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Validation Case Studies - Invitation to Participate

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INTRODUCTION

Validation Case Studies is an ongoing feature in the Journal of Validation Technology (JVT). This feature has provided a forum for validation professionals to discuss their actual work experiences – problems and solutions to problems that may be helpful to other validation professionals. A similar feature has been published in the Journal of GXP Compliance addressing problems and solutions related to the compliance responsibility. The ideas for these features came from several managers in validation an quality. They agreed on the idea to discuss their respective experiences and subsequent corrective actions that were initiated in response. We hope and intend that Validation Case Studies – by discussing problems and their solutions – will help readers gain from the experiences of others by introducing new ideas or reaffirming approaches. Managers have told us that anything that helps solve problems will be worth the effort.

PAST PUBLICATIONS

Validation Case Studies has addressed a broad range of validation problems and solutions in past publications. The following lists all previously published case studies:

1. Equipment Cleaning Validation Including Visual Evaluation. JVT, V16, #1, 2010.
2. Questionable Equipment Qualification, JVT, V 16, #1, 2010.
3. Process Validation Failure of a Liquid Product Batch Size Increase – “Identical” Manufacturing Tanks. JVT, V16, #3, 2010.
4. Cleaning Validation Failure – Unknown HPLC Peaks. JVT, V16, #4, 2010.
5. Substandard Data and Documentation Practices. JVT, V17, #2, 2011.
6. Should Acceptable Product Yield (Not GMP Yield) be a Validation Requirement? JVT, V17, #2. 2011.
7. “Like-For-Like” Changes – Is Validation Testing Needed? JVT, V17, #2, 2011.
8. Erroneous False Negative Cleaning Validation Results. JVT, V22, #5, 2016

VALIDATION CASE STUDY SUMMARIES

Brief summaries of all previously published case studies follow. These examples were provided by multiple validation and quality managers from multiple companies communicated primarily at various IVT meetings. Some of these provide examples of problems and a general corrective action. For example, a similar corrective action – verifying equipment operation after motor installation – was applied to multiple like-for-like equipment problems. Others are very specific and describe a unique problem, an unexpected root cause,

and a unique solution. For example, a manufacturing tank thought to be identical and used interchangeably with other tanks for many years was found to be different which negatively affected the mixing process of a specific formulation. These studies demonstrate the broad scope of validation problems and the often unexpected root causes for problems.

1. Equipment Cleaning Validation Including Visual Evaluation

The case study described equipment cleaning and inspection of cleaned equipment. One specific equipment was found to have visible residue on the equipment despite being cleaned by the validated cleaning procedure and inspected by manufacturing and QA personnel. Investigation of this individual event indicated multiple related problems. Three issues were investigated:

- Equipment cleaning – residue was found on the equipment after cleaning. Why did this happen?
- Cleaning validation -- the equipment had been cleaned by a validated cleaning procedure. Has something changed?
- Equipment cleanliness evaluation -- the cleaned equipment was evaluated as clean by multiple individuals. Why was the residue not observed during inspection?

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. Several site improvements were also implemented.

- Investigations. 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 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 – the process design stage of process validation. In the event above, the rinsing procedure was not adequately defined, resulting in 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. 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.

2. Questionable Equipment Qualification

A case study involving fundamental problems in equipment qualification at a contract drug product packaging facility was discussed. The event comprised review of documentation associated with qualification of a cartoning machine. This review demonstrated a serious lack of understanding fundamental qualification practices and requirements. Suggested CAPA for implementation included the following:

- Equipment qualification activities. Use of the cartoning machine was stopped until a properly

prepared and approved protocol was developed and executed to provide documented evidence that the equipment is properly installed and performing its function.

- Basic validation / qualification procedures. Procedure should be established requiring that prior to execution all qualification/validation protocols must be typed and approved by the quality unit and a technical representative (e.g., Production, Validation, Engineering).
- Investigation procedures. A procedure should be established to investigate any deviations from the pre-approved protocol including changes to data.
- Validation training. All personnel involved in equipment qualification and/or process validation should undergo training in the proper way to conduct qualification and validation studies.
- Documentation practices training. All personnel should under training in proper documentation to understand the issues involved with changing data without proper documentation to justify the change. Training should also address the requirements to sign documents when entering data.
- Data. Handling. Data transfer practices should be documented in a written procedure that requires independent verification that the data were properly transferred.
- GMP training. GMP Training should be conducted to ensure that all personnel are familiar with basic GMP and documentation requirements.

Although the contractor had good intentions and understood that the new cartoning machine required qualification, the company failed to understand some of the basic principles of qualification and documentation. The lack of a pre-approved protocol based on written requirements and specifications, use of handwritten protocols, lack of control of data transfer, lack of approval of documentation, and lack of the signature of the person executing the protocol indicate a poor understanding of the basic principles of qualification/validation and GMPs.

3. Process Validation Failure of a Liquid Product Batch Size Increase – "Identical" Manufacturing Tanks

A case study involving a batch size increase for a liquid solution product was described. The batch size increase was considered to be a relatively simple change since other similar products at the site were already manufactured at the same increased batch size, and the equipment to be used was identical to other site equipment. Management argued that validation was not necessary because of the long history of interchangeable tank usage. Although the fill volumes of all tanks were the same, there were mixing impeller differences that significantly affected processing of different formulations. Manufacturing was started and the formulation ingredients did not dissolve in the vehicle -- the validation PPQ was a failure. Mixing in the tank was not sufficiently rigorous to dissolve the formulation ingredients. CAPA activities initiated included the following:

- Manufacturing process. A new manufacturing process was developed using a reduced solution volume at an intermediate process stage which enabled successful manufacturing
- Equivalent equipment. Equipment qualification and equipment equivalence documentation was reviewed and modified.
- Post-validation monitoring. Post-validation lots confirmed acceptability of the new process.

This incident reminded all groups at the site that they must be sensitive to perceived minor differences in equipment. The two-impeller and three-impeller tanks in this example were originally designated as equivalent many years ago when the site manufactured relatively simple solution formulations. These formulations contained very soluble ingredients that dissolved quickly in all tanks. All tanks provided equivalent performance when these simple formulations were manufactured. However, when more complex formulations requiring enhanced mixing were manufactured, differences between mixing tanks, i.e., two impellers vs. three impellers, became apparent. Validation professionals must be vigilant even when apparently mundane changes are initiated. "Identical" may really not be so.

4. Cleaning Validation Failure – Unknown HPLC Peaks

A case study involving cleaning validation and the observation of unknown peaks in HPLC chromatograms was described. Unknown peaks were observed from testing of swab samples following cleaning of suspension products containing insoluble active drug, suspending agents, colors, and flavors. Equipment was visually clean. Following the original cleaning validation failures, a "shotgun" approach with a new cleaning procedure was attempted but was unsuccessful. Technical personnel then conducted laboratory studies using multiple cleaning agents based on the physicochemical properties of the product residues to develop a new cleaning procedure. Analytical scientists determined that the unknown peaks were associated with the hydrophobic flavoring ingredients in the formulation. The following CAPA and associated activities were conducted:

- New cleaning Procedure. A new cleaning procedure based on results of laboratory studies was developed. Cleaning process parameters such as exact liquid volumes, concentrations of cleaning agents, rinsing times, etc., were specified for all steps.
- Inspection. The visual inspection procedure for cleaned equipment of these products was enhanced with increased lighting and specific examination of problem areas
- Documentation. All work associated with the original validation failure including technical cleaning method development and analytical determination of unknown peaks was documented and filed in the validation library.
- Site approach to cleaning validation. The analytical lab proactively tested other formulation ingredients that might potentially become "unknown HPLC peaks" in future unsuccessful cleaning validation.

The primary lesion learned from this experience was the implementation of a scientific and technical approach to cleaning method development and problem solving. The approach started with an understanding of the chemical and physical properties of formulation ingredients and product residues. Once these properties were understood, development of a new cleaning procedure with appropriate cleaning agents was accomplished.

5. Substandard Data and Documentation Practices

Test data and results generated as specified in the validation protocol are a continuing problem. Actual examples associated with validation and quality documents were described. Problems discussed included data recording and storage, data signature responsibility and verification, data transfer, and other substandard documentation practices. Test data and results generated as specified in the validation protocol are critical in the validation process because they provide the basis for the final validation report and the judgment that the item of interest is validated. Validation managers suggested development or enhancement of documentation practices associated with validation documents.

- Review of original data by the VAC as part of validation report approval process. When the VAC is reviewing a validation report containing test data or other results, the documentation containing original data must also be reviewed. Implementing this practice will eventually eliminate data recording on paper towels and similar unacceptable media. If original data are still recorded on individual sheets of paper or other sources, these must be considered primary documents and be retained and stored appropriately. They must be reviewed in addition to the data provided in the validation report. All data numbers must be verified.
- Storage of original data in validation documents. Original data may be stored as part of the approved validation report in the validation library. The validation library should be a secure area from which validation documents cannot be removed. If a site does not have document storage system or a bound notebook system and is unwilling to implement such a system, storage of original data in the validation document package should be done. The validation report must be supported by original retrievable data.
- Training. The above recommendations necessitated the development and strengthening of several procedures in the organization. Training on these procedures is mandatory. The examples provided

by validation managers indicated significant misunderstanding of fundamental procedures and serious non-compliance. Manufacturing and engineering personnel are often not as familiar with data-recording procedures as QA or GMP analytical lab personnel. Training and periodic retraining must be considered depending on the overall competence of the organization. The site VAC must be especially well trained in these procedures for their roles as surrogate regulatory auditors of validation documents.

- Senior management support. Just as with any major policy or procedural change in an organization, senior management must be supportive of changes in data and documentation practices. Senior management may not be familiar or have interest in data or documentation problems. Efforts to upgrade data and documentation practices in the organization that require significant changes without senior management support will be futile.

6. Should Acceptable Product Yield (Not GMP Yield) Be A Validation Requirement?

A compliance case study involving a validated manufacturing process is described. The process met all acceptance criteria and was judged to be validated. Products from the manufacturing process had a significant level of waste and rejects. Eventually the defect level became so high that business people intervened and requested investigation. The defect problem was caused by a major excipient with significantly different particle size distributions obtained from a new supplier. FDA GMP requirements regarding yield require that product be formulated to provide 100% of the labeled amount and that actual yields and percentages of theoretical yield shall be determined at the conclusion of each appropriate phase of manufacturing. Percent of theoretical yield means that all materials assigned to the batch must be quantitatively reconciled, but does not require a level of acceptable product. Meeting GMP requirements may not be indicative of a well-controlled manufacturing process. Acceptable product yield provides much more useful information regarding the process than percent of theoretical yield. High rejects and high waste demonstrates formulation or process problems that should be investigated. Yield data including acceptable product, rejected product, and waste should be monitored in a timely manner. Reviews should begin during development to develop a product history. Reviews should continue post validation during commercial manufacturing. Monitoring these yields will provide far more useful information than GMP percent of theoretical yield data and can also be used as a measurement of process robustness. Modern monitoring analysis techniques such as control charting should be used. Validation personnel must understand that just being compliant with GMP percent theoretical yield requirements is not sufficient for good manufacturing process control.

7. “Like-For-Like” Changes – Is Validation Testing Needed?

“Like-for-like” changes are usually considered to be minimal changes not requiring confirmatory validation testing. The discussion addresses situations in which “like-for-like” changes did not perform as expected due to incorrect installation of the replacement equipment. Several actual occurrences are described, one of which required FDA involvement and a significant product recall. Others resulted in reduced product yields or products not meeting specifications. All changes, including “like-for-like” changes, should be evaluated by the Quality Assurance function and the site Validation Approval Committee (VAC) to standardize evaluation processes and carefully consider associated risks. Emergency changes may be initiated as needed by maintenance or other management. However, these changes should ultimately be reviewed by Validation and Quality for final disposition.

One reason for erroneous judgments regarding “like-for-like” changes is to avoid the burden of validation documentation. Site engineers hope to avoid preparation of protocols, VAC approvals, execution, and so on by judging changes to be “like-for-like.” Documentation attesting to correct installation of high risk “like-for-like” equipment can be accomplished by simple approved verification memo requiring reasonably simple justification for judgments and approval of function management. This approach provides certainty of successful equipment installation while reducing burdensome documentation requirements.

8. Erroneous False Negative Cleaning Validation Results

This case study described 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. 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 with the first two lots (technician working alone) 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 optimized to clean the extended release formulation. An improved cleaning process with increased cleaning agent concentration, extended cleaning time, and higher temperature was developed, implemented, and ultimately validated.

Cleaning validation sampling technicians must have good understanding of their work, and must know the technical reasons for the procedures they perform, and potential problems if procedures are not correctly executed. Sampling personnel training should include a quantitative demonstration of acceptable sampling by means of analytical testing. Training exercises should include worst case sampling such as with volatile solvents, multiple equipment, and other potential variations in sampling. In this case study, sampling by two different technicians enabled erroneous results to be discovered. Regarding the cleaning process, inactive ingredients in a formulation may have a very significant effects on cleaning processes; cleaning of residues does not depend solely on the properties of the API.

FUTURE CASE STUDIES -- WE NEED YOUR HELP

The studies described above have been very well received by readers, and publication of new cases has been repeatedly requested. Several new case studies are currently in progress by authors. We need your help to continue the success of Validation Case Studies – more examples are always needed. Case studies are always anonymous with no connection to companies or organizations. This feature will be most useful when the validation and quality community submits experiences and ideas for system improvements. Please contact coordinators Paul Pluta at paul.pluta@comcast.net or Melissa Carella at Melissa.carella@cbinet.com with comments, suggestions, topics, and events for discussion.

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Paul Pluta, Ph.D, has extensive pharmaceutical industry and university academic experience, and has been involved with the Journal of Validation Technology and Journal of GXP Compliance as a writer and editor-in-chief...
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