Alternate Raw Material Supplier Validation

Melissa Valerín Díaz
Master of Engineering in Manufacturing Engineering
Advisor: Dr. Rafael A. Nieves Castro
Industrial and Systems Engineering Department
Polytechnic University of Puerto Rico

Abstract *— This article 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.*

Key Terms *— DMAIC, Process Validation, Raw Material, Supplier Qualification.*

INTRODUCTION

GSK is a Global Pharmaceutical Manufacture Facility that produces Over the Counter (OTC) products. GSK Puerto Rico site main products are analgesics and dietary supplements. This manufacturing site consumes more than 60% of all Ibuprofen required by Consumer Operations Network. Ibuprofen is a widely used non-steroidal anti-inflammatory drug (NSAID) currently marketed worldwide. In addition to the anti-inflammatory properties of ibuprofen, it also has pain-relief (analgesic) and fever-reducing (anti-pyretic) properties. This facility is responsible for the 100% of the Ibuprofen family products for US domestic sales. Ibuprofen family represents 58% of GSK Puerto Rico 2019 volume plan.

Ibuprofen, USP is approved for use in multiple OTC drug products marketed by GSK. The primary ibuprofen drug substance supplier for GSK Ibuprofen family products informed that they have not recovered from a natural disaster. As a result of this natural disaster, the supplier shut down production of ibuprofen indefinitely. The supplier has not committed to a timeframe for its ability to return to operation and support GSK with ibuprofen supply to full-capacity. GSK ibuprofen family products currently consume approximately 200 metric tons of ibuprofen per month, with primary supplier supplying 60% of the ibuprofen consumed by GSK monthly. This current shut down for an extended period will impact the supply of ibuprofen for the Ibuprofen family OTC products.

Research 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.

Research Objectives

The following are the objectives of this research project:

- Alleviate ibuprofen drug shortage imposed by primary supplier's facility shut down.

- Increase the flexibility in raw material suppliers.

Research Contributions

With the validation of an alternate supplier for ibuprofen raw material, GSK will mitigate the drug shortage imposed by the primary supplier of Ibuprofen. As an OTC medicine, the Ibuprofen family products provide consumers access to convenient treatment for sudden symptoms and minor ailments. These OTC brands are relied upon by consumers to treat common, self-treatable health conditions and symptoms such as those caused by the common cold, minor pain, allergies and other conditions that impact large segments of the population. Research has indicated that 81 percent of adults use OTC medicines as a first response to minor ailments.

Since GSK Puerto Rico is responsible for 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.

BACKGROUND

Effective process validation contributes significantly to assuring drug quality. The basic principle of quality assurance is that a drug should be produced that is fit for its intended use. 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.

Before any batch from the process is commercially distributed for use by consumers, a manufacturer should have gained a high degree of assurance in the performance of the manufacturing process such that it will consistently produce APIs and drug products meeting those attributes relating to identity, strength, quality, purity and potency [2].

Process design will not be discussed for this project since the manufacturing process is currently validated, the purpose of the process validation is to confirm the performance of the product using an alternate API supplier. The process design will remain the same as the one established, the expected change to monitor will be the quality attributes regarding the input of a different supplier for the raw material.

Process Qualification

During the process qualification (PQ) stage of process validation, the process design is evaluated to determine if it is capable of reproducible commercial manufacture [3]. This stage has two elements: (1) design of the facility and qualification of the equipment utilities and (2) process performance qualification (PPQ). Successful completion of Stage 2 is necessary before commercial distribution.

This project is focused in stage 2 (PPQ) since the product is currently validated for commercial production using the previously validated facilities. Stage 1, design of the facility and qualification of the equipment utilities, will not be discussed.

The PPQ combines the actual facility, utilities, equipment and the trained personnel with the commercial manufacturing process, control procedures and components to produce commercial

batches. A successful PPQ will confirm the process design and demonstrated that the commercial manufacturing process performs as expected. A manufacturer must successfully complete PPQ before commencing commercial distribution of the drug product. Data from quality control (laboratory) and pilot studies can provide additional assurance that the commercial manufacturing process performs as expected.

A written protocol that specifies the manufacturing conditions, controls, testing and expected outcomes is essential for this stage of process validation. The protocol should discuss the following elements:

- Manufacturing conditions including operating parameters, processing limits and raw materials.
- Data to be collected, when and how it will be evaluated.
- Tests to be performed (in process, release, characterization) and acceptance criteria.
- Sampling plan: sampling points, number of samples, frequency of sampling. The number of samples should be adequate to provide sufficient statistical confidence of quality both within a batch and between batches.

A report documenting and assessing adherence to the written and executed PPQ protocol should be prepared to summarize data collected and analyze as specified by the protocol. This report should state a clear conclusion as to whether the data indicates that the process met the conditions.

Continued Process Verification

The goal of the third validation stage is continued assurance that the process remains in a state of control (validated state) during commercial manufacture [3]. A system for detecting unplanned deviations from the process as designed is essential to accomplish this goal. Adherence to the cGMP requirements, collection and evaluation of information and data about the performance of the process will allow detection of undesired process variability. Evaluating the performance of the process identifies problems and determines whether the action must be taken to correct, anticipate and prevent problems so that the process remains in control [3].

An ongoing program to collect and analyze product and process data that relate to product quality must be established [1]. The data collected should include relevant process trends and quality of incoming materials, components, in-process material and finished products. The data should be statistically trended and reviewed by trained personnel. The information collected should verify that the quality attributes are being properly controlled throughout the process. Data gathered during this stage might suggest ways to improve and/or optimize the process by altering some aspect of the process or product, such as the operating conditions (ranges and set points), process controls, component or in-process material characteristics.

METHODOLOGY

DMAIC is a data-driven quality strategy used to improve processes [4]. 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 [5]. 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.

DMAIC methodology will be applied in this project in order to accomplish project objectives and to validate the raw material alternate supplier for the commercial production of Advil Family Product in GSK Puerto Rico.

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 are 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.

The Process Qualification Study will cover the complete manufacturing process of Ibuprofen OTC family product. The manufacturing process consists of the following stages: Weighing, Wet Granulation, Blending, Compression, Film Coating and Branding. The study will consist of three (3) consecutive batches to establish with a high degree of assurance that the process is capable of producing a consistent product with acceptable physical and chemical characteristics and to confirm that the change in the raw material supplier does not have an impact in the finished product quality attributes. Testing will be conducted from Weighing Process, Blending and Compression Stages in addition of Batch Release Testing.

RESULTS AND DISCUSSION

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

Weighing Process Stage

Physical testing for the three (3) batches (2001088737, 2001085888, and 2001088739) of Ibuprofen used in the validation was performed for characterization purpose. 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. Ibuprofen batches 2001088737, 2001085888, and 2001088739 were sampled at the weighing stage. For this purpose, a sample of NLT 300 grams from each batch was taken in plastic bags and submitted for testing.

Results, summarized in Figures 1 and 2, show a graphical view of the testing conducted and the uniformity of the results obtained for each evaluated batch.

Data obtained showed a comparable behavior for each of the physical tests evaluated. No significant differences were observed between the three (3) control numbers of Ibuprofen used during the validation with range values of (0.34-0.35) g/ml for bulk density, (0.57-0.60) g/ml for tapped density, and (0.04-0.06) %w/w for moisture content.

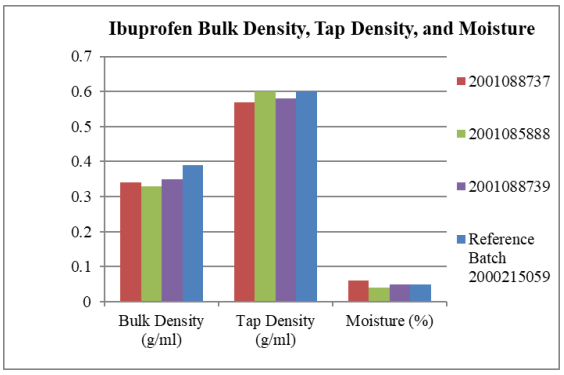

Figure 1
Ibuprofen Bulk and Tap Density and Moisture

Particle size distribution results show that most of the material was retained at the 140 mesh for the three batches, 2001088737, 2001085888 and 2001088739 during the screen analysis. The results were also compared to a previous validation exercise using Ibuprofen from primary supplier of Ibuprofen. A difference in the percent retained in each mesh is observed compared with the reference validation batches.

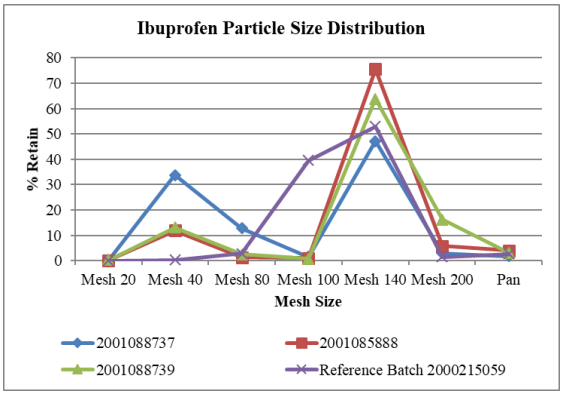

Figure 2
Ibuprofen Particle Size Distribution

Blending Stage

According to protocol design, samples for chemical analysis were collected at the blending stage. Batches AH0347, AF3997 and AF3998 were sampled for blend uniformity. According to protocol sampling plan, ten (10) samples in triplicate were collected after the final blend from ten locations of the V-Blender for each batch and analyzed for blend uniformity.

According to the results, blend uniformity for the V- Blender show 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. All results were within limits for stage I Standard Deviation ≤3.0%. The data for all the validation batches present minor variations and demonstrate uniformity across all ten-sample points of every validation batches. Graphical presentation is illustrated in Figure 3.

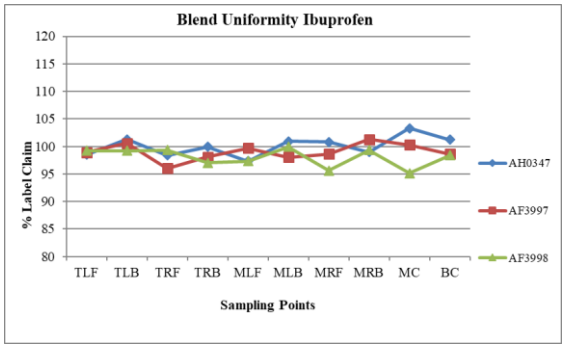

Figure 3
Blend Uniformity Individual Data Ibuprofen

Compression Stage

Batches AH0347, AF3997 and AF3998 were sampled through the compression run. Testing was conducted to the core product for content uniformity, single point dissolution, and assay. Sampling consisted of forty (40) sampling points evenly distributed of the compression run, collecting not less than 21 caplets from each sampling point. Content uniformity was analyzed from 20 locations including the beginning, middle and end of the run. An amount of three (3) caplets per each sample point were weighed and analytically tested for content uniformity. Single point dissolution was performed by testing 6 tablets at the beginning, middle and process end. Assay was conducted from a composite sample from the beginning, middle and end of the validation batches.

Content Uniformity criteria define that all individuals are within 75.0 – 125.0% LC and meet 90% Confidence/95% Lower Bound Probability for n=60. Content uniformity 20 points results for batches AH0347, AF3997, and AF3998 comply

with Stage I acceptance criteria (All individuals are within 75.0 -125.0 % L.C. and meet 90% Confidence/95% Lower Bound Probability for n=60). 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.

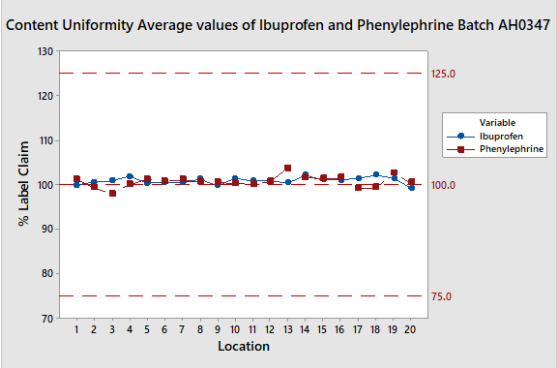

Figure 4
Average Value Content Uniformity % of Label Claim Batch AH0347

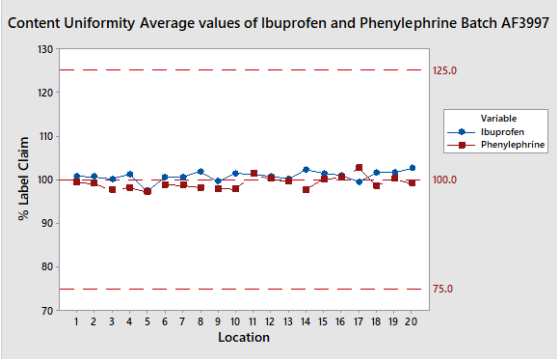

Figure 5
Average Value Content Uniformity % of Label Claim Batch AF3997

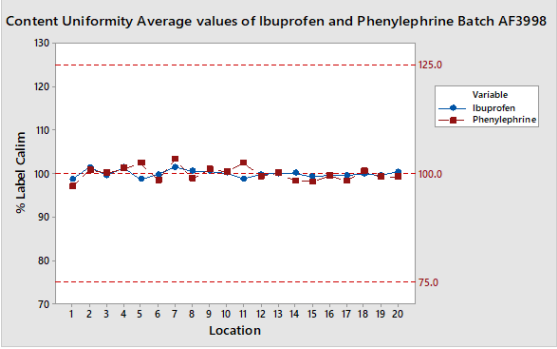

Figure 6
Average Value Content Uniformity % of Label Claim Batch AF3998

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%to 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 in Figure 7 illustrating the test conducted.

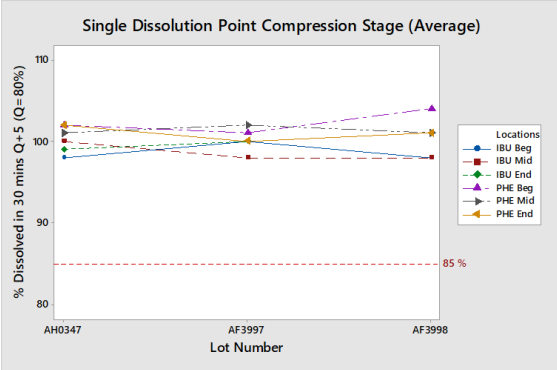

Figure 7
Single Point Dissolution Ibuprofen and Phenylephrine

Assay performed from the three (3) sampling points 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% to 102.0% for Ibuprofen. The three (3) validation batches: AH0347, AF3997 and AF3998 met acceptance criteria of (95.0-105.0)% L.C. Assay results from the three (3) batches are presented on Figure 8.

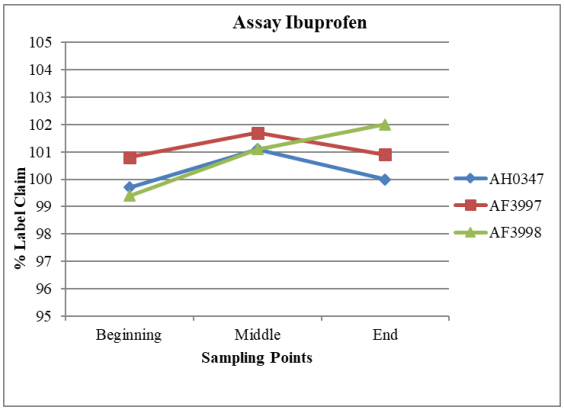

Figure 8
Assay Ibuprofen

Batch Release Testing

As part of the Master Batch Record a sample from the three validation batches were collected for release monograph testing after the completion of the branding process. According to the testing conducted for monograph release all results were within specification. All batches complied with the monograph release specification. Content uniformity results conforms USP/NF, <905> "Dose Uniformity" criteria. Dissolution conducted for each batch manufactured shows results are within the specification of NLT 85% in 30 minutes. AQL complied with product defect criteria for the three validation batches.

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.

Next step after improvement (implementation) stage, is control stage. In control stage a continued process verification will be conducted annually during routine commercial production in order to assure that that the process remains in a state of control. For this third stage of validation process, statistical analysis is included to verify that the validated process remains in control.

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