Reduction in Dissolution Test Results Variability of A/B Capsule Product

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Abstract *— Since the origins of the agency, the Food and Drugs Administration (FDA), a scientific, regulatory, and public health agency had been dedicated to consumer protection. The FDA, provides standardized regulations and guidance to pharmaceutical industry. Under the agency umbrella are covered different organizations: The Center for Drug Evaluation and Research (CDER) performs an essential public health task by making sure that safe and effective drugs are available to the people. The CDER works in the publication of diverse guidance for industry that include, scale up and post approval changes (SUPAC), testing of immediate release (IR) and modified release (MR) dosage forms, and the Investigation of Out-of-Specification (OOS) Test Results for Pharmaceutical Production. Any failure or violations on drug products is considered to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 351(a)(2)(B)]and the current Good Manufacturing Practices (cGMP). Considering this, a recognized failure in dissolution testing is considered adulteration of the drug product with negative consequences to the manufacturing facility.*

Key Terms *— Dissolution, Failure, Guidance, Requirements.*

PROJECT STATEMENT

The A/B capsule product is indicated for the treatment of hypertension. A/B capsules are immediate release and are administered orally in dosages of 37.5/25 mg and 50/25 mg. During the manufacturing process of A/B capsules 50/25 mg highly variable dissolution results were obtained during finished product testing.

An investigation was conducted under DEV-11-0065, including extensive reviews of the raw materials and manufacturing process. See Table 1.

Table 1
A/B Capsules Formulation Composition

Code	Material	mg/capsule	kg/batch	Percentage
1936 or 1689	A USP	50.0	170.85	26.3%
1973 or 1922	B USP	25.0	85.35	13.2%
2095	Lactose Monohydrate NF	97.9	334.35	51.5%
2101	Povidone USP	3.8	12.98	2.0%
2161	Purified Water USP	Removed	69.00	N/A
2035	Magnesium Stearate NF	13.3	45.45	7.0%
N/A	**Total (Fill Weight)**	**190.0**	**648.98**	N/A
5666	Capsule	38.0		
2040	Corn Starch NF	Trace		
N/A	**Gross Weight**	**228.0**		

Attributes of each raw material that could potentially explain variation in dissolution were evaluated, such as particle size and tapped density of the active ingredients and specific surface area of the Magnesium Stearate. No correlation was found between raw material attributes and dissolution performance.

Through the investigation, the dispensing, granulation, drying, milling and encapsulation processes were found to not contribute to the variable dissolution performance observed for Batch 191983. A change in the blending process, from the use of one asset of the 1415-liter twin-shell blender to another, was identified as the most likely cause for the variable dissolution performance.

The investigation report for DEV-11-0065 concluded the following: “The variable dissolution performance for lot 191983 is directly related to the variability in the disintegration performance of the capsule cores. The variable capsule core disintegration performance is attributed to over lubrication of the blend given the increased quantity

of Magnesium Stearate present in the formula. A downward shift and widening of the dissolution range has been observed which is associated to the use of 1415 liter blender #8 and after the decommissioning of blender #15 with trunnions on the blender walls. Blender #8 does not have the trunnions and is not equipped with an intensifier bar. The absence of trunnions on the blender wall for blender #8 may optimize the mixing affect for the in-process material when compared to blender #15. Therefore, the use of blender #8 without trunnions has a more efficient blending affect leading to over lubrication of A/B 50/25 Capsule blends and subsequently impacting the finished product dissolution performance" [1]. Refer to Figure 1.

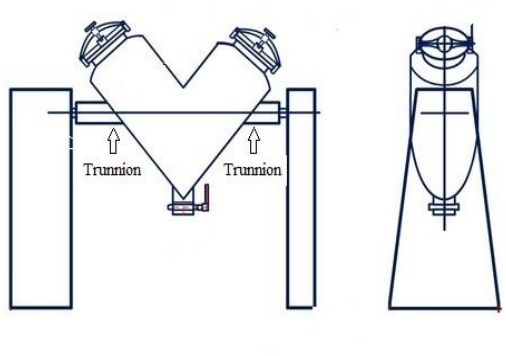

Figure 1
Trunnions in a Twin-Shell V Blender

Investigation identified two probable causes:

- Increased quantity (7%) of Magnesium Stearate present in the formula,
- Switch from animal-derived to vegetable-derived Magnesium Stearate.

As a result of this deviation, A/B 50/25mg Capsules batch 191983 was destroyed, the manufacturing of this product line was placed on hold on May 2011, a voluntary recall of this product in coordination with the FDA was conducted in November 2011 and Preventative Action Commitment PAC-11-0231 was initiated to evaluate and optimize the blending time for A/B 50/25mg Capsules to prevent over-lubrication of the blend to reduce variability in the dissolution performance for this product.

The increased variability appears to be a result of the following:

- Change in Magnesium Stearate from animal to vegetable;
- Segregation during discharge;
- Post-blending material handling steps.

Research Description

This project has been outlined with the purpose of classify and evaluate the increased variability in the A/B capsule product process in order to reduce or eliminate the variability in the product and re-start the manufacturing of the product line. Multiple factors, including raw materials, manufacturing process, batch size, analytical methods, equipment type and equipment set-up have been evaluated over the course of a number of experiments, to better understand the potential causal factors for the dissolution variability.

Research Objective

The experimentation for A/B Capsules 50/25 mg was focused on the following:

- Reduction of batch size to fit in an 800-liter Intermediate Bulk Containers (IBC).
- Elimination of rapid movement of the blend.
- Control of tamping during encapsulation.

Research Contributions

With the project implementation, the A/B capsules product process will obtain improvement on the manufacturing process, eradicate the variability in the testing errors and therefore give a much needed boost to operational efficiency. This assessment could be applied to other products with similar tendencies or related situations due to possible failures in testing compliance. This increases the chance of quality products and compliance.

LITERATURE REVIEW

The current manufacturing process of the A/B capsules allows for discharge from the twin-shell blender into two 800-liter intermediate bulk containers (IBCs) or one 1400-liter IBC. Since

most Capsule Filler Machines at the manufacturing site can only support 800-liter IBCs, it was decided to focus future development efforts in the 800-liter IBC.

The current commercial process includes 3 granulating sections. In order to not change the granulation process and to fit into one 800 L IBC, the batch size must be reduced to 1 or 2 sections. The working capacity of an 800 L IBC is 160 – 680 L. The lowest bulk density obtained during process validation of this product was 0.608 g/mL. Each section is 216.35 kg, or 356 L, based on this bulk density. Two sections (712 L) would be too large to fit into the working volume range of an 800 L IBC. The highest bulk density obtained during process validation of this product was 0.635 g/mL. A single section of 216.35 kg at this bulk density would occupy 341 L, which is within the working volume of an 800 L IBC. Thus, the batch size will be reduced to 1/3 of the current commercial batch size, by reducing from three granulating sections to one. The development study also evaluates the change in blending time, from an original blend time of 18 minutes to a new blend time of 30 minutes [2].

The evaluation of the A/B product process should be conducted by collect the necessary data, evaluate, analyze and catalog all blending and encapsulation process history and details. Once the processes data is gathered, it must be validate, before the execution of any change to ensure process and system compliance to make the effective change. These changes could reduce the variability in dissolution testing and shall be completed with the required change documentation to prevent any remark by regulatory agencies.

The roots of Six Sigma as a measurement standard can be traced back to Carl Frederick Gauss (1777-1855) who introduced the concept of the normal curve. Six Sigma as a measurement standard in product variation can be traced back to the 1920's when Walter Shewhart showed that three sigma from the mean is the point where a process requires correction. Many measurement standards (Cpk, Zero Defects, etc.) later came on the scene but credit for coining the term "Six Sigma" goes to a Motorola engineer named Bill Smith. The key objective of the Six Sigma methodology is the implementation of a measurement-based strategy that focuses on process improvement and variation reduction through the application of various Six Sigma methodologies including the key processes like DMAIC (Figure 2) and DMADV.

Figure 2
DMAIC Continuous Cycle

Six Sigma is a methodology of continuous improvement aimed at reducing defects by using the model Define-Measure-Analyze-Improve-Control (DMAIC), which is further developed through the Design for Six Sigma, which is based on creating a robust design that meets customer requirements and Lean Six Sigma, which is based on the processes and ways to increase their efficiency.

DMAIC refers to a data-driven quality strategy for improving processes, and is an integral part of the company's Six Sigma Quality Initiative. DMAIC is an acronym for five interconnected phases: Define, Measure, Analyze, Improve, and Control. Each step in the cyclical DMAIC Process is required to ensure the best possible results. The process steps are:

- Define: Identify the requirements and problem statement;
- Measure: Identify and document the process;
- Analyze: Collect data to determine cause;
- Improve: Select the best solution in order to improve;
- Control: Revised process to hold the gains.

Each of the previous stages involve and promote the use of tools for process improvement, reduction in variation and customer satisfaction [3].

METHODOLOGY

In order to achieve the proposed objectives, this section provides an overview of procedure and methodology that will be applied in the design project. The project methodology to be used is DMAIC improvement strategy coming from Six Sigma principles. DMAIC is an acronym that has five phases: Define, Measure, Analyze, Improvement and Control.

- **Define Phase**: This phase consists in defining the scope, goals and project statement. It will use a project charter in order to describe the process and identify the possible opportunities of improvement.
- **Measure Phase**: The objective of this phase is the collection of the key aspects of current process and relevant data. As well as the identification of potential factors that may affect the process. It will use data collection and detailed process flow diagram. The tools to be use to show visual representations of the current state are graphs, charts, and flowcharts.
- **Analyze Phase**: This phase consists on identifying deep causes with the objective of validate them with relevant data. The key components of this phase include cause-effect, root cause and value- non value added analysis. It will used Value stream map and cause-effect diagram.
- **Improvement Phase**: The objective of this phase is optimizing the current process based on data analysis. The key components for this phase include lean manufacturing tools, optimized process parameter settings and standardized work.
- **Control Phase**: This phase includes designing and documenting the new controls and procedures, in order to hold the gains. Key components to this phase are visual workplaces, periodic audit exercises and training process to monitor the success.

RESULTS AND DISCUSSION

This chapter present the problem analysis and improvement results using the Lean Six Sigma Methodology and DMAIC tool.

Define Phase

The results obtained during the manufacturing of the A/B 50/25mg Capsules batch 191983 for dissolution testing reflects variability in the results obtained. The failure in obtain results that comply with the acceptance criteria specification in considered a potential violation on drug products that could be considered adulterated. The manufacturing of this product line was placed on hold until the definition of the potential causes were initiated to evaluate and optimize the blending time for A/B 50/25mg Capsules to prevent over-lubrication of the blend to reduce variability in the dissolution performance for this product. As the result of define the problem the increased variability appears to be a result of the following:

- Change in Magnesium Stearate from animal to vegetable
- Segregation during discharge
- Post-blending material handling steps

Measure Phase

The evaluation of the A/B product process should be conducted by collect the necessary data, evaluate, analyze and catalog all blending and encapsulation process history and details. Once the processes data is gathered, it must be validate, before the execution of any change to ensure process and system compliance to make the effective change.

This development study was executed with an intermediate blend time of 30 minutes. This batch was encapsulated on a Bosch/DMW 2000. Eight samples were submitted for dissolution profile testing from this batch, including three additional samples (#50, #51 and #52) collected after the batch was technically finished. The developmental

study results are presented in the Figure 3 for product A and Figure 4 for product B.

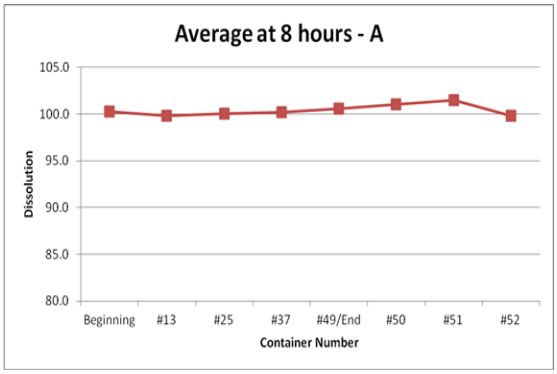

Figure 3
Dissolution Results Product A First Development Study

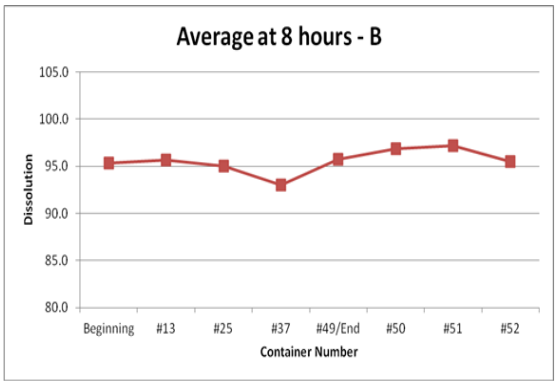

Figure 4
Dissolution Results Product B First Development Study

All samples had high average values, with low variabilities. All samples pass Stage 1 dissolution criteria for both active ingredients. A dissolution profile comparison was conducted evaluating the entire encapsulation run, with f2 results calculated for both active ingredients between the Beginning sample and the End (#49) sample, simulating the process validation test that will ultimately be performed. The f2 results were 98 for A and 97 for B, indicating that dissolution performance is comparable between the beginning and end of the lot [2].

The dissolution results were significantly better than expected, and therefore it was hypothesized that the raw material lots selected for this batch led to the reduced dissolution variability.

The results suggest that an earlier conclusion, that switching from animal-derived Magnesium Stearate to vegetable-derived Magnesium Stearate was not an impactful change, may need to be re-visited. The change in Magnesium Stearate was made in 2006. An Engineering Study was conducted, on commercial batch 163745 in August 2006. This batch had high dissolution results with low variability. The immediate conclusion had been that the switch in the raw material source did not have an impact on the finished product. However, the data summarized in this report shows that segregation could be occurring during discharge. Magnesium Stearate is the only extra-granular excipient added to the formulation and tends to be finer than the dried granulation. This manufacturing process utilizes 7.0% Magnesium Stearate, which is far greater than the typical 0.5% usage of this raw material. Some products have an increased level of Magnesium Stearate of 1.0%, 1.5% or even 2.0%, with virtually no formulations having greater than 2.0%. With such a high level of Magnesium Stearate in this formulation, the change in source may have more of an impact than originally thought.

In addition, n=10 capsule samples from start-up and run-out of encapsulation were submitted for as-is and weight corrected content uniformity testing [4]. The as-is results are presented in the tables 2 and 3:

Table 2
A/B Capsules Content Uniformity Results (Process Beginning) First Development Study

Start-Up As-Is	Mean	RSD	Bergum RSD Criteria (n=30)	Bergum RSD Criteria (n=90)
A	92.2	2.1	NMT 2.40	NMT 2.93
B	91.1	1.8	NMT 2.13	NMT 2.59

Table 3
A/B Capsules Content Uniformity Results (Process End) First Development Study

Run-Out As Is	Mean	RSD	Bergum RSD Criteria (n=30)	Bergum RSD Criteria (n=90)
A	101.5	1.5	NMT 3.76	NMT 4.57
B	100.8	1.7	NMT 3.96	NMT 4.81

A final development study was manufactured using the new Bosch 2500, which is an automated encapsulation machine, like the MG Planeta, but

within the same Scale-Up and Post Approval Changes (SUPAC) class and sub-class (dosing disk) as the current manufacturing process. Ten samples were submitted for dissolution profile testing from this batch, including one (Start-Up) collected before the initial Z-test was performed and one (Run-Out) collected after the batch was technically finished. Due to a QC Laboratory instrument error, only 2 capsules were reportable from the Start-Up sample. All samples were tested with the new Ultra High Performance Liquid Chromatography (UHPLC) method. Refer to Figure 5 for a graphical summary of the 8-hour dissolution results for product A and Figure 6 for product B.

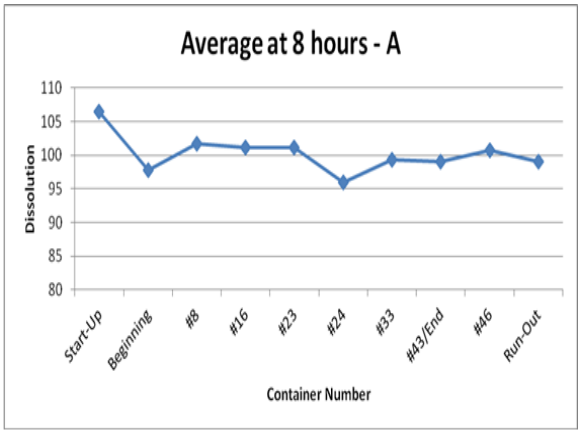

Figure 5
Dissolution Results Product A Second Development Study

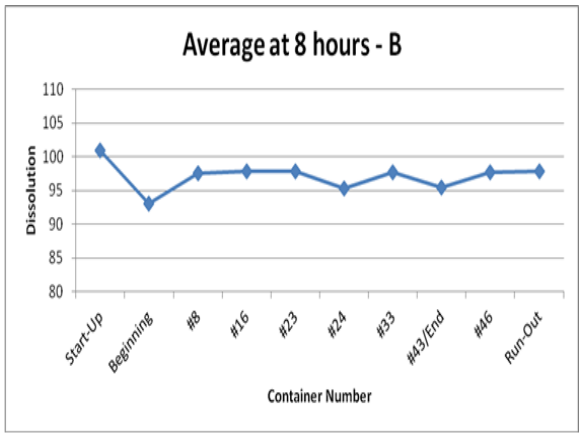

Figure 6
Dissolution Results Product B Second Development Study

All samples had high average values, with low variabilities. All samples pass Stage 1 dissolution criteria for both active ingredients. A dissolution profile comparison was conducted evaluating the entire encapsulation run, with f2 results calculated for both active ingredients between the Beginning sample and the #43/End sample, simulating the process validation test that will ultimately be performed. The f2 results were 84 for A and 82 for B, indicating that dissolution performance is comparable between the beginning and end of the lot. [2]

In addition, a 12-hour sample will ultimately be needed when performing an f2 analysis between a future validation lot and an earlier exhibit lot, thus one sample (#24) was tested out to 12 hours for additional informational purposes only, while all other samples were only tested out to the specification time of 8 hours. The 12-hour result was slightly higher than the 8-hour result, as expected.

In addition, n=10 capsule samples from start-up and run-out of encapsulation were submitted for as-is and weight corrected content uniformity testing [4]. The as-is results are presented in the Tables 4 and 5:

Table 4
A/B Capsules Content Uniformity Results (Process Beginning) Second Development Study

Start-Up As-Is	Mean	RSD	Bergum RSD Criteria (n=30)	Bergum RSD Criteria (n=90)
A	105.2	1.1	NMT 2.73	NMT 3.33
B	102.3	1.3	NMT 3.53	NMT 4.30

Table 5
A/B Capsules Content Uniformity Results (Process End) Second Development Study

Run-Out As Is	Mean	RSD	Bergum RSD Criteria (n=30)	Bergum RSD Criteria (n=90)
A	97.4	0.8	NMT 3.63	NMT 4.42
B	98.7	1.2	NMT 3.91	NMT 4.76

The as-is results were expectedly further from target weight, since weight had not yet been dialed in for the start-up samples and weight control may have been lost for the run-out samples.

Analyzed Phase

The experimentation conducted demonstrates that the increased dissolution variability is a result

of the change in Magnesium Stearate from animal-derived to vegetable-derived, which is possibly exacerbated by segregation or over-blending during discharge of the twinshell blender to the Intermediate Bulk Container and post-blending material handling steps.

The following changes are recommended to correct the impact of the above and to return the process to a higher level of capability:

- Change in blender from 1415-liter V-blender to 800-liter IBC.
- Corresponding reduction in batch size from 3 sections (3,416,000 capsules) to 1 section (1,138,684 capsules).
- Corresponding decrease in blend speed, from 14 RPM to 6 RPM.
- Corresponding increase in blend time, from 18 minutes to 30 minutes, with a proven acceptable range of 8 – 42 minutes.
- This represents a change in the SUPAC sub-class, from V-Blender to Bin Blender, while retaining the SUPAC class of Diffusion Mixer.
- Change in encapsulator from the non-automated "Bosch or DMW Rotary Filler" to the automated "Bosch 2500".
- Retaining the lower level of tamping (14.0 mm dosing disc).
- This represents no change in SUPAC class, Encapsulator, or SUPAC sub-class, Dosing Disk.
- Change in analytical method for dissolution from High Performance Liquid Chromatography "HPLC" to "HPLC or UHPLC".

The process flow diagram for the proposed manufacturing process is shown Figure 7, along with the in-process controls and in-process tests.

The improvement phase was performed under the execution of a Process Performance Qualification. This process performance qualification (PPQ) study was conducted as a requalification of the manufacturing process of A/B Capsules 50/25, Catalog Number 2715, Formula A, and Theoretical Yield 1,140,000 units. This study meets the validation master plan (VMP) commitment of a full PPQ study for the product.

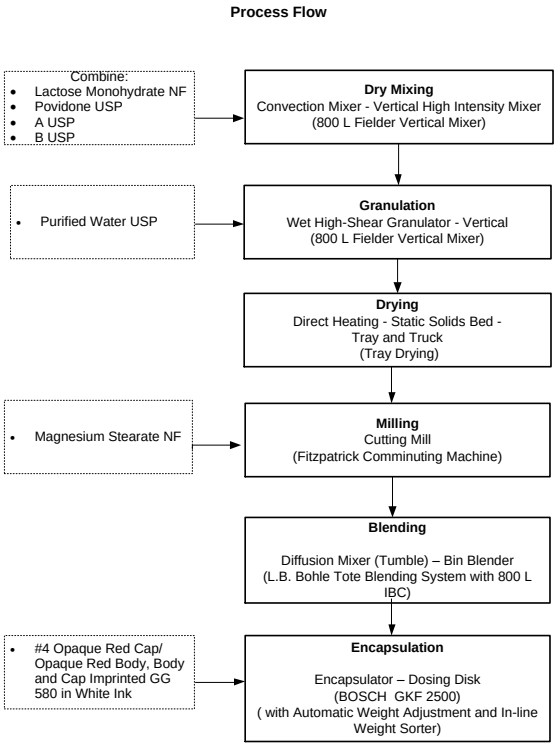

Figure 7
Proposed Manufacturing Process

Improvement Phase

The following changes were represented in the PPQ study:

- Batch size reduction from 3,416,000 units to 1,140,000 units.
- Blender change from the 1415 L Patterson Kelly to the 800 L Bohle Intermediate Bulk Container.
- Blending time change for final blend from 18 minutes to 30 minutes.
- Rotary Filler Machine changed from the Bosch or DMW Rotary Filler to the Bosch GKF 2500.

Five batches of AB Capsules 50/25 —CB1506, CB1507, CB1508, DR3301, and DR3302—were manufactured in this validation study. All sampling and testing plans were performed per protocol.

All lots met the variation acceptance criteria for content uniformity and dissolution as defined in the PPQ protocol. The manufacturing process of

AB Capsules 50/25 as described in this report is validated.

The dissolution results were represented in the following graphs [5]. Refer to Figure 8 for product A and Figure 9 for product B.

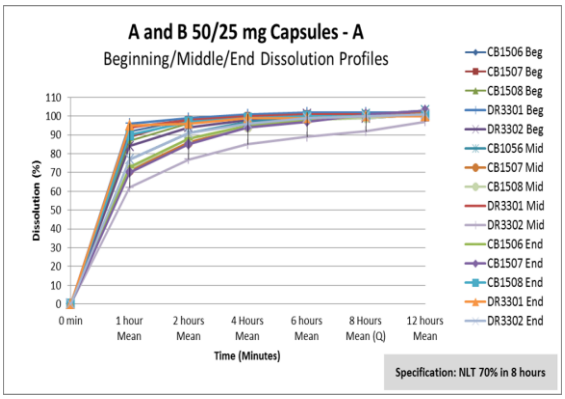

Figure 8
Dissolution Results Product A Validation Process

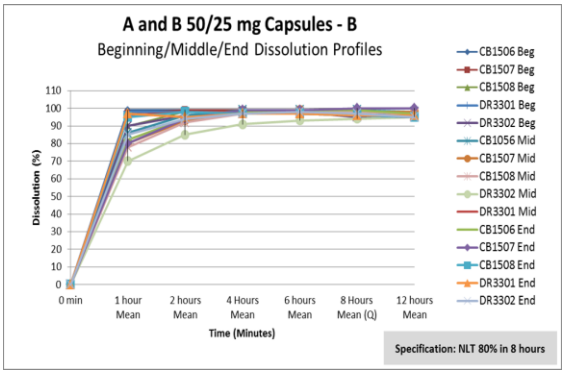

Figure 9
Dissolution Results Product B Validation Process

Control Phase

The purpose of DMAIC control phase is to provide a control plan to prevent the counter measures and solutions in place that can be controlled to prevent future problems and provide a sustainable financial benefit.

It is recommended that Stage 3—Continued Process Verification (CPV) be limited to the monitoring of:

- In-process controls (IPCs) for the manufacturing processes studied in the PPQ protocol;
- critical process parameters (CPPs) for the manufacturing processes;
- enhanced monitoring of dissolution (maintain PPQ level of testing), and
- trending of the critical quality attributes (CQAs) of content uniformity, dissolution, assay, and related compounds.

Those controls were made in order to maintain and ensures the standard work, key to continually improve a process.

CONCLUSIONS

From start to finish, DMAIC tool provides a structured way for business improvement with a road map for solutions. This technique allowed the identification, evaluation and categorization of opportunities under their impact and difficultly. After a deep analysis performed, for the A/B capsules 50/25 product, the product returns to the market in were has a market participation of 20%. It shows a reduction on the variability of the product; that result in a reduction in testing time and product approval. Also, increase the production of batches for the product; this is the first re-launch of a product for this manufacturing site since 2010. In addition, the implementation achieves the elimination of waste and standardized work, never compromises the quality and compliance.

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