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VCS #10. Cleaning Validation Equipment Sampling Locations

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"Validation Case Studies"provides a forum for validation practitioners to share information about actual validation events experienced in their facilities. These discussions respect confidentiality and proprietary considerations. Our objectives include dissemination of useful information to help readers anticipate and prevent problem situations. Previous discussions have addressed a wide range of activities including the following:

1. Visual Observations, Journal of Validation Technology (JVT), Volume 16, #1. 2010
2. Equipment Qualification, JVT, Volume 16, #1, 2010
3. Identical mixing Tanks, JVT, Volume 16, #3, 2010
4. Cleaning HPLC Peaks, JVT, Volume 16, #4, 2010
5. Documentation Practices, JVT, Volume 17, #1, 2011
6. Yield, JVT, Volume 17, #2, 2011
7. Like-for-Like Changes, JVT, Volume 17, #2, 2011
8. Erroneous Negative Cleaning Validation Results. JVT, Volume 22, #5, 2015
9. Unapproved Materials from Approved Suppliers. JVT, Volume 27, #4, 2021.

"Compliance Case Studies" provides an equivalent forum for Quality function practitioners to share information about actual quality and compliance experiences. These experiences are presented in the Journal of GXP Compliance.

Readers are invited to participate and contribute manuscripts for both Validation Case Studies and Compliance Case Studies; we encourage sharing helpful information and successful practices with others. Please contact coordinators Paul Pluta or Stacey Bruzzese through the comments section below with questions, suggestions, or submissions for publication.

INTRODUCTION

The validation of cleaning processes is an important requirement in pharmaceutical manufacturing. Cleaning process validation assures product integrity, *i.e.*, there is no contamination of product with drug residue from prior manufacturing. After completion of a cleaning procedure, processes are validated by sampling cleaned equipment at specified locations, quantitatively determining the amount of residue in samples, and then comparing the respective residue levels vs. residue level acceptance criteria.

An extremely important factor in cleaning validation is the selection of cleaning validation sampling sites used to test the cleaned equipment. Quantitative residue level data from these sites are critical in proving that the cleaning process is validated. Sampling locations for these samples must be carefully chosen to represent worst-case locations for cleaning. If worst-case equipment locations can be proven to be clean, all other locations on equipment are assumed to be clean. Very simply and using common-sense logic -- if the floor in the middle of a room is clean, we cannot be confident that the corners of the room are also clean.

Quality Risk Management

The selection of sampling locations in cleaning validation must be dictated by risk assessment, *i.e.*, surface material, access for cleaning, level of contamination, and other factors that may impact cleaning must be considered when designing cleaning validation. For example, an apparently difficult to clean equipment part which is able to be removed from the equipment, submersed in cleaning liquid, thoroughly scrubbed, and easily examined to observe residual soil may be reliably cleaned. In contrast, an apparently easily cleaned part not able to be removed from equipment main assembly may be difficult to clean due to restricted access. Risk judgments for sampling locations must be thorough and comprehensive.

Regulatory Guidelines

Guidelines from regulatory agencies and cleaning validation literature clearly recommend the selection of worst-case sampling locations for cleaning validation (1-8). Approaches to determine sampling locations, however, are not specifically stated in these guidelines. Expectations for supportive documentation addressing selection of worst-case cleaning locations is also not described.

Discussion Topics

This case study describes a validation event in which sampling locations for cleaning validation were determined to be arbitrarily selected, i.e., rationale for selection of worst-case sample locations was not available. An investigation was initiated and a strategy for identifying worst-case sampling locations on equipment was developed. CAPA activities were then completed addressing this deficiency. Details of this event were provided by a Validation Manager who requested anonymity.

VALIDATION EVENT

A new tablet product containing a potent drug was developed and regulatory submission filed. Regulatory investigators were conducting the product pre-approval inspection at the manufacturing site. The new product was a relatively simple compressed tablet manufactured by wet granulation, drying, sizing, blending, and tablet compressing unit operations. Manufacturing documentation including process validation was reviewed; no issues were identified. Cleaning validation documentation was requested and reviewed. All cleaning validation data for sampling locations on each equipment were also acceptable; 3 or 4 samples were tested on each equipment. The regulatory auditor requested rationale for the locations of worst-case sampling on equipment. The validation manager explained that sampling locations were chosen based on historical precedent from previous cleaning validations, however, no written descriptive rationale for selection of sampling locations was available. The regulatory investigator suggested future corrective action to define worst-case sampling locations for cleaning validation. Although all validation documents presented were acceptable, the lack of justification for cleaning validation sampling locations reflected poorly on the site validation program.

INVESTIGATION

An investigation to address the lack of documented rationale for sampling locations was initiated. Rationale for equipment sampling locations to be used in cleaning validation was to be developed and documented. Sampling templates for cleaning validation protocols would be prepared. The following activities were performed:

1. Sampling Location Categorization. General categories of sampling locations on equipment were identified. This listing served as a checklist for identifying potential contamination locations on all site equipment. Most equipment had sampling locations in multiple categories. For example, equipment may have locations where most residue accumulated and where access for cleaning was limited. The following were categories of sampling locations:

- Sampling locations representative of all equipment surfaces. For example, most equipment was composed of stainless steel
- Sampling locations in areas of possible non-uniform contamination in the next product. These were locations that may flush residue into subsequent product
- Sampling locations in most difficult to clean areas of equipment. These were corners, 90° bends, piping, ad other problematic locations
- Sampling locations that accumulate maximum process residue
- Sampling locations that have maximum product contact
- Sampling locations for specific product-contact material. Equipment components composed of plastics, gaskets, and other non-stainless-steel components.

2. Sampling Methods. Equally important in the performance of cleaning validation is the selection of sampling methods appropriate for sampling sites. The sampling method is the procedure used to sample the equipment surface for eventual analytical testing for the presence of chemical residue. Swab sampling and rinse sampling were the two sampling methods selected for use in site equipment.

3. Evaluation of Sampling Locations and Methods. Considerations impacting the selection of sampling locations and sampling methods were identified. Activities involved included the following:

- Technical analysis of equipment. Problematic cleaning areas were identified from theoretical equipment evaluation
- Observation of equipment after processing. Areas with significant residue accumulation after completion of processing were noted
- Review of equipment disassembly. The equipment disassembly process prior to cleaning was reviewed
- Review of equipment cleaning procedures. The equipment cleaning procedure was reviewed
- Manufacturing experience with cleaning. Cleaning technician opinions during actual equipment cleaning were reviewed; what equipment areas were problematic for cleaning?

The above evaluations required input from Engineering, Quality, Validation, and Operations personnel. Experiences of manufacturing technicians who performed actual equipment cleaning was critical in this activity. A checklist of questions was developed for all involved, for example:

- What are most difficult to clean locations on equipment? Why difficult?
- Are certain products more difficult to clean than other products? Products with film residues vs. particulate residue?
- Possible changes to equipment to make cleaning easier or improve cleaning? Areas that accumulate rinse water, poor drainage, extreme angles, and other poorly designed areas?
- Possible changes to cleaning procedure to make cleaning process easier or faster?
- Auxiliary equipment needed to improve cleaning or to help evaluate cleaning (additional light, telescoping mirrors, etc.)?
- Any other comments regarding cleaning this equipment?

Content in these evaluations was the primary information supporting the identification of worst-case sampling locations for cleaning validation.

4. Recommendations. After equipment evaluation as described above, sampling locations and methods for a specific equipment were recommended. The sampling method (swab or rinse) was listed along with the sampling location. A general hierarchy of sampling locations evolved; these included:

    - **Primary Sampling Locations**

        - Most difficult to clean location on equipment
        - Non-uniform contamination locations
        - Sampling locations that accumulate maximum process residue.
        - Representative sampling locations. Areas easy to clean when representative locations comprise essentially all equipment surfaces.
    - **Secondary Sampling Locations**
        - Sampling locations that have maximum product contact.
        - Random sampling locations.
    - **Special Sampling Locations**
        - Sampling locations for specific product contact material. Used when specific product contact material is a significant component of the total surface area
        - Equipment with potential to contaminate product due to air flow or other reasons such as lyophilizer shelves or oven walls.

Trials to confirm the above approach on several representative equipment were then conducted. Representative sampling templates with equipment pictures/diagrams identifying sampling locations were prepared and evaluated for routine use in cleaning validation protocols.

CAPA

Activities implementing use of the sampling location strategy and application to actual cleaning validation included the following specific activities.

1. **Sampling Determination Procedure.**A site procedure to evaluate sampling locations on equipment was developed. This procedure described the equipment evaluation process and identification of sampling locations and sampling methods as described above. The approach was then utilized for new equipment, new products, and other applications in advance of actual cleaning validation. Subsequent review of this approach by regulatory investigators received favorable comments. When an auditor asked how equipment sampling sites and methods were determined, this procedure was provided.
2. **Equipment Evaluations.**These include the complete evaluation process including operator interview documentation for each equipment. Equipment evaluations followed the above procedure to determine sampling locations on site equipment. Activities included equipment technical evaluation, observation of equipment after processing, equipment disassembly review, cleaning procedure review, and cleaning actual experiences. The final result of the equipment evaluation was recommendations and rationale for equipment sampling. When an auditor asks how equipment sampling sites and methods have been determined for a specific equipment, the corresponding report for the selected equipment was provided.
3. **Equipment Sampling Templates for Cleaning Validation Protocols.**These are the documents to be used in cleaning validation protocols. These documents were approved by the site Validation Approval Committee and were controlled documents subject to change management. Equipment evaluation documentation was filed along with the sampling templates. The approved Equipment Sampling Templates were used in all cleaning validation protocols. When a new cleaning validation was initiated and the process train determined, appropriate Equipment Sampling Templates were are assembled and used in the cleaning validation protocol. Use of the same sampling procedures in all cleaning validation protocols provided continuity and consistency to the site cleaning validation program.

SUMMARY AND FINAL THOUGHTS

This case study demonstrated an approach used to identify equipment sampling locations and sampling methods for cleaning validation. If sampling sites and methods are not correctly chosen, the cleaning validation is questionable. Regulatory guidelines clearly state that sampling locations for cleaning validation must include worst-case sampling locations. Documentation affirming the selection of sampling locations and methods must be available.

Sampling locations and sampling methods must be selected based on risk of contamination in subsequent product manufacturing. Specifics of the approach used in this case study included the following.

1. **Sampling locations.** Multiple categories of sampling locations were identified.
2. **Sampling methods.** Primary types of sampling methods used at the site were described.
3. **Approach for selection of sampling locations and sampling methods.** Selection of sampling locations and methodologies should be accomplished by a logical and reliable method including equipment technical analysis, observation of equipment after processing, equipment disassembly, cleaning procedure review, and cleaning actual experiences.

Content in the above analysis is documented and retained as justification for selection of sampling locations and methods for cleaning validation. This activity was the most important in addressing the case study deficiencies identified by the regulatory investigator.

4. **Sampling locations and sampling method recommendations.** Worst-case locations and methods were identified and justified base on the above sequence of activities and corresponding analysis.

CAPA activities in response to the investigator's observations included development of an equipment evaluation procedure to identify worst-case sampling, utilizing this procedure on site equipment, and developing sampling templates for use in cleaning validation protocols.

Other Benefits

Aside from the stated objective of the work to justify sampling locations for cleaning validation, several unintended consequences of the above activities also occurred. Review of equipment resulted in modifications to facilitate cleaning. Design deficiencies were corrected including modification of 90° piping bends to lesser angles to facilitate powder flow and minimize obstruction. Pipe lengths were shortened to facilitate cleaning. Areas with rinse water accumulation were modified to improve drainage. Several equipment disassembly procedures and equipment cleaning procedures were also improved. This activity heighted employee attention to cleaning processes, caused improved equipment designs to facilitate cleaning, and generally increased site awareness of cleaning validation.

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