The Scilife Success Guide

How to Prepare for EU GMP Annex 1

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01
Introduction

The latest version of the legally binding EU GMP Annex 1 was issued on August 22, 2022. It provides technical guidance and GMP guidelines on manufacturing sterile medicinal products. This new annex will come into effect later this year on August 25, 2023, with the exception of Chapter 8.123 "Product Transfer/Loading/Unloading Areas for Lyophilizers," which will become relevant on 25 August 25, 2024.

The changes in this new annex will significantly affect the manufacture of sterile products, as it introduced several new requirements and clarified some aspects that were not adequately defined before.

However, Annex 1 is a dense document to read and interpret; and some changes will require expert interpretation. That's why we are highlighting and discussing the main changes of the new annex in this article.

The first modification in Annex 1 goes beyond specific technical aspects. The new version represents a significant shift in perspective, focusing on the connection between Annex 1 and risk management.

Overall, the objective of the annex is still to define the requirements to "minimize the risk of microbiological, particulate and pyrogen contamination in sterile products."

Yet, in any manufacturing environment where human operators are present, microbial contamination is an unavoidable reality, even with the most stringent cleanroom protocols. It is unrealistic to expect zero contamination in all areas during every aseptic processing operation due to contamination risks from personnel, utilities, and equipment. Additionally, it is impossible to completely prove the sterility of the aseptic processing environment and the surfaces that come into contact with the product.

What contamination sources are there?

- **Primary sources:** personnel and water (including aerosols)
- **Secondary sources:** air, surfaces, and equipment

Are you ready? Let's begin.

02
Main Changes

Despite the unchanged goal of establishing requirements to reduce the likelihood of contamination in sterile products, three new concepts have been incorporated into the scope and opening sections of the annex:

02. A. The potential application of the concepts outlined in Annex 1 to non-sterile product areas

A common practice in non-sterile laboratories was to apply some specific points of the legacy Annex 1 that was not reflected in the regulation. The classification of cleanrooms into grades or microbiological control limits during routine monitoring is one example. Thanks to this addition in the new version, these cases become more meaningful and are now well-reflected.

02. B. Introduction of the Quality Risk Manager (QRM) and Pharmaceutical Quality System (PQS) principles

The new annex has moved from an almost residual mention of the concept of risk to the application of a more emphatic and reinforced Quality Risk Manager (QRM) approach in all activities. QRM has become an essential methodology to use at the level of procedures, equipment, facilities, services, personnel, and processes. The incorporation of the two concepts was necessary to align the guideline with other current guidelines, such as ICHQ9 and ICHQ10.

02. C. The implementation of the Contamination Control Strategy (CCS)

The new annex places a stronger emphasis on thorough oversight and examination of sterile product areas through a **Contamination Control Strategy (CCS)**. CCS is presented as a mandatory document, which should define all critical control points, measures, and assessment of effectiveness to control all risks associated with product contamination.

To attain a state of control that ensures product Quality and patient safety, the annex requires organizations to design an effective CCS based on a scientific assessment, understand the process, and implement QRM principles. These principles must provide a proactive means of identifying, scientifically evaluating, and controlling potential risks to Quality.

The annex not only considers the current state of control but also **underlines the need for innovative technology or techniques** to fill any gaps.

03
Premises

03. A. Cleanrooms, areas, and barrier technologies

The new annex places a strong emphasis on using new barrier technologies to prevent contamination from materials or personnel shredding in Grade A areas.

There is another change in the section of the premises. Now, Grade A is considered a critical zone for high-risk operations, whereas Grades B, C, and D are considered cleanrooms.

This classification is achieved by using unidirectional airflow in Restricted Access Barrier Systems (RABS) or isolators.

What is a Restricted Access Barrier System (RABS)?

A Restricted Access Barrier System (RABS) is a localized airflow protection system used to control the environment in which sterile products are manufactured. This system provides a physical barrier between the operator and the product while maintaining an aseptic environment inside the RABS unit.

In the legacy version of Annex 1, Grade A was met by using a laminar airflow. Now, laminar airflow has been replaced by unidirectional airflow.

With unidirectional airflow, air enters in only one direction, thus reducing the possibility for particles to fall into the cleanroom.

How does unidirectional airflow work? Unidirectional flow is maintained through the use of laminar airflow hoods that direct air jets downward in a straight path.

To achieve this, the access of personnel into the Grade A area should also be limited through the design of facilities, equipment, processes, and procedures.

Air pressure differentials must now be continuously monitored; and there must be an alarm system in case of out-of-limit values. In contrast, the legacy version only required this to be recorded periodically.

03. B. Airlocks

The new annex recommends separating personnel airlocks for entry and exit from those used for the movement of materials between different areas or cleanrooms.

What is an airlock?

An airlock is an enclosed space with interlocking doors constructed to maintain air pressure control between adjoining areas or cleanrooms. The airlock is used to prevent the entry of particles and microorganism contamination from lesser-controlled areas.

The annex also recommends having an interlock mechanism in place for Grade A and B areas, although it would seem logical to apply this principle to all cleanroom grades.

Please note that the entry and exit doors of airlocks leading to Grade A and B areas should not be opened simultaneously. This can be achieved by using an interlocking system.

However, in the case of airlocks leading to Grade C and D areas, a visual and/or audible warning system is sufficient.

What is an interlocking system in a cleanroom?

An interlocking system is designed to control access into a cleanroom and prevent its contamination. An interlocking system consists of doors, airlocks, and other access points that are connected to an electronic control system. The control system ensures that the cleanroom is not entered or exited unless the proper procedures have been followed and the environment is in a suitable state.

For example, an interlocking system might require personnel to pass through an airlock before entering a critical area. This airlock might have two doors, and the control system would ensure that the first door cannot be opened until the second door is closed.

This helps prevent contaminated air from entering the cleanroom and protects the products during manufacturing.

The interlocking system can also be used to control airflow and the operation of other environmental control systems, such as HEPA filters, to maintain a required level of cleanliness and sterility.

If the CCS indicates a high risk of cross-contamination, the annex states that separate changing rooms for the entry and exit of personnel should be considered.

03. C. Entry of personnel

Personnel that enters the space should flow from lower to higher grade areas of increasing cleanliness (for example, from Grade D to C, from C to B, and then from B to A). However, the new annex does not state the flow of personnel who leave the space, which potentially allows for skipping grades on the way out.

03. D. Entry of materials

The movement of materials from lower-grade cleanrooms to higher-grade areas should be subject to cleaning and disinfection, depending on the risk and the CCS.

03. E. Airflow visualization

Airflow patterns and complex gas flows within cleanrooms and zones should be visualized to demonstrate that air does not ingress from lower grade (i.e., more contaminated) to higher grade (i.e., less contaminated) areas.

03. F. Cleanroom monitoring

The new annex strongly focuses on environmental monitoring since continuous cleanroom monitoring and environmental monitoring is the most effective way of reducing contamination risk.

However, this should not be a substitute for poor environmental control. It means that **Quality by design** and risk assessment principles need to be introduced in the process design beforehand. Cleanroom monitoring should be part of the overall CCS.

The controls and monitoring practices are to be based on sound scientific reasoning and should be able to effectively assess the cleanroom environment, airlocks, and pass-through hatches. Ensure that these conditions are properly monitored and evaluated.

What is the purpose of environmental monitoring?

- Provide information about any adverse trending data on the Quality of the environment during manufacturing
- Apply preventive actions to avoid future microbiological contamination
- Prevent the release of a potentially contaminated batch
- Identify environmental controls
- Provide a cleanliness status of the manufacturing site
- Study the pattern of microbiological species to identify those that are more resistant

How is contamination monitored?

- Viable counting methods (e.g., settle plates, air-samplers, contact plates, or swabs)
- Particle counting
- Rapid microbiological methods (e.g., spectrophotometric or biofluorescent counters)

03. G. Cleanroom and clean air equipment qualification

It is obvious that cleanrooms and clean air equipment must be classified and qualified for the manufacture of sterile products. However, the legacy document did not define what tests would need to be executed for this.

For the first time, the new annex includes a list of tests to perform for the qualification of cleanrooms. Qualification should include testing

for: filter system, airflow, air pressure, microbial contamination, temperature, humidity, recovery, and containment leak.

The classification of cleanrooms is based on the total particle concentration limits (at 0.5 microns and 5 microns), and is part of the cleanroom qualification process.

The initial classification should be performed during simulated operations in both “at rest” and “in operational” states.

In addition, the qualification of cleanrooms is completed by the **determination of microbial contamination level**. The number of samples taken and their sampling locations should depend on the risk assessment.

What do “at rest” and “in operational” mean?

“At rest” means with the main manufacturing equipment installed as specified but not operating and without personnel present in the room.

“At operational” means with the maximum number of personnel present, performing or simulating routine operational work. This is the worst case, which is essential for routine assessment.

The speed of air criterion for unidirectional airflows (homogeneous values within 0.36-0.54 m/s) is maintained at the working position unless scientifically justified in the CCS.

The legacy annex included microbial contamination limits for the monitoring of clean areas or areas in operation. The new annex specifies that the microbial concentration level must be determined during qualification both “at rest” and “in operation” and must be verified by three methods indicated in Table 2 (Chapter 4.31).

Otherwise, adequate justification must be given for not carrying out any of the methods.

There are two changes in the maximum permitted microbial contamination levels appearing in the new annex:

> The average calculation of results is not considered in the table; and
>
> No growth of microbial contamination should be seen for Grade A cleanrooms.

The annex specifies for the first time the frequency or maximum time interval for qualification:

> 6 months for Grade A and B areas; and
>
> 12 months for Grade C and D areas.

The document also requires the maximum number of people present in the clean area during operation.

Requalification is also needed whenever there is a change to equipment, facility, or process, and based on the change management process.

Moreover, it is not enough to qualify or validate facilities, equipment, and processes. Continuous verification and regular reviews must be conducted.

03. H. Disinfection

The new annex places a stronger focus on cleaning and disinfection protocols.

Cleaning needs to take place before disinfection. However, cleaning must not leave residues, as these may interfere with disinfectants.

Different types of disinfectants can be used, as they have different modes of efficacy in order to increase the spectrum of disinfection. A sporicidal agent must be included in the disinfection plan across all grades of cleanrooms.

The disinfection process must be supported by the use of validated disinfectants and be assessed through the environmental monitoring program, including different types of organisms that are potentially resistant.

The annex requires any disinfectant that is diluted to be assessed for its microbial content, including hold times and expiry times.

The text requires that disinfectants and **detergents used in Grades C and D** may also **require sterilization when determined by the CSS**. When they are prepared by the manufacturer, microbial contamination should be monitored by the supplier; when supplied "pre-diluted", the supplier's certificates of analysis can be accepted as long as the supplier is qualified.

The cleaning validations should respect the expiry dates of the prepared solutions.

04
Equipment

Some points of the equipment section have been expanded in the new annex to provide general guidance on the design and operation of equipment:

> A detailed description of equipment and services (process and instrumentation diagrams) should be available at the initial qualification and kept up to date as part of the continuous review of the CCS.
>
> Process and equipment alarms should be evaluated for trends.
>
> Direct and indirect product contact parts (parts in contact with sterilized critical components) should also be sterilized.
>
> Particle counters, including their sampling tubing, should be qualified. The new annex specifies that the length of the tubing must not exceed 1 meter and should have a minimum number of bends.

05
Utilities

The previous annex did not go into much detail on utility systems such as gas, water, and vacuum. The new annex incorporates the following requirements:

The criticality of each utility system needs to be assessed as part of the CCS and covered by a risk assessment. Higher-risk utilities in descending order of criticality include:

- Major risk: Utilities that directly contact product, such as water for washing and rinsing, gases, and steam for sterilization.
- Utilities that contact materials that will ultimately become part of the product.
- Utilities that contact surfaces that come into contact with the product.
- Other utilities that may directly impact the product.

Results of critical parameters and **Critical Quality Attributes (CQA)** of high-risk utilities need to be trended regularly to ensure the system's suitability. For example, trends of pressure differentials, steam Quality, and water Quality.

Pipes and ducts are to be avoided in cleanrooms. Our interpretation of this requirement is to minimize their impact on the cleanliness and contamination control of the environment. Cleanrooms need to be designed with minimal airborne and surface contamination, so the presence of pipes, ducts, and other utilities that penetrate the walls or ceiling can introduce contaminants from other areas into the cleanroom.

05. A. Water systems

The requirements for water systems focus on actions that prevent microbiological contamination, particulate matter, and endotoxins/ pyrogens.

Water for injections (WFI) that is free from microorganisms, particulates, and endotoxins should comply with the current monograph of the European Pharmacopeia. Water should be in constant circulation at a temperature above 70ºC to maintain Quality and minimize the risk of microbiological growth. Special care should be taken for **microbial contamination** from vent filters installed in storage tanks. Legs in pipelines should be avoided wherever possible.

Biofilm formation is another challenge. The risk of microbial adhesion and biofilm formation in the pipes can be minimized if the water flow is turbulent, and sterilization, disinfection, or regeneration of water systems is planned.

Special care should be taken due to **seasonal variation**. After disinfection is done, testing must be carried out before using the water system.

Continuous TOC and conductivity monitoring must be in place in WFI systems. These values can indicate the performance of the water system and alert probable excursions before they happen,

Values exceeding the alert levels should be documented and include a trend analysis to determine if this is an isolated event or if it is indicative of loss of control or deterioration of the system. The root cause and impact on the Quality of products or processes in which it is involved should be determined.

05. B. Steam used as a direct sterilizing agent

Pure steam generators must be designed, qualified, and operated in such a way as to comply with the defined specifications of chemical substances and endotoxins.

When steam is used as a direct sterilization agent of materials or surfaces in contact with the product, the condensates must comply with the current EP monograph for WFI. A regular sampling plan must be in place to ensure representative samples of pure steam are tested for analysis in which additionally non-condensable gases, dryness value and superheat must be analyzed.

05. C. Gases and vacuum systems

Gases that come into direct product contact must be of the appropriate chemical, particulate, and microbial Quality, including oil and water content.

The design of the gas and vacuum system should prevent backflow to avoid potential risks of contamination.

In the case of gases used in aseptic processes, an additional filtration step is needed to remove basic bacteria. A sterilizing grade filter with a pore size of a maximum of 0.22 microns needs to be used at the point of use.

05. D. Heating and cooling and hydraulic systems

There is a risk of spillage and cross-contamination with heating, cooling, and hydraulic systems. To avoid this risk, it is recommended that they are placed outside the filling room. In the event of leakage, a warning alarm should be in place.

06

Personnel

The basic requirement of having **trained, qualified, and experienced personnel** with a focus on sterile product protection is maintained in the annex. It is the manufacturer's responsibility to ensure that sufficient appropriate personnel is available.

Particular importance is given to training, specifying the areas in which relevant staff must be trained: hygiene, microbiology, cleanroom practices, contamination control, aseptic techniques, behaviors, gowning, and protection measures.

The training should be comprehensive, being in accordance with the criticality of the activities and areas of work to be carried out by each person.

The entry of non-qualified personnel to Grade A and B cleanrooms in operation is restricted. For exceptional cases where access is necessary, written procedures outline the situations in which access is allowed and what steps are to be taken, including direct supervision by a qualified and authorized person.

Clothing with low particle shedding is required. Appropriate garments for sterile areas must be worn prior to entry to Grade B areas and visually inspected for their integrity.

Reusable clothing must be cleaned using a **qualified procedure** that ensures clothing is not damaged and contaminated.

The annex mentions that personnel qualification procedures and a disqualification system must be in place. To reinstate a disqualified employee for aseptic practices, retraining and requalification is required.

07
Production and Specific Technologies

Not much has changed regarding production technologies for terminal sterilization. The CCS should **identify the risks of contamination in different areas and cleanrooms**. If a high risk of contamination has been identified in the processing of bulk solutions, a filtration step should be used to reduce the bioburden levels prior to the filling process. The cleaning of primary packaging containers and components should also be validated. The new annex encourages the use of RABS, isolators, and robotics to reduce the risk of contamination and the need for human interventions.

07. A. Human interventions

Human interventions during aseptic processing are serious issues. They can increase the risk of introducing contamination into the aseptic filling area. The new annex requires that human interventions are carefully designed, evaluated via risk assessment, and qualified.

Interventions can disrupt first air. So, we can say that the best practice is to **avoid any kind of intervention whatsoever**. If this is not possible, we should limit the number and complexity of human interventions as much as possible.

Non-qualified interventions should be performed exceptionally with the authorization of the Quality unit, which should perform a risk assessment, an investigation, and an evaluation prior to batch disposition.

What kind of interventions are there?

There are two main types of interventions: routine and non-routine:

- Routine interventions are part of the process and are performed in every bath manufactured.
- Non-routine interventions are usually not part of the process. They are referred to as corrective interventions due to a problem or failure during manufacturing.

Due to the potential for microbial growth, manufacturers should typically conduct studies to define acceptable hold times for process intermediates. There should be a maximum permissible time for each specific product and preparation.

What is holding time?

Holding time is the amount of time that a preparation remains in a controlled, sterile environment after it has been prepared but before it is used. The holding time is intended to prevent contamination of the item during the interval between preparation and use.

07. B. Sterilization

The new annex includes a large section on sterilization technologies:

> Sterilization by heat
>
> Moist heat sterilization
>
> Dry heat sterilization
>
> Sterilization by radiation
>
> Sterilization with ethylene oxide
>
> Filter sterilization

The following guiding principles are essential:

> Use scientific principles in the selection of the sterilization procedure.
>
> Validate the sterilization process - repeatability and reliability - by physical measurements and biological indicators.
>
> Use heat sterilization, which is the preferred system; otherwise use another method described in the current **European Pharmacopeia**.
>
> There are some concerns with the use of ethylene oxide. It should only be used when no other method is practicable, because of the difficulty to ensure that no residues or reaction products are controlled at acceptable limits.
>
> Review and verify the sterilization process at scheduled intervals according to the risk assessment and CCS.

> Deviations must be investigated.
>
> Sterilization records should be reviewed and approved for batch release purposes by a knowledgeable person.

The new annex describes other areas of aseptic sterilization that are out of the scope of this article, like packaging systems and other processes: form-fill-seal (FFS), blow-fill-seal, lyophilization, closed, and single-use systems (SUS).

08

Environmental and Process Monitoring

As an important verification tool in the CCS, the environmental program will ensure the air cleanliness of cleanrooms and equipment and will detect deviations from established acceptance criteria. All **controls are effective when they are considered holistically and not individually.** The guidance applies to ongoing routine monitoring.

Environmental monitoring comprises the following:

> Particle monitoring (the particle monitoring program should be risk-based to establish samples locations, types of samples and methods selected, samples sizes and volumes, sampling time, frequency, and strategy for personnel monitoring)
>
> Viable particle monitoring
>
> Temperature monitoring
>
> Relative humidity monitoring
>
> Aseptic process simulation (APS) or media fill

These parameters are **good indicators of the areas' cleanliness** and their good aseptic processing conditions.

Temperature and humidity are important environmental parameters that can affect the stability and shelf life of the product. It can also impact the growth and survival of microorganisms, which can pose a risk of contamination to the product.

It is important to note that the annex considers positively the use of rapid monitoring methods, appropriately validated, which speed the early detection of microbial contamination.

Alert levels and action limits need to be established based on qualification tests. Trending data should be reviewed periodically. In the case of having out-of-alert/action limits, they should be investigated to find the root cause and apply appropriate CAPAs.

The annex describes that APS or media fill is periodic verification effectiveness that should be done based on Risk Assessment of the aseptic process (e.g., qualification, validation, or after changes). APS should cover aseptic manipulations and interventions, as well as worst-case scenarios.

What is aseptic process simulation (APS) or media fill?

Aseptic process stimulation (APS) or media fill **is a simulation of the aseptic manufacturing process** that evaluates the capability of the aseptic process to ensure product sterility in all aseptic operations associated with routine manufacturing.

Microbiological growth-promoting media **is used in place of the product.**

The media is made to contact all product contact surfaces of the equipment chain, container closure, critical environment, and process manipulations that the product itself will undergo.

Media is then incubated and inspected for **microbial growth**.

This information is used to assess the potential for product units to become contaminated during the aseptic processing operations.

All routine monitoring data obtained in production should be trended and used as part of the routine batch release and periodic assessments. Trends should include different types of excursions, such as increasing numbers of excursions, consecutive excursions, isolated excursions, or changes in microbial patterns.

09

Quality Control

The QC part of the annex includes requirements on:

- QC/QA personnel training and experience
- Specifications
- Types of microbiological tests (e.g., bioburden or sterility)
- Sampling
- Method verification/validation
- Parametric release
- Data review

10

Final Considerations

In the end, it is important to recognize that the Annex only sets out the minimum requirements. Pharmaceutical manufacturers should continually focus on preventative strategies, including proactive risk assessments and controlled changes, supported by trending, investigations, corrective and preventive actions (CAPA), root cause determination, and the use of robust investigational tools. Producing sterile medicinal products is all about continuous improvements.

Discover how a tailored Smart Quality Platform for Pharmaceutical companies can help you get ready for all the changes in the EU GMP Annex 1!

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