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Compliance Case Studies - An Invitation

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INTRODUCTION

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

PAST PUBLICATIONS

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

1. Equipment Cleaning and Visual Evaluation, published in Journal of GXP Compliance (JGXP), Volume 13, Number 1, Winter 2009.
2. Questionable Equipment Qualification, JGXP, V 14, #1, 2010.
3. Manual Processes – Performance, Responsibility, and Training, JGXP, V 14, #1, 2010.
4. Cleaning Validation Unknown HPLC Peaks, JGXP, V 14, #1, 2010.
5. Secondary Packages with Defective Glue Joints, JGXP, V 14, # 2, 2010.
6. Identical (?) Mixing Tanks, JGXP, V 14, #3, 2010.
7. Broken Punches, JGXP, V 14, #3, 2010.
8. White Spots on Tablets, JGXP, V 14, #4, 2010.
9. Substandard Data and Documentation Practices, JGXP, V 15, #2, 2011.
10. False Negative Cleaning Data, JGXP, V 18, #3, Spring, 2014.
11. Glass (?) Fragments in a Parenteral Product. JGXP, V18, #3, 2014
12. Consistent Sampling, Results, and Original Data. JGXP, V18, #4, 2014
13. Yellow Discoloration on White Coated Tablets After Commercial Distribution. JGXP, V18, #4, 2014
14. Like-for-Like" Changes – What, if Anything. Should be Done? JGXP, V19, #1, 2014
15. Manufacturing Support Audit Observations. JGXP, V19, #2, 2014

CASE STUDY SUMMARIES

Brief summaries of all previously published case studies follow. These examples were provided by multiple quality and validation managers from multiple companies communicated primarily at various IVT meetings. Some of these provide numerous examples of problems and general corrective actions. Others are very specific and describe a unique problem, an unexpected root cause, and a unique solution. In one case, for example, the root cause was found to be dusty counting trays in the pharmacy – not in the manufacturing plant -- that provided the opportunity for chemical drug interactions and a visible product defect. This case study demonstrates that compliance professionals must keep an open mind when investigating potential root causes.

1. Equipment Cleaning and Visual Evaluation

The case study described equipment cleaning and inspection of cleaned equipment. Problem root cause was determined to be inadequate rinsing of equipment due to undefined steps in the cleaning procedure. CAPA addressed the specific root cause as well as implementing multiple improvements to the site cleaning procedures, equipment inspection procedures, and operator training program.

2. Questionable Equipment Qualification

A case study involving fundamental problems in equipment qualification at a drug product packaging facility is 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 specific equipment qualification activities, basic validation / qualification procedures, investigation procedures, training, data handling, and other practices.

3. Manual Processes, Performance, Responsibility, and Training

This case study involved manual cleaning of equipment; performance and responsibilities of manufacturing personnel, supervisors and QC personnel; and training supporting all involved personnel. Root cause was determined to be inadequate job performance by several individuals. CAPA addressed the specific root cause as well as implementing multiple improvements to the site cleaning procedures, equipment inspection procedures, and the site training program.

4. Cleaning Validation Unknown HPLC Peaks

A case study involving cleaning validation and the observation of unknown peaks in HPLC chromatograms is discussed. 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. Most important benefit was the demonstration of a scientific and technical approach to problem solving, cleaning method development, understanding residue chemistry, specifying process parameters, and so on – a scientific and technical basis for cleaning validation.

5. Secondary Packages with Defective Glue Joints

This case study discussed intermittent defective secondary packages of a pharmaceutical product – 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 shutdown and startup such as occurring with employee work breaks and lunch periods. Problem-solving required efforts far beyond usual investigative efforts. A joint effort with the packaging contractor was essential to successful problem -solving.

6. Batch Size Increase with Identical (?) Mixing 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. The supposedly identical tank did not have the same impeller arrangement as the other mixing tanks. Although the fill volumes of all tanks were the same, mixing impellers differences significantly affected processing. CAPA activities included a new manufacturing process, training, documentation, process validation, post validation monitoring, equipment qualification, and application of lessons learned to other site products.

7. 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.

8. White Spots on Tablets

A case study involving unexpected white spots on a blue tablet product was described. Initial speculation was that the white-spot problem was either grease spots or microbial growth. Chemical change of the blue dye in alkaline pH was determined to be the cause of the white spots. Incorrectly assembled milling equipment causing materials to not be milled to the correct particle size exacerbated the problem. CAPA involved a new milling equipment assembly procedure, new milling process, and operator training. This study demonstrated highly unlikely causes of a serious compliance problem – an inactive excipient and incorrect equipment setup interacting to cause a serious problem. Compliance personnel must keep an open mind without preconceived beliefs when investigating problem root causes.

9. Substandard Data and Documentation Practices

Test data and results generated as specified in the validation protocol is 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, and other substandard documentation practices. Recommended actions to address these problems were proposed including policies and practices, training on data and documentation practices, and routinely repeated training. Senior management support of activities to address data and documentation problems is mandatory and must be visible.

10. False Negative Cleaning Data

This case study described a cleaning validation event in which two different technicians provided swab sampling for cleaning validation of a new product. The first technician testing (two lots) resulted in no drug residue being detected – apparently successful cleaning. The second technician test results (third lot) were significant failures with high levels of residue remaining on equipment. Investigation indicated a sampling technique problem with technician #1 resulting in false negative data. The presence of drug residue indicated an inadequate cleaning method for the product. The cleaning procedure was ultimately modified. Technician #1 was retrained to correct inadequate sampling technique. Understanding process steps in swab sampling is critical for successful cleaning validation performance.

11. 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 carbonate-free closure. This case study demonstrated an unlikely root cause of a compliance problem -- chemical interaction with primary packaging commodities.

12. Consistent Sampling, Results, and Original Data

This discussion addresses problems and potential problem-solving approaches associated with sampling, sample results, and original data. Sampling problems may have very significant consequences. When there are problems with sampling, there likely are problems with results. Original data associated with sampling and test results must be consistent, must comply with good documentation practices, and be quickly retrievable. Other problems associated with original data include data numerical transpositions, data verification, and typographical errors in reports.

13. 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.

14. “Like-for-Like” Changes – What, if Anything. Should be Done?

“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. 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 Quality and Validation for final disposition. Documentation attesting to correct installation of high risk “like-for-like” equipment can be accomplished by simple approved verification memo. This approach provides certainty of successful installation while reducing burdensome documentation requirements.

15. Manufacturing Support Audit Observations

This case study discussed actual regulatory audit observations received by quality and compliance managers in the US and Europe. Regulatory observations were noted for manufacturing support functions such as training, calibration, and preventive maintenance. Regulated manufacturing facilities must continually

operate with preparedness for regulatory audits and should focus on highest risk activities. Unfortunately, however, lesser supporting activities may be delayed or overlooked when action on higher priority activities is required. Training, calibration, and preventive maintenance (PM) are perceived as being less important and prone to regulatory observations.

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 repeated requested. Several new case studies are currently in progress by authors. We need your help to continue the success of Compliance Case Studies – more stories are always needed. Case studies are always anonymous with no connection to companies or organizations. This feature will be most useful when the quality and compliance community submits experiences and ideas for quality 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.

ABOUT THE COORDINATORS

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