demanded from the manufacturers in order to comply with current Good Manufacturing Practices (cGMP).

The main aim of the new Annex 1 is to widen the sterilization focus from inspecting the sterility of the end product to monitoring and controlling the sterility of the whole process of manufacturing including facilities, equipment, systems, personnel, and procedures used for the production of sterile end products.

What we can help with

Are the updated Annex 1 requirements causing you concern? Unsure if you are ready for the changes? Rest assured, Wickham Micro is your reliable partner in this journey.

Our dedicated services are designed to support you in achieving full compliance with the latest EU GMP Annex 1. Explore our microbiological environmental monitoring solutions and let us assist you in meeting the new standards effectively.

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+44 (0)1329 226600 sales@wickhammicro.co.uk

Key concepts and changes of Annex 1

1 - Quality Risk Management (QRM) approach

This approach represents the guidelines and principles that should be applied to the holistic manufacturing process to ensure the prevention of microbial, particulate, and endotoxin/pyrogen contamination in the final product.

2 - Pharmaceutical Quality System (QMS)

The basic role of a manufacturer's PQS in relation to annex 1 requirements, is to track, address, and control the sterility specifications required for product manufacturing, and also to ensure that the risk of microbial, particulate, and endotoxin/pyrogen contamination is minimized. The new Annex 1 added other requirements to be included in PQS such as:

- Integration of effective risk management systems into all stages that a product goes through during manufacturing.
- The manufacturer has the necessary expertise in product manufacturing and equipment engineering that directly affect product quality .
- Suitable corrective and preventive actions (CAPA) are taken in cases of procedural, or equipment failure by performing root cause analysis and successfully addressing contamination risks.

- Risk management is also applied to monitor the Contamination Control Strategy (CCS) , to address, evaluate, reduce, and control the risks of contamination in production.
- Senior management should review the risk management outcome and monitor the overall state of control on a regular basis.
- Sterile products should be stored and transferred appropriately to maintain sterility.
- Persons responsible for the release of sterile products should have access to the necessary manufacturing and quality information of the product to be able to decide whether the product manufacturing was done in accordance within the required quality specifications.
- Risk management processes should be well documented at each stage.

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3 - Holistic Contamination Control Strategy (CCS)

The CCS approach is one of the new requirements in the updated Annex 1, which:

- The CCS should be introduced to the whole facility of manufacturing to be able to address critical control points and evaluate the state of all controls, also monitoring the aspects of risk management of the product quality and safety.
- As mentioned above, CCS should be routinely reviewed, appropriately managed, and continuously updated in line with best practices in cGMP.
- The CCS should include a cascade of events and measures and its development requires deep knowledge of potential sources of contamination due to microbial and cellular debris (e.g. pyrogen, endotoxin) or particulate (e.g. glass and other visible and sub-visible particles).
- CCS should include (but not be limited to):
    - Premises and equipment.
    - Personnel.
    - Utilities.
    - Raw material controls – including in-process controls.
    - Product containers and closures.

- Vendor approval, such as key component suppliers, sterilization of components and single-use systems (SUS), and critical service providers.
- Management of outsourced activities and availability/transfer of critical information between parties.
- Process risk management.
- Process validation.
- Validation of sterilization processes.
- Preventative maintenance: maintaining equipment, utilities, and premises.
- Cleaning and disinfection.
- Monitoring systems: including an assessment of the feasibility of the introduction of scientifically sound, alternative methods that optimize the detection of environmental contamination.
- Prevention mechanisms: trend analysis, detailed investigation, root cause determination, corrective and preventive actions (CAPA), and the need for comprehensive investigational tools.

Key concepts and changes of Annex 1

4 - Environmental monitoring

Environmental and process monitoring program forms part of the overall CCS.

- The purpose of environmental monitoring is to ensure that cleanrooms, utilities, and associated equipment constantly supply the required quality of clean air.
- Environmental monitoring should be established and documented.
- The CCS should highlight the point at which investigation and assessment of risk to product quality is required.
- Procedures of monitoring should define the approach to trending which could include:
    - Assessing the numbers of excursions from action limits or alert levels.
    - Assessing excursions from alert levels.
    - Regular but separated excursion from action limits that may have a common cause.
    - Changes in microbial flora type and numbers and predominance of specific organisms.

The elements included in the environmental monitoring programs are :

- Environmental monitoring: total particles.
- Environmental and personnel monitoring: viable particles.
- Aseptically Manufactured Product (APS)
- Temperature, relative humidity, and other specific characteristics.

Data collected from applying these systems should be used for routine batch release and for regular evaluation whenever the process is reviewed.

Key concepts and changes of Annex 1

Environmental monitoring: total particles.

- Total particle monitoring includes setting up the maximum limits allowed for total airborne particles for particles ≥0.5 and ≥5 µm according to the area grade (from A-D) where grade A has the lowest allowable limits for particulates and D has the highest allowable limits for particulates.
- Depending on the need during manufacture a laboratory or cleanroom of appropriate grade is chosen by assessing the impact of contamination of the product from the environment. Often there is a cascade in clean room areas to allow performance of different activities of the manufacturing processes.
- For grade A areas, monitoring is full-time during the critical stages of production even during equipment assembly. This continuous monitoring is performed by obtaining a suitable sample flow rate so that any particle concentration changes during the process are captured and then each sample result is correlated to the alert level and action level, hence addressing when the alert level exceeds.
- In cases where contaminants result from the manufacturing process itself (e.g. live organisms, powdery products, and radiation hazards) that could cause an imbalance in particles in the environment the monitoring strategy, and sampling frequency should be adjusted to maintain the same environmental categorization before and after exposure to contamination risk. More viable particle monitoring is strongly recommended in these cases.

Environmental and personnel monitoring: viable particles

- Viable particle monitoring is not only measured during the process of manufacturing but also should be monitored within cleanrooms when no normal action is taking place, this could include post-disinfection, before starting the manufacturing process, once the batch production is completed, for example.
- Viable particle monitoring should include a sampling of personnel at regular time intervals without compromising the quality of the process.
- All microorganisms that are detected in grades A, B areas should be identified at the species level and their potential effects on final product quality should be evaluated.

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Key concepts and changes of Annex 1

Aseptic Process Simulation (APS) (AKA media fill)

The APS should not be considered as primary validation for aseptic processes especially when surrogate materials are used during simulation.
The aseptic process design and accordance with CCS and PQS should be the primary measures of aseptic process effectiveness.

The APS process should closely mimic the routine aseptic manufacturing process and should include all critical stages, specifically:

- Evaluation of all aseptic processes performed as a consequence of sterilization and decontamination cycles of the materials used in manufacturing.
- Evaluation of any additional aseptic procedures for non-filterable formulation.
- Replacing inert gas that is needed sometimes for aseptic manufacturing with air in the simulation process if possible.
- Replacing the additional sterile powder needed for some processes with surrogate material in the same containers.
- Separate simulations of individual unit operations should be avoided.

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While developing the APS plan, the following points should be considered:

- Worst-case conditions should be addressed considering all the relevant variables such as container size and line speed, and their effect on the process. Justification of the selected variables is also considered.
- Deciding the representative container/closure sizes combination that should be used in the process.
- Set up a limit for the time the sterile product and equipment should be exposed during the aseptic process.
- The container should be filled enough for the media to be in contact with component surfaces and also, leave enough above space to detect the potential growth of microorganisms.
- The method of detection of microorganisms should be justified to make sure that all possibly present microorganisms are successfully detected.
- The time for the aseptic simulation process should be long enough to detect any potential challenges.
- Simulation should also include all normal pauses during aseptic manufacturing when the process is on hold due to shift changeovers, recharging dispensing vessels, etc.
- Maintaining normal environmental monitoring during the simulation.

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