

# When clean is critical—the importance of understanding the parameters and definitions of clean

## Key words

Critical environments, clean, clean room, contamination prevention, clean parameters, validation, cleanliness standards.

Working within a critical environment such as a clean room necessitates high-quality materials and equipment. Even microscopic amounts of foreign material can render batches or materials unusable, resulting in wasted time and money. It is therefore essential that products used in critical environments, such as plastic bottles, vials, carboys, caps, and other materials conform to the accepted standards of cleanliness; it's important to reduce the possibility that there is anything in your containers other than the formulations that you've added.

To provide products that meet the needs of the applications, materials and consumables must conform to a variety of specified standards. These might include achieving a required low level of particulates, or sterility assurance levels (SALs) that reach or even exceed USP standards. For example, USP <788>, "Particulate Matter in Injections," sets the limits of particulates in a final product—specifically for injections and parenteral infusions—yet may still be inappropriate for the consumables used to produce these products, which all contribute to that particle load. Manufacturers may wish to consider setting their own acceptance standards below those laid out in USP <788>, in order to provide an enhanced level of service.

When considering which containers or equipment to use in a critical environment, there are a number of considerations to bear in mind:

- Do you have sufficient time, financial resources, and expertise internally to produce containers and other materials that conform to the required levels of cleanliness? Or would relying upon a third party be more efficient?



- Do you need product or process validation? Or do you need something in between? Are you aware of the differences between validating your product vs. the equipment on which it is processed?
- Have you established the precise levels of cleanliness your critical environment requires, and fully understood the options or limitations specific to these clean parameters?

Having answers to these questions requires a comprehensive understanding of precisely how clean parameters are defined and validated.

## Defining clean parameters

It's easy to assume that particular parameters used to define cleanliness are understood. However, with so many terms and complexities, those parameters can quickly become ambiguous. While the main drivers behind selecting a particular product are often functions defined as low particulate, low pyrogen, etc., there are additional aspects that may require clarification. Does irradiating or autoclaving, for example, mean that a product is sterile? What does steam or gamma sterilization achieve? Often there can be more than one answer to these queries and thus defining these terms is important for maintaining critical environment conditions. Different applications will often require different processes in order to achieve the required levels of cleanliness (Table 1).

**Table 1. Cleaning process suitable for critical environments definitions and common associated applications.**

Process	Definition
Irradiation	Application of a radiation dose in an attempt to destroy all viable forms of life, including bacterial spores. A typical radiation dose required to reach a desired sterility assurance level (SAL) of $10^{-6}$ is 25–40 kGy. Simply being “irradiated” is not a guarantee of sterility (see “Sterile” below).
Autoclaving	Application of steam, heat, and pressure in an attempt to destroy all viable forms of life, including bacterial spores. The amount of time, heat, and pressure can vary depending upon several factors. Simply being “autoclaved” is not a guarantee of sterility (see “Sterile” below).
Sterile	Sterilization involves the application of steam, heat, and pressure (autoclaving), irradiation (gamma, e-beam, etc.) or chemicals (EtOH, $H_2O_2$ , etc.) to destroy all viable forms of life, including bacterial spores, to an acceptable sterility assurance level (SAL) of $10^{-6}$ that has been fully validated. Validation generally includes a statistically significant sampling plan, multiple lots, and use of validated equipment/processes.
Particulate cleaning	Water filtered to submicron levels (e.g., USP water or water for injection (WFI)) is used for the particulate cleaning process. Water is heated and used to “wash” items in multiple cycles. Materials are then dried and packaged, all in clean room environments to keep particulates low. Simply being “particulate washed” is not a guarantee of sterility (see “USP <788>” below).
USP <788>	Compliance to USP <788> requires that either a product is produced in a clean environment or be particulate-washed, such that you can achieve a validation of this low particulate limit. Validation generally includes a statistically significant sampling plan, multiple lots, and use of validated equipment and/or processes.

## How valid is this validation?

Conformity of the equipment or materials entering a critical environment to your requirements, need proper validation—often of the equipment used in the process, the product claims, or both. Which one you opt for can depend on both your intended application and the risks.

Process validation data provides assurances that the equipment used in the process (of cleaning and autoclaving, for example) pass Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ). This provides documented evidence and a high degree of confidence that the process being used will consistently yield a product of predetermined quality. Validating the process facilitates validating product claims later. Relying on the process validation, which certifies that the equipment is used in the processes only, and results in a certificate of processing for customer documentation purposes. This is generally the fastest and lowest cost validation method, although it also carries the highest level of relative risk if you are using it to make assumptions about a product claim. Product validation on the other hand, includes putting the finished product through biological, chemical, and physical testing protocols to ensure that it consistently meets a certain criteria or claim (e.g., sterility). This can require multiple production lots, statistical sampling, and real-time shelf life analysis, depending upon the user's particular requirements. Following a full validation, the product is typically exempt from subsequent release testing for that particular parameter, unless changes are made that require it. Product validation results in a certificate of analysis, certifying the final product. While this offers the lowest relative risk, it also requires more time and additional financial costs.

Ultimately the validation options are up to the user and should be based on the intended application—is this for a clean room waste container, a media-mixing vessel where the media will be filtered and sterilized, or is it for a final drug product stability sample? You may determine that each carries different levels of risk and therefore requires different levels of validation. A middle ground, where a partial product validation is executed for example, could make use of smaller sampling sets or analysis of only the accelerated shelf life; maybe it also includes release testing for extra security. There are numerous options available within the existing validation system to accommodate individual needs.

## DIY or outsource?

Cleaning and preparing equipment to critical environment standards is challenging, and carrying out this work internally comes with costs of both resources and capital. Producing validated containers and materials involves several important components:

- Dedicated facility space
- Autoclave purchase, installation, validation, and routine maintenance
- Washers/dryers (people or equipment) purchase, installation, validation, and routine maintenance
- Water system purchase, installation, validation, and routine maintenance
- Protocol development
- Validation report development
- Sourcing of base materials (container, closure, etc.) to be washed
- Revalidation and upkeep as required
- Personnel to perform all of the above

This may be an option for some, but for others this can be an order too tall to fulfill. Large amounts of budget can be consumed, while substantial amounts of valuable time are taken up with sourcing the right equipment and people, devising and implementing protocols, and maintaining all of this to exacting standards. In these cases, outsourcing to a third party can save substantial amounts of time and effort.

## The benefits of an outside service provider

Making use of a provider with experience in this area can have direct benefits to product quality. A trusted and experienced partner for those needing critical environment products and services can provide high-quality products that have been processed in an ISO-certified facility. Our product quality is assured via multiple inspection points both before and after washing and packaging. That quality is further maintained through a structured approach for dealing with product quality and supported with corrective action processes, change control, and customer notifications for changes or other important information. During the container processing, we make use of extensive washing and sterilization capabilities:

- Advanced devices that include vial, bottle, carboy and cap washers capable of accommodating a range of sizes from microliters to in excess of 50 L
- On-site autoclave facilities and an external partner for gamma irradiation and e-beam treatment for sterilization
- An array of packaging options to accommodate individual or multiple packs, partitioned cartons, bags, trays, and other custom options.
- Class 1000 clean room production area and Class 100 packaging

Additionally, where procedures call for other special product claims, we can produce products with low pyrogens, low total organic carbon (TOC), and silanized for low binding properties (although these cannot be combined with a low particulate parameter as well).



## Overall workflow

Clearly, the levels of certification, validation, and assurance are up to the user to decide, based on willingness to take on various risks, intended application, and current circumstances. This allows for a highly customizable approach to critical environment products and processes, in which experienced partners for outsourced services can help streamline the whole process from start to finish. For those embarking upon this process for the first time, it is worthwhile to establish answers to some fundamental questions from the outset:

- First, determine the specific product requirements based on your individual goals—be clear about “must have” vs. “nice to have.”
- Determine which parameters can and cannot be combined (for example, sterile and low particulate can be combined, whereas in some cases, sterile and depyrogenated cannot).
- Evaluate the level of risk in your process if one of these requirements are not met. For example, is this a waste container, where low particulates are only a concern as it relates to bringing particulates into a clean room, or is it a final bulk drug product that cannot be filtered, where any particulates can add to the final product particulate levels?
- Consider whether process and equipment validation, product validation, or both are required for the specific application.

Now think about your capabilities for achieving all that is needed internally. If you opt for a third-party supplier, check to see if the product or packaging that you need already exists in a predefined configuration. For example, if a particular carboy or bottle, washing, packaging, and sterility method is already validated for the product, it could provide huge cost-savings to choose such a preexisting configuration. Making careful decisions about all of these concerns and questions early will enable an informed decision about what is required and how to proceed, whether or not you opt to perform the work internally or rely upon an experienced third party.

## Conclusion

Making sure that equipment and materials used within critical environments meet the demanding standards of cleanliness—and understanding those cleanliness definitions—can be a challenging process. For these reasons, Thermo Fisher Scientific offers vast experience in this area as a trusted third-party supplier. With capabilities to generate a broad combination of cleanliness parameters and certifications, as well as custom packaging options, we can help meet your precise specifications and requirements.

To learn more about our critical environmental products and services, go to [thermofisher.com/criticalenvironment](https://thermofisher.com/criticalenvironment)

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