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# GXP Talk– Question #77: Cleaning Validation in the Lab?


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*"GXP Talk" provides a forum for addressing compliance issues identified by readers of the Journal of GXP Compliance.*

*"GXP Talk" is the longest running continuing series in the Journal of GXP Compliance. A total of 76 questions on GXP topics have been previously discussed. We discuss #77 this issue. Previous discussions have addressed a wide range of compliance activities covering essentially all sections of the US GMPs. Responses to questions and associated opinions have been contributed by representatives from multiple pharmaceutical industries and regulatory agencies. In the current format, questions and answers are presented together.*

*Readers are invited to participate ad contribute questions, answers, and discussion for this series – please share your successful practices with other readers. This column succeeds when we are able to address current GXP issues submitted by interested readers. Please contact column coordinators Jerry Lanese at jerry@lanesegroup.com, Rich Poska at richposka@gmail.com, or Melissa Carella at melissa.carella@ivtnetwork.com with comments, or submissions for publication. We welcome your questions, opinions, or other input.*

**QUESTION #77**

Cleaning methods for pharmaceuticals are developed and validated for use in the cleaning of manufacturing equipment. Are these same methods required to be used in the analytical laboratory for cleaning glassware, tubing, and other analytical equipment? Must these laboratory cleaning methods also be validated?

**ANSWER**

Cleaning methods and the validation of cleaning methods is intended for application to manufacturing equipment. The FDA CGMPs specifically address the cleaning of manufacturing equipment and utensils in 21 CFR 211.67, Equipment cleaning and maintenance (1) and the documentation of cleaning manufacturing equipment in 21 CFR 211.182, Equipment cleaning and use log (2). There is no specific mention of cleaning laboratory equipment in 21 CFR 211.160, Laboratory Controls (3). There is also no mention of cleaning laboratory equipment in Validation of Cleaning Process (7/93) (4), FDA's most recent specific guidance on cleaning validation. Other major global regulatory cleaning documents also do not comment on cleaning of laboratory equipment (5,6,7,8).

FDA comments on cleaning of laboratory equipment in "Questions and Answers on Current Good Manufacturing Practices. Equipment Question #9. Should laboratory glassware be included in a firm's cleaning validation program?" (9) is relevant. Specifically,

> *"FDA does not expect laboratory glassware to be included in the processing equipment cleaning validation program. Glassware must, of course, be clean, and CGMP regulations consider laboratory equipment to be included within the scope of 21 CFR 211.67. "*

These comments state that laboratory glassware must be clean, but does not need to be sampled, quantitatively tested for residue, or validated as expected for manufacturing equipment. The lab may choose to test cleaned glassware for interfering residue in cases of sensitive test methods. Residual drug on glassware may affect the accuracy of subsequent analytical determinations of highly potent drug molecules.

FDA further comments regarding the importance of laboratory glassware cleaning (9):

“Glassware that is not properly cleaned can make it difficult to determine if the source of aberrant analytical results is related to the unclean glassware or residues from manufacturing equipment. We expect firms to maintain laboratory equipment in a clean and sanitary manner to provide confidence in the analytical results.”

One cautionary CAPA note also in the FDA comments (9), suggesting problems with laboratory cleaning:

> “Contaminated laboratory equipment, however, should not be a frequent excuse for rejecting or discarding aberrant results.”

**Discussion Topics**

Several topics related to the above question on cleaning warrant further discussion. In brief:

- Objective and focus of cleaning and cleaning validation, including cleaning manufacturing equipment surfaces and cleaning limit calculations. Patient dosage is the primary focus.
- Objective and focus of lab glassware and equipment cleaning, including analytical interferences, dedicated equipment, and avoiding incompatible materials. Analytical method accuracy is the primary focus.
- Application of R&D and cleaning technical information to laboratory equipment cleaning. Cleaning methods, both in manufacturing and in the laboratory, should be technically based whenever possible.
- Case studies demonstrating the above.

This discussion focuses specifically on the cleaning of residues and cleaning validation in the lab. Safety of personnel must also be considered as part of lab cleaning and testing procedures, but is beyond the scope of this discussion.

**OBJECTIVE OF CLEANING AND CLEANING VALIDATION – MANUFACTURING ENVIRONMENT**

The objective of cleaning validation is to confirm the effectiveness of a designated cleaning procedure on specific manufacturing equipment to reduce drug and other potentially pharmacologically-active residues to an acceptable level. This is intended to minimize transfer of residues to the following manufactured batch through contact on shared equipment surfaces. For example, if Product A is the first manufactured lot and cleaning of Product A residue is not effective, patients receiving the subsequent Product B lot could have pharmacologic activity from transferred Product A residue. Cleaning and cleaning validation is complex – hydrophilic compounds, hydrophobic compounds, highly potent compounds, highly toxic compounds, biologic compounds, solids, liquids, semisolids, and so on. All of these factors are considered when developing a cleaning methods and subsequent validation testing. To briefly summarize: The focus in cleaning validation is on shared manufacturing equipment and cross-contamination between products causing a drug effect when contaminated product is administered to patients.

**Residue Limits Determination**

Cleaning validation requires reduction of surface residue to a calculated quantitative level that will be determined in analytical testing. This limit is calculated from the minimum pharmacologic dose of Product A drug, maximum dose of Product B administered to the patient, equipment surface area contacted by both products, and batch size of Product B – Product A residue is transferred to second product and dosed to the patient. Note the maximum Product B patient dosage term in the calculation. Cleaning validation confirms Product A residue levels are below the pharmacologically active limit dosed to the patient.

**Comparison to the Laboratory – No Patient Involvement**

Contrast the above production-oriented discussion with potential cross contamination in the laboratory. While Product A residue may be transferred to Product B solution being analyzed through surface contact of shared laboratory equipment, there is no opportunity for patients to receive contaminated solution. There is no possible residue administration to the patent in the laboratory situation.

**ANALYTICAL METHODS CONSIDERATIONS**

The objectives of cleaning laboratory equipment are much different than cleaning manufacturing equipment – none of which involve administration to patients. Consider the following: Glassware and other laboratory equipment with residue from prior laboratory preparations (Product A) is cleaned after completion of testing. If prior residue is not adequately removed, subsequent testing (Product B) may be adversely affected due to the presence of contaminant. Transfer occurs because equipment surfaces containing Product A contaminant contacts Product B test solutions during sample preparation.

Cleanliness of laboratory equipment is expected to ensure accurate, unbiased, and reproducible test results. Cleaning residue could interfere with subsequent analyses causing erroneous test results, chromatography, or other interferences causing an out-of-specification or procedural deviation. Laboratory glassware and other lab equipment may actually require higher standards of cleanliness than manufacturing equipment. Manufacturing equipment requires cleanliness to a sub-pharmacologic level of cleaning; laboratory cleanliness levels are concerned with potential interference with analytical determinations. Even trace contamination may cause analytical problems. Laboratory cleaning methods may utilize specific solvents to dissolve residue, may utilize dedicated equipment, may require specialized tubing that does not interact with drug analyte, or may utilize disposable equipment – all to accomplish accurate analytical determinations.

**CLEANING METHOD DEVELOPMENT TECHNICAL INFORMATION**

Although the above discussion justifies laboratory personnel not being required to utilize the same validated cleaning method for cleaning laboratory equipment as is used for manufacturing equipment, laboratory personnel should consider information developed as part of cleaning method development for possible use in laboratory cleaning. For example, cleaning methods for manufacturing equipment utilize solubility properties of product residues to optimize residue removal from equipment surfaces; a typical manufacturing cleaning procedure might require aqueous sodium hydroxide solution to remove most residues followed by surfactant cleaning agent to remove oil-soluble formulation ingredients. Laboratory personnel might utilize alcohol, organic solvents, or other atypical reagents to clean glassware; these would not normally be utilized to clean large-scale equipment for reasons of cost, toxicity, safety, or explosivity. Studies addressing residue recovery from surfaces may also provide useful information applicable to laboratory cleaning in different percentage recoveries and variation (10,11). Laboratory equipment must be scrupulously clean to provide accurate test results without potential for analytical interferences. Using optimal technical methods perhaps including organic solvents in the laboratory to eliminate potential interfering contaminants should be considered. Analytical methods may require use of dedicated equipment or disposable equipment for performance of certain testing such as with low concentration solutions. Certain materials such as silicone tubing may be avoided because they may absorb or adsorb a hydrophobic drug causing erroneous low analytical determinations. All of the above considerations should be known and understood through product R&D studies and cleaning method development studies, and should be useful for analytical laboratory methods and cleaning.

**CASE STUDIES**

The following case studies relating manufacturing cleaning to laboratory cleaning were described by managers from multiple companies. The successful resolution of these problems demonstrates the importance of a firm's knowledge management system. Knowledge management is an important Quality System enabler identified in ICH Q10, Pharmaceutical Quality System (12).

**Case Study #1. Cleaning Validation Unknown HPLC Peaks – Application to Laboratory Cleaning**

A manager reported unknown HPLC peaks in manufacturing equipment samples submitted for testing in cleaning validation (13). Active drug was adequately cleaned, but unknown compounds were observed in the HPLC chromatogram. These observations were noted several times in repeated cleanings and testing. Further laboratory testing determined that the unknown peaks were associated with hydrophobic flavoring oils in the product formulation. The manufacturing cleaning procedure was modified to include cleaning with an acidic cleaner followed by a proprietary alkaline surfactant cleaning agent. The laboratory also modified their standard cleaning procedure to include cleaning of manufacturing cleaning changes and laboratory cleaning changes – were made, successful cleaning validation was accomplished. Technical information utilized in

developing the manufacturing cleaning procedure was used to improve the laboratory cleaning procedure.

**Case Study #2 – Alcohol-Soluble Residue Cleaning – Application to Laboratory Cleaning**

A quality manager was auditing manufacturing operators who were cleaning small parts associated with a liquid filling operation. The validated cleaning method utilized a proprietary alkaline surfactant mixture. Equipment parts such as filling needles and polymer tubing were placed into a plastic tub; the tub was then filled with cleaning liquid for manual agitation and rinsing of equipment parts. The manager observed that an acidic proprietary cleaning agent was used instead of the alkaline cleaner. The acid cleaner was used at full strength (85% phosphoric acid); the acid liquid was not diluted as was the normal use of this cleaner. When confronted about not following the validated cleaning procedure, the supervisor stated that the alkaline cleaner never successfully cleaned the small parts, and the operators simply used an alternate method they knew would work (a compliance problem!). Operators "didn't have time to fix the procedure and accomplish cleaning validation." They were proud to do "whatever it takes" to get the job done – despite required procedures!

The site cleaning SME was consulted regarding the cleaning problem. Drug solubility information indicated that the active drug was highly insoluble in water, but very soluble in ethanol. Cleaning of equipment parts was moved to an explosion-proof room, and a new cleaning procedure using ethanol was validated.

During implementation of changes with the equipment cleaning procedures, an analytical laboratory technician described difficulty in cleaning pipets with the standard laboratory cleaning procedure. All pipets in the lab were cleaned by using an automatic pipet rinsing apparatus. When pipets were inspected after cleaning, insoluble material was always visible in the pipets. A new procedure in which pipets and other equipment were manually rinsed with ethanol before the standard cleaning procedure was implemented. Technical information utilized in developing the manufacturing cleaning procedure was applied to improve laboratory cleaning methods.

A new procedure in which pipets and other equipment were manually rinsed with ethanol before the standard cleaning procedure was implemented. Technical information utilized in developing the manufacturing cleaning procedure was applied to improve laboratory cleaning methods.

**FUTURE Q&A – WE NEED YOUR HELP**

The Q&A reported in GXP Talk over many years have been very well received by readers, and publication of new topics have been repeatedly requested. Several new Q&A discussions are currently in progress by authors. We need your help to continue the success of GXP Talk. This feature will be most useful when the compliance community submits questions or topics for discussion. Please contact column coordinators Jerry Lanese at jerry@lanesegroup.com or Rich Poska at richposka@gmail.com with comments, questions, or other input.

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