

Thinking beyond sterility— a tiered approach

Identify the right level of clean for your bioproduction processes

Within bioproduction facilities, different applications carry various levels of risk, and require different levels of cleanliness and validation. A sterility level of 10^{-6} has become an industry standard, however, Thermo Fisher Scientific is going beyond this to help ensure that USP <788> standards are met and even exceeded, in addition to complying with USP <30> and USP <85> standards. Implementing the correct level of clean to meet the needs of an application can help manage batch quality, ensure regulatory requirements are met, and improve the overall efficiency of the entire pipeline.

Deciding which rigid containment products to use can be a complex decision. When selecting a container that comes into direct contact with the biopharmaceutical product, resins, contact surfaces, and container parameters need to be considered. It's crucial to define the cleanliness needs

of the application and source containers that match those needs—for example, sensitive biopharmaceutical drug substances require the cleanest contact surfaces, so the containers used for these applications should have various certifications, very low particulate levels, and validated sterility.

This eBook is designed to offer an overview about clean containers and process requirements beyond sterility to professionals in quality department, project managers, and procurement managers.

Read on to find out why understanding different levels of container cleanliness is key to successful bioproduction workflows, and how a collaborative relationship with a trusted vendor can help to optimize output quality and streamline processes.

90% of industry experts surveyed* are concerned about particulates, yet only 41% are familiar with USP <788>.

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* According to the 2019 Thermo Scientific™ Bioprocessing Particulate Contamination Survey.

Understanding clean parameters

Understanding and monitoring cleanliness levels helps enable management teams to keep the total particulate load of pharmaceuticals at a level that complies with current good manufacturing practices (cGMP) regulations, while adhering to ISO Class 5 cleanroom specifications. A clear understanding of the different cleanliness standards is an essential aspect of this risk mitigation strategy. These include:

- Sterility assurance level (SAL) of 10^{-6} inside and outside the containers
- Certified low endotoxin—per USP <85>
- Certified low particulates—per USP <788>

Navigating and understanding these parameters can be challenging, especially for those who are new to the sector or to a quality-based role. The primary drivers behind product tiers are often particulate and pyrogen levels, but there are additional aspects that often need clarification, especially as different applications require different processes to obtain the required level of cleanliness.

Industry experts considered sterility the most important factor when selecting containers for their manufacturing needs. When asked, only 11% chose USP <788> as the top factor, despite 90% being concerned about particulates.

Process	Definition
Sterilization	<p>Sterilization involves the application of steam, heat, and pressure (autoclaving), irradiation (gamma, e-beam, etc.) or chemicals (EtOH, H₂O₂, etc.) to destroy all viable forms of life, including bacterial spores, to an acceptable, validated SAL of 10^{-6}.</p> <p>Validation generally includes a statistically significant sampling plan, multiple lots, and use of validated equipment and processes.</p>
Particulate cleaning or rinsing	<p>Water that is filtered to submicron levels is used for the particulate cleaning process. The water is heated and used to “rinse” items in multiple cycles. Materials are then dried and packaged in cleanroom environments to keep particulates low. Simply being “particle-rinsed” is not a guarantee of sterility (see “USP <788>” below).</p>
USP <788>	<p>Packaging is not only important in the protection of the low-particulate products, but also in the manufacturing step down process.</p>

Ways to overcome subvisible particulate contamination: USP <788>

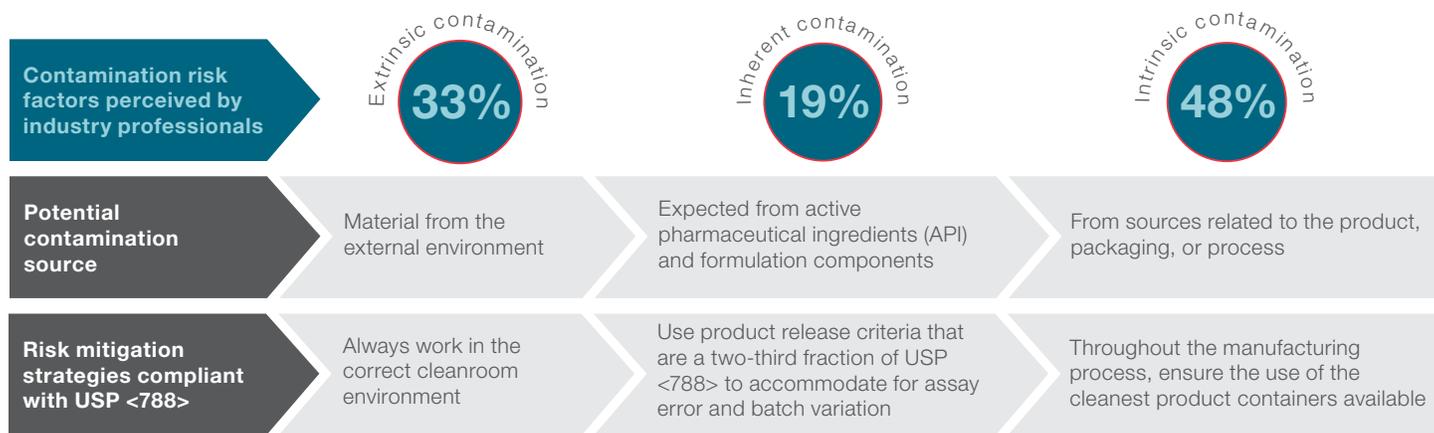
When working in bioprocessing applications, sterility and visible particulate contamination are common concerns, however, potential subvisible particulate contamination is an equally important concern when producing injectables and parenteral infusions.

In a recent survey of experienced professionals in industry, 41% said that they track the level of particulates at each and every step of their manufacturing process, which allows them to see where and when particulate contamination buildup may arise.

USP <788> outlines practices and methods used to measure particle size and count in injections and parenteral preparations. This regulation places strict limits on levels of allowable subvisible particulate matter—ensuring product quality and patient protection.

Particulate contamination can build up throughout each step of the manufacturing process, and potential contamination can arise from multiple sources. There are several ways to reduce the risk of batch noncompliance with USP <788>:

- Setting product release criteria at 2/3 of the USP <788> allowable limits will allow for assay error and batch-to-batch variation
- Using containers that have been certified to contain less than 1/3 of the USP <788> allowable limits



* According to the 2019 Thermo Scientific Bioprocessing Particulate Contamination Survey.

The importance of certifications

Access to certifications and other accompanying data can ensure that the right containers are being used for the specific needs of the application, right from the start of the process.

Once validations and cleanliness parameters have been selected by the customer, data are collected from the vendor and reviewed internally by the quality and project management teams. Evaluating the data based on the specific application, processes, and intended use can help mitigate risk, ensure project timelines are met, and manage regulatory affairs.

The data provided includes:

- Validation binders, providing information on resin suitability (testing and processing certificates for sterility and particulate levels should be readily available, while change notification procedures can help to maintain traceability and documentation)
- Easily accessible certificates for sterility and particulate levels, as well as notifications to any relevant change to help maintain document traceability

Having access to this data gives valuable information that can be used as evidence when managing regulatory affairs. The data provided by certificates, validation binders, and extractables studies help to demonstrate to regulatory inspectors that the standards of cleanliness within a facility are being met.

The value of vendor relationships

A misinformed decision on the most suitable level of cleanliness for a product or process can lead to increased risks of batch contamination, resulting in various issues for both quality and project managers. For quality managers, batch contamination could lead to serious problems such as regulatory noncompliance.

Collaborating with a vendor that has a proven track record of product excellence and dedicated customer support can help facilitate quality managers' decisions regarding which containers best minimize risks for a specific application, optimize processing efficiency, and reduce the risk of pipeline delays. An experienced vendor can not only recommend the correct level of cleanliness needed to minimize the risk of processing delays for a specific project, but can also advise on container lead times and delivery logistics.

Choosing the best containers

When assessing which clean container to select for a given application, there are several important factors to consider—both process and potential product claim validations can help the user to select containers of appropriate quality while also reducing the level of risk.

Claims can be complex, especially in the context of various cleaning processes. Therefore, it's essential to have an in-depth understanding of these claims and their implications, so it's possible to make the most informed decisions about which containers suit the needs of the application. Common process and product validation claims about containers include:

Sterility assurance—validated to ensure that every lot meets the defined SAL level, but sterility is not an indication of particulate level

Low particulate—validated with standards such as USP <788>, indicating a quantifiable particulate load that is lot-to-lot tested

Although these claims can be complex, the decision-making process can be facilitated by a number of factors, including:

- **Resin**—Does the application require a prequalified resin, chemical resistance, biological compatibility, or gas permeability? What temperature range will the resin be subjected to?
- **Container shape and size**—What volume is required? What are the dimensions for storage and shipping? What fluid transfer process and connections will be used? What are the storage and shipping requirements?
- **Clean**—What are the quality and regulatory requirements? What particulate level is tolerable? What endotoxin and bioburden limits are applicable? What are the sterilization requirements?

65% said material of construction and shape were the top two considerations when choosing containers.

The tiered portfolio of Thermo Scientific™ Nalgene™ containers is tailored to meet the different application requirements of bioproduction facilities:

Standard clean	<ul style="list-style-type: none">• Manufactured from high-quality resins• Available as sterile or nonsterile• Single-walled outer packaging of carton
Certified clean	<ul style="list-style-type: none">• USP <788> compliant• <0.5 EU/mL endotoxin• SAL of 10⁻⁶ in both inside and outside of the container• Triple-layer packaging with two interior heat seals that qualify as sterile barriers• Double-walled outer packaging of carton
Certified platinum clean	<ul style="list-style-type: none">• Rinsed with water for injection (WFI) to certify below 1/3 allowable USP <788> particulate limits• <0.25 EU/mL endotoxin• SAL of 10⁻⁶ in inside and outside of the container• Triple-layer packaging with two interior heat seals• Double-walled outer packaging of carton

Conclusions:

ensuring confidence in the chosen level of clean

When working in a critical environment, such as a cleanroom, or when producing critical biopharmaceuticals, even microscopic amounts of contamination can have a disastrous impact, potentially rendering whole batches or materials unusable, with obvious cost, time, and productivity implications.

Therefore, in order to maintain an effective, streamlined pipeline and adhere to cGMP regulations, the selection containers used need to be of the appropriate quality level, safeguarding both intermediates and final product.

It is possible to reduce the risk of batch noncompliance with USP <788> by taking simple steps. These include setting product release criteria which are a 2/3 fraction of USP <788>—allowing for accommodating assay error and batch-to-batch variation. Working within a clean environment and with the cleanest certified containers will reduce the potential risk of particulate contamination.

Establishing strong, collaborative vendor relationships is crucial to support and inform quality departments and project management teams, thus ensuring final products are produced using well-suited equipment and consumables. Speaking to experienced vendors can help the management teams better understand the complexities that surround cleanliness parameters and regulatory standards, and source the right products for the application needs.

The long-term risks and costs associated with using low-quality products may be averted by conversion to a vendor that offers support at every stage of the process.

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Find out more about Thermo Scientific clean containers at
thermofisher.com/uspclean

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