White Spots on Tablets—Compliance Case Study #8

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“Compliance Case Studies” discusses compliance situations useful to practitioners in compliance and validation. Each case presented deals with a specific compliance problem, elements of which are described to demonstrate strategy to solve compliance problems. We intend this column to be a useful resource for daily work applications. The main objective of this column: Useful and practical information.

Reader comments, questions, and suggestions are needed to help us fulfill our objective for this column. Case studies illustrating compliance issues submitted by readers are most welcome. Please send your comments and suggestions to journal coordinating editor Susan Haigney at shaigney@advanstar.com.

KEY POINTS DISCUSSED

The following key points are discussed:
• A case study involving unexpected white spots on a previously problem-free blue tablet product is described.
• Initial speculation was that the white-spot problem was either grease spots or microbial growth.
• FD&C Blue #2 was the colorant in the tablet formulation.
• Chemical change (chemical reduction in alkaline pH) of the blue dye was determined to be the source of the white spots.
• Manufacturing personnel indicated that there was potential for incorrectly assembled milling equipment causing materials to not be milled.
• Comparative testing of control tablets and experimental tablets under accelerated temperature conditions indicated that the unmilled excipient was the cause of the distinct white spots in the tablets. FD&C Blue #2 was chemically incompatible with the alkaline excipient.
• A new milling equipment assembly procedure and a new milling process was developed.
• Training of manufacturing personnel was conducted.
• Process validation was completed.
• All investigations, analyses, and conclusions were documented to close the corrective action and preventive action (CAPA). All investigation documentation was reviewed by US Food and Drug Administration investigators.
• Additional monitoring of manufacturing was conducted to confirm successful corrective action.
• This case study further demonstrated highly unlikely causes of a serious compliance problem—an inactive excipient and incorrect equipment setup.
• Compliance personnel must keep an open mind without preconceived beliefs when investigating problem situations.

INTRODUCTION
This case study was provided to the Journal of GXP Compliance by a reader who requested anonymity. The event described is an actual occurrence.

A small molecule pharmaceutical company had produced an uncoated blue tablet product for many years. A large number of product complaints were unexpectedly received from customers. Complaints described distinct white spots on the blue tablet product. The cause of the problem was not easily determined. Speculation ranged from grease spots to microbial growth.

This discussion provides:
• Process description background. The manufacturing process for the tablet product is briefly described.
• Compliance event. A description of the event, the key issues to be addressed, and applicable current good manufacturing practice (CGMP) requirements.
• Investigation. Interviews and actions conducted to investigate the event.
• Discussion. Key information, activities, and analysis.
• Corrective action and preventive action (CAPA). Actions and improvements implemented.
• Post CAPA. Lessons learned. Maintaining validation and performance.

PROCESS DESCRIPTION BACKGROUND
The manufacturing process in this case study involved manufacture of an uncoated blue tablet product. The manufacturing process for the product comprised a typical wet-granulation process. The following describes the manufacturing process:
• The active pharmaceutical ingredient (API) and other inactive excipients were milled using an impact mill.
• Wet granulation was performed using an aqueous binder solution containing a polymeric binder.
• Wet granulation was dried using a fluidized bed dryer.
• Dried granules were sized using a sifting apparatus. Oversized granules were milled using an impact mill.
• Remaining formulation ingredients were milled using an impact mill. This included FD&C Blue #2 as colorant in the formulation.
• All ingredients were mixed in a twin-shell blender.
• Tablets were compressed.

COMPLIANCE EVENT
A small molecule pharmaceutical company had produced an uncoated blue tablet product for many years. The product was a relatively large volume Rx product. Product attributes and process performance were reliable and reproducible. Annual product reviews and process monitoring for several years indicated no ongoing problems or process trends. A large number of product complaints were unexpectedly received from customers. Complaints described easily visible distinct white spots on the tablet product. Complaints were received on several different batches of product, but not all lots had complaints. Manufacturing personnel speculated the cause to be grease spots from the compressing process, a problem occasionally observed in the past. Samples of problem tablets were received. Speculation from the appearance of the spots was that microbial growth was occurring on tablets. No instances of microbial growth had previously been reported for this or any other products at the site.

What are the Issues?
There were several critical issues to be investigated as follows:
• What was the composition of the white spots?
• What was the source of the white spots?
• Why were white spots not detected in tablet inspection?
• Why did the white spot complaints suddenly occur?
• Did manufacturing operators follow batch record directions properly?

CGMP Requirements
Relevant CGMP (1) requirements potentially applicable to the above event are listed as follows:
• Subpart D–Equipment.
  • 211.63. Equipment Design, Size, and Location.
  • 211.65. Equipment Construction.
• Subpart F–Production and Process Controls.
  • 211.110. Sampling and Testing of In-process Materials and Drug Products.
  • 211.113. Control of Microbiological Contamination.
  • 211.134. Drug Product Inspection.
• Subpart J–Records and Reports.
  • 211.180. General Requirements.
  • 211.188. Batch Production and Control Records.
  • 211.192. Production Record Review.

INVESTIGATION
Investigation and ultimate resolution of this event required involvement of several groups. These included personnel involved in the incident (manufacturing and quality assurance [QA]) and technical personnel responsible for the manufacturing formulation and process. There were many details that needed to be investigated or confirmed. Personnel from all groups were interviewed and interacted to address the above issues.

Product Testing
Products with white spots were submitted for analytical testing for all product attributes. All test results were acceptable. Products were fully potent regarding active drug. Dissolution test data were acceptable and showed no slowing of the product dissolution performance. Despite the white spots, there did not seem to be any adverse effects on the other product attributes.

Manufacturing Personnel Interviews
Manufacturing personnel affirmed that all batch record directions were performed as specified. Manufacturing operators had manufactured this product many times in the past. The manufacturing staff comprised experienced operators and some newly trained operators. All processes were considered to be well established and problem-free. There were no training issues or variation in performance thought to be associated with the manufacturing procedure.

QA Personnel Interviews
QA personnel reviewed inspection records from problem lots. Tablet inspection occurred periodically throughout the compressing process. Laboratory personnel conducted a final tablet inspection of a composite sample in the analytical laboratories—different people in different areas inspected the tablets. All tablet inspection records were acceptable. No instances of white spots on tablets were reported.

Technical Personnel Investigation
Technical personnel conducted parallel investigations addressing possible causes of the white spot problem. These included microbiological testing, elemental analysis, changes in formulation materials, and FD&C Blue #2 chemistry. As investigations indicated potential causes for the problem, leads would be pursued.

Microbiological testing. White spots were removed from the tablet surface and submitted for microbiological testing. No microbial growth was observed. The moisture content of the tablets would not support microbial growth. Microbial growth was eliminated as a cause of the problem.

Elemental analysis. White spots were removed from the tablet surface and submitted for microscopic elemental analysis. Samples of greases used in the tablet compressing process were also submitted for comparison. No evidence of contamination by grease was observed. The elemental composition of the white spots was identical to the tablet formulation components. Grease spots were eliminated as a cause of the problem.

Changes in formulation materials. The purchasing history of all product ingredients was reviewed. There were no changes in materials. There were no changes in suppliers of formulation materials. All materials and suppliers had a good quality history. Material changes were not a cause of the problem.
**FD&C Blue #2 chemistry.** Technical personnel investigated the chemical properties of FD&C Blue #2, the blue colorant used in the formulation. Chemical change (chemical reduction in alkaline pH) of the blue dye was determined to be the source of the white spots. FD&C Blue #2 is a widely used synthetic blue dye and is used in the dying of blue jeans. FD&C Blue #2 is also known as Indigotin, Indigo dye, and E132 in Europe. In alkaline pH, this dye is chemically reduced to indigo white or leuco-indico, which is white in color. The formulation of the blue tablet product contained excipients that maintained an alkaline pH in the tablet. This pH was necessary for API product stability. The alkaline pH of the tablet core caused reduction of the blue dye to indigo-white, which in turn caused white spots. However, because of the sudden change in the appearance of the tablet when there had been no changes in the formulation, materials, or manufacturing process was unknown.

**Manufacturing equipment.** When problems with the blue dye were identified, manufacturing management further probed FD&C #2 handling and processing. Discussions with manufacturing operators indicated that there was potential for improperly assembled milling equipment. It was possible that the milling screens were not correctly installed. If this occurred, unmilled particles would escape the milling chamber and would not be milled. Correct equipment setup was necessary for good milling.

Experimental trials were designed to test this hypothesis, as follows:

- **Control milling.** The impact mill was assembled properly. Alkaline excipient was successfully milled. Sieve analysis was conducted to characterize the milled material.
- **Problem milling.** The impact mill was assembled incorrectly. Alkaline excipient was milled. Unmilled powder was observed escaping the milling chamber. Sieve analysis was conducted to characterize the milled material. Data indicated that a small percentage of particles were not milled, resulting in relatively large alkaline particles in the tablet core. It was hypothesized that these large particles reacted with blue dye to cause white spots in the blue tablets.

- **Control tablets.** Product tablets were manufactured with correctly milled material.
- **Problem tablets.** Product tablets were manufactured with improperly milled material.

Comparative testing of control tablets and experimental tablets under accelerated temperature conditions was then conducted. Samples of respective tablets were also stored under refrigeration. Tablets manufactured with the improperly milled material stored at high temperature developed distinctly visible white spots. It was concluded that the large particle-size excipient was the cause of the distinct white spots in the tablets. Comparison of tablets stored under accelerated conditions to the refrigerated tablets indicated that the refrigerated tablets were slightly darker in color than the heated tablets. This result indicated that the FD&C Blue #2 was chemically incompatible with the alkaline excipient. However, as long as the alkaline excipient was finely milled, color change was slow, diffuse, and generally unnoticeable to the naked or untrained eye.

**DISCUSSION**

Information obtained through interviews and subsequent experimental work enabled good understanding of the problem, determination of the root cause, and ultimate corrective and preventive action. Original speculation as to potential causes of the problem were tested and disproven. Investigative and experimental work by the technical group conclusively determined the root cause of the white spot problem. FD&C Blue #2 dye in the formulation was chemically reduced to indigo white, a white substance. Large particles of alkaline excipient, which had not been milled, caused the localized chemical reaction resulting in the formation of the distinct white spots. The alkaline excipient in the formulation was not milled because the milling screens were incorrectly installed in the impact mill. Comparative testing conclusively proved that the improperly milled alkaline excipient was the cause of the white spot problem. Comparison of heated tablets to refrigerated tablets confirmed the susceptibility of the FD&C Blue #2 to alkaline chemical reduction. As long as the alkaline excipient was finely milled, lightening of the blue tablets was not noticeable. The importance of
the milling process, and especially of correct installation of screens in the impact mill, was clearly demonstrated.

CORRECTIVE AND PREVENTIVE ACTIONS
The following CAPA and associated activities were conducted:
- New milling equipment assembly procedure
- New milling process
- Process validation
- Training
- Documentation
- Communication to other sites
- Other similar products manufactured at the site.

New Milling Equipment Assembly Procedure
The importance of equipment assembly in the milling process indicated that greater control was required. A new and more detailed assembly procedure was implemented. Also, the manufacturing supervisor checked and approved (signature) the assembly of the mill by the manufacturing operator. Signoff by the supervisor was added to the manufacturing batch record.

New Milling Process
A new milling procedure and control test was also implemented for this product. The alkaline excipient that was determined to be the cause of the white spot problem was milled twice through the impact mill. After milling, the milled material was sampled and tested for passage through an appropriate screen. Any unmilled particles would not pass through the screen. If unmilled particles were observed, the process was stopped and a supervisor was immediately notified.

Process Validation
Product manufactured using the new milling process was validated. The amount of alkaline excipient comprised a very low percent of the formulation. The amount of potentially smaller particle size of this ingredient did not impact the particle size distribution in the blended granulation and did not affect the flow properties or compressing process for the product.

Training
All personnel were trained on the new equipment assembly procedure and milling process procedure. The importance of the milling process in manufacturing this product and the correlation of improper milling to the white spot problem were well communicated. Training on proper setup of milling equipment was applicable to all products manufactured at the site. Essentially all products included milling as part of their manufacturing process.

Documentation
All work associated with the original validation was completed. All investigations, analyses, and conclusions were documented to close the CAPA. Development of the new manufacturing process including trial runs was documented and filed in the validation library as supporting information for the validation process qualification (PQ) runs. US Food and Drug Administration investigators visited the manufacturing site in response to customer complaints. All investigation documentation was reviewed by FDA investigators. No FDA 483 observations were issued.

Communication to Other Sites
The incident described herein was communicated to other global sites licensed to manufacture this product.

Other Similar Products Manufactured At The Site
The milling problem described was unique to the specific product. Other products did not contain the same colorants or formulation containing the alkaline excipient.

POST CAPA MONITORING
Additional monitoring of manufacturing was conducted to confirm successful corrective action. A final report summarizing all monitoring data was prepared after three months (many lots) of manufacturing. No instances of improper machine set up were observed. No milling difficulties were reported. No customer complaints on product lots that were manufactured after the process changes were received. Corrective action was successful.
CONCLUSIONS
A case study describing a compliance event in which a large number of product complaints involving distinct white spots on a tablet product was discussed. The cause of the problem was not easily determined. Speculation on the problem source ranged from grease spots to microbial growth. The product had been successfully manufactured for many years without any incidence of this type of complaint. Technical personnel conducted parallel investigations addressing possible causes of the white spot problem. These included microbiological testing, elemental analysis, changes in formulation materials, and chemistry of FD&C Blue #2, the colorant in the formulation. Chemical change (chemical reduction in alkaline pH) of the blue dye was determined to be the source of the white spots. All other potential problem causes were disproven.

Manufacturing personnel determined that there was potential for improperly assembled milling equipment causing material that was not milled. This in turn caused formation of the white spots. Experimental trials confirmed this hypothesis. This work also indicated that the FD&C Blue #2 was chemically incompatible with the alkaline excipient. However, as long as the alkaline excipient was finely milled, color change was slow, diffuse, and generally unnoticeable. The importance of the milling process, and especially of correct installation of screens in the impact mill, was clearly demonstrated.

CAPA and associated activities conducted included a new milling equipment assembly procedure to prevent improper equipment setup, a new milling process, process validation of the new process, training of manufacturing personnel, and documentation of all activities. The documentation was almost immediately useful when FDA audited the site in response to customer complaints to the Agency. This event and its corrective actions were communicated to other corporate sites manufacturing the same product. No other products manufactured at the site were susceptible to this problem. Additional monitoring of manufacturing was conducted. No instances of improper machine set up were observed. No milling difficulties were reported. No complaints on product lots that were manufactured after the process changes were received. Corrective action was successful.

This case study demonstrated highly unlikely causes of a serious compliance problem. Chemical properties of inactive ingredients are not a typical cause of problems. The milling process is also not considered to be a problematic manufacturing process. These two unlikely causes combined to cause a very significant problem. Compliance personnel must be aware that all ingredients in the formulation, not just the active drug, may have significant negative effects on the product. Compliance personnel must not assume simple manufacturing processes to be problem free. The inactive ingredients are important components of products. The performance of even presumably mundane processes such as milling must be seriously considered. Compliance personnel must keep an open mind without preconceived beliefs when investigating problem situations.

REFERENCE

ABOUT THE AUTHOR
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