Case Study #1—Equipment Cleaning and Visual Evaluation

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Welcome to “Compliance Case Studies.”

This column discusses compliance situations useful to practitioners in compliance and validation. Each case presented deals with a specific compliance problem, elements of which are described with the intention of enriching the knowledge of those responsible for solving a firm’s compliance problems. We intend this column to be a useful resource for daily work applications.

“Compliance Case Studies” presents actual compliance events submitted by readers of the Journal of GXP Compliance. These events are briefly described, the issues are identified, relevant CGMP requirements are noted, and the actions taken in response are presented.

Reader comments, questions, and suggestions are needed to help us fulfill our objective for this column. Case studies illustrating compliance issues submitted by readers are welcome. We need your help to make “Compliance Case Studies” a useful resource. Please send your comments and suggestions to journal coordinating editor Susan Haigney at shaigney@advanstar.com.

KEY POINTS DISCUSSED

The following key points are discussed in this case study:

• A compliance case study involving equipment cleaning and inspection of cleaned equipment
• The event comprised cleaning of multiple equipment per procedure. Manufacturing residue was observed in only one specific equipment after cleaning.
• Three issues were investigated: (1) Equipment cleanliness evaluation—the cleaned equipment was evaluated as clean by multiple individuals; (2) Equipment cleaning—residue was found on the equipment after cleaning; and (3) Cleaning validation—the equipment had been cleaned by a validated cleaning procedure
• Investigation and root cause determination involved personnel interviews and cleaning procedure technical evaluation
• Root cause was determined to be inadequate rinsing of equipment because of undefined steps in the cleaning procedure
• Corrective action and preventive action (CAPA) addressed the specific root cause as well as implementing multiple improvements
to the site cleaning procedures, equipment inspection procedure, and training program
• CAPA activities included impact assessment on previous manufactured lots and application to other site cleaning procedures
• Post CAPA activities verified and maintained the continuing success of CAPA initiatives.

INTRODUCTION
This case study was provided to the Journal of GXP Compliance by a reader who requested anonymity. The circumstances presented describe an actual occurrence. This discussion provides the following:
• Background. A description of the event, the key issues to be addressed, and applicable current good manufacturing practice (CGMP) requirements.
• Investigation. Interviews and actions conducted to investigate the event.
• Discussion. Key information and analysis.
• CAPA. Actions and improvements implemented. These included the cleaning procedure change, equipment inspection procedure change, training on new procedures, cleaning validation, and associated activities.
• Post CAPA. Verifying and maintaining validation and performance.

Comments and recommendations from the authors are included.

BACKGROUND
The circumstances of the event were as follows: Pharmaceutical manufacturing plant, end of the second shift, weekday night. Operator Doe, an experienced operator working the PM shift, cleaned the manufacturing equipment he had used during his shift. Equipment included a manufacturing tank, mixer, associated tank small parts, particle size reduction mill, filtration apparatus, and transfer lines to a holding tank prior to filling into final packaging. This equipment was used to manufacture an oral solution product.

The cleaning performed was a manual cleaning process that included equipment disassembly, scrubbing with alkaline cleaning agent, rinsing with purified water, and drying with compressed air. After completion of the cleaning process and associated documentation per site procedure, Operator Doe requested that his manufacturing supervisor sign the cleaning record to affirm completion of the cleaning procedure and that the equipment was clean.

Operator Doe and his supervisor were both experienced employees at the company. The supervisor signed the cleaning record. Per procedure, the supervisor then requested the quality control (QC) supervisor to check the equipment for cleanliness and to approve the cleaning record. The QC supervisor, also an experienced worker, inspected the equipment and signed the cleaning record.

When the plant reopened the following morning for manufacturing, Operator Smith, working the AM shift, noted that some of the equipment was not clean. The mixing tank had a thin film of residue on the inside of the tank. Manufacturing could not be initiated without re-cleaning the equipment. The AM manufacturing supervisor confirmed that the mixing tank was not clean. All other associated equipment (e.g., mixing blades, transfer lines, filtration equipment, mill, and other small parts) were clean—no residue was observed. A swab sample of the mixing tank residue was taken by the technical group to determine the composition of the residue. Operator Smith then re-cleaned the mixing tank prior to initiation of subsequent manufacturing.

What are the Issues?
There are three primary issues to be investigated in the presented event as follows:
• Equipment cleanliness evaluation. The cleaned equipment was evaluated as clean by multiple individuals during a relatively short time frame (all PM end of shift), but was subsequently (next morning, eight hours later) observed to have residue.
• Equipment cleanliness. The equipment had been cleaned per procedure, but certain equipment was found to have residue from previous manufacturing. The mixing tank had residue;
all other equipment including mills, filtration equipment, and small parts were clean.

- Cleaning validation. The validated cleaning procedure was used to clean the equipment. There should have not been any residue.

**CGMP Requirements**

Relevant GMP requirements applicable to the presented event are listed as follows:

- Subpart D – Equipment
  211.67. Equipment cleaning and maintenance
- Subpart J – Records and Reports
  211.180. General Requirements
  211.182. Equipment cleaning and use log.

**INVESTIGATION**

Investigation and ultimate resolution of this event required involvement of several groups. These included personnel involved in the incident (operations and QC) and technical personnel responsible for the cleaning procedure. The following details needed to be investigated and/or confirmed:

- Why was the mixing tank dirty after cleaning? Was the equipment unusually dirty after processing, causing the cleaning procedure to be ineffective? Was cleaning performed as directed in the cleaning procedure? Why did the mixing tank have residue while all other equipment were clean? Is it possible that the mixing tank was not cleaned?
- Was the mixing tank actually observed to be clean after the cleaning procedure was completed? Was the equipment dry when the cleaned equipment was evaluated? Were any differences noted between the mixing tank and other equipment?
- When the residue was discovered, was the residue from PM manufacturing or was it contaminated with other soil? What was the nature of the soil? Could the equipment have become contaminated overnight? What parts of the equipment were not clean? Were the mixing tank and all associated parts uniformly dirty? Were the dirty areas localized?
- Is the cleaning procedure adequate? Is there a technical reason for residue on the mixing tank but not on other equipment? Any reason why most of the equipment was clean, but the mixing tank had residue? Wasn't this a validated cleaning process? Was the actual cleaning procedure different from the process that had been validated?

**Personnel Interviews**

Personnel involved in the incidence included Operator Doe (PM operator), PM manufacturing supervisor, PM QC supervisor, Operator Smith (AM operator), and the AM manufacturing supervisor.

Operator Doe confirmed that nothing unusual had occurred associated with equipment cleaning. The equipment was not unusually soiled or difficult to clean after the previous manufacturing. All cleaning procedure steps were performed as required. The equipment was examined after cleaning and appeared clean. Evaluation occurred after the equipment was dry. The PM manufacturing supervisor confirmed that all cleaning procedure steps were performed as required. He examined the mixing tank and associated equipment after cleaning, and all appeared clean. Evaluation occurred after the equipment was dry. The PM QC supervisor confirmed that all equipment was examined after cleaning and appeared clean. Evaluation occurred after the equipment was dry.

Operator Smith confirmed that the mixing tank was not clean when he initially examined the equipment prior to starting manufacturing in the morning. He rubbed his hand over the tank surface and noticed a uniform thin film of residue. The residue was a white powder. The residue was not obvious when simply looking at the tank. It was only noticed when he rubbed his gloved hand over the tank surface. All other equipment parts were clean and did not have any residue. The AM manufacturing supervisor confirmed that the mixing tank was not clean. He also rubbed his gloved hand over the equipment surface and noted a uniform thin film of residue. The residue was uniformly distributed and was not observable when simply looking at the equipment. All other equip-
ment and small parts were clean and did not have any residue.

**Technical Evaluation**

Technical personnel explained that all equipment was cleaned using essentially the same procedure (i.e., same cleaning agent, same cleaning process, and sequence of cleaning steps). Although all equipment was cleaned in the same way, there were slight differences based on the nature of the equipment. For example, small parts were disassembled from the main equipment and washed and rinsed in the sink. They were easily and thoroughly rinsed and dried. The particle size reduction mill was moved to a wash area and cleaned by scrubbing, rinsing, and drying. The mill was easily cleaned because all parts were readily accessible and able to be seen during cleaning. The mixing tank was permanently installed and not able to be moved. It was manually scrubbed, rinsed, and dried in place. Rinsing was accomplished by spraying water into the mixing tank and draining the rinse water from the tank. After rinsing, the tank was dried.

The fact that the mixing tank was the only equipment with residue suggested that the rinsing procedure for the tank was suspect. All other equipment was easily rinsed. The mixing tank, however, required that the rinse water be completely drained from the tank to effect complete rinsing. If the rinse water in the tank was not emptied, residue would not be expelled from the tank. The cleaning procedure did not clearly specify that complete draining of the tank during rinsing was required. Depending on the operator and sequence of cleaning activities, the mixing tank may or may not have been drained.

When the morning personnel noticed the presence of residue, technical personnel obtained a swab sample of the residue. The sample was analyzed to determine if the residue was product or another substance. The results of the analysis indicated that the residue contained both product residue and cleaning agent residue. These data further confirmed the inadequacy of the rinsing process. The amount of active drug residue and cleaning agent residue was quantitated by the analytical method.

**DISCUSSION**

The interviews and technical discussion described were key to determining the root cause of the event. Multiple trusted and reliable people (PM people) affirmed that the equipment was clean when they completed their inspection. However, their inspection was entirely visual; they did not touch the equipment surfaces (this was not required per procedure) when inspecting the equipment. There were no distinct or obvious appearances of residue on the equipment when observed visually. All equipment had been cleaned. Morning personnel only observed residue on the mixing tank when they touched the equipment. Residue would not have been observed if the morning personnel had not touched or rubbed the surface of the mixing tank, which created a contrasting surface. All other associated equipment and small parts were clean and did not have residue. The description of the residue on the equipment by the Monday AM personnel indicated that this was not typical residue after manufacturing (i.e., the tank residue was evenly dispersed over the tank surface). The fact that only the mixing tank had residue suggested that rinsing of the tank was not adequate. All other equipment was easily rinsed and had no remaining residue. Finally, the details of mixing tank rinsing explained by the technical personnel (i.e., that it was expected to allow the tank to completely drain during rinsing) indicated that complete emptying of the tank during rinsing must be clearly defined in the cleaning procedure.

Several changes in the cleaning procedure were implemented as a result of this investigation. Technical personnel recommended an additional rinsing step using tap water to be added to the cleaning procedure following scrubbing with alkaline cleaning agent. This would enable thorough rinsing without depleting the purified water reservoir. The tap water rinsing step was also quantified to ensure adequate rinsing. After scrubbing, the equipment was rinsed with tap water (maximum open flow
rate) for a specified time. Also, the mixing tank was required to be completely drained when it became filled with rinse water. Multiple drainings of the mixing tank were required. This was determined to be the root cause of the problem. Because the tank was not completely drained, residue in the rinse water was not flushed from the tank and was re-deposited on the tank surface in a uniform film. Complete emptying of the mixing tank during rinsing was not clearly specified in the original cleaning procedure. Subsequent rinsing with purified water and drying then completed the cleaning procedure.

Several changes in the clean equipment inspection procedure were also implemented. Additional lighting and a hand-held mirror were provided to enhance the inspection procedure. The mirror aided in the inspection of equipment undersides. Technical personnel also recommended a “white glove” test to evaluate the cleaned equipment. This step would mimic the procedure that had alerted everyone to the thin film of residue on the equipment.

Technical personnel also prepared plates with residue of known concentrations to mimic the residue originally observed on the equipment. The swab sample analysis of the actual residue was used to demonstrate the actual residue level on the mixing tank. These plates confirmed that the equipment appeared visually clean when untouched because the residue was uniformly dispersed. After touching and rubbing the surface, however, residue could be observed.

Be careful of premature judgment! Initial review of the details of this event suggested that Operator Doe, the PM supervisor, and the PM QC supervisor might have not adequately fulfilled their responsibilities: Doe might not have adequately cleaned and inspected the equipment post cleaning; the PM supervisor might not have adequately inspected the equipment; and the PM QC supervisor might not have adequately inspected the equipment. If true, all three signing documentation affirming same would have been a very serious GMP violation. Weekday late night, end-of-shift circumstances might have implied that work and subsequent inspections might have been hurriedly performed. In reality, all personnel followed procedures and performed their required tasks as trained. These individuals, as well as the technical people who developed the cleaning procedure, were not aware that evenly dispersed residue is very difficult to see. It was only by rubbing the surface of the equipment (which was not the usual practice) that the evenly distributed residue film was observed. The detailed description of the residue appearance by the AM workers was key to determining the root cause of the problem—insufficient rinsing in the cleaning procedure.

CORRECTIVE ACTIONS AND PREVENTIVE ACTIONS

The following CAPA and associated activities were conducted:

- **Cleaning procedure change.** Multiple changes were implemented that significantly improved the cleaning procedure described. An additional rinsing step with tap water was added to the equipment cleaning procedure following scrubbing with alkaline cleaning agent. The tap water rinsing step was followed by rinsing with purified water. Parameters for both tap water rinsing and purified water rinsing was defined (i.e., rinsing was required for a specified amount of time with a known volume of water). Adding the tap water rinsing step enabled extensive rinsing without concern for depleting purified water reserves. An important change included multiple complete drainings of the tank during rinsing. This enabled complete flushing of residue and cleaning agent and prevented re-depositing of residue on the mixing tank surface.

- **Review of other cleaning procedures.** The lessons learned as described in this case study were considered in the other cleaning procedures used in the facility. Other cleaning procedures that might also have inadequate rinsing were clarified or modified. An additional tap water rinsing step was also added to these procedures. Rinsing parameters (volumes and times) were also added to other cleaning procedures. Requirements to completely drain
other mixing tanks during rinsing were also added to these procedures.

- **Equipment inspection procedure change.** Visual examination of equipment was improved by use of additional lighting and hand-held mirrors to aid in inspection of equipment. Mirrors aided the inspection of areas that were difficult to directly observe. A “white glove test” was also added to inspection procedures. This required touching or rubbing the equipment surface to verify that there was no residue.

- **New procedures.** Procedures were changed reflecting the above changes. These included cleaning procedure changes and cleaned equipment inspection procedure.

- **Training on new procedures.** Training for all manufacturing and QA personnel was conducted on the changed procedures. Training included both classroom discussions and “on-the-job training” to demonstrate the important aspects of the new procedures.

- **Cleaning validation.** Cleaning validation was conducted on all new cleaning procedures. A matrix approach including worst case products was used to validate the new cleaning procedures. The aforementioned training on new cleaning procedures and inspection procedures was helpful in successfully accomplishing cleaning validation without difficulty.

- **Communication.** The incident was discussed with all manufacturing and QC individuals at a plant meeting to emphasize the importance of the event, reinforce correct actions, reinforce training, and demonstrate management commitment to the quality principles involved.

- **Impact on past manufacturing.** Past manufacturing history was reviewed. The maximum amount of possible residue remaining on equipment was determined by laboratory analysis. The amount of residue was far less than that which would cause a pharmacological response in subsequent manufactured products. There was no impact on previously released products.

**POST CAPA—VERIFYING AND MAINTAINING VALIDATION AND PERFORMANCE**

The previously described actions enabled closure of the CAPA associated with this case study event. However, post event monitoring was implemented to verify success of the CAPA and maintain performance. Elements of this program addressed the following:

- **Cleaning validation and cleaning procedures changes.** The site cleaning monitoring program was enhanced to enable ongoing review of the new cleaning procedures and maintenance of the validated state. Because all cleaning at this facility was manual, it was decided to conduct periodic analytical testing of worst case products and procedures. This practice, along with review of cleaning deviations, non-conformances, other changes, and an enhanced training program provided good confidence that cleaning processes were well controlled.

- **Equipment inspection procedure changes.** The improved visual examination of equipment and new “white glove test” was established as regular practice. These changes also enhanced confidence in the site-cleaning program.

- **Training.** Training for all concerned on the equipment cleaning procedures and cleaned equipment inspection procedures was required to be repeated annually for all personnel. The annual retraining requirement provided repeated emphasis on the importance of the cleaning procedure and inspection procedure, especially when in cases where cleaning is a manual process.

**CONCLUSIONS**

This case study illustrated several important points, including solution to the specific problem of the event, application to associated procedures and processes at the site, and continued verification and maintenance of corrective and preventive actions. The following improvements were also implemented:

- **Investigations.** Investigations must be thoroughly conducted. In the example above, a thorough investigation resulted in a defined
root cause for the cleaning event, a specific solution to the identified root cause, a comprehensive solution addressing associated and contributing elements to the problem, and subsequent improvements in processes and procedures. The identified root cause affected only specific equipment (mixing tank) within the otherwise acceptable cleaning procedure that included multiple equipment and associated parts.

- **Cleaning procedure.** There must be a good technical basis and understanding of the cleaning procedure. In the event presented, the rinsing procedure was not adequately defined, resulting in process variation and an actual cleaning failure. The revised cleaning procedure clearly defined process parameters and added additional steps to insure successful cleaning. The improvements developed for the cleaning procedure of the specific event were then applied to other cleaning procedures at the site.

- **Equipment inspection.** This event prompted evaluation of the cleaned equipment inspection procedure, again resulting in several improvements that were applied to all equipment inspections at the site.

- **CAPA.** All CAPA activities associated with the event must be carefully and thoroughly completed. These included the impact of the problem procedure on previously manufactured lots and possible application to other cleaning procedures. This event caused several other site cleaning procedures to be significantly improved.

- **Post CAPA.** Activities to verify and maintain operator performance and maintain the validated state of the cleaning program were implemented. These included enhancements to the cleaning monitoring program, cleaned equipment inspection program, and training program. These enhancements also provided timely maintenance and review of the cleaning program.

- **Improvements.** The review and evaluation of specific activities and programs prompted by the event of this case study resulted to several specific improvements for the site.