Application of Processing Guidance: Case Study of Cleaning Validations on Flexible Endoscopes

Nupur Jain, S. Darbi Chavez, and Alpa Patel

About the Authors

***Nupur Jain**, BS, MBA, is director of sterility assurance and reprocessing at Intuitive in Sunnyvale, CA. Email: nupur.jain@intusurg.com*
Corresponding author

***S. Darbi Chavez**, BS, RM(NRCM), is senior validation engineer—reprocessing at Intuitive in Sunnyvale, CA. Email: darbi.chavez@intusurg.com*

***Alpa Patel**, BS, RM(NRCM), is a principal scientist at Nelson Laboratories, LCC, in Salt Lake City, UT. Email: apatel@nelsonlabs.com*

Abstract

In 2015, the Food and Drug Administration (FDA) updated its guidance on test methods for cleaning validations for reusable medical devices. The changes include the condition and contamination of devices, test samples and controls, cleaning process performed during validation, extraction methods, and endpoints. This article reviews the FDA's changes to cleaning validations. Examples are presented using flexible endoscopes in order to provide a practical guide to performing cleaning validations.

As part of the Food and Drug Administration's (FDA's) 21 CFR Part 820.30 (Quality System Regulation) requirements, the medical device manufacturer (MDM) of a reusable medical device is required to provide instructions "to ensure that the device can be effectively reprocessed and safely reused over its use life."[1]

The first step in processing a reusable medical device is to remove contamination from the device, thereby allowing it to be further processed or ready for clinical use. This is the definition of cleaning. The cleaning steps must be validated to ensure that the reusable medical device is safe for patient use and fulfills the 21 CFR Part 820.30 requirement. Therefore, MDMs perform cleaning validations on all reusable medical devices to develop and provide instructions for use (IFUs) for healthcare facilities.

In 2015, the FDA published guidance, titled *Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling*,[2] that changed the methodology for cleaning validations performed on reusable medical devices. The guidance, which addressed agency concerns from its review of cleaning validations, sought to standardize scientific processes performed during cleaning validations and reduce variability between validations.

The goal of this article is to provide practical guidance on following the cleaning validations described in the FDA's guidance document. Six of the changes introduced in the guidance are outlined using examples that have been submitted to and cleared by the FDA.

The guidance document applies to validation methods that should be used for reusable medical devices. To analyze the risk of infection using the Spaulding classification, medical devices are placed in three categories: critical, semicritical, and noncritical. The guidance applies to all three categories, but for this article, examples of cleaning validations of semicritical flexible endoscopes will be described. Flexible endoscopes were selected because of the high volume of healthcare-acquired infections related to them.[3]

The changes outlined in the guidance document that will be discussed in this article are:

- Using clinically relevant test soils.
- Applying simulated clinical use conditions to the device.
- Designing a worst-case validation plan.
- Selecting clinically relevant endpoints to evaluate the processes with predetermined limits.
- Using test devices with multiple controls.
- Validating the extraction method.

Cleaning Validations

A cleaning validation consists of a series of consecutive steps that must be followed in a specific order. The first step starts with performing repeated cycles of simulated use to bring the test articles to a "used condition."[2] The cycles consist of simulated clinical use contamination, cleaning, disinfection, and/or sterilization to mimic the use life of the device in a healthcare setting. Once completed, the device is subjected to the cleaning

validation as follows:

- Contaminating the device using simulated use conditions with an artificial test soil consisting of clinically relevant organic and/or inorganic materials
- Drying the test soil on devices to simulate delayed processing and time between transport and cleaning
- Performing a cleaning procedure as outlined in the IFU using worst-case conditions for the processing steps
- Extracting the devices for analysis of residual test soil

This four-step process allows for variability based on the clinical use of the medical device while maintaining consistency in the process.

Four-Step Process of Cleaning Validation

1. Contamination: Test Soils and Simulated Use Process

The first step to evaluate any cleaning process is to establish the contamination procedure to simulate what the reusable medical device would encounter during clinical use. As native (human) soil is not readily available or appropriate for validations, the industry has developed simulated use test soils that closely mimic what the device would be exposed to during use in various procedures. Simulated use test soils have been formulated to closely represent various native soils.

Both ASTM F3208-20[4] and ISO/TS 15883-5:2005[5] provide a list of clinically relevant test soils that can be used to represent clinical procedures. These test soils incorporate the building blocks of the native soil, such as protein, blood, mucus, serum, and organic carbons (e.g., carbohydrates, lipids).

The most common test soils used for cleaning validations are protein- and blood-based test soils. However, selecting a test soil that is clinically relevant for the device being validated is important. For example, the test soil used to contaminate a duodenoscope is formulated from two test soils: a blood-based test soil and a mucous-based test soil. The combined test soil is used to simulate clinical contamination to which a duodenoscope would be exposed during clinical use. Often, duodenoscopes are used for endoscopic retrograde cholangiopancreatography procedures, where the distal end of the scope is introduced through the mouth, then through the digestive tract and into the bile and pancreatic ducts for diagnosis. The endoscope often is used with a surgical tool to help remove tissue samples from areas of concern for further observation. During this procedure, the working channel and distal end of the duodenoscope are contaminated with bodily fluids that consist predominately of blood and mucus; therefore, a combined test soil is selected.

After the test soil is determined, its application on the reusable medical device must be evaluated to simulate its clinical use in a healthcare facility. The simulated use should match the clinical use of the device. Because of the lack of direction prior to the release of the FDA guidance document, cleaning validations were performed using extreme worst-case conditions. Often, simulated use test soils and other contaminants were used to challenge the devices without assessing for clinical relevancy. However, with the help of the guidance document, the contamination method was further defined to specify that cleaning validations should "mimic worst-case clinical use conditions"[2] while ensuring that all difficult-to-clean locations on the medical device that would be contaminated clinically are contaminated.

To be clinically relevant, the contamination process also should mimic the actual use of the device. This includes actuating the device and/or using tools and accessories associated with the device. To illustrate this, the contamination method used for a flexible bronchoscope is outlined as an example.

The flexible bronchoscope is inserted into the lung through the mouth to perform minimally invasive peripheral lung biopsies. The bronchoscope's physical characteristics allow it to reach the peripheral portions of the lung, but this introduces tight bends in the process. To perform cleaning validation on this device, the bronchoscope is positioned in a way that introduces two tight bends, in order to challenge its bend radius and mimic the clinical procedure. The instruments that are designed to be introduced into this channel during clinical use

were inserted and removed multiple times while the distal end was immersed in the test soil.

This simulated procedure stressed the device to its maximum capacity while maintaining a clinically relevant contamination process. Similar test methods should be applied to all channels of flexible endoscopes to maintain clinical relevancy while ensuring clinically worst-case contamination.

After contamination and before the cleaning procedure, a worst-case drying time is required as part of the validation to simulate operational practices at healthcare facilities. The FDA guidance document states that "drying of soil might occur and cleaning might not be performed immediately after use, the validation methods should allow soils to dry for a length of time that simulates worst-case (longest duration)."[2] This is another instance where clinical relevancy also should be considered as part of the validation. For example, some flexible endoscope IFUs specify a maximum time limit allowed between use and processing. If it's understood that this time is not met clinically, then a validation with an extended drying time should be considered in the validation plans. This is the final step required as part of the simulated use contamination outlined in the guidance document.

2. Cleaning Process: Using Worst-Case Conditions

After the simulated clinical use contamination process has been established, the next step is to outline the worst-case cleaning process. The guidance document is very clear regarding what is considered "worst case" when it comes to performing the cleaning validation: "The cleaning validation protocols should use the shortest times, lowest temperatures, weakest dilutions, etc., for each step of the cleaning instructions. You should perform a detailed, side-by-side comparison of the text of the cleaning instructions and the text of the validation protocols to identify and account for all worst-case processing conditions."[2]

Examples are given in the document to expound on the text quoted above, but at no point is the MDM required to omit portions of the process. In fact, the FDA requires that "you should validate the cleaning process you provide in your labeling."[2] The guidance document specifically requires the IFU to include a point-of-use process, as needed, and a method of cleaning with enough detail that all appropriate parameters can be controlled to reach a cleaned state.

This aligns with 21 CFR Part 820.30, which "require(s) manufacturers to validate the design, including processing instructions, of reusable devices to ensure that the device can be effectively processed and safely reused over its use life, as intended."[1] For a flexible bronchoscope, the cleaning validation process was conducted in a worst-case manner by reducing all the manual cleaning steps outlined in the IFU. All soak times and flush volumes were reduced by 10%, with other steps reduced in a similar fashion.

3. Validation Test Methods: Endpoints and Controls

Endpoints used to validate the efficacy of the cleaning process are based on the building blocks of the clinically relevant test soil. The intended use of the device helps the MDM select what analyte would be best suited for evaluation. The guidance document has helped clarify and narrow the scope of the analyte testing required for cleaning validations. The FDA requires testing with clinically relevant analytes that would be most appropriate to assess the cleanability of a device. The FDA directs MDMs as follows: "The artificial test soil chosen should allow at least two clinically relevant soil components to be quantified for validation testing (e.g., total organic carbon, protein)."[2]

Proteins are naturally occurring building blocks of human tissue. They are among the analytes used for evaluation and have become necessary components for all cleaning validations. Proteins left behind after cleaning are a source of contamination (e.g., prions) and can further affect patient risk. Other analytes (e.g., hemoglobin, total organic carbon) often are tested as the second required analyte.

The MDM must consider the test soil that will be used to challenge the test device for cleanability when determining the correct analytes tested in the validation. For example, for flexible endoscopes, test soils composed of blood, mucin, and proteinaceous material often are used for cleaning validations. Therefore, protein and hemoglobin analytes would be suitable endpoints.

Controls are needed as part of the validation to further support the method used to evaluate the cleaning validation. Because of the lack of specificity regarding test method controls for cleaning validations prior to the current FDA guidance, additional controls were added to the document (a negative device control, negative sample control, positive device control, and positive sample control). These controls allow the agency to compare and evaluate test methods used for all cleaning validations of reusable medical devices.

Negative device control. The definition of a negative device control used in a validation is a device that is not contaminated but is subjected to the cleaning process. This control is used to assess whether any interferences (e.g., detergents) present in the test system could give a false-positive result.

Negative sample control. The negative sample control is a sample of the extraction fluid and is used as a "blank" during analyte analysis. Both negative controls are tested for the endpoint analyte and should have low values (i.e., close to limit of detection), showing no interference in the test system.

Positive device control. A positive device control is contaminated, not subjected to the cleaning process, and extracted in the same way as the test devices. It provides an understanding of the maximum values that could be seen for each of the endpoint analytes tested during a cleaning validation if the cleaning steps are not effective.

Positive sample control. Last, a positive sample control consists of an aliquot of test soil added to the extraction fluid. A comparison of the positive device control and positive sample control should demonstrate whether any interferences could give false-negative results.

These controls are in place to verify the interaction of the entire test system. They ensure that the correct analytes are tested for the specific test soil. Simulated use test soils may contain clinically relevant components that negatively affect the analytical tests. If these components are used in cleaning validations, the analytes may be masked, thus causing false negatives or augmenting a signal and causing false positives. For example, clinical dyes may be used for procedures involving flexible endoscopes. During a cleaning validation, adding a dye to the test soil may be relevant. However, clinical dyes work by binding to organic material, such as protein or hemoglobin, and their interaction may affect the analytical assays. Implementing these controls in the test methods for each analyte evaluates the test system for interference and can indicate whether a different analyte may need to be evaluated in the validation.

4. Extracting the Test Sites

The final step in the cleaning validation is extraction. The goal of the extraction method used during a cleaning validation is to remove residual soil from the medical device after the cleaning process. It is performed using an appropriate extraction fluid. Depending on the design of the device, the extraction method could be simple (e.g., submerge the device in extraction fluid) or extensive (e.g., submerge and sonicate the device in extraction fluid). Regardless of the extraction process, it must be validated using a recovery efficiency method.

The recovery efficiency method can be performed via an exhaustive or inoculated extraction process. In an exhaustive extraction, the device is contaminated in the same manner as described above (i.e., a clinically relevant simulated use), then subjected to the extraction process repeatedly until the results are below the limit of detection of the analyte being tested.

Using flexible bronchoscopes as an example, three bronchoscopes were inoculated with a protein-based (mucus and blood) test soil. The devices were contaminated as outlined previously and allowed to dry for 65 minutes at room temperature. After drying, the three devices were extracted four times and the extracts tested for protein and hemoglobin. The percent recovery efficiency of the three devices was calculated using the following formula:

$$\% \text{ Recovery efficiency} = \frac{\text{Analyte level from first extraction}}{\sum \text{Analyte levels from all extractions}} \times 100$$

The percent recovery efficiency results for the three flexible bronchoscopes were averaged, resulting in averages of 83% protein recovery efficiency and 76% hemoglobin recovery efficiency.

The percent recovery efficiency value demonstrates how well the analyte can be removed from the device or what percentage of the total contamination was removed in the first extraction. The raw analyte results obtained from the test and control devices following extraction then are divided by the recovery efficiency value to present an accurate depiction of residual test soil on the devices. For example, if 20 µg hemoglobin was removed from the device outlined above, this would only represent 76% of the total residual hemoglobin on the device and would need to be corrected by the recovery efficiency value. Therefore, the actual residual value of hemoglobin would be 26 µg.

$$\text{Corrected residual value} = \frac{\text{Raw analyte value}}{\text{Recovery efficiency}}$$

$$26 \text{ µg hemoglobin} = \frac{20 \text{ µg hemoglobin}}{0.76}$$

After extraction and testing of analytes are completed, the data obtained are evaluated against acceptance criteria for each analyte, as established by the MDM prior to testing. If the process was successful, the MDM will use the cleaning validation to develop the device IFU.

Conclusion

The six changes outlined here demonstrate two objectives of the FDA's 2015 guidance document on test methods for cleaning validations for reusable medical devices[2]: (1) cleaning validations should be based on the intended clinical use of the medical device and (2) cleaning validations should be designed to reduce variability.

Before designing a cleaning validation, understanding the intended clinical use of the medical device so that appropriate test soils are selected (or designed) is vitally important. As part of the cleaning validation, applicable use conditions are simulated and correct endpoints are selected. Further, using worst-case testing parameters, additional controls, and validating the extraction method allow for standardization of cleaning validations and help identify variability in the test method. These changes (and other changes in the FDA guidance document) help streamline testing for consistency and ensure that the medical device industry will develop effective cleaning processes for reusable medical devices.

The direction specified in the FDA guidance document has helped MDMs design cleaning validation plans that are based on scientific justification and clinical relevance. The guidance has given the industry a more robust test method for defining the accuracy of the test results by providing addi-

tional controls and recommended test methods to evaluate a device's cleanability.

Subject matter experts responsible for performing cleaning validations should understand how the device is clinically used such that an appropriate contamination methodology is used and technically appropriate endpoints are selected. Further, they should understand the purpose of different controls, such that interference from the test system can be detected and investigated.

Following release of the FDA guidance document in 2015, the sterilization community has endeavored to update standards so that they are aligned with the guidance. Currently, AAMI's sterilization working group ST/WG 93 is creating a standard (ST98, *Cleaning validation of health care products—Requirements for development and validation of a cleaning process for medical devices*) that will help define how cleaning validations should be performed. Once released, ST98 will replace AAMI TIR30:2011/(R)2016 (*A compendium of processes, materials, test methods, and acceptance criteria for cleaning reusable medical device*).[6] ST98 and the FDA guidance document will aid MDMs in creating compliant and scientific cleaning validations.

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