LIGHTHOUSE
WORLDWIDE SOLUTIONS

OVERVIEW OF EU GMP ANNEX 1:2022

Lighthouse Worldwide Solutions

Overview

The EU GMP Annex 1 is a set of guidelines that outline the requirements for the manufacture of sterile medicinal products. It is a standard that is enforced by the European Medicines Agency (EMA) for all manufacturers of sterile medicinal products in the European Union (EU). The Annex 1 standard was first introduced in 1992, and since then, it has undergone several revisions.

The latest revision of the Annex 1 standard was published in March 2021 and became effective in September 2022. The key changes in the revised standard include a stronger emphasis on risk management, more specific requirements for the design and operation of cleanrooms and controlled environments, updated requirements for environmental monitoring and controls, and new requirements for personnel training and hygiene.

The European Untion (EU)

The European Union (EU) is a political and economic union of 27 member states located primarily in Europe. The EU was established by the Treaty of Rome in 1957, and its primary objectives are to promote peace, stability, and economic prosperity in Europe.

EU GMP stands for European Union Good Manufacturing Practice. It is a set of guidelines and regulations that ensure that pharmaceutical products are consistently produced and controlled according to the highest quality standards. The EU GMP is enforced by regulatory authorities in the European Union (EU) and applies to all manufacturers of medicinal products intended for human use within the EU.

Compliance with EU GMP guidelines is essential for pharmaceutical manufacturers that wish to distribute their products in the EU. Manufacturers must demonstrate that they comply with the guidelines through regular inspections by regulatory authorities. Failure to comply with EU GMP guidelines can result in regulatory action, including suspension or revocation of a manufacturer's license to operate.

Some of the Key Areas Covered by the EU GMP Annex 1 Standard Include:

- **Design and Operation of Cleanrooms and Controlled Environments: The standard outlines specific requirements for the design and operation of cleanrooms and controlled environments, including air quality, airlocks, and gowning procedures.**
- **Sterilization: The standard provides guidance on the various methods of sterilization, including steam sterilization, dry heat sterilization, and sterilization by irradiation.**
- **Environmental Monitoring: The standard requires that manufacturers regularly monitor the environment in which sterile products are produced to ensure that it meets the necessary standards for cleanliness and sterility.**
- **Personnel: The standard outlines requirements for personnel training and hygiene, including the use of appropriate protective clothing and regular hand washing.**
- **Quality Control: The standard requires manufacturers to implement a robust quality control system to ensure the quality and safety of their products.**

Environmental Monitoring

Environmental monitoring is a critical component of the manufacturing process for sterile medicinal products, as it helps to ensure that the production environment is maintained at the necessary standards for cleanliness and sterility. The EU GMP Annex 1 provides specific requirements for environmental monitoring that manufacturers of sterile products must adhere to.

The requirements for environmental monitoring are set out in Chapter 9 of the Annex 1 standard. The chapter covers a range of topics, including:

1. **Frequency of Monitoring: The standard requires that environmental monitoring be conducted at appropriate intervals, taking into account the risk of product contamination and the nature of the manufacturing process. The frequency of monitoring should be established based on a risk assessment of the process.**
2. **Sampling Methods: The standard provides guidance on the appropriate methods for sampling the environment, including the use of settle plates, contact plates, and air sampling. The standard also specifies the minimum number of samples that should be taken in each area of the production environment.**
3. **Acceptance Criteria: The standard sets out specific acceptance criteria for the results of environmental monitoring. These criteria are based on the microbial limits for different areas of the production environment.**
4. **Trending and Investigation: The standard requires manufacturers to trend environmental monitoring data over time and to investigate any trends or deviations from established limits. Manufacturers must also have a system in place to investigate and address any environmental excursions.**
5. **Reporting: The standard requires manufacturers to document and report the results of environmental monitoring, including any trends or excursions, as part of their quality management system.**
6. **Verification of Cleaning and Disinfection: The standard requires that manufacturers verify the effectiveness of their cleaning and disinfection procedures through environmental monitoring. This is typically done by conducting monitoring after cleaning and disinfection to ensure that the microbial counts are within acceptable limits.**

EU GMP Annex 1 provides specific requirements for environmental monitoring in the manufacture of sterile medicinal products. These requirements cover the frequency of monitoring, sampling methods, acceptance criteria, trending and investigation, reporting, and verification of cleaning and disinfection. Adhering to these requirements is essential for ensuring the safety and efficacy of sterile products.

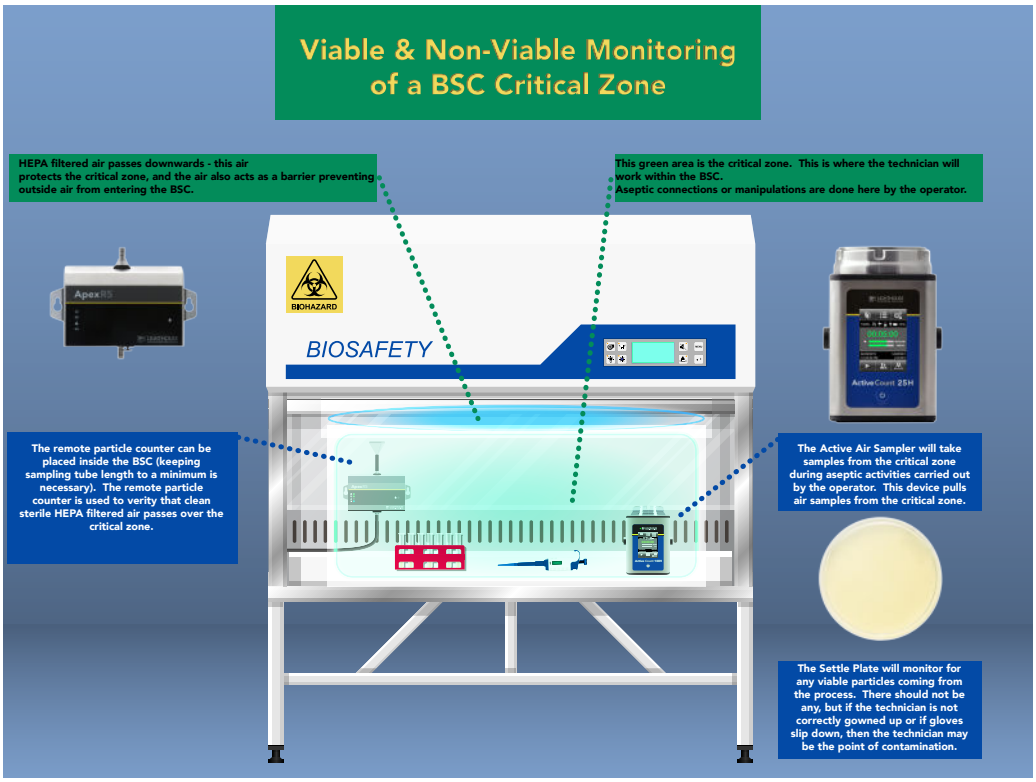
How is Environmental Monitoring achieved?

EU GMP Annex 1 provides specific requirements for environmental monitoring in the manufacture of sterile medicinal products. These requirements are achieved through a systematic approach that involves the following steps:

Risk Assessment: The risk assessment should evaluate the potential sources of contamination and the likelihood of contamination occurring. It should take into account factors such as the product being manufactured, the manufacturing process, the personnel involved, and the facility and equipment used. The assessment should also consider any regulatory requirements or guidelines that apply.

Sampling Plan: The sampling plan should be based on the results of the risk assessment and should include the frequency of sampling, the sampling locations, the types of samples to be taken, and the methods of sampling. The plan should also consider any relevant regulatory requirements or guidelines.

Sampling Methods: The appropriate sampling methods will depend on the area being sampled. Settle plates, contact plates, and air sampling are commonly used methods. The sampling method should be validated to ensure its effectiveness in detecting microbial contamination.



Biological Safety Cabinet is monitored for viable and non-viable particulates based on Risk Assessment.

Acceptance Criteria: The standard provides specific acceptance criteria for the results of environmental monitoring. These criteria are based on the microbial limits for different areas of the production environment, and any results that exceed these limits must be investigated and addressed.

Trending and Investigation: Environmental monitoring data should be trended over time to identify any trends or deviations from established limits. Any deviations or trends should be investigated to identify the root cause and to implement appropriate corrective and preventive actions.

Reporting: The results of environmental monitoring should be documented and reported as part of the manufacturer's quality management system. The reporting should include any trends or deviations, as well as any corrective and preventive actions taken.

Verification of Cleaning and Disinfection: Manufacturers must verify the effectiveness of their cleaning and disinfection procedures through environmental monitoring. This is typically done by conducting monitoring after cleaning and disinfection to ensure that the microbial counts are within acceptable limits.

What Types of Environmental Monitoring Does EU GMP Annex 1 Discuss?

1. **Settle plates: Settle plates are petri dishes containing a nutrient medium that is exposed to the air in the environment being monitored. The plates are left in place for a specified period of time, typically one to four hours, and then incubated to allow any microorganisms present to grow. The number and type of microorganisms that grow on the plates can provide an indication of the microbial contamination present in the environment.**
2. **Contact plates: Contact plates are similar to settle plates but are placed directly onto surfaces in the environment being monitored. They can be used to assess the level of microbial contamination on surfaces such as workbenches, floors, and walls.**
3. **Air sampling: Air sampling involves the use of specialized equipment to capture and analyze the air in the environment being monitored. The equipment may use impaction, filtration, or centrifugation to collect particles from the air, which are then analyzed for the presence of microorganisms.**
4. **Surface swabbing: Surface swabbing involves the use of sterile swabs to collect samples from surfaces in the environment being monitored. The swabs are then analyzed for the presence of microorganisms.**

5. **Passive air sampling: Passive air sampling involves the use of a settling dish that collects particles from the air over a period of time, typically one week. The particles are then analyzed for the presence of microorganisms.**
6. **Particle counting: Particle counting involves the use of specialized equipment to measure the number and size of particles in the air. The data collected can provide an indication of the level of particulate contamination in the environment.**
7. **Water sampling: Water sampling involves the collection and analysis of samples from water sources in the environment being monitored. The samples are typically analyzed for the presence of microorganisms and other contaminants.**

What is Routine Monitoring?

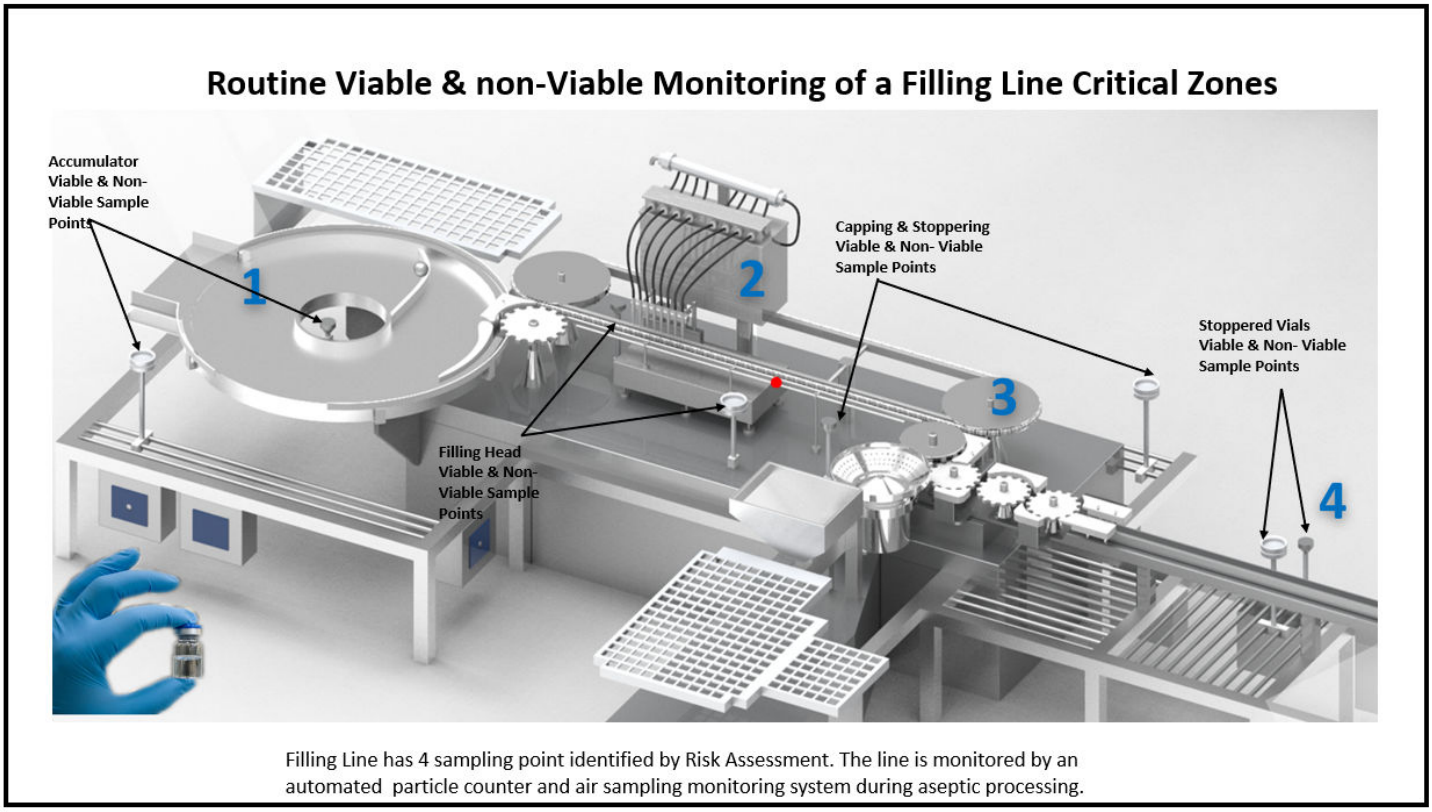
Manufacturers of sterile medicinal products are required to establish a routine environmental monitoring program that includes monitoring of air, surfaces, personnel, and water. The frequency of monitoring should be based on a risk assessment of the process.

EU GMP Annex 1:2022 standard requires that manufacturers of sterile medicinal products establish a routine environmental monitoring program that includes monitoring of air, surfaces, and personnel.

Specifically, the standard states that manufacturers must monitor the viable and non-viable particulate contamination in the areas where the product is exposed to the environment, using appropriate sampling methods and acceptance criteria. The standard also requires that manufacturers establish a routine program for monitoring the quality of the water used in the manufacturing process.

The standard further requires that the frequency of environmental monitoring be established based on a risk assessment of the process, taking into account factors such as the type of product being manufactured, the manufacturing process, and the equipment and facilities being used.

In general, the standard recommends that environmental monitoring be conducted at appropriate intervals to ensure that the manufacturing environment is maintained at the necessary standards for cleanliness and sterility. The frequency of monitoring should be sufficient to detect any deviations from established limits and to identify any trends or issues that may require corrective and preventive actions.



Example of sensor placement on filling line and routine monitoring of critical points along the Filling Machine

Section 8.4.2 of the Annex further requires that "Environmental monitoring shall be conducted in accordance with a defined program, which takes into account the risk to the product and process, and shall include monitoring for microbiological and particulate contamination." This means that manufacturers must conduct regular monitoring of the cleanroom environment for the presence of microorganisms and particles.

The Annex also emphasizes the importance of integrating the data from continuous monitoring and environmental monitoring to provide a comprehensive understanding of the cleanroom environment. For example, section 8.4.2.2 states that "Data from continuous monitoring and environmental monitoring shall be combined and evaluated to provide a complete picture of the environmental conditions."

To give some examples of how this integration of data can be used, section 8.4.3 of the Annex recommends the use of statistical process control (SPC) to evaluate the data from continuous monitoring and environmental monitoring. This can help identify trends and patterns in the data that may indicate a potential issue with the manufacturing environment.

Another example can be found in section 8.5.5.5 of the Annex, which requires that "the frequency and locations of environmental monitoring shall be justified based on risk assessment." This means that manufacturers must carefully evaluate the risk of microbial and particulate contamination at different points in the manufacturing process and adjust the frequency and locations of environmental monitoring accordingly.

Overall, the EU GMP Annex 1 2022 emphasizes the importance of integrating continuous monitoring and environmental monitoring to ensure the control of the sterile manufacturing environment and the safety and efficacy of sterile medicinal products.

Contamination Control Strategy

EU GMP Annex 1:2022 standard provides guidance on contamination control strategies for the manufacture of sterile medicinal products. According to the standard, a contamination control strategy is a systematic approach to preventing contamination and ensuring the quality of sterile medicinal products.

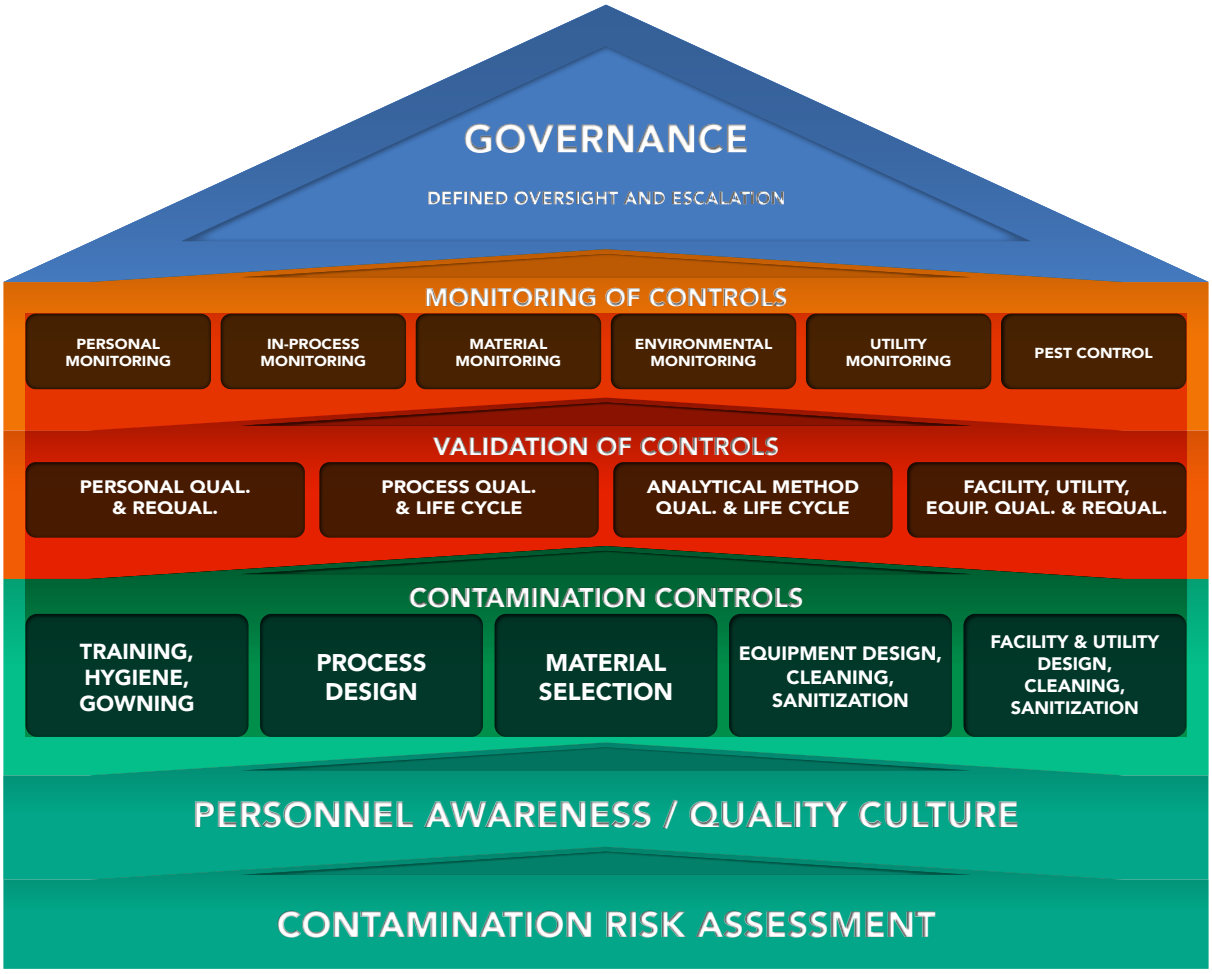
The standard states that manufacturers must develop a contamination control strategy that is based on the principles of quality risk management and that takes into account the specific risks associated with the manufacturing process. The strategy should be designed to minimize the risk of contamination at every stage of the process, from raw materials and equipment to personnel and the environment.

The goal of a CCS is to make sure that a manufacturing process is running smoothly and safely, and that the products being made are of high quality. By using tools like monitoring and control, a CCS can help make sure that everything is working as it should be. The CCS is a facility wide and Environmental Monitoring is a subset of the CCS governance.

The CCS is there to ensure that products are manufactured in a controlled environment that is free from contamination, which could compromise the safety, quality, or efficacy of the final product.

The Contamination Control Strategy Should Include the Following Elements:

- **Risk assessment:** The contamination control strategy should be based on a risk assessment that evaluates the potential sources of contamination and the likelihood of contamination occurring at each stage of the manufacturing process.
- **Design and layout of facilities:** The facilities should be designed and laid out to minimize the risk of contamination. This includes using appropriate materials for construction and finishes, providing appropriate air filtration and ventilation, and ensuring that there is proper separation between different areas of the facility.
- **Equipment and process design:** The equipment and manufacturing processes should be designed to minimize the risk of contamination. This includes using appropriate materials for equipment, designing processes that minimize the potential for contamination, and ensuring that equipment is properly cleaned and maintained.
- **Personnel:** Personnel should be trained and qualified to perform their duties and to maintain a high level of cleanliness and hygiene. This includes appropriate gowning and hygiene practices, as well as regular training on contamination control.
- **Environmental monitoring:** The manufacturing environment should be regularly monitored to ensure that it is maintained at the necessary standards for cleanliness and sterility.
- **Cleaning and disinfection:** The cleaning and disinfection procedures should be designed and validated to ensure that they effectively remove and control microbial contamination.
- **Process validation:** The manufacturing processes should be validated to ensure that they are capable of producing sterile medicinal products of the required quality.



Principals of a Contamination Control Strategy outlined in EU GMP Annex1:2022

Think of a CCS as a superhero that helps keep a factory or manufacturing plant running smoothly. Just like how a superhero has special powers and tools to fight crime, a CCS has special tools and processes to make sure that everything is working as it should.
One of the main tools that a CCS uses is called monitoring. Monitoring means keeping track of different parts of the manufacturing process to make sure that everything is working as it should be. For example, if you're baking a cake, you might use a timer to monitor how long the cake is in the oven, and a thermometer to monitor the temperature of the oven to make sure it's not too hot or too cold.

A CCS does something similar but on a much bigger scale. It might monitor things like the temperature of a machine, the pressure in a pipe, the level of a liquid in a tank, or particle counts in a room. If the CCS sees that something is going wrong or is about to go wrong, it can send an alert to the people in charge so that they can fix the problem before it gets worse.

Another important part of a CCS is called control. Control means using different tools and processes to make sure that everything is working correctly. For example, if you're driving a car, you might use the brakes to slow down or stop the car if you need to. In a manufacturing process, a CCS might use control valves to regulate the flow of a liquid, or sensors to make sure that something is in the right place at the right time.

Pharmaceutical Water System Monitoring

Manufacturers must also establish a routine program for monitoring the quality of the water used in the manufacturing process. The frequency of monitoring for water should be based on a risk assessment of the process and should take into account factors such as the source of the water and the potential for contamination.

The standard requires that water used in the manufacture of sterile medicinal products be of suitable quality and that it meet the requirements of the European Pharmacopoeia or other appropriate standards.

The standard specifies that manufacturers should monitor the quality of water used for the following purposes:

1. **Water for Injection (WFI): Water used for the preparation of parenteral products, such as injections, must meet the requirements of the European Pharmacopoeia or other appropriate standards. The standard requires that WFI be monitored for microbial contamination, endotoxins, conductivity, and other relevant parameters.**

Water for injection (WFI) is a type of water that is used in the pharmaceutical industry for the preparation of sterile medicinal products, particularly for parenteral preparations such as injections, intravenous infusions, and ophthalmic solutions.

WFI is a highly purified form of water that meets the requirements of the European Pharmacopoeia or other appropriate standards. It is used as a solvent for active pharmaceutical ingredients (APIs) and excipients, and it is also used for reconstituting lyophilized products.

2. **Purified Water (PW): Water used for the preparation of non-parenteral products, such as oral liquids and topical preparations, must also meet the requirements of the European Pharmacopoeia or other appropriate standards. The standard requires that PW be monitored for microbial contamination, conductivity, and other relevant parameters.**

PW is required to meet strict specifications for microbial contamination and other impurities. It is typically produced through a process of reverse osmosis or ion exchange, followed by a process of ultrafiltration to remove impurities and further purify the water.

3. **Water used for cleaning and disinfection: Water used for cleaning and disinfection must also be of suitable quality. The standard requires that this water be monitored for microbial contamination and other relevant parameters.**

Water used for cleaning and disinfection in the pharmaceutical industry is typically referred to as "cleaning water." This type of water is not required to meet the same level of purity as water for injection (WFI) or purified water (PW), as it is not used directly in the manufacturing process.

Liquid Particle Counters That Can be Used to Monitor WFI and PW

Liquid Particle counters like the LS-20 and LS-60 can be used to monitor water batches from WFI systems and PW systems to do routine testing on the water quality.

Batch samples from the point of use on WFI and PW systems can be taken and sampled routinely to ensure that the WFI OR pw system is working correctly and consistently producing sterile and clean water for injection. In pharmaceutical manufacturing Quality Control WFI is used for the preparation of reagents, standards, and samples in analytical testing methods such as High-Performance Liquid Chromatography (HPLC), Gas Chromatography (GC), and Mass Spectrometry (MS) to ensure the quality and purity of the finished products.

WFI is a critical component in the manufacturing process of sterile pharmaceutical products, and it is used in multiple stages of the process to ensure the safety, purity, and efficacy of the final product. LPC's play a vital role in providing visibility and recording particle data to ensure WFI is as pure as it can be.

Remote Liquid Particle Counters

Remote LPC's monitor multiple points on WFI systems in real time to ensure that the filtration and RO processes are sufficiently working and currently delivering WFI that is pure as intended for use.

Product Batch Testing

Liquid Particle Counters are used to test batch products to ensure these products are free of particulate contaminants.

EU GMP Annex 1 2022 states in Section 8.5.5.3 of Annex 1 states that "The design of the LPC sampling point shall ensure a representative sample of the batch is taken" and goes on to provide specific requirements for the location and design of the sampling point. appropriate acceptance criteria."

The Annex also requires that "The LPC sampling shall be carried out at a frequency that is representative of the batch" and that "The results of the LPC shall be evaluated against appropriate acceptance criteria."

The acceptance criteria for LPC can vary depending on the type of product being manufactured and the intended use of the product. Generally, the acceptance criteria for LPC are based on the size and number of particles observed in the sample.

For example, the US Pharmacopeia (USP) <788> provides guidance on the maximum allowable limits of particles for various types of parenteral products, including injectable solutions, suspensions, and emulsions. The limits vary depending on the size of the particles, with smaller particles generally being more critical than larger ones.

In addition to setting acceptance criteria, the evaluation of LPC results may also involve investigating the root cause of any particle excursions and implementing corrective and preventive actions to prevent a recurrence.

Overall, the evaluation of LPC is an important aspect of ensuring the quality and safety of sterile medicinal products, and manufacturers must ensure that their LPC procedures and acceptance criteria are in compliance with relevant regulations and standards.

LPC's can be implemented into the Contamination Control Strategy and digital results can be sent to the CCS system software to enable more data points to be analyzed and Quality Control managers can make faster decisions. The following are the maximum allowable limits of particles per container or per milliliter of solution as per USP <788>:

Injections for intravenous use:

Particulate matter ≥10 µm: Not more than 12 particles per mL
Particulate matter ≥25 µm: Not more than 2.9 particles per mL

Going Digital to Meet the Contamination Control Strategy

Environmental Monitoring in the digital age we are in does not have to be that painful paper-based system that we have endured since the 1960's. Particle Counting technology has moved fast in the last 5 years with particle counters becoming mini-computers and with the installation of audit trail and 21CFR11 compliance for data integrity the data governance and data lifecycle particle counters can be easily integrated into digitalized systems. These systems mitigate against human errors associated with sampling and data entry.

To give some examples of how this integration of data can be used, section 8.4.3 of the Annex recommends the use of statistical process control (SPC) to evaluate the data from continuous monitoring and environmental monitoring. This can help identify trends and patterns in the data that may indicate a potential issue with the manufacturing environment.

Digital Cleanroom Certification enhances your Contamination Control Strategy with instant data

1. Cleanroom Operator takes particle room samples using a digital particle counter

2. All Data is uploaded to a centralized data analysis system instantaneously

3. Data is screened and used within the system to make process decisions quickly.

Digital Cleanroom Certification enhances your Contamination Control Strategy with instant data.