Alternate Raw Material Supplier Validation

Author: Melissa Valerín Díaz

Advisor: Rafael Nieves

Manufacturing Engineering

Abstract

This project discusses the Process Validation of Over the Counter Pharmaceutical Product using alternate supplier of raw material. The primary ibuprofen drug substance supplier for GSK Ibuprofen family products informed that they have not recovered from a natural disaster that impacted their facilities. As a result of this natural disaster, the supplier shut down production of ibuprofen indefinitely. In order to alleviate ibuprofen drug shortage imposed by primary supplier's facility shut down, GSK Puerto Rico has identified potential alternate supplier of Ibuprofen for the current Ibuprofen OTC products. To conduct this project, DMAIC methodology was used in order to have a better understanding of the process to increase efficacy and identify areas of opportunity to improve. GSK Puerto Rico is responsible for the 100% of the Ibuprofen family products for US domestic sales and Ibuprofen family represents 58% of GSK 2019 volume plan. The company will be able to supply the expected volume of Ibuprofen family products to the customers and the volume plan will be achieved with the validation of alternate ibuprofen supplier for Ibuprofen family products.

Project Description

This project will focus in the validation of an alternate ibuprofen supplier for Ibuprofen family OTC products to alleviate the possible impact in 100% of the Ibuprofen family products for US domestic sales and 58% of GSK 2019 volume plan that Ibuprofen family represents.

Objectives

- Alleviate ibuprofen drug shortage imposed by primary supplier's facility shut down
- Increase the flexibility in raw material suppliers

Background

Effective process validation contributes significantly to assuring drug quality. Process validation is defined as the collection and evaluation of data, from the process design state through commercial production, which establishes scientific evidence that the process is capable of consistently delivering quality product [1]. Process validation involves a series of activities taking place over the lifecycle of the product and process. The process validation activities are described in three general stages:

- Stage 1-Process Design: The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.
- Stage 2-Process Qualification: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.
- Stage 3-Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.

This project is focused in stage 2 (PPQ), since the product is currently validated for commercial production using the previously validated facilities.

Methodology

DMAIC is a data-driven quality strategy used to improve processes [2]. It is an integral part of a Six Sigma initiative, but in general can be implemented as a standalone quality improvement procedure or as part of other process improvement initiatives such as lean [3]. DMAIC is an acronym that stands for Define, Measure, Analyze, Improve and Control. It represents the five phases that make up the process, including the tools to use to complete those phases. Each of these five steps implement different strategies focused on reducing waste, increasing efficiency, and improving quality of the process.

For the project, the five steps will be described as follow:

Define- Problem Statement: The primary supplier of ibuprofen drug substance for GSK Ibuprofen family products informed that they have not recovered from a natural disaster that impacted their facilities. As a result of this natural disaster, the supplier shut down production of ibuprofen indefinitely. In order to alleviate ibuprofen drug shortage imposed by primary supplier's facility shut down, GSK Puerto Rico has identified potential alternate supplier of Ibuprofen for the current Ibuprofen OTC products.

Measure-Process Validation Execution: Generate a Process Qualification Protocol in order to validate the use of an alternate ibuprofen raw material supplier for the commercial production of Ibuprofen OTC family products.

Analyze- Summary of results and analysis: Summarize data collected during protocol execution and analyze data as specified by the protocol. At this stage conclusion as to whether the data indicates the process met the conditions established in the protocol and whether the process is in a state of control should be stated.

Improve-Optimize process performance: Implement the expected change if the results were successful, in this case use alternate supplier of ibuprofen raw material for commercial production of Ibuprofen OTC family products.

Control-Continued Process Verification: Statistical analysis to verify that the validated process remains in control. As part of process controls, Bill of Materials and Master Batch Records will be revised in order to include the alternate supplier of ibuprofen raw material as part of the cGMP documents that are used in the manufacturing process of Ibuprofen OTC family products.

Results and Analysis

As part of the Analyze Stage, results of Process Qualification Protocol were analyzed. The analysis consisted of statistical and graphical analysis during the manufacture of Ibuprofen family product.

During Weighing process physical testing for the three (3) batches of Ibuprofen used in the validation was performed. Ibuprofen was tested for Ro-Tap Screen Analysis (mesh no: 20, 40, 80, 100, 140, 200 and Pan), moisture (Karl Fischer method), and poured/tapped density. Results are summarized in **Figures 1** and **2** shows a graphical view of the testing conducted and the uniformity of the results obtained for each evaluated batch.

Results and Analysis (cont.)

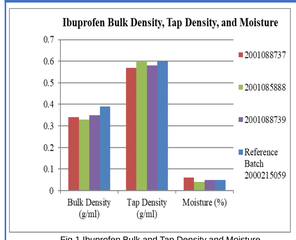

Fig 1 Ibuprofen Bulk and Tap Density and Moisture

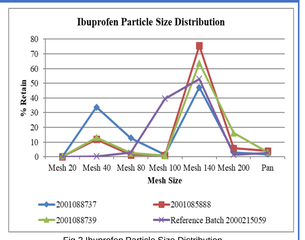

Fig 2 Ibuprofen Particle Size Distribution

No significant differences were observed between the three (3) control numbers of Ibuprofen used during the validation. Particle size distribution results show that most of the material was retained at the 140 mesh for the three batches, during the screen analysis.

According to the results, blend uniformity shows that granulation blend presents a homogeneous blend within the blend components. Results for Ibuprofen and Phenylephrine in the V-Blender were within the acceptance criteria for the three (3) validation batches sampled. The data for all the validation batches present minor variations and demonstrate uniformity across all ten-sample points of every validation batch. Graphical presentation is illustrated in **Figure 3.**

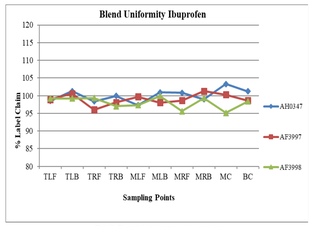

Fig 3 Blend Uniformity Ibuprofen

Batches were sampled through the compression run. Testing was conducted to the core product for Content Uniformity, Single Point Dissolution, and Assay. All batches met the content uniformity acceptance criteria. A graphical view of the content uniformity (20 points) average value is displayed in **Figures 4 to 6**.

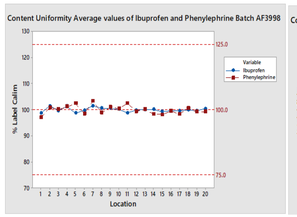

Fig 4 Content Uniformity Batch AF3998

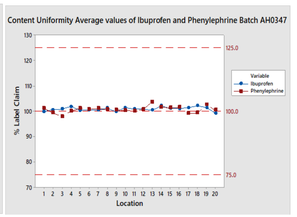

Fig 5 Content Uniformity Batch AH0347

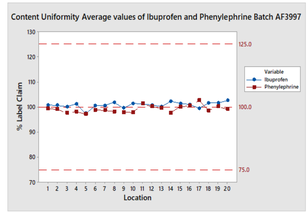

Fig 6 Content Uniformity Batch AF3997

Results and Analysis (cont.)

Single Point Dissolution was performed from the three (3) sampling point collected through the entire run representing the beginning, middle and end of the compression run of each validation batch, with average results from (98- 101) % for Ibuprofen. The single point dissolution data for all batches manufactured met Stage I criteria for dissolution with NLT 85% dissolved in 30 minutes. All samples complied with Stage I criteria. A summary of single point dissolution testing is presented at **Figure 7** illustrated the test conducted**.**

Assay was performed from the three (3) sampling point collected through the entire run represented the beginning, middle and end of the compression run of each validation batch, with average results from (99.4- 102.0) % for Ibuprofen. The three (3) validation batches met acceptance criteria of (95.0-105.0) % L.C. Assay results from the three (3) batches are presented on **Figure 8.**

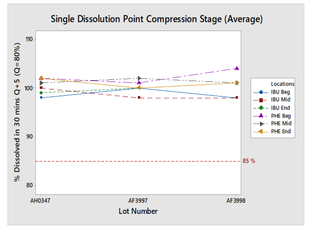

Fig 7 Single Dissolution Point

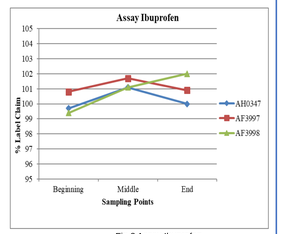

Fig 8 Assay Ibuprofen

Conclusion

Using DMAIC Methodology to gather data, analyze results and improve the process was a successful approach for the supplier drug shortage problem that GSK Puerto Rico was experiencing. Process Qualification Protocol requirements were successfully completed obtaining results that met all requirements and specifications established for Ibuprofen OTC family products. According to the results obtained, the Process Validation exercise demonstrates the alternate supplier of Ibuprofen is equivalent to the current primary supplier of Ibuprofen used in Ibuprofen OTC family products manufacturing process. Therefore, the manufacturing process of Ibuprofen OTC family products using Ibuprofen from alternate Ibuprofen supplier is considered validated. Since all release test criteria were met it is recommended to include alternate supplier of ibuprofen in manufacturing process official documents (Bill of Materials and Master Batch Record). Alternate supplier of Ibuprofen is recommended for the commercial production of Ibuprofen OTC family products.

References

[1] U.S. Department of Health and Human Services Food and Drug Administration (2011) Guidance for Industry. *Process Validation: General Principles and Practices*

[2] Shaikh, S., & Kazi, J. (2015) A Review on Six Sigma (DMAIC) Methodology. *International Journal of Modern Engineering Research*. 5(11-16)

[3] Ahmed, S., Antony, J. & Abdul S. (2015) A systematic review of Lean Six Sigma for the manufacturing industry. *Business Process Management Journal*. 21(665-691)