Compliance Case Study #6
Process Validation Failure—Liquid Product Batch Size Increase

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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 a batch size increase for a liquid solution product is described
• The batch size increase was considered to be a relatively simple change because 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
• Manufacturing was started and the formulation ingredients did not dissolve in the product solution—The validation performance qualification was a failure. Mixing in the tank was not sufficiently rigorous
• The supposedly identical tank did not have the same impeller arrangement as the other large mixing tanks at the site. Although the volume of all tanks was the same, the mixing impellers were different
• A new manufacturing process was developed using an intermediate reduced solution volume that enabled successful manufacturing
• Corrective action and preventive action (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
• Several other products were also manufactured using the new manufacturing procedure
• Minor equipment differences may have significant effect in manufacturing. “Identical” may really not be so.

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 required a batch size increase for a liquid solution product to meet increased commercial demand. The batch size increase was considered to be a relatively simple change because other similar products at the site were already manufactured at the same increased batch size. The need for validation was questioned because the product and process were “identical” to other product manufacturing, and the equipment to be used was “identical” to all other mixing tanks. A one-lot confirmatory validation batch was ultimately planned because this change was considered to be of minimal risk. Equipment to accomplish the increased batch size was available. An infrequently used mixing tank was the appropriate size to make the large batch solution. Manufacturing was started. The unexpected happened; manufacturing had to be aborted during the batch due to mixing failure. Ingredients did not dissolve in the product solution. The validation was a failure.

This discussion provides the following:
• Process description background. The manufacturing process for the increased batch size 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 are given
• Investigation. Interviews and actions conducted to investigate the event are discussed
• Discussion. Key information, activities, and analysis are presented
• Corrective action and preventive action (CAPA). Actions and improvements implemented are detailed. These include development of a new manufacturing process, training, documentation, process validation, post-validation monitoring, equipment qualification, and application to other similar products at the site
• Post CAPA. Lessons learned, maintaining validation and performance, and other actions and improvements implemented as result of knowledge gained and activities associated with the incident are discussed.

PROCESS DESCRIPTION BACKGROUND
The manufacturing process in this case study involved manufacture of an aqueous solution in a standard mixing tank. Ingredients in the formulation included the active drug, hydrophilic polymer to increase viscosity, buffer salts to maintain pH, preservatives, flavor, color, hydrochloric acid, sodium hydroxide, and purified water. The manufacturing process for the product comprised the following steps:
• Approximately 85% of purified water was added to the mixing tank. Solution volume was measured with a dip stick
• The mixer was started
• Solid ingredients were added to the mixing tank through a port at the top of the mixing tank. Powder adhering to the side of the tank was rinsed into the solution with a small amount of purified water
• After all ingredients were added, the solution was mixed for 60 minutes
• Solution pH was measured. If necessary, pH was adjusted with hydrochloric acid solution or sodium hydroxide solution
• Additional purified water was added to make the final solution volume. Solution volume was measured with a dip stick
• The solution was mixed for 15 minutes
• Solution was filtered and filled into the commercial packaging.

COMPLIANCE EVENT
A small molecule pharmaceutical company required a batch size increase for a liquid solution product. Plant management and supply chain personnel ordered an increase in batch size for commercial supply and cost reduction purposes. Equipment to accomplish the
increased batch size was available—an infrequently used mixing tank was the appropriate size to make the large batch solution. The mixing tank was the same size as several other tanks in the facility and was thought to be identical to all other tanks. However, it was a backup tank that had not been used for several years. The validation group prepared a process validation protocol as requested by plant management. The product to be scaled-up was an oral solution product. The plant manufactured several other oral solution products at the same increased batch size in other tanks. Management assumed that there would be no problem with the increased batch size and ordered an immediate batch size increase. The product had a good manufacturing and quality history at the smaller batch size. One lot was requested to validate the increased batch size because several other similar products were already manufactured at this same large batch size. The existing batch record documentation was modified to manufacture the increased batch size. No problems were expected.

Manufacturing operators manufactured the larger batch size according to the specified directions. The procedure used was scaled from the smaller batch size procedure. The procedure used was also the same as used for other products at a similar batch size. When certain inactive ingredients were added to the mixing tank, these materials floated on the top of the water in the tank but did not dissolve. Mixing continued for several hours. The inactive ingredients still did not dissolve. The manufacturing process was terminated. The validation performance qualification (PQ) conformance lot had failed.

What Are The Issues?
There were several critical issues to be investigated as follows:

- Did manufacturing operators follow batch record directions properly?
- Did all associated groups approve the batch record change?
- Did the technical group approve the batch record change?
- Why did the process validation fail?

CGMP Requirements
Relevant good manufacturing practice (GMP) requirements applicable to the event are listed as follows:

- Subpart D–Equipment. 211.67. Equipment Cleaning and Maintenance
- 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 process validation. There were many details that needed to be investigated or confirmed. Personnel from all groups were interviewed and interacted to address the issues.

Manufacturing Personnel Interviews
Manufacturing personnel affirmed that all batch record directions were performed as specified. Manufacturing operators had manufactured the equivalent products at large batch size using an equivalent procedure at the site many times. They had also manufactured the specific product of this case study at small batch size many times. There were no training issues or variation in performance associated with the manufacturing procedure.

Batch Record Review And Approval
All relevant personnel had reviewed and approved the manufacturing batch record. The change had been evaluated by the validation approval committee and one PQ conformance lot was recommended. There was no expectation that the process would not be completely successful. Other products in the plant had been successfully manufactured at the same batch size. These lots had been manufactured in what was thought to be an equivalent mixing tank. Validation documentation indicated that all mixing tanks were equivalent.

Technical Personnel Evaluation
Technical personnel affirmed that there should have been no problem with manufacturing the increased
The manufacturing process was straightforward as follows:
- Approximately 85% of purified water was added to the mixing tank
- Solid ingredients were added to the mixing tank
- The solution was mixed for 60 minutes.

All ingredients were expected to dissolve within the 60-minute mixing time.

**Key Information**

The general manufacturing process was used to manufacture a small batch size many times. This same process was proposed for use for the increased batch size. The engineering staff was requested to evaluate the mixing tank used for the failed PQ conformance run. The mixing tank that was used to manufacture the increased batch size was an infrequently used tank. This tank did not have the same impeller arrangement as the other large mixing tanks at the site. All mixing tanks except the tank used for the process validation had three pitched-blade turbines located at the top, middle, and bottom of the mixer shaft. The tank used for the failing batch had only two pitched-blade turbines located at bottom and mid-level on the mixer shaft. The mixing tank with two impellers did not provide adequate axial flow to pull solid ingredients into the bulk liquid to effect dissolution. The mixing tank used in the failed PQ run was significantly different from all other mixing tanks at the site. However, because this tank was a backup tank that had not been used for several years, no one was aware of the difference. Although the volume of all tanks was the same, the mixing impellers were very different (see Figure).

**DISCUSSION**

Information obtained through interviews and subsequent experimental work enabled good understanding of the problem and an ultimate solution. Technical personnel conducted experimental runs and proposed processing changes to enable manufacturing in all mixing tanks. Two experimental runs were conducted.

**Run #1**

The first run comprised addition of purified water to the two-impeller mixing tank. The amount of water added was measured to be just above the middle impeller. This water level provided good mixing as evidenced by a strong vortex and did not cause excessive splashing. Approximately 55% of the final solution volume was required to cover the impeller. Mixing was initiated and observed to provide a vortex that would dissolve the ingredients. The hydrophilic polymer was known to be the slowest dissolving of all ingredients. The required amount of hydrophilic polymer was added to the purified water in the tank. The polymer was quickly drawn into the liquid and easily dissolved.

**Run #2**

A second trial run was conducted using all ingredients except the active pharmaceutical ingredient. Not including the active ingredient considerably reduced the cost of the trial run. Purified water was added to the mixing tank at 55% of the final volume. Mixing was initiated. All inactive ingredients were then added to the purified water. All ingredients quickly dissolved. This second run confirmed that all formulation ingredients would be dissolved in the 55% solution volume during the mixing process. The trial run greatly increased the confidence of all involved that the process validation would be
successful. Because the active ingredient was readily soluble in water, it was not expected to impact the solution process.

A new batch record was developed using the newly developed mixing process. New validation documentation was also developed. Three PQ runs were recommended because the manufacturing process was completely new to the site. Manufacturing, QA, engineering, and technical support management approved the change and all associated documentation.

CORRECTIVE AND PREVENTIVE ACTIONS
The following CAPA and associated activities were conducted:

- New manufacturing process
- Training
- Documentation
- Process validation
- Post-validation monitoring
- Equipment qualification
- Other similar products manufactured at the site.

New Manufacturing Process
A new manufacturing process comprising the following was implemented when the backup tank was used:

- Approximately 55% of purified water was added to the mixing tank
- Mixing was started
- Solid ingredients were added to the mixing tank
- After all ingredients were added, the solution was mixed for 60 minutes
- Purified water was added to the mixing tank to 95% of the final volume
- Solution pH was adjusted with hydrochloric acid solution or sodium hydroxide solution if necessary
- Purified water was added sufficient to the make the final solution volume
- The solution was mixed for 15 minutes
- Solution was filtered and filled into the commercial packaging.

Training
All personnel were trained on the new manufacturing procedure. The importance of adding only 55% of the final solution volume to the mixing tank was stressed in the training. This procedure was used only when using the two-impeller mixing tank.

Documentation
All work associated with the original validation was completed. All investigations, analyses, and conclusions were documented to close the original validation. Development of the new manufacturing process including trial runs was documented and filed in the validation library as supporting information for the validation PQ runs.

Process Validation
The increased batch size manufacturing process for product in the two-impeller manufacturing tank was validated. Three lots were tested. All test data passed acceptance criteria.

Post-Validation Monitoring
Additional monitoring of manufacturing the increased batch size product was conducted to confirm the successful process validation. Visual observation of the mixing and dissolution process was required for subsequent lots manufactured during the next three months. One lot was manufactured each month. The manufacturing process using the new process was successful in all batches. Visual observation of the manufacturing process was documented and filed in the validation library.

Equipment Qualification
The installation qualification (IQ) for the manufacturing tank with the two impellers was reviewed to be sure that its documentation correctly stated its impeller arrangement. The IQ documentation for all other tanks was also reviewed. These records incorrectly indicated that all tanks were interchangeable because they all contained the same volume. Documents were changed to indicate that the two-impeller tank was not listed as equivalent to the other three-impeller tanks. While the manufacturing volumes of all tanks
were identical, the mixing capabilities of the tanks were significantly different because the impellers on the tanks were different.

**Other Similar Products Manufactured At The Site**
Manufacturing batch records for other products with large batch sizes were reviewed. Master batch records for all products were modified to exclude the two-impeller tank from optional use in manufacturing. All products specified initial addition to 85% of purified water to the mixing tank. This volume would have resulted in inadequate mixing. If the two-impeller tank would be needed for manufacturing flexibility of other products, the master batch records of the other products would be changed to add 55% of purified water to the mixing tank in the first step of the manufacturing process.

**POST CAPA**
Several other products were required to be manufactured in the two-impeller tank in the following months. Manufacturing experience with the initial product, including trial runs, was used as supporting justification to modify the respective master batch records of the additional products. The formulations for all products were essentially identical excepting the active ingredient. In all cases, the active ingredient was readily soluble in purified water.

**CONCLUSIONS**
The batch size increase discussed in this case study was considered to be a relatively simple change because other similar products at the site were already manufactured at the same increased batch size. The need to actually demonstrate successful processing in validation was even questioned because the product and process were identical to other manufacturing, and the mixing tank was thought to be identical to all other tanks. There was no possibility of any problems occurring. Manufacturing was started and the unexpected happened—ingredients did not dissolve in the product solution and the manufacturing batch was a complete failure.

The cause of the failure was easily determined. The impellers on the mixer in the specific mixing tank used for the increased batch size were different than all other site mixing tanks. Mixing in this tank was inadequate. A new manufacturing process was ultimately developed that enabled adequate mixing and successful manufacturing. All associated documentation affirming that all mixing tanks were equivalent was corrected.

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 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.

This case study demonstrates the need for compliance professionals to be vigilant even when apparently mundane changes are initiated. “Identical” may really not be so (see reference).

**REFERENCE**

**ARTICLE ACRONYM LISTING**
CAPA  Corrective Action and Preventive Action  
CGMP  Current Good Manufacturing Practice  
GMP  Good Manufacturing Practice  
IQ  Installation Qualification  
PQ  Performance Qualification  
QA  Quality Assurance

**ABOUT THE AUTHOR**
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