RevereIT LLC

Cleaning Validation – Introduction

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CLEANING VALIDATION

Cleaning Validation is used to show proof that the cleaning system consistently performs as expected and provides scientific data that consistently meets pre-determined specifications for the residuals. The cleaning validation process must be written into protocols and standard operating procedures which are detailed and specific for the different pieces of equipment and instrumentation used by the facility for each type of drug product produced. Other protocols and SOP's are also required if cleaning is performed based on the type of product manufactured or process used (such as a batch or bulk process or shared versus dedicated equipment).A final report on the cleaning validation system will attest that the studies and data prove that the process is in control and clean as expected. This report will also detail when and why revalidation needs to take place.

CLEANING VALIDATION METHOD

A Cleaning Validation Method involves testing for acceptable residues on pharmaceutical manufacturing or medical device surfaces. The validation involves:

· Identifying Residue
· Selecting a Residue Detection Method
· Selecting a Sampling Method
· Setting Residue Acceptance Criteria
· Validation Methods and Implementing Recovery Studies
· Writing Procedures and Training Operators
· Directory of Cleaner Residue Detection Methods for Detergents

This procedure is used to document acceptable residues 3 or more times and then a rational monitoring program, to maintain a validated state that can be put in place. If you are changing any part of the cleaning procedure including the cleaner, you must revalidate. To do this first clean the new way, collect data and then clean the old way before using any equipment. Follow these steps until the new procedure is fully validated.

Identifying residue—in a medical device environment involves:
-the process fluids, polishing compounds, mold releases, bioburden, endotoxins, cleaning agents and any degradation or interaction products.
This document is intended to help with the cleaner residue identification.

Selecting a residue detection method—for cleaners, may involve choosing a specific method or a non-specific method. Specific methods test for a specific ingredient includes: high-performance liquid chromatography (HPLC), ion selective electrodes, flame photometry, derivative spectroscopy, enzymatic detection and titration. Non-specific methods test for, the presence of a blend of ingredients, such as: total organic carbon, pH, and conductivity. The FDA prefers specific methods, but will accept non-specific methods with adequate rationale for their use. For investigating failures or action levels, a specific method is usually preferable.

Selecting a sampling method—for cleaners, involves choosing between rinse water sampling, swabbing surfaces, coupon sampling and placebo sampling. ***Rinse water sampling*** involves taking a sample of an equilibrated post-final rinse that has been recirculated over all surfaces.

Rinse samples should be correlated to a direct measuring technique such as swabbing. ***Swabbing*** uses a swab, or wipe, moistened with high purity water (WFI), that is drawn over a defined area using a systematic, multi-pass technique always moving from clean to dirty areas to avoid recontamination. A typical swabbing pattern might begin with ten side by side vertical strokes, followed by ten horizontal strokes and then ten strokes with the flip side of the swab in each diagonal direction. You then cut off the head of the swab and place it in the pre-cleaned TOC vial. For TOC analysis very clean low background swabs or wipes and sample vials such should be used. The Texwipe large Alpha Swab 714A and 761 have been used successfully. These are available in kits with clean sample containers. For UV testing, Texwipe TX 762 swabs have been used in conjunction with running a swab blank to set the zero level on the UV visible analyzer. Quartz glass fiber filter papers have also been used successfully. ***Coupon sampling*** involves the use of a coupon or a removable piece of actual pipe that is dipped into high purity water to extract residues for analysis. ***Placebo testing*** is done using placebo products and analyzing for residues from the previous batch.

Setting residue acceptance criteria—acceptance criteria are set based on potential for the residue to effect biocompatibility, toxicity, or functionality of the finished device. Where historical data, on particulate contamination, from existing successful manufacturing processes exists, it can be used to set acceptance limits for particulate levels. This will serve as a general control and facilitate cleaning consistency. For existing devices with a history of acceptable performance, the mean level of residue plus three standard deviations can be used for particulates and other types of residues. For a new device, a series of residue spiking biocompatibility studies at different levels can be done to determine the failure point. A lower level, possibly half the failure point, could be used to perform an analysis demonstrating that device performance was not affected and toxicity levels were not exceeded. When testing a new device, you can determine the expected level of residue, spike the device at a suitably higher level of residue and then evaluate for biocompatibility and functionality. If it passes, then that is where to set the limit. With cleaning agents and process fluids, consider systemic toxicity based limits. These can be derived if systemic toxicity is known. If not, estimate the acceptable daily intake (ADI) from LD50 (lethal dose for 50% of the population by compatible route of exposure depending on device) and a conversion factor using the equation below.

Acceptable Daily Intake = LD50 (mg/kg) x body weight(kg)/conversion factor Conversion factors will vary from 100 to 100,000 depending on the type of device and duration of exposure. Higher risk devices have higher conversion factors. According to the equation above, acceptable residue per square centimeter will depend on the size and quantity of devices being used. Consider the following example. A cleaner has an LD50 of greater than 500 mg/kg. An acceptance criterion is to be set for a device with less than one week of patient exposure. A safety factor of 10,000 is appropriate and the resulting limit should not exceed acute biocompatibility limits such as irritation. The calculation for a 70 kg adult would be: ADI/Device = 500 mg/kg x 70 kg/10,000 = 3.5 mg/device. The size of the device is then be factored into the calculation. If the device had a surface area of 100 square cm, then the surface residue limit for that detergent would be 35 micrograms per square cm (3.5 mg/device / 100 square cm). Of course, a process requirement of visually clean might very well be more stringent. In this example, we are working with a fairly non-toxic detergent, a fairly short contact time medical device and the resulting safety-based limit is fairly high. When working with more toxic residues on devices with greater exposure risk, such as implantable devices, conversion factors would be higher and acceptance limits lower. In such cases visibly clean levels might not stringent enough.

Validating methods and implementing recovery studies
Involves validating your residue detection method by establishing accuracy, precision, linearity, reproducibility, selectivity, specificity (if it is a specific method), limits of detection, limits of quantization, and ruggedness of the analytical residue detection method. Recovery studies involve the use of the sampling and detection methods on known spiked surfaces at representative levels. Typically, spikes are set at 50%, 100% and 150% of the acceptable limit and at lower than expected actual levels. This helps show linearity with documented % recovery as analyzed. It can also help determine the limits of detection and quantitation. Ideally, the expected values and limits should be multiples of the limits of quantitation. The % recovery is used to correlate amount detected with amount of assumed surface residue found acceptable. For example if 100 µg of residue was spiked on the surface and only 90 µg was detected after swabbing, extracting and analyzing, then there was 90% recovery. When used in a cleaning validation, any results would have to be adjusted by this recovery factor. In this example, a result of 90 µg per swabbed area would have to be interpreted as actually being 100 µg per swabbed area to adjust for the 90% recovery. This is a good time to consider wipe and rinse sample storage conditions as well time frame for sample analysis. A rinse ability profile, showing complete rinsing of an individual detergent ingredient, should be done when the solubility of that ingredient or its rinse ability after drying is in doubt. If your analytical detection method is only sensitive to one ingredient in the detergent, document that all ingredients rinse at the same rate or that the ingredient that you are testing for is the last to rinse away. If you cannot demonstrate either of these, provide a rationale that explains why you believe one or both to be true. For example, a surface active agent, or surfactant, is a good candidate to represent the entire detergent formulation. A scientific rationale can be made for this. Because a surfactant is attracted to the solution-surface interface, it is likely to be the last ingredient to rinse away. However, this is only true if the other detergent ingredients are significantly water soluble at the rinse concentrations. Infact, in the cases where all detergent ingredients are at least somewhat water soluble, have solubility greater than 10,000 ppm, they should all rinse at similar rates when tested using detergent spiked coupons in sequential rinses. To test by this method, dip coupons in rinse water, then analyze water for the detergent ingredients. In this crude form of testing, expect no detectable difference in rinse rate for somewhat water soluble ingredients at typical cleaning concentrations within the solubility limit of the detergent ingredients. This can be verified by comparing rinse rate for a specific ingredient analyzed by a specific method with rinse rate for a non-specific method such as TOC. In some cases, bioburden/endotoxin levels may need to be validated. As this takes longer, it is recommended that this process be done separately from the validation of the cleaning process so.

Writing procedures and training operators—are necessary components of cleaning validation in both medical device and pharmaceutical industries. Written procedures should include the following: assigned responsibilities; protective clothing requirements; equipment disassembly and monitoring procedures; documentation requirements; labeling instructions, for in process and cleaned equipment, that include cleaning expiration date, post cleaning inspection procedures, storage conditions and inspection requirements before next use. The operators must then be trained and certified in the procedures.

Directory of cleaner residue detection methods for detergent

- Anionic surfactant analysis methods

- Nonionic surfactant analysis
- Direct UV/Visible determination
- Phosphate detection Methods
- Total Organic Carbon (TOC) analysis
- When rinsing with deionized water
- Citric Acid analysis
- Ion selective electrode or flame photometry
- Propylene glycol ether detection by GC

Please contact Mr. A Gupta at 603-889-3000 X 107 for more details.