IVT NETWORK
INSTITUTE OF VALIDATION TECHNOLOGY | an informa business
Unlimited Validation Knowledge Awaits...
Published on *IVT Network* (http://www.ivtnetwork.com)

Validation Case Studies and Compliance Case Studies – Invitation to Participate

By **Paul L. Pluta**

Aug 26, 2020 10:42 am EDT

INTRODUCTION

Validation Case Studies and Compliance Case Studies are ongoing features in the *Journal of Validation Technology (JVT)*and *Journal of GxP Compliance (JGXP)*, respectively. These features have provided a forum for validation and compliance professionals to discuss their actual work experiences – problems and solutions that may be helpful to other industry professionals. The ideas for these features came from several Validation and Quality managers at various IVT meetings. They agreed on the idea to discuss their respective experiences and subsequent corrective actions. We intend that the case studies discussed in these features 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.

CASE STUDY CONTENT AND FORMAT – A NEW APPROACH

Content and format for the respective case studies has previously been as written word in the IVT journals. More than 25 case studies on a wide range of topics have been reported. This format will continue in the future along with a new option for authors to verbally discuss their case studies. IVT has introduced a weekly podcast "Voices of Validation" that discusses topics of interest to validation and compliance professionals. A recent podcast by Cliff Campbell verbally discussed "Intrinsic Compliance: A Model for Process Validation Optimization," originally published in JGXP Volume 24, #4, in July 2020; the podcast further discussed the importance of knowledge management activities related to compliant process validation. The Campbell paper is reprinted in this issue of JVT along with a link to the corresponding podcast. This combined approach – hardcopy and podcast - applied to Validation and Compliance Case Studies provides readers/listeners an enhanced opportunity to learn actual problem solving approaches, methods, and CAPA, as well as additional comments from the author associated with the case study. The podcast format has been very well received by presenters and journal readers.

EXAMPLE CASE STUDIES

The following are some example case studies published in either JVT or JGXP. These examples were provided by multiple validation and quality managers from multiple companies communicated primarily at various IVT meetings. The content of these case studies is broad – technical, theoretical, compliance, documentation, performance technique, and so on. Some 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 published case studies and the often unexpected root causes for problems. Several example case studies published in either JVT or JGXP demonstrating the broad scope of these case studies follow.

1. Questionable Equipment Qualification

A case study involving fundamental problems in equipment qualification at a contract pharmaceutical 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 principles and practices. Suggested CAPA 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 functioning.
- **Basic validation/qualification procedures.** Procedure should be established requiring that prior to execution all qualification/validation protocols must be approved by the quality unit and technical representatives (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 activities.
- **Documentation practices.** 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 data were properly transferred.
- **GMP training.** GMP training should be conducted to ensure that all personnel are familiar with basic GMP 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 indicated poor understanding of the basic principles of qualification/validation and GMPs.

2. 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, the mixing impellers were not identical; some tanks had three impellers while others had two. 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 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 became apparent.

Validation professionals must be vigilant even when apparently mundane changes are initiated. “Identical” may really not be so.

3. 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 Validation Approval Committee (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 practices. 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 must be verified.
- Storage of original data in validation documents. Original data should 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. 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.

4. 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 businesspeople 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. Monitoring analysis techniques such as control charting is recommended. Validation personnel must understand that just being compliant with GMP percent theoretical yield requirements is not sufficient for good manufacturing process control.

5. “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.

6. 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 causing 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. 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.

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.

7. Secondary Packages with Defective Glue Joints

This case study discussed intermittent defective secondary packages of a pharmaceutical product at a contract packaging facility – glue application was not reliably applied to all packages. Process defects were not able to be determined by routine product sampling. It was ultimately determined that defects were associated with equipment shutdowns and startups such as occurring with employee work breaks and lunch periods. Problem-solving required efforts far beyond usual investigative efforts. Attention to equipment operational details on the manufacturing floor was lacking and determined to be the cause of defects. A joint effort with the packaging contractor was essential to successful problem-solving.

8. Broken Tablet Punches

A case study describing manufacturing of a tablet product in which an abrupt and unexpected change in the manufacturing process occurred. Tablet compressing became extremely difficult including breakage of numerous tablet punches. The observations of manufacturing operators regarding a change in the physical properties of the granulation was key to initiating the direction of the investigation. Problems were associated with a new vendor source of lactose. CAPA involved restriction of manufacturing to initial lactose vendor, developing a new powder density specification for incoming lactose, improvements in master production records, operator training, and a new procedure for the evaluation of new vendor materials.

9. Glass (?) Fragments in a Parenteral Product

This case study describes a compliance event in which finished product defect inspectors reported observation of glass fragments in a sterile liquid product. Initial problem-solving focus assumed some form of glass container damage during the vial preparation and/or vial filling processes. Elemental analysis of fragments indicated the presence of calcium and phosphorous – not glass residues. The particulate that was previously thought to be glass was actually a calcium hydroxyphosphate salt with a glassy appearance. The problem root cause was determined to be an interaction between calcium carbonate in the rubber closures and sodium phosphate in the product formulation. Trace amounts of calcium apparently leached from the rubber closure into the product solution resulting in the calcium phosphate precipitate. CAPA entailed the replacement of the rubber closure with a calcium carbonate-free closure. This case study demonstrated an unlikely root cause of a compliance problem -- chemical interaction with primary packaging commodities.

10. Yellow Discoloration on White Coated Tablets After Commercial Distribution

A small molecule pharmaceutical company received multiple field complaints describing the presence of yellow discoloration observed on a commercially marketed white film-coated tablet. The yellow discoloration was connected to the presence of sulfasalazine, a compound not found in use or in inventory within the company manufacturing facility. Experimentation demonstrated that sulfasalazine interacts with polyethylene glycol 1450, the plasticizer in the tablet film coating. Tablets that contacted sulfasalazine residue on pharmacy counting trays at the time of pharmacy dispensing developed yellow spots and streaks that were the cause of product complaints. An acceptable alternate coating was developed and ultimately used in commercial product. This case study illustrates two unexpected occurrences:

1. Inactive ingredients in a formulation are not always inert and may be reactive, and
2. Problems may be caused by sources completely unrelated to the product ingredients, manufacturing process, product storage, or other causes associated with the manufacturing site.

NEW CASE STUDIES - WE NEED YOUR HELP

The case studies described above have been very well received by readers. We need your help to continue the success of Validation Case Studies and Compliance Case Studies – more examples with corrective actions are always needed. Case studies are anonymous with no connection to companies or organizations. The addition of podcasts to the written publication provides additional discussion of case studies and will enhance the application of case study information. Case study features will be most useful when the validation and compliance communities submit experiences and ideas for quality system improvements. Please contact coordinators Paul Pluta at paul.pluta@comcast.net or Stacey Bruzzese at stacey.bruzzese@informa.com with comments, suggestions, topics, and events for discussion.
