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# The Importance of Aseptic Sampling Devices in a Bioburden Reduction Strategy

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## Introduction

Microbial control is mandatory for all sterile drug manufacturers. Bioburden reduction represents a significant proportion of risk mitigation efforts. The Parenteral Drug Association released Technical Report No. 69: Bioburden and Biofilm Management in Pharmaceutical Operations. It provides background on the causes and control strategies of bioburden in pharmaceutical production processes, as well as the risks of biofilm, the challenges of removing it, and actions to help reduce the incidence of biofilm formation.

PDA Technical Report No. 69 strongly suggests the use of aseptic | sterile sampling devices. Alternative sampling methods can lead to false positive-results, and contribute to process fouling by bioburden and biofilm formation.

This White Paper delves deeper into aseptic sampling devices to explain how they offer exceptional performance in the effort to control contamination.

**Find out more:** [www.sartorius.com/takeone](http://www.sartorius.com/takeone)

## What is an Aseptic Sampling Device?

An aseptic sampling device is a self-contained device that has

- a means for aseptic withdrawal of fluid from a vessel,
- multiple and independent sampling pathways,
- appropriate sample collection vessel(s) at the end of each sampling pathway, and
- a method for aseptic removal of the sample collection vessel after sampling.

Aseptic sampling devices are typically offered in two forms: 1) a single-use and preassembled device (Figure 1) and 2) reusable devices with single-use sampling lines. The supplier sterilizes the assembled device or sampling lines, usually by gamma irradiation. The external product-contact surfaces of the device are sterilized by the routine steam-in-place (SIP) conducted on the process vessel after the aseptic sampling device has been connected.

The device performs aseptically, meaning that before, during, and after sampling, external contaminants are not introduced to the process vessel or to the sample itself. It is not necessary to sterilize between sampling events, making sample collection quick and simple.

Aseptic sampling devices have multiple, independent sampling lines that remain unused until the sampling event. This feature facilitates the collection of perfectly representative samples, which provide insights into what's happening in a vessel at any particular time. Because samples are collected through unused, independent, and fully contained fluid pathways, there should be no doubt that a bioburden hit in a sample means the vessel is contaminated. This was not always the case with outdated sampling techniques.



Figure 1: Takeone® Aseptic Sampling Device

## The Challenges of Biofilms

Biofilms are a major focus of PDA Technical Report No. 69 and represent a significant concern for pharmaceutical and biopharmaceutical manufacturing companies.

A biofilm is a colony of microorganisms embedded in extracellular polymeric substances and attached to a substratum (Parenteral Drug Association, 2015). Technical Report No. 69 offers several characteristics of biofilms:

- They are difficult to remove, even with high-shear fluid flow and aggressive chemical cleaning agents.
- They act as protective barriers to sanitizers for the bacterial colony contained within.
- Bacteria in or on a biofilm unpredictably and episodically desorb from the biofilm and foul the production fluid.

Technical Report No. 69 suggests that the best way to tackle biofilm formation is to monitor and prevent microbial contamination, since this is how biofilms originate.

# Bioburden and Biofilm Monitoring Strategies

Technical Report No. 69 recommends aseptic | sterile sampling devices for measuring bioburden throughout the production process (Figure 2).

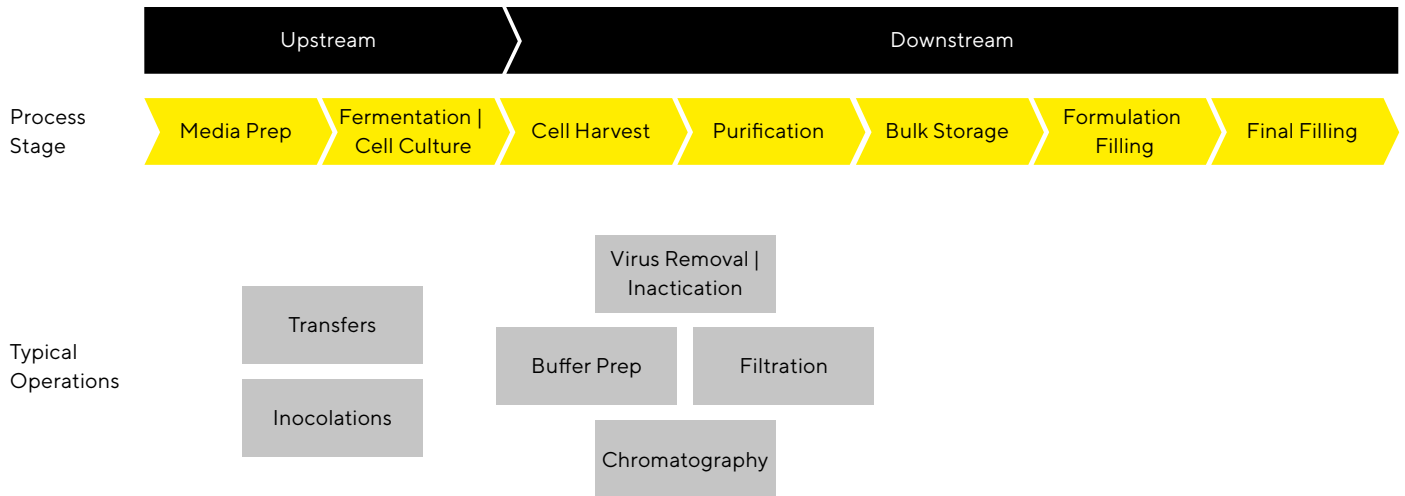


Figure 2: Bioprocess Production Map

Conditions for the propagation of bioburden are ideal in nutrient-rich upstream manufacturing steps. Biofilm growth predominates in downstream operations, where conditions may not be as conducive to microbial proliferation (Parenteral Drug Association, 2015). Therefore, continuously monitoring bioburden in solution using aseptic sampling devices is crucial to an effective bioburden and biofilm control strategy.

Generally, aseptic sampling should be done:

- just before feeding media into a vessel,
- just after media has been added to the vessel, and
- at the conclusion of each batch.

Bookending process stages with aseptic sampling is a critical component of a contamination control program.

## Previous Methods for Bioburden Collection

Employing an aseptic | sterile sampling device is a more integrated approach than previous sampling methodologies. Examples of prior sampling systems include in-house-built steamable valve assemblies. The user builds an assembly of valves, fittings, and tubing, which is usually autoclaved and then connected to a steamable valve assembly on the vessel. After a steam sterilization step, the sampling system would be ready to use.

Sampling systems like these usually have only one sampling line so subsequent samples require additional steam sterilization steps to re-sterilize the fluid pathway. Even after steaming operations, the sampling pathway holds remnants of fluid from previous samples, introducing ambiguity to sample analysis.

Subsequent samples require the connection of new assemblies or sample vessels. With each connection, the system is opened to the environment. Any open manipulation of components connected directly to a process vessel is an opportunity for bioburden to enter the system or the sample itself.

The assembly and re-installation steps, the multiple SIP cycles and the open manipulations make these systems undesirable.

Technical Report No. 69 discourages the “open grab” method since that carries even greater risk of inadvertent bioburden introduction. An open grab sample is one where the user opens a new sample bottle, opens a valve on the tank, lets the fluid pour into the bottle, closes the valve and replaces the cap or lid on the sample cup. This form of sample collection presents an easy opportunity for a microbe to enter either the sample or the valve connected to the vessel. Technical Report No. 69 instructs users to ensure that samples collected for microbiological testing are not compromised, citing that “the use of open grab samples is discouraged because this practice can lead to false-positive results due to sample contamination. For best results, aseptic or sterile sampling devices should be used whenever feasible for collecting bioburden or non-host samples.” (Parenteral Drug Association, 2015).

## Benefits of Single-Use

The incorporation of single-use technologies in the biotech industry is a significant improvement in biofilm prevention. A single-use component has never been used in processing, handled by operators, and will not be used on future batches. As a result, the risk of introducing microorganisms is very low and biofilm propagation is abated.

The story is different for multi-use components. Yet, reusable equipment remains in use and will continue to be for some time. Clearly, the integration of single-use components helps mitigate the risk of bioburden introduction.

Technical Report No. 69 includes a section on life-cycle management of soft parts (also known as multi-use or reusable parts). It emphasizes its importance to an effective bioburden and biofilm control and monitoring program. Let us consider soft part management in the context of sampling devices, including the types of aseptic sampling devices that include multi-use components (Figure 3).

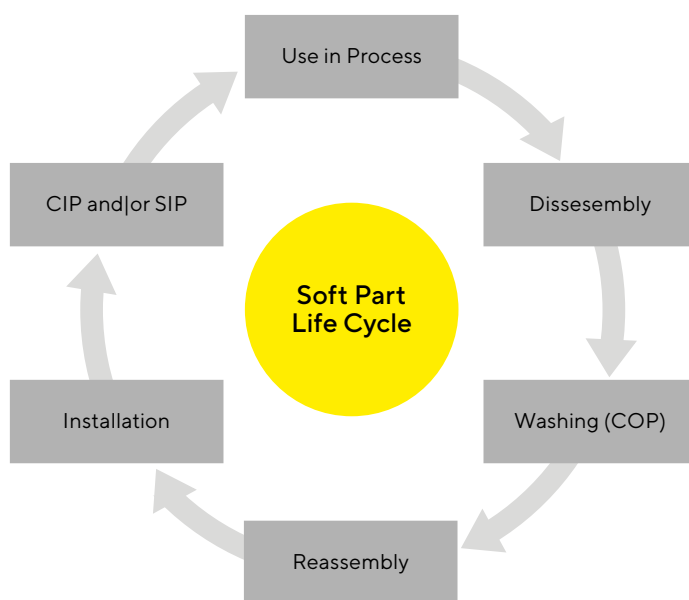


Figure 3: Management of the reusable (soft part) equipment life cycle is essential in bioburden control.

Assemblies that include soft parts are typically removed from process equipment, disassembled, and cleaned out of place (COP) before being reassembled for reuse. The maintenance of multi-use stainless steel parts should be closely monitored during its lifetime to preserve the thin passive oxide layer which is intrinsic to the surface when new (Cluett, 2001). Corrosion or breakdown of this ultra-thin layer, be it chemical or physical, becomes safe harbor points for bioburden and biofilm formation (Cluett, 2001) even after clean-in-place (CIP) and COP processes.

## Conclusion

Once reassembled and installed on process equipment, the microbial colonies in biofilm may desorb and foul the production process (Parenteral Drug Association, 2015).

If they must be used, Technical Report No. 69 recommends routine preventative maintenance of soft parts, including inspection and replacement of damaged parts. The useful life of soft parts should be determined by validation of the following:

- Number of SIP cycles
- Number of CIP|COP cycles
- Number of production processes

The risks of biofilm formation and added validation efforts are supportive of preassembled and single-use systems. Choosing an aseptic sampling device that uses soft parts requires added vigilance of life-cycle management and perpetual risk of biofilm formation and bioburden fouling. Ultimately, preassembled and single-use aseptic sampling devices simplify validation and remove risk.

## Environmental Controls

The environment that the drug product is produced in, as well as the environment of the support operations, including equipment cleaning and assembly areas, may also contribute to bioburden introduction. The location where assemblies are built, and the components the assembly is built from, need to be bioburden controlled. An effective bioburden management strategy becomes a complex web of validation of facilities, equipment, and processes.

Consequently, an easier solution and popular trend is to purchase preassembled single-use systems, including aseptic sampling devices.

Technical Report No. 69 highlights the need for adherence to strict aseptic techniques and good microbial controls to reduce the risk of adventitious contamination.

Routine and well-designed bioburden monitoring programs using aseptic sampling devices help manufacturer track and respond to out-of-specification bioburden findings.

The selection of a preassembled and single-use aseptic sampling device reduces bioburden contamination risk. It is a valuable tool to combat biofilm formation through an effective prevention and monitoring program.

## References

Parenteral Drug Association, 2015, Technical Report No. 69; Bioburden and Biofilm Management in Pharmaceutical Operations, Bethesda, MD. Cluett, J.D., 2001, Cleanability of certain stainless steel surface finishes in the brewing process, Rand Afrikaans University, Johannesburg, South Africa.

## A Profile of Sartorius Stedim Biotech


Sartorius is a leading provider of cutting-edge equipment and services for the development, quality assurance and production processes of the biopharmaceutical industry. Its integrated solutions covering fermentation, cell cultivation, filtration, purification, fluid management and lab technologies are supporting the biopharmaceutical industry around the world to develop and produce drugs safely, economically and in a timely manner. Sartorius focuses on single-use technologies and value-added services to meet the rapidly changing technology requirements of the industry it serves. Strongly rooted in the scientific community and closely allied with customers and technology partners, the company is dedicated to its philosophy of “simplifying progress.”

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