

Five Steps to Validating the Cleaning Process of Medical Devices

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Many modern medical devices are composed of high-tech materials such as metallic alloys or synthetic plastics. Their production may require the use of various agents to aid in the manufacturing process or produce contaminants that require later removal. These devices must be clean to ensure patient safety, and to ensure the device will continue to function as intended. Listed here is a five step process to help keep contaminants out and ensure cleanliness.

Medical devices are regulated under 21 CFR Part 820 – Quality System Regulation and several sections are directly relevant to device cleanliness, specifically: 820.3 Definitions and 820.70 Production and process controls.

For manufacturers, the challenge is to validate the cleaning process to ensure devices are free of residue (chemical and particulate). The following framework can help.

Step 1: Evaluate the process

A thorough understanding of the manufacturing process will facilitate the validation process. Start with a step-by-step audit. Focus on identifying any chemicals that come into contact with the device during manufacturing and cleaning (lubricating oils, mold release agents, rinsing streams, detergents, etc.). Examine procedures that may produce a potential contaminant (e.g., cutting parts may produce particulate).

While a manufacturer will know its own processes, it must be equally informed about components supplied from outside sources. Include raw material components, as well. Any chemical residue on a supplied raw material could potentially remain throughout the manufacturing process. Be sure to communicate with raw material suppliers.

Step 2: Determine the limits

Once potential residuals have been identified, examine their health effects. Determine the acceptable limits of contamination on two key criteria:

- Health: How much can be there before it begins to hurt people?
- Product impact: How much can be there before the product starts to fail?

The limits chosen should be achievable, logical, scientifically justifiable – and set for each potentially harmful chemical residual that could remain at the end of the manufacturing process. When determining limits, take into account the toxicity of the residual as well as the device usage. The residual limit of a chemical on a device

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that will briefly come into contact with a patient's skin will likely have a different limit than if it were implanted inside a patient's skull. The application of safety factors to the limit can help where assumptions are made. It is convenient to set limits in units of amount per area (e.g., mg/cm²).

For chemicals, Material Safety Data Sheets (MSDS) provide basic, critical information on toxicity and harmful effects. Use this data to begin to determine limits. Obtain MSDS documents for each chemical used and examine for information such as toxicity, LD50 or No Observable Effect Level (NOEL). All can be useful in determining safe residual levels.

Step 3: Identify the analytical test

Once limits are determined, an analytical method must be identified to test for the contaminant. Here, many manufacturers, lacking the analytical capabilities and experience internally, will turn to an outside contract laboratory.

The laboratory will determine the best analytical method for testing — choosing either a specific method (examples are HPLC and GC), a non-specific method (examples are TOC and gravimetric analysis), or a combination of the two. The choice of a specific vs. non-specific method will be based on the residuals of interest and their limits. Each has their advantages and disadvantages.

Specific methods, which involve measuring specifically for Contaminant A and/or Contaminant B, are typically more difficult and more expensive to run. Specific methods may need to be developed for the residual of interest. The benefit is in knowing exactly how much of Contaminant A or Contaminant B is present. This may be useful if the residual of interest is particularly toxic or detrimental to the device. Specific methods typically have lower detection limits than non-specific methods.

In contrast, non-specific methods can provide results for many different contaminants in a single assay, but without being able to give a true value for any of them. An assumption has to be made that the assay result is the same for each of the contaminants of interest. Non-specific assays are routinely used in cleaning validations. They are typically cheaper, quicker to run, and require little method development.

Or, the laboratory could require a combination of methods. This could occur when testing for different types of residuals is required, e.g. lubricating oil and a cleaning agent.

Step 4: Validate the method for use

Once selected, testing methods must be validated as to their ability to repeatedly provide accurate results. In addition to typical analytical method validation parameters (specificity, accuracy, linearity, limit of detection, precision), this includes validating the sampling procedure (usually extraction or swabbing).

The extraction or swab recovery validation typically involves performing a spike and recovery study. This involves taking a clean part and applying a known amount of contaminant, performing the extraction/swabbing, and measuring using the

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analytical method. The recovery study samples may be generated by the testing lab or the manufacturer but are generally tested at the lab.

Based on the results, the decisions and methods selected in Step 3 may need to be adjusted.

Step 5: Validate the cleaning process

In Step 5, the manufacturer and laboratory work jointly to validate the cleaning process itself.

Ideally, newly manufactured samples are obtained, assayed for residuals, and examined to determine if the cleaning process has achieved the desired results. If these devices are not available, devices may be spiked in the worst-case (hardest to clean) areas with the contaminant of interest and sent through the usual cleaning process before testing. The spike amount is typically 10X the limit — or another justifiable amount based on knowledge of the manufacturing process.

Beyond the 5 Steps

Start to finish, the five-step process could take 1 to 2 months to complete depending on a number of variables — including how well a manufacturer and its suppliers know their processes, and the capabilities and experience of the testing lab.

Periodic verifications of the cleaning process should be undertaken throughout the lifetime of the device. Moreover, if any changes are made to the device or component configuration, the manufacturing process, supplied components, cleaning process, or the like — a repeat of some or all of the validation process may be required.

Validating cleaning methods for medical devices need not be a headache. Coupling a step-by-step approach with a strong knowledge of the manufacturing process and access to a broad range of analytical capabilities will go a long way towards providing clean, contaminant-free products.

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