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COMPLIANCE CASE STUDY #19
PRIMARY CONTAINER PROBLEMS

"Compliance Case Studies" provides a forum for compliance practitioners to share information about actual compliance experiences. Previous discussions addressed a wide range of compliance activities. Previous case study titles discussed in this series include the following:

1. Equipment Cleaning and Visual Evaluation, Journal of GXP Compliance (JGXP), V13, #1, Winter, 2009.
2. Questionable Equipment Qualification, JGXP, V14, #1, Winter, 2010.
3. Manual Processes – Performance, Responsibilities, and Training, JGXP, V14, #1, Winter, 2010.
4. Cleaning Validation Unknown HPLC Peaks, JGXP, V14, #1, Winter, 2010.
5. Secondary Packages with Defective Glue Joints, JGXP, V14, #2, Spring, 2010.
6. Identical Mixing Tanks, JGXP, V14, #3, Summer, 2010.
7. Broken Punches, JGXP, V14, #3, Summer, 2010.
8. White Spots on Tablets, JGXP, V14, #4, Autumn, 2010.
9. Substandard Data and Documentation Practices, JGXP, V15, #2, Spring, 2011.
10. Change Control for "Like-For-Like" Changes, JGXP, V16, #2, Spring, 2012.
11. "Glass" Fragments in a Parenteral Product, JGXP, V18, #3, Autumn 2014.
12. Yellow Discoloration on White Coated Tablets After Commercial Distribution, JGXP, V18, #4, Winter 2014.
13. Consistent Sampling, Results, and Original Data. JGXP, V18, #4, Winter 2014.
14. "Like-for-Like" Changes – What, if Anything, should be Done? JGXP, V19, #1, Spring, 2015.
15. Manufacturing Support Audit Observations. JGXP, V19, #2, July 2015.
16. Microbial Contamination from Food. JGXP, V24, #6, November 2020.
17. Spots on Tablets – An Investigation. JGXP, V25, #2, March 2021.
18. Culture vs. Compliance. JGXP, V25, #5, November 2021.

Readers are invited to participate with manuscripts for this journal series, for the IVT blog, and for "Voices in Validation" podcasts – please share your successful practices with others. Please contact journal editor-in-chief Paul Pluta et or journal managing editor Stacey Bruzzese through the comments section with questions, comments, or submissions for publication.

ABSTRACT

Example events in which product primary containers caused compliance problems are described. Pharmaceutical containers are safe for use in products and are generally considered to be non-reactive and inert. However, containers may be reactive under various conditions or when in contact with certain ingredients or formulations. Compliance professionals must consider the potential for container interactions and utilize outside expertise as necessary when investigating technical product problems.

INTRODUCTION

Compliance Case Studies has described compliance events and associated problem-solving for an extensive range of occurrences. Most reports have addressed problems whose causes were much different from the obvious. For

example, problem white spots on tablets were caused by incorrect machine assembly (1); broken tablet punches were caused by an ingredient supplier change (2); faulty carton sealing was caused by stopping equipment operation for employee lunch breaks (3). Another highly unexpected event involved the presence of yellow discoloration on a white film-coated tablet caused by product contact with drug residue on pharmacy counting trays (4).

Several new problem examples communicated by readers are described in the following discussion. These involved routinely used packaging components generally expected to be non-reactive with product. Problems described in the following discussion involved product primary containers, i.e., containers with direct product contact.

Pharma Product Containers

Product primary containers may include glass bottles, rigid plastic containers, flexible plastics, molded containers, blow/fill/seal containers, and a variety of other configurations that have direct contact with manufactured product. Each of these packages are complex formulations with multiple ingredients to provide desired properties. Each material is available from different suppliers, and each supplier may have a different manufacturing process including subtle differences to ultimately produce the container. Further, labels with adhesives, inks, colored pigments, surfactants, and other ingredients are affixed to these primary containers.

Container Reactivity. When compliance personnel discuss reactivity, they usually are thinking chemical reactivity, i.e., a drug molecule chemically degrades to a different molecular structure. What must be considered are both chemical and physical reactivity or physical changes. Physical reactivity comprises solubility, permeability, absorption, adsorption, leaching, extraction, and equivalent descriptive terminology – all physical effects with no changes in molecular composition. Molecules (drugs, formulation ingredients, label ingredients such as inks) may **dissolve (solubility)** and be **absorbed** (note "b") into the container; when dissolved, they may permeate and migrate through the container. Drugs may be **adsorbed** (note "d") onto a container surface. Ingredient materials (plasticizers, inks, activators, others) in the container formulation may be **extracted** and **leach** into the product solution. Regulatory, USP, and industry organizations have published guidelines on extractable/leachable testing (5,6); ICH Q3E on assessment and control of extractables and leachables is currently in progress (7).

Key points in this discussion are that product primary containers must not be considered to be inert or non-reactive. A container with many years of successful product use may be unacceptable when used with a new product formulation. Further, the technology supporting these materials and manufactured containers is complex; pharmaceutical organizations usually do not have in-house expertise to fully understand these materials. Technical expertise outside the company may be critical in problem-solving; the importance of relationships and agreements with suppliers is vital in these situations.

Discussion Topics

This discussion will describe several compliance events involving seemingly inert pharmaceutical containers -- materials typically thought to be of no consequence in usual pharma manufacturing. These examples were provided

to the *Journal of GXP Compliance* by multiple readers who requested anonymity. Events described involve pharmaceutical primary packaging – containers with direct product contact; a related laboratory "container" application is also described. Subsequent discussions are planned to address events involving elastomeric closures and in-process manufacturing materials such as lubricants and filters. After a drug product is successfully manufactured, packaged in a suitable packaging system, and released for commercial distribution, drug interactions with administration devices to patients may also be problematic.

Readers are invited to submit other examples of compliance events to be included in future *Compliance Case Studies*, in the IVT blog, or in *Voices in Validation* podcasts. Readers appreciate these examples; they serve as reminders of possible compliance issues and approaches to investigate root causes.

PRIMARY CONTAINER PROBLEMS

Event #1. Product Potency Loss on Stability

The drug potency of a new high potency (low concentration) ophthalmic drug product solution being developed into LDPE squeeze bottles was experiencing an apparent loss of potency as a function of time during routine product stability studies. However, there was no related increase in the degradation products to correspond with the decrease in drug potency. Further, as the initial drug solution concentration was very low, this situation resulted in a significant drop in potency on a percentage basis even if there was only a slight potency loss. The drug product was as an aqueous solution; however, the drug had some inherent lipophilic properties.

Problem investigation included a review of any manufacturing changes and a reassessment of the analytical methods. The analytical stability test methods determined to be stability indicating, fully validated, and approved with no issues. The decrease in potency was also found to be reproducible in testing multiple lots. The drug potency met acceptance specifications at the start of stability studies. The investigation suggested that as there was no drug degradation, however, the drug was apparently being "lost" somewhere – it was thought that the loss could probably be with the LDPE packaging.

An extraction and analytical test method was designed to determine if the drug was being absorbed into or adsorbed onto the LDPE bottle. Bottles of drug product that experienced the decrease in potency, along with "time zero" product as a control, were first rinsed with the drug product analytical mobile phase and tested; no drug was found, thus ruling out drug adsorption.

The next step into investigation entailed cutting up pieces of the drug product's bottles that had the decrease in potency along with freshly bottled drug product solution as a control into fixed sizes. These pieces were then soaked in a fixed volume of the drug product analytical method's mobile phase in order to have a constant surface area to volume ratio of LDPE to mobile phase. The product bottle pieces, and mobile phase were then stored in a closed container and placed upon stability. After just only a few days of storage, the drug was indeed found to be present in the mobile phase indicating that the drug was being absorbed (i.e., dissolved) into the LDPE. Further, there was mass

balance between the observed potency loss and the amount of drug recovered from the extraction system. In other words, all of the drug was indeed present in each bottle, but the drug was migrating into the plastic due to its inherent lipophilic properties – demonstrating "likes dissolving likes."

Corrective action comprised successful conduction compatibility studies with various LDPE formulations in order to select a compatible resin. The implementation of newly selected LDPE resin did not result in any loss of potency in the drug product.

Event #2. Glass Ampoules Delamination

A new drug as a phosphate salt was being developed using Type I amber glass ampoules. Upon routine accelerated stability testing, small particulates were observed in the drug product solution; however, the drug potency was fine. Microscopic and electron microprobe analysis examination of the particulates along with SEM observation of the interior of glass surfaces indicated glass attack. That is, the phosphate salt of the API (remembering that phosphates can also serve as detergents) was interacting with the glass, causing a physical delamination of the glass resulting in visual flakes.

Compatibility studies were then performed using USP Type I glass from various glass manufacturers. It was determined that glass attack would take place with drug product solution from certain glass manufacturers, while glass attack did not occur with ampoules form other glass manufacturers. Discussion was then held with the glass manufacturers to determine why some manufacturers of Type I glass had glass attack while others did not. None of the manufactures would reveal their glass formulations or process parameters; it was surmised that their USP Type I formulations were all very similar. What was gleaned, however, was that there were differences in the glass manufacturing processes utilized in making the Type I glass ampoules. More specifically, it was hypothesized that the manufacturer that employed a slow and long (and more expensive) glass annealing process resulted in glass that was more resistant to glass attack for this drug product solution. Because the resultant glass was more resistant to attack, the manufacturer stated that the additional use of a sulfur dioxide, ammonium bifluoride or equivalent treatments, for example, were deemed unnecessary for increased resistance. The conclusion was the successful use of the glass ampoules from the manufacturer with the annealing process that resulted in the more resistant glass.

Event #3. Label Ink Migration

Routine analytical stability testing of a new ophthalmic aqueous drug product solution filled into LDPE bottles indicated the presence of an unknown impurity. Via the use of LC-MS/MS, the impurity was identified as an organic solvent ingredient used in non-aqueous inks for the printing of the labels. However, the use aqueous (i.e., water-based) -- not solvent-based inks -- was specified to be used for the product labels. It was not immediately known how an ingredient from a solvent-based ink could have been present in the aqueous inks.

The problem solvent was obtained and separately placed in the bottom of a closed glass desiccator vessel along with filled LDPE bottles containing drug product solution. The vessel was then stored at controlled room temperature for

48 hours. The solvent was found to migrate through the LDPE bottle into the product solution within the 48 hours of storage suggesting that the solvent is very volatile and transmissible through LDPE. Data were shared with the label vendor demonstrating the presence and the extreme volatility of the found solvent. The label vendor was extremely cooperative and then supplied all of the print ink ingredients to be tested for the presence of this solvent – no solvent was found in any of the aqueous based ink ingredients.

With the vendor's permission, a visit to the label printing plant was then performed; label-printing equipment was examined. It was learned that the same machines were used for both solvent and water-based label printing with equipment cleaning performed between the changeovers. The equipment was sampled after cleaning following use of solvent-based inks; residual solvents were found in some of the piping, suggesting possible carry-over and cross-contamination. The label vendor then changed the printing processes such that only designated equipment would separately be used for solvent and water-based inks. However, the printing of labels took place in the same processing area with the use of designated equipment. Solvent was still found in the aqueous based printed labels suggesting cross-over occurring via air transmission. These designated machines were then placed in separate rooms to prevent the chance of cross-contamination via air. These improvements were determined to be successful.

This case was an excellent example of open and transparent cooperation between the pharmaceutical company and the vendor. Representatives from both organizations worked together to resolve a problem on a priority basis resulting in improved quality and compliance levels for both companies.

Event #4. Laboratory "Container" Application

A similar event to the primary container examples described above with laboratory testing of a potent drug (<1 mg drug content) tablet product. Dissolution test results indicated immediate tablet disintegration and rapid initial drug dissolution. However, final dissolution test data at the specification timepoint was only ~60% of drug content – a dissolution failure. Initial interpretation of results focused on tablet dissolution performance; the tablet was fully potent in chemical testing, but failed dissolution. Observation of the dissolution media during testing indicated no presence of residual tablet.

Investigation on several fronts was initiated. Tablet processing parameters potentially impacting tablet dissolution performance received major attention. Tablets with optimized process parameters were prepared; all process permutations enhancing dissolution performance were unsuccessful. Laboratory investigation of test parameters was simultaneously initiated. Drug solution contact with glassware, tubing, filters, needles, and other test method components was evaluated. Data indicated drug adsorption into glass surfaces. This finding led to focus on the glass dissolution vessels. Drug recovery studies from the dissolution vessels using non-aqueous solvents was performed. Quantitative drug was recovered from the vessel surface; combined drug in solution and drug on the vessel surface resulted in complete drug recovery. Drug adsorption onto dissolution vessel surface was confirmed.

The dissolution test volume was reduced to a minimum volume to increase drug dissolution results. Dissolution testing calculations were also modified to include a final recovery step in the dissolution test to normalize test results. Supportive experimental data confirming drug adsorption in testing was critical to finalize the dissolution test procedure. Drug adsorption to the dissolution test "container," i.e., the dissolution vessel, was the root cause of the problem. The new dissolution test method was successfully defended to regulatory auditors.

SUMMARY AND FINAL THOUGHTS

This discussion described a variety of causes for unanticipated product problems in pharmaceutical primary package materials, each of which are often considered to be inconsequential or inert. This discussion focused on product primary containers and included physical effects causing product problems.

Lessons learned from this compilation is to look beyond the obvious when conducting compliance investigations. In nearly all of the above events, initial speculation as to the causes of the events by experienced professionals were not correct. The investigations required continued persistence to determine the root cause of problems. The investigations followed direction as dictated by technical data.

Also vital in problem-solving was team competence and people with appropriate expertise, skill sets, and education. Team members include internal and external personnel, i.e., vendor representatives for container suppliers. Internal people must evaluate problems, understand the limitations of their capabilities, and involve representatives with appropriate expertise and capabilities from external sources.

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