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# Perspective of Aseptic Sampling Product Manager on the PDA Technical Report No. 69

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## Introduction

Microbial control is a major objective for all sterile drug manufacturers, with bioburden reduction representing a significant share of risk mitigation efforts. The Parenteral Drug Association recently released PDA Technical Report No. 69: Bioburden and Biofilm Management in Pharmaceutical Operations, which 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 strategies to help reduce the incidence of biofilm formation.

The document emphasizes the importance of sampling throughout the process, from upstream manufacturing through downstream purification, culminating in bulk and final filling operations. PDA Technical Report No. 69 strongly suggests the use of aseptic | sterile sampling devices. Alternative sampling methods can lead to false positive results, and can contribute to process fouling by bioburden and biofilm formation.

This paper delves deeper into aseptic sampling devices to explain how they offer superior performance in the effort to control contamination.

**Find out more:** www.sartorius.com/en/products/fluid-management/transferring-sampling/takeone

## What Is an Aseptic Sampling Device?

To understand how aseptic sampling devices improve sampling operations, it's necessary to understand what they are and how they function.

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 and 2) single-use sampling lines which can be installed into reusable hardware. The supplier renders the assembled device or sampling lines sterile, 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 to the empty vessel. 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 required 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 allows for collection of perfectly representative samples. Perfectly representative samples provide data of exactly 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 — that was not always the case with outdated sampling techniques.

Image 1: Takeone® Aseptic Sampling Device

## The Challenges of Biofilms

A major concern for pharmaceutical and biopharmaceutical manufacturing companies, biofilms are a main focus of PDA Technical Report No. 69. A biofilm is a colony of microorganisms embedded in extracellular polymeric substances, which is 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.

In conclusion, Technical Report No. 69 suggests that since biofilms originate from bioburden in solution, the real challenge for manufacturers is designing and managing processes to reduce the risk by preventing and monitoring bioburden so that the biofilm does not form in the first place.

# Bioburden and Biofilm Monitoring Strategies

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

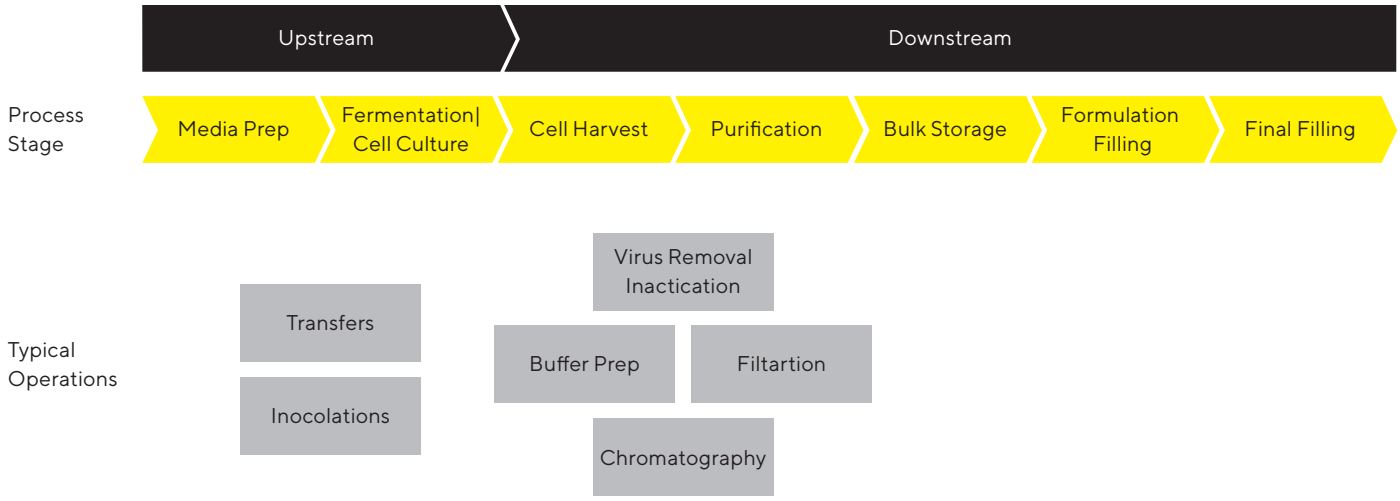



Image 2: Bioprocess Production Map

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

Generally speaking, 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 for bioburden monitoring is a critical component of a contamination control program.

## Previous Methods for Bioburden Collection

Use of 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 normally 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 previously used fluid pathway. Even after following steaming operations, the sampling pathway holds remnants of fluid from previous samples, which can introduce ambiguity to sample analysis.

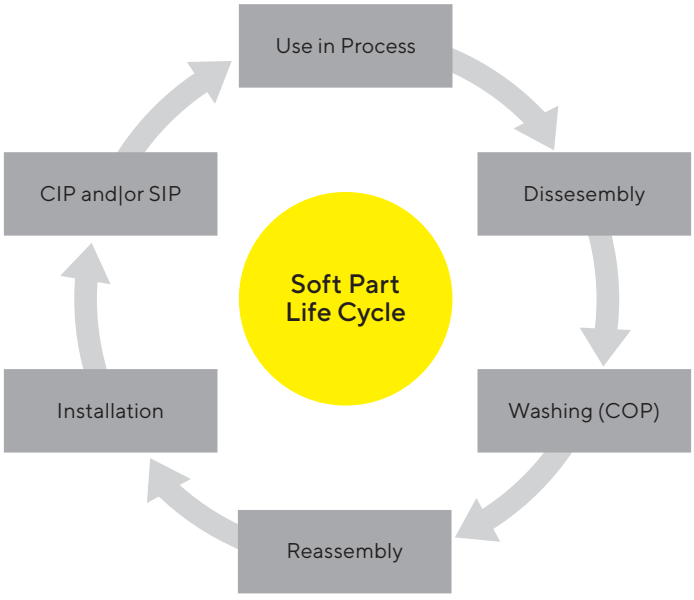
Subsequent samples require connection of new assemblies or sample vessels. With each connection the system is opened to the environment. Any open manipulation of components that are connected directly to a process vessel is an opportunity for bioburden to enter the system or the sample itself.

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

Technical Report No. 69 discourages the "open grab" method since that carries even more risk of inadvertent bioburden introduction. An open grab sample is one where the user opens a new sample cup or 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 bacterial microbe to enter either the sample or the valve connected to the vessel. The report 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 components in the biotech industry is a major improvement in biofilm prevention. A single-use component has never been used in processing, has never been handled by operators, and will not be used on future batches. The introduction of microorganisms is very low and biofilm propagation is abated.




The story is different for multi-use components. And yet, reusable equipment remains in use and will continue to be for some time. It stands to reason that integration of single-use components, wherever possible, is helpful in mitigating 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) and 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.

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. 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 to include 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 a 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 place where assemblies are built needs to be bioburden controlled and the components the assembly is built from must be bioburden controlled. An effective bioburden management strategy becomes a very complex web of validation of facilities, equipment and processes.

To reduce the chance of bioburden, an easier solution and popular trend is to purchase preassembled single-use systems, including aseptic sampling devices.

## Conclusion

The 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 manufacturerstrack and respond to out-of-specification bioburden findings.

Selection of a preassembled and singleuse aseptic sampling device reduces bioburden contamination risk and is a key component 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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