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Validation Case Study: Erroneous Negative Cleaning Validation Results

By **Paul L. Pluta**

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1. *Visual Observations, Journal of Validation technology (JVT), Volume 16, #1.*
2. *Equipment Qualification, JVT, Volume 16, #1.*
3. *Identical mixing Tanks, JVT, Volume 16, #3.*
4. *Cleaning HPLC Peaks, JVT, Volume 16, #4.*
5. *Documentation Practices, JVT, Volume 17, #1.*
6. *Yield, JVT, Volume 17, #2.*
7. *Like-for-Like Changes, JVT, Volume 17, #2.*

Readers are invited to participate and contribute manuscripts for this series -- we encourage sharing successful practices with others. Please contact journal editor-in-chief Paul Pluta at paul.pluta@comcast.net or content specialist Dustin Henderson at dustin.henderson@cbinet.com with comments or submissions for publication.

ABSTRACT

This case study describes a cleaning validation event in which failing results for API residue from a small molecule extended release tablet dosage form were observed. The initial two lots in the cleaning validation were successful. The third lot failed acceptable residue limits. Investigation of the failure comprised cleaning process development and performance; residue sampling, sample handling, sample analysis, and evaluation of the analytical method. Investigation of this event initially involved interviews of relevant personnel and reviews of associated documentation. Two areas were identified for further evaluation – residue sampling and the cleaning process. Regarding sampling, a newly trained technician, working alone, sampled the first two acceptable lots, while an experienced technician working with a colleague sampled the third failing lot. Evaporation of sampling solvent occurred causing residue to be insufficiently recovered from the equipment surface resulting in erroneous false negative test results. Regarding the cleaning process, manufacturing operators commented that the new extended release formulation was more difficult to clean than the original immediate release formulation although the same cleaning procedure was utilized for both products. Evaluation of the cleaning process indicated that the process parameters were not optimal to clean the new extended release product. An improved cleaning process with increased cleaning agent concentration, increased cleaning time, and higher temperatures was developed, implemented, and ultimately validated.

Cleaning validation sampling personnel must have good technical understanding of their work, and must know the technical

reasons for the procedures they perform, and potential problems if procedures are not correctly performed. Sampling personnel training for cleaning validation should include a quantitative demonstration of acceptable cleaning by means of analytical testing. Training exercises must also include worst-case sampling such as with volatile solvents, multiple equipment, and other potential variations in sampling. SOPs must be carefully written to describe potential problems and include performance constraints to minimize variation and risks. There is an inherent danger when variation is not deliberately introduced into a validation project – material variation, manufacturing operator variation, and in this case study, sampling personnel variation. Sampling by two different technicians enabled erroneous results to be discovered. Regarding the cleaning process, inactive ingredients in a formulation may have very significant effects on cleaning processes. Cleaning of residues does not depend solely on the properties of the API.

INTRODUCTION

The compliance event involved cleaning validation for cleaning of residue from a new small molecule extended release tablet dosage form. The active ingredient in the tablet was a potent drug – dosage of the active ingredient was low and cleaning was expected to be successful. The site already had a successful history of cleaning a marketed immediate-release tablet containing a lower dose of the same active drug. No changes in the cleaning method were required for the new product. After cleaning, the target residue level was below “visually clean” and required the residue level to be determined by swab sampling and chemical analysis. Three lots were required for cleaning validation.

The following are discussed:

- Compliance event. A description of the cleaning validation event
- Investigation. Interviews and actions conducted to investigate the event
- Discussion. Key information, activities, and analysis
- CAPA. Actions and improvements implemented in the cleaning process, sampling process for cleaning validation, and training of sampling personnel
- Cleaning validation of modified cleaning process. Implementation of the new cleaning process and subsequent validation.

BACKGROUND

The process of validation typically comprise the following sequence of activities:

1. **Change desired.** An equipment or process change is needed or required. This may be a necessary change or a desirable improvement.
2. **Development work**. Appropriate Stage 1 development work is completed in support of the change.
3. **Validation plan**. A formal request to initiate the validation process is submitted to the validation approval committee (VAC). Development reports may be included in the request in support of the change. The change request includes a proposed level of work to confirm the acceptability of the change. The level of work is based on risk to the patient and to the organization. The VAC approves the change request. The approved change request document is stored in the validation library.
4. **Protocol.** A protocol is written specifying detailed sampling and testing to confirm the acceptability of the change. The VAC approves the protocol. The approved protocol is stored in the validation library.
5. **Validation work**. Stage 2 PPQ validation work is performed according to the protocol. Sampling and testing are completed. Data and other results are generated and recorded.
6. **Validation report**. A report containing all test results with discussion and conclusions is prepared and submitted to the VAC for approval. The report is approved and the process or equipment change is implemented. The approved validation report is stored in the validation library.
7. **Validation closure**. If no other work is needed, the validation project initiated by the change request is closed.
8. **Continued verification.** Stage 3 post-validation monitoring confirming acceptability of the change continues throughout the product / process lifecycle.

The issue addressed in this case study occurs in #5 and #6 above. The actual work conducted to confirm the acceptability of the validation project is performed by technical people. In this case study, samples were removed and tested for residue content.

VALIDATION EVENT

A small molecule pharmaceutical company conducted initial cleaning validation on a new extended release tablet product containing a water-insoluble API as active ingredient. The new product was a line extension -- an extended release formulation of a marketed immediate-release tablet product. The new product contained a polymeric matrix to enable prolonged release and once-daily dosage to patients.

The cleaning validation exercise was expected to be successful. Although the product contained a highly potent active drug which required low residue levels on cleaned equipment, the company had extensive experience with the cleaning procedure over several years. The original immediate-release product cleaning was relatively easy and had a long successful history of performance. Several previous cleaning validations had been successfully accomplished. The analytical method for residual API from swab samples was easily performed and very reliable.

Sampling of three lots of new product was planned for cleaning validation. The manufacturing process comprised several unit operations. Sampling of unit operations for cleaning validation was performed on multiple days for each lot. The first lot was manufactured and cleaning completed on all equipment. Equipment was visually clean. Swab sampling was done by the sampling technician. Cleaning validation analytical test data indicated no active drug present in all swab samples – all acceptable results. A second lot was manufactured. Cleaning was completed. Swab sampling was done. Cleaning validation analytical test data again indicated no levels of residual drug in all swab samples. A third lot was manufactured. Cleaning was completed. Swab sampling was done. Cleaning validation analytical test data indicated extremely high residue levels significantly above the required acceptance criteria. Test results on the third lot indicated a significant failure of the cleaning process.

This event prompted multiple questions to be investigated and answered.

1. Cleaning process performance. Did manufacturing personnel correctly perform the cleaning process in the third (failing) lot? Which operator cleaned the equipment? Were manufacturing personnel adequately trained in the cleaning procedure? What was past history with use of this cleaning process? Were repeat cleanings required in past cleaning? Were deviations required?
2. Cleaning process development. How were the cleaning process parameters developed? What was the history of this method with the immediate release product? We any changes made for cleaning the extended release product?
3. Sampling. Did the sampling technician correctly sample the recommended equipment surfaces? Were sampling personnel adequately trained?
4. Residue samples. Was the integrity of residue samples adequately protected during transport to the lab? Could samples have become contaminated causing the test failures? Were samples correctly and quickly transferred to the lab for analysis? Were samples handled during transport and storage according to procedures? Were samples exposed to high temperatures during transport and storage?
5. Analytical laboratory. Was the analysis correctly performed? Which technician performed the analysis? Were laboratory technicians adequately trained? Was analytical equipment qualified for use for the API analysis? Was system suitability below required limits?
6. Analytical R&D. Were there any problems with the analytical method? Was the analytical method correctly developed? Was the analytical method validated?

INVESTIGATION

Investigation of this compliance event initially involved interviews of relevant personnel and reviews of associated documentation. Personnel related to the compliance event included manufacturing personnel, QC personnel, cleaning sampling technicians, and the technical personnel responsible for product formulation and process, cleaning method

development, technical support, and analytical testing. There were many details and variables that needed to be investigated and/or confirmed. Personnel from all groups interacted to address the above issues.

Documentation reviews included manufacturing documentation, cleaning documentation, equipment inspection records, laboratory records, analytical method development reports, validation reports, and other records. All applicable manufacturing SOP's and analytical SOPs were reviewed.

Cleaning Process Performance

Manufacturing personnel correctly performed the cleaning process in all three lots. Cleaning procedure documentation for all lots was reviewed and found to be perfectly executed. No deviations were issued. Different operators executed cleaning of multiple equipment in the validation lots. An experienced operator executed cleaning in the third (failing) lot. Training records for all operators were reviewed and found to be acceptable. Operators commented that the new extended release product was more difficult to clean than the original immediate release product. The extended release polymer made removal of the product residue more difficult that was typical with the original immediate-release product. This observation reflected operator experience with manual cleaning of small parts. Product was able to be removed from equipment surfaces and yield visually-clean surfaces. No repeat cleanings were required. No deviations were issued.

Cleaning Process Development

The cleaning process for the immediate release product had been previously developed. An alkaline cleaning agent that was used on several other products in the plant was used. Because the API in the new extended release product was the same as in the immediate release product, no changes were made to the cleaning method. Technical personnel were unaware of any difficulty in cleaning the extended release product.

Sampling

Two different sampling technicians performed sampling in the three lots. A newly-trained technician sampled lots #1 and #2, both of which had acceptable low residue levels. The newly-trained technician worked alone to accomplish sampling since no other sampling technicians were available. Lot #3 was sampled by an experienced technician. The experienced technician worded with a colleague who helped sample the recommended equipment surfaces and complete required documentation. Both sampling personnel were adequately trained as evidenced by training documentation.

Residue samples

Residue samples were packaged in protective wrapping for transfer to the lab. Samples were immediately closed and not contaminated. Transport to the lab was rapid and without exposure to unusual environmental conditions or excessive heat.

Analytical laboratory

The laboratory analysis was correctly performed. Experienced technicians performed the analysis. All technicians were adequately trained. Analytical equipment was qualified for use for the API analysis. Lab documentation indicated acceptable execution of the analytical procedure.

Analytical R&D

The same analytical method was used for the original irradiate-release product and for the new extended-release product. Analytical R&D verified that the test method performed acceptably for the new product. There were no problems with the analytical method. The analytical method was validated.

DISCUSSION

Interviews and discussion of the above questions did not clearly indicate an obvious cause for the problem. Manufacturing personnel confirmed that they performed cleaning as required by procedure. Equipment was cleaned by automated methods wherever possible. All associated small parts were manually cleaned was cleaned according to procedure. The manufacturing supervisor verified that procedures were followed and that the equipment was visually clean. Quality unit personnel who

inspected the equipment also verified that all equipment and small parts were visually clean. All inspections were conducted after the equipment was dry. Samples were transported to the lab quickly and according to procedure. Samples were also quickly stored in the laboratory upon receipt and under specified security conditions. Laboratory personnel confirmed acceptable performance of analytical procedures. Analytical standards over a range of concentrations tested along with the actual cleaning validation samples yielded accurate results. Analytical R&D scientists confirmed acceptable performance of the validated test method.

Two areas were identified for further investigation. These included:

1. Swab sampling. A newly trained technician, working alone, sampled the first two acceptable lots. All samples in these lots were acceptable. An experienced technician, working with a colleague, sampled the third failing. Was something different about the third lot, or was the failing data due to the difference in sampling personnel?
2. Cleaning process. Manufacturing operators commented that the new extended release formulation was more difficult to clean than the original immediate release formulation. The same cleaning procedure was utilized for both products.

Swab Sampling

Swab sampling for the three lots was done by two different sampling technicians. The first two lots were sampled by a newly-trained person. Data for these lots indicated minimal or no residual soil – acceptable results. The third lot with failing data was sampled by an experienced technician who worked with a colleague.

The sampling method required wetting of the swab with organic solvent to dissolve residue from the equipment surface. The new technician did all sampling alone. The experienced technician performed sampling with a colleague to accomplish the sampling procedure in minimum time. She explained the necessity of the rapid sampling technique because evaporation of the sampling solvent must be minimized. The new technician was not aware of the time limitation in sampling. Although not conclusively proven, it was suspected that evaporation of solvent occurred causing residue to not be adequately recovered from the equipment surface. The new technician worked slowly and carefully, and completed all necessary steps. However, the time required for performance, especially since she worked alone, may have caused residue recovery to be incomplete or minimal. The analytical lab confirmed that if sufficient solvent was not present on the swab, residue recovery would be unsuccessful.

Cleaning Process

Technical personnel responsible for the cleaning process had no previous experience with the cleaning method. The cleaning method for the original product had been established many years ago and never required new technical evaluation. Manufacturing management decided to use the well-established cleaning method without involvement of technical personnel. Management’s rationale was that since the API in the original product had been reliably cleaned for many years, there was no need to evaluate the cleaning process for the new product. Technical personnel had not been requested to evaluate the cleaning process used in the failed cleaning validation. In light of the cleaning failure, technical personnel recommended laboratory studies to evaluate available cleaning agents, cleaning process parameters, and related factors in a systematic way. Evaluation of the cleaning process indicated that the process parameters were insufficient to clean the new product. The polymeric matrix in the new product (methylcellulose mixture) was much more difficult to clean than the original immediate release product. Technical personnel conducted studies to establish new cleaning process parameters suitable for the extended release product. A new cleaning method with increased cleaning agent concentration, increased cleaning time, and higher temperatures was developed.

CORRECTIVE ACTION / PREVENTIVE ACTION (CAPA)

Two CAPA activities corrected the problems experienced in the original cleaning validation. These involved new training of swab sampling personnel and a modified cleaning process for the extended release product.

Swab Sampling Training

Personnel who perform cleaning residue sampling using swabs wetted with volatile solvents were taught the importance of rapidly performing swab sampling. Many of the swab sampling technicians did not have a technical background and did not

understand solvent volatility and the consequences for swab sampling. Studies confirmed that the new technician, who worked alone in the sampling activity, did not perform swab sampling quickly. When sampling was not performed quickly, solvent evaporated and surface residue was not able to be dissolved. Analytical results on evaporated swab samples indicated extremely low or no levels of residue which erroneously passed cleaning validation acceptance criteria – a false negative due to solvent evaporation.

Future training of swab sampling technicians included new test procedures to require rapid performance of sampling procedures. The previous qualification test did not utilize a volatile solvent and did not require rapid performance. The new qualification test required technicians to demonstrate rapid sampling in order to become a qualified sampling technician. Sampling teams (two technicians) were required when volatile solvents were used in sampling. Technicians were required to quantitatively recover residue in training to be qualified for residue sampling. Training was repeated on an annual basis. SOPs describing cleaning sampling methods using volatile solvents were strengthened to require rapid sampling and working in teams. The combined emphasis of new training and new procedures that both underscored the risks and potential variation in residue sampling strongly addressed the issues described in this case study.

Modified Cleaning Process for Extended Release product

Technical personnel evaluated the cleaning process and determined that process parameters were not optimal to reliably clean process residues. The cleaning agent concentration was increased, the temperature was increased, and the cleaning time was increased in the new procedure. These parameters enhanced the cleaning process to more effectively and more efficiently remove the polymeric residue.

CLEANING VALIDATION OF MODIFIED CLEANING PROCESS

The new cleaning process was implemented. Manufacturing operators confirmed that new cleaning process parameters significantly improved the cleaning process. Three product lots were manufactured. Cleaning was performed on required equipment in three lots. Worst-case locations on equipment were swab sampled by two-person teams of sampling personnel. Two-person teams ensured minimal solvent evaporation and rapid sampling procedures. All test results passed the acceptance criteria.

SUMMARY AND FINAL THOUGHTS

A case study describing a compliance event in which erroneous false negative analytical data was generated in cleaning validation. These data caused a mistaken conclusion that a cleaning process for a new modified release dosage form was acceptable. The cause of the problem was not easily determined – all test data were acceptable. Initial investigation of potential problem areas indicated that everything was done according to procedure – nothing was done incorrectly. It was ultimately determined that the sampling process for product residue was not sufficiently controlled, and that the equipment cleaning process was not adequate for the modified release formulation. The sampling error, i.e., loss of solvent in sampling, had a major effect on cleaning validation. The sampling technician did not understand the importance of working quickly to minimize solvent loss. This lack of understanding resulted in a false negative test result and an erroneous conclusion that the cleaning process was acceptable. Fortunately the error was discovered when a different technician correctly and rapidly sampled the equipment surfaces. The combined emphasis of new training and new procedures that both emphasized the risks and potential variation of sampling strongly addressed the sampling issues described in this case study. Observations by manufacturing personnel caused the cleaning process to be evaluated by technical personnel, and a new cleaning process with optimized process parameters was developed. The new cleaning process was ultimately validated.

Lessons Learned

Several important lessons may be learned from this case study.

- **Sampling personnel understanding of sampling process and training.** Sampling personnel must have good technical understanding of their work. They must know the reasons for the procedures they perform. They must know potential problems if procedures are not correctly performed.

- **New procedures.** SOPs describing cleaning sampling methods using volatile solvents were strengthened to require rapid sampling and working in teams. Time constraints were added to all affected procedures. SOPs must be carefully written to identify potential risks and minimize variation.
- **Sampling personnel training.** Training of cleaning validation sampling technicians is a critical activity. Training exercises must include a quantitative demonstration of acceptable cleaning by means of analytical testing. Training exercises must also include worst-case sampling such as with volatile solvents, multiple sampling equipment, and other potential variations used in sampling. Retaining of technicians at some defined and reasonable frequency should be considered.
- **Inactive ingredients effects on cleaning.** Inactive ingredients may have very significant effects on cleaning processes. Cleaning of residues does not depend solely on the properties of the API. Formulation ingredients may significantly affect the cleaning process. In this case study, an extended release polymer in the formulation caused difficulty in the cleaning process. Inactive ingredients such as dyes and flavors may also greatly influence cleaning, and may actually be the most difficult ingredients to clean in a formulation. All components in a formulation must be considered when developing a cleaning process.
