Microbial Control for Nonsterile Drug Manufacturing Product Contact Surfaces

Antonio Ortiz, STERIS Corporation, Life Sciences

Abstract

There is a fairly good understanding of how cleaning processes for pharmaceutical equipment used in aseptic operations are implemented not only for controlling drug product cross-contamination, but also for the initial reduction in bioburden prior to sterilization. However, there is limited guidance on bioburden limits for product-contact surfaces of equipment used to manufacture nonsterile products. This lack of information and regulatory requirements prompts questions on whether it is necessary to have a separate sanitization or disinfection step after cleaning of equipment product-contact surfaces for nonsterile drug manufacturing. Per USP <1115>, microbial limits and the design for cleaning and other associated processes should be based on risks assessed and the level of control necessary based on the product. It would be beneficial to implement processes that can address both residual product and microbial contamination of equipment surfaces. Multiple factors play into the design of an effective and efficient cleaning process. When adequate controls are implemented for the cleaning process and its associated factors, a separate sanitization or disinfection process may not be needed for product-contact surfaces when data is able to demonstrate that the cleaning process and the other preventive measures are able to control microbial contamination of those surfaces.

Background

Per USP <1115>, Bioburden Control of Nonsterile Drugs and Substances:

"In terms of microbiological contamination risk control, there are two broad categories of drug products: (a) sterile products, in which the bioburden is essentially eliminated using validated methodologies, and (b) nonsterile products for which the final product bioburden is controlled to appropriate levels based on product attributes, route of administration, and target patient population"[1].

There are multiple regulations, standards, and guidance documents that describe definitive requirements for the sanitization and disinfection processes and limits for the overall contamination control strategy of cleanroom areas and equipment used for aseptic operations[2,3,4]. However, for nonsterile drug manufacturing, is it necessary to have a separate sanitization or disinfection step after cleaning of equipment product-contact surfaces? And what would the product-contact surface limits be when processing nonsterile drug products?

This poster provides guidance on how a well-designed cleaning process, along with other preventive measures, can control microbial contamination of product-contact surfaces for nonsterile drug manufacturing operations.

Regulatory Overview

Below are some general regulations and guidelines that need to be addressed in nonsterile manufacturing facilities.

FDA CFR part 211 section 67:

"Equipment and utensils shall be cleaned, maintained, and, as appropriate for the nature of the drug, sanitized and/or sterilized at appropriate intervals to prevent malfunctions or contamination…"[5].

FDA's Guide to Inspections: Validation of Cleaning Processes:

"it is important to note that control of the bioburden through adequate cleaning and storage of equipment is important to ensure that subsequent sterilization or sanitization procedures achieve the necessary assurance of sterility"[6].

EU Guidelines for GMP, Annex 15: Qualification and Validation, section 10.7:

"The risk presented by microbial and endotoxin contamination should be considered during the development of cleaning validation protocols"[8].

FDA's Draft Guidance for Industry: "Microbiological Quality Considerations in Nonsterile Drug Manufacturing":

"While non-sterile drugs do not require to be sterile, there is a threshold of microbiological content above which safety and efficacy of a given nonsterile drug may be adversely impacted"[9].

FDA 21 CFR 211.113(a):

"Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed"[5].

Per regulatory and guidance documents, there is an expectation for implementing controls to limit the introduction of microbiological contamination during the manufacturing process as the main control. Preventive measures are preferred over remediation processes once contamination is inadvertently introduced during the manufacturing process.

Setting Limits for Nonsterile Processing Equipment

There are sources that provide guidance on the requirements for setting limits, such as maximum allowable carryover (MACO), for cleaning validation purposes[3,6,10,11,12], however, what is not as clear is how to set limits for bioburden on equipment product-contact surfaces used to manufacture nonsterile products.

Manufacturing facilities need to identify the controls and acceptance criteria necessary for microbiological contamination in the manufacturing process to meet the specified bioburden limits for the finished product[9]. Per USP <1115>[1], the design for cleaning and other associated processes should be based on risks assessed and the level of control necessary based on the product. The proposed controls should consider drug product and manufacturing process characteristics, such as dosage form, water activity, and other aspects that may contribute to microbial contamination. Activities performed around equipment product-contact surfaces shall be controlled to reduce or eliminate the possibility of contamination of product-contact surfaces from those external sources. When setting limits, it is necessary to understand the equipment conditions that can promote microbial growth and the next product being processed in shared equipment. Microbial testing data, collected through verification and validation studies, should be analyzed and risk-assessed to confirm the validity of the limits selected.

Design of Cleaning and Associated Processes

The first step in the cleaning validation lifecycle is the cleaning process design stage. Using the principles of Quality by Design (QbD)[13], risk assessments are performed to understand contamination risks throughout the facility, specifically on product-contact surfaces. Developing a robust, efficient, and easily validated cleaning process requires an understanding of the influences from the factors listed in Table 1[14]:

Table 1 – Factors to Consider for Microbial Control

Factors	Evaluate the following for influence on cleaning process
Cleaning parameters	Temperature, Action, Chemistry/Concentration/Coverage, Time (TACT), perform lab-scale studies to understand and optimize process parameters
Raw materials	Adequate storage conditions, water activity, natural vs synthetic materials, bioburden load
Nature of product residue	Dosage form, water activity, manufacturing process (temperatures, wet vs dried, baked-on, pH)
Surface and equipment design	Materials of construction, smooth, non-porous, cleanability, drainability, compatibility with cleaning agent, rouge
Personnel	Personnel protective equipment, hygiene, behavior, training
Cleaning process	Automated vs manual, coverage, effectiveness, robustness, consistency, training, experience

In addition to the factors listed above, the following (next column) are considered cleaning-associated processes or factors that should be assessed or designed to prevent microbial contamination on product-contact surfaces for nonsterile manufacturing equipment[1,4,9,14].

Preservatives in a formulation are not a substitute for a comprehensive approach to preventing microbial contamination of nonsterile drugs and should not be presumed to reduce in-process bioburden during manufacturing[9].

Selection of Cleaning Agent

- Broad-spectrum cleaning performance
- Antimicrobial effectiveness
- Substrate compatibility
- Stability and shelf life
- Analyzability
- Environmental considerations
- Manufacturing quality

Control of Utilities

- Water quality
- Air quality
- Chemical purity
- Microbial load

Dirty Hold Time

- Nature of soil
- Minimized time to limit proliferation
- Considered during cleaning studies

Cleaning and Drying Process

- Residues may be nutrient source
- Cleaner with multiple mechanisms provides broad-spectrum efficacy
- pH and temperature extremes impart hostile environment
- Rinsing, drying, and draining effectiveness

Clean Hold Time

- Effective drying process
- Full drainability
- Clean, segregated storage conditions

Preventative Maintenance

- Surface quality impacts cleaning process
- Preventive stainless-steel maintenance
- Inspection, testing, and/or replacement of parts to maintain cleanable surfaces

Environmental Monitoring

Environmental monitoring for nonsterile manufacturing facilities should be implemented using a risk-based approach based on data collected[1]. Established microbial contamination controls for areas and procedures in place for processing and handling of equipment, as described above, will help prevent contamination of product-contact surfaces. Environmental monitoring will confirm the effectiveness and consistency of the controls implemented. Environmental monitoring results should be evaluated for trends and prompt root cause analysis, along with corrective and preventive measures, that should be employed when abnormal trends are observed

Key Takeaways

- Existing regulations are general for microbial control of nonsterile product-contact surfaces
- A well-designed cleaning process will help control microbial contamination on product-contact surfaces
- Preventive measures for contamination control are preferred over corrective methods
- Risk analysis tools should be implemented to understand processes and implement scientifically sound controls
- Continued monitoring of cleaning and associated processes prompts continuous improvement for contamination control

Conclusion

Historically, cleaning processes for shared equipment have been developed to address concerns about cross-contamination from one product to the other with clear approaches for determining acceptable residue limits. Cleaning validation regulations or guidance documents are not definitive on setting limits for bioburden on equipment product-contact surfaces used for nonsterile manufacturing. There are only general references stating that when developing a cleaning process, risks concerning microbial contamination need to be addressed. Cleaning and the associated processes and factors listed here are critical elements of contamination control strategy that may have a direct impact on microbial control of product-contact surfaces. As described here, a holistic approach for controlling microbial contamination should be implemented where preventive controls are the preferred method, rather than relying on cleaning and disinfection processes for remediating microbial contamination introduced during the manufacturing process. All process development activities should be carried out using a risk-based approach where manufacturing and finished product characteristics drive the development of contamination controls needed. Unless mandated by a regulatory body, a separate sanitization or disinfection process may not be needed for product-contact surfaces when data is able to demonstrate that the validated cleaning process and the other preventive measures listed here are able to control microbial contamination of those surfaces. In keeping with QbD principles, cleaning verification and environmental monitoring data collected should be evaluated and previous risk assessments should be routinely re-visited to determine whether the implemented contamination controls need to be revised or improved. Routine evaluation of cleaning process data drives continuous improvement to the overall contamination control strategy.

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