Anti-inflammatory Drug Elution Rate Variability Reduction

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Abstract — *This project was focused in the Drug Elution Rate Variability of an Anti-inflammatory Drug used in a Medical Device Company. The project is based on the manufacturing and bonding process of a DXA Drug Collar that is a component of a lead manufacturing company. As part of the Lot Acceptance testing for drug collars, elution testing is performed. Results must comply both individual and mean values in order to be considered acceptable. A failure in a drug collar lot could result in a cost of scrapping or a field action. Therefore, there is a need to implement changes that reduce the variability of the elution testing.*

The methodology selected for this project is DMAIC. A process map will be developed to identify elements that could be providing variability in elution rate and provide recommendations for manufacturing process enhancement. An implementation plan will be create for proposed changes implementation.

Key Terms — *DMAIC (Define, Measure, Analyze, Implement, Control), DXA (Dexamethasone Acetate), FDA (Federal Drug Administration), Lot Acceptance Test.*

PROBLEM STATEMENT

Currently, the variability of elution testing of drug collar lots is too high and have provided failing lots that end up in engineering investigations, cost due to scrap, leads manufacturing line stop and compliance issues. There have been three failures during on the last year that resulted in the scrap of two drug collar lots. A failure in a drug collar lot could result in a cost of scrapping one lot of drug collars with a cost of $17,274 and more than $100,000 on leads that already had the drug collar bonded.

Research Description

These project will focus in determine the root cause and recommend actions to reduce the variability in elution rate. Failures in drug testing is been resulting in a cost for the company and in compliance risk. This project is being develop as a problem solving project within the BSC organization to decrease the variability of elution rate percent for one drug collar product which will result in minimizing the risk of failing lot acceptance or stability testing of dug collars therefore reducing the risk of scrap and compliance issues.

Research Objectives

The purpose of this project is to provide recommendation that will reduce the variability of elution rate of the Drug Collar Manufacturing and/or Bonding process. These will be achieved by evaluating each main process of the Drug Collar Manufacturing and Bonding to determine any step that is providing the highest variability in drug collars elution rate within the process and recommend actions to minimize this variability. The outcome of this project will be to reduce the variability of elution results while maintaining product quality and compliance as the main goal.

Research Contributions

Reducing the variability of the elution testing results for the Drug Collar will result in a cost avoidance due to scrap of drug collars or leads, time of engineering personnel in investigations and time of developing new products since the I improve process will have a reduced variability and

therefore there is no need for additional time of process improvements.

LITERATURE REVIEW

The Medical device industries have been producing what is called a Combination Product. By definition by the Federal Drug Administration (FDA), a combination product is comprised of two or more regulated components that are physically, chemically, or otherwise combined or mixed and produced as a single entity[1]. That is the case for Implantable Pacing Leads.

A Pacing lead (or pacemaker lead) are electrical conductors that transmit electric impulses from a pulse generator (pacemaker) to the hearth and vice versa[2]. The history of pacemakers starts on the late 1950's when Dr. Graeme Sloman clinically used external temporary pacemaker electrodes and the large external Zoll pulse generator[3]. Also, on 1959 Furman had experimented with a "home-made" transvenous lead consisting of a Cournand catheter containing a steel wire which was soldered distally to a piece of tin foil cathode electrode [3]. As part of the continued improvement of pacemakers and implantable leads, the use of a steroid have been introduced to the medical device. Is been proved that the use of implantable leads for pacemakers produce inflammation response at the electrode-tissue interface what can be treated with the steroid application. The Dexamethasone Acetate (DXA) has been used as a steroid-elution (anti-inflammatory) collar or plug[4].

As part of the lead manufacturing process, the drug is considered a component. The manufacturing process of the DXA Drug collar X consists of the following main steps: Formulation, Molding, Cut, Final Inspection, Lot Acceptance Tests/Release. As part of the Lot Acceptance testing, drug collars are bonded on leads or tips (which represents the part of the lead where the drug collar are assembles) since it should represents what the patient will be receiving. The bonded tips are tested for elution rate with a specification requirement for individual and mean values. Bonded tips must comply both individual and mean values in order to be considered acceptable. This testing is also performed to the stability lot that represents each year of drug collars manufacturing.

PROJECT METHODOLOGY

In order to achieve the goal of the Drug Elution Rate Variability Reduction Project the DMAIC Methodology will be used to complete the project objectives. DMAIC is a structured five-step problem-solving procedure that can be used to successfully complete projects by proceeding through and implementing solutions that are designed to solve root causes of quality and process problems, and to establish best practices to ensure that the solutions are permanent and can be replicated[5].

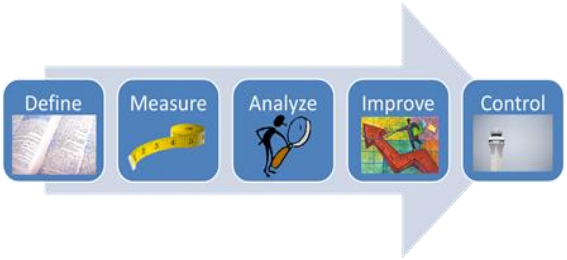

Figure 1
DMAIC Methodology

Five main phases are defined for the project (See Figure 1):

- Define
- Measure
- Analyze
- Implement
- Control

This research is focused on the Drug manufacturing and bonding process of one product at a Medical Device Company in Puerto Rico. The detail of the execution of each phase of the DMAIC methodology is described below:

- Define: A process Map will be developed for the Drug Manufacturing and Bonding Process. In order to start developing the process under investigation, all inputs to the process needs to be identified and then will be categorize in

using a Cause and Effect Diagram into the following categories: Mother Nature, Measurement, Machine, Material, and Method. Figure 2 includes an example of the Fishbone Diagram.

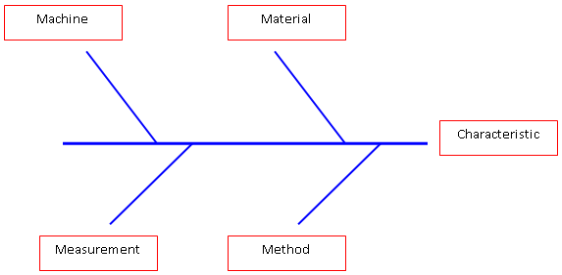

Figure 2
Cause and Effect Diagram

- Measure: During the Measure Phase, each step of the manufacturing and bonding process will be monitored, including different operators in order to get a general idea of the different constraints that could be presented. Having several monitoring processes will provide some areas for process standardization. In addition, historical data will be used to determine timeframe of several processes. This historical data will be gathered from the "Automatic traceability system" used to document each step of the manufacturing process. Data queries will be performed to gather data required to complete the measurement assessment.
- Analyze: During the Analyze Phase, the measures data will be verified and tested using different statistical tools as applicable based on the type of data collected. Each category in the Cause and Effect diagram will be analyze to discard or prove that it is related to the elution variability and failures been evaluated.
- Improve: As part of the Improve phase, any recommendation will be presented to for Management Review in order to establish priorities for implementation of process improvement opportunities. The intent is to reduce the variability of the elution testing values that will results in a cost avoidance due to scrap of drug collars or leads, time of engineering personnel in investigations and time of developing new products. A detail schedule will be developed for the area of opportunity identified and approved for implementation.
- Control: The Process control will be done by implementing clear instructions on the current manufacturing and bonding procedures and to assure that personnel qualification contains the necessary guidance and training. Also, the implementation could end up with a change in the manufacturing or bonding process that could require process validation and regulatory submission. In addition, initial verification and validation (V&V) of the changes implemented should include at least one month or at least three lots tested with the improvements implemented to monitor that changes performed have been conducted in accordance with the initial proposal. The control phase will not be part of this design project due to time constraints since changes to the drug manufacturing or bonding process will require regulatory submission.

RESULTS AND DISCUSSION

This section discusses all the activities performed and results gathered for each of the phases of the DMAIC Methodology used during the research project.

Define

A process Map was developed for the Drug Manufacturing and Bonding Process. The drug manufacturing consist in the following processes: Mixing (manual and mechanical), molding with the use of a press and a dedicated fixture, cut by the use of a fixture and bonding process which is done manually.

To start developing the process under investigation, Cause and Effect Diagram was done

based on the inputs identified that could affect the elution rate are the following:

- Product Builder Variability during mixing or during samples preparation (Bonding process)
- Drug Mixing and Molding equipment
- Drug cutting fixtures
- Drug storage conditions
- Environmental conditions during processing
- Manufacturing Instructions
- Sample preparation Instruction
- Mixing Components (DXA, LSR)
- Sample preparation components
- Elution rate calculation – Measurement

Figure 3 includes the Cause and Effect Diagram with the inputs defined categorize into: Mother Nature, Measurement, Machine, Material and Method.

Measure

Once the possible inputs to the variability of the drug collar elution rate were established, it was necessary to gather the data for analysis which of the input could be consider the most probable root cause for the out of specification elution results. During the Measure Phase, historical data was obtained in order to evaluate each input such as:

- Data for product builders involved in any of the manufacturing or bonding for the drug collars in order to compare results per product builder.
- Equipment evaluation was performed to confirm if they were within specifications during calibrations or if there was any out of tolerance investigation.
- Drug collars of several lots were measured to compare dimensions in order to determine any change in the fixtures related to molding process or cut process that could affect the elution rate.
- Environmental conditions for the timeframes where the lot involved in the investigation was manufactured and when samples were bonded was verified.
- History of changes in any materials or components used as part of the manufacturing or bonding process.
- Manufacturing instructions and bonding process were monitor to identify any area of opportunity related to the elution rate result.

All data gathered was analyzed based in the cause and effect to identify the possible root cause.

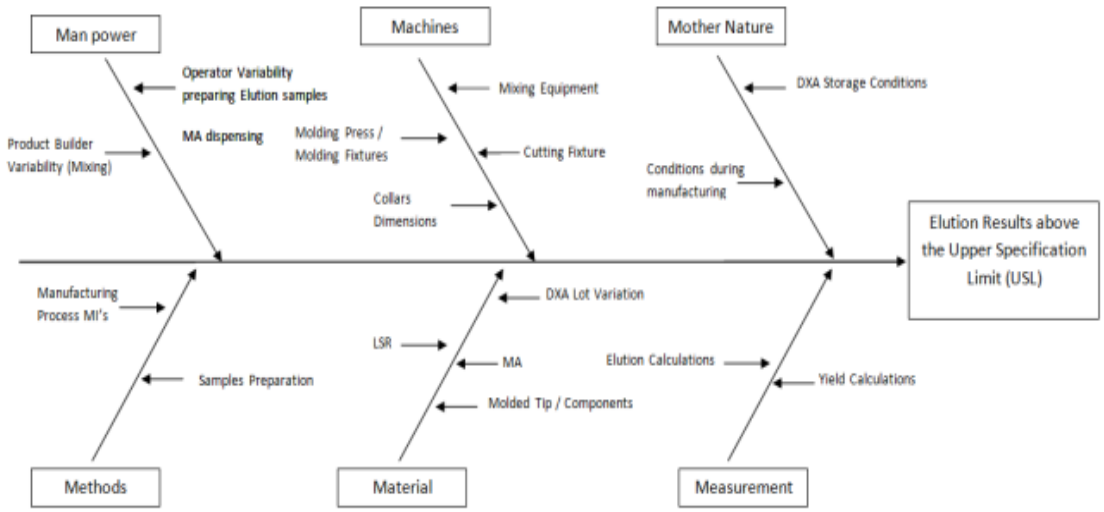

Figure 3
Cause and Effect Diagram

Analyze

During this phase, we evaluated any cause and effect category (Mother Nature, Measurement, Machine, Material and Method).

- Mother Nature: Manufacturing Processes are performed in controlled temperature, relative humidity and pressure environments as established in Company procedures. Also, DXA material is storage inside a Smart Desiccator. It was confirmed that the Drug collar lot that fail elution rate testing was mixed and molded within appropriate conditions. In addition, no changes were performed to room requirements during the timeframe of the failures. Therefore, Mother Nature was discarded as a possible root cause.
- Measurement: The only measurements performed in the manufacturing process are the Dexamethasone acetate (DXA) and Liquid Silicone Rubber (LSR) weight performed in the Mixing process and the Yield calculation thru the manufacturing process. Yield calculation does not affect elution result and therefore no evaluation is required. The DXA and LSR weight is documented in the traceability System what assures that the amount of DXA and LSR used is the correct one. Furthermore, if an incorrect amount of DXA or LSR is used for the drug collars manufacturing, it will be directly reflected in the Potency results and all results obtained for potency were within specification and within the normal lot variability. Therefore, Measurement was discarded as a possible root cause.
- Man Power: The manufacturing processes that could be impacting elution results due to man power variability are Mixing process and Samples preparation. Results obtained for Elution at 24hrs of the lots manufactured by each product builders that performed mixing process for lots used during specification development and lots from 2012 were compared to verify variability and any practical difference that could impact elution results. Four (4) experienced Product Builders have been involved in the mixing process for this product. No practical difference is observed that could be attributed to the shift in elution results. Figure 4 includes the product builder comparison.

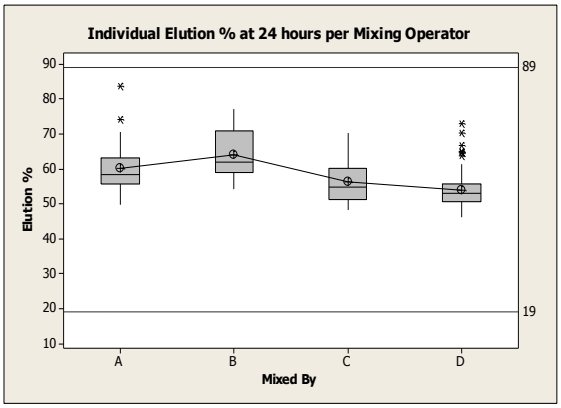

Figure 4
Product Builder Variability – Mixing

The bonding process of this product have been performed by several personnel since development process started. In order to see a difference between product builders that performed bonding process a Line Plot per product builder was done, refer to Figure 5. It can be observed that the same operators performed bonding processed on lots from 2010 and 2012 and there was a difference between their results for elution.

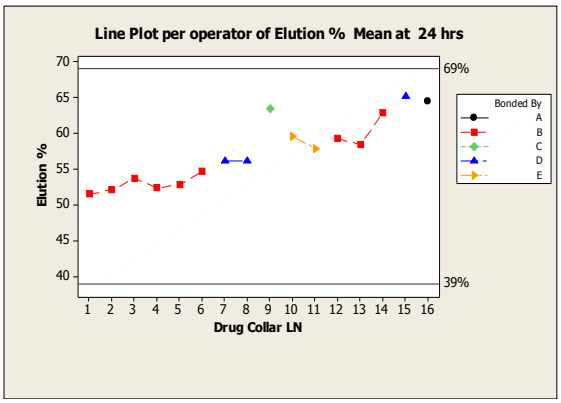

Figure 5
Product Builder Variability – Molding

In order to verify any trend, product builders that bonded more than one lot were evaluated. Figure 6 and 7, includes elution results for different product builders on different times/lots.

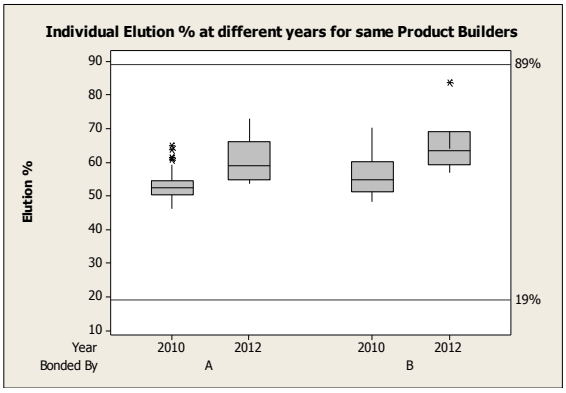

Figure 6
Product Builders Bonding Variability at different times (Individual)

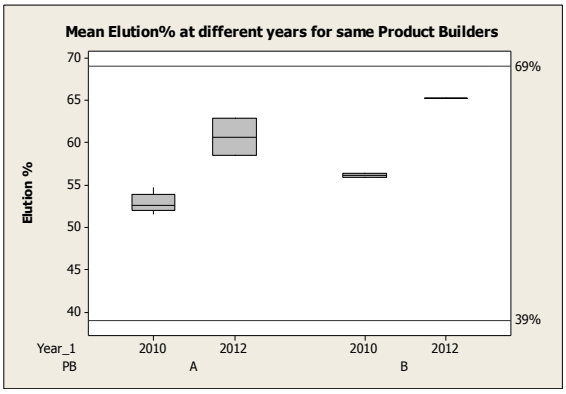

Figure 7
Product Builders Bonding Variability at different times (Mean)

It can be observed in this data that the same product builder produces different elution results at different times. Also, for both product builders there are higher elution results on 2012 versus 2010. Therefore, the product builders variability for bonding process is not considered significant.

Based on the results obtained for the mixing and bonding process product builders variability, Man Power is discarded as a possible root cause for the Elution shift and out of specification.

- Machine: Equipment related to the Drug Collars manufacturing process was evaluated to determine any non conforming event during the manufacturing timeframe of the lots that could affect elution value. All equipment have been used within calibration tolerances and there have been no investigations related to the failures.

The molding fixtures could impact the drug collar internal or external diameters. In order to determine any significant difference between molding fixture cavities, drug collar dimensions were measured and compared. A boxplot was done with the data of the measurements taken. Figure 8 and 9 includes the comparison of the internal diameter (ID) and outside diameter (OD) of drug collars manufactured on each molding cavity. No practical difference was observed.

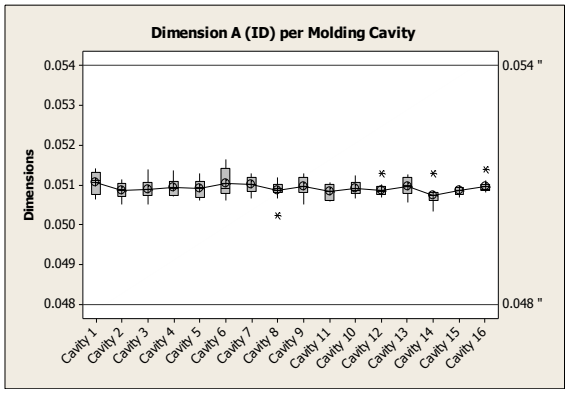

Figure 8
Boxplot of Drug Collar ID Dimensions per Molding Cavity

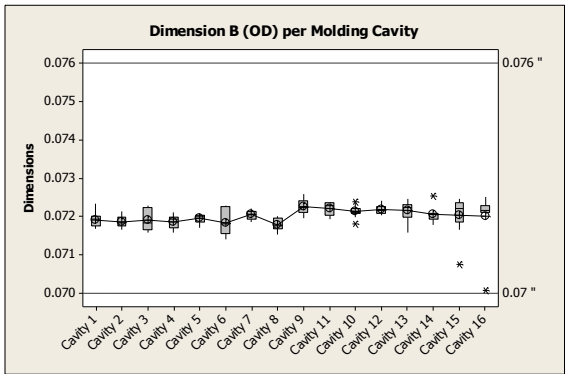

Figure 9
Boxplot of Drug Collar OD Dimensions per Molding Cavity

The drug manufacturing process requires the use of a Cutting fixture to provide the required length of the drug collars. The cutting fixture used blades and in order to cut the collars for the required dimensions, the fixture use blades that need to be aligned properly in order to obtain the required length. Any impact of the cutting process could be reflected in the drug collar dimensions and therefore proportional to the elution results. In order to determine if the cutting fixture could have an impact in the elution failure, drug collars of one lot were measured to ensure the thickness (length) was in compliance with the design requirement. The length obtained for the collars was confirmed to be within the design specifications.

Based on the results obtained for manufacturing equipment evaluation, Machine was discarded as a possible root cause.

- Material: The material used for the mixing process and bonding process was evaluated to confirm any change that could impact elution results. All drug collar lots for this product have used the same DXA raw material. In addition, there have been no changes to the MA or materials associated to the bonding process. There have been three lots of LSR involved on the manufacturing of this product during 2011 and 2013. In order to determine if the change in LSR lots impacted elution results, a comparison of elution % at 24 hrs per LSR lot was done, refer to Figure 10.

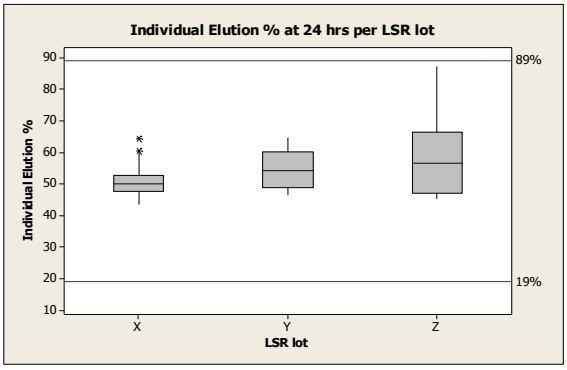

Figure 10
Boxplot of Individual elution per LSR Lot

This boxplot for does not have a practical difference in the mean. Based on the results obtained for the Material and components used during manufacturing or bonding process, Material was discarded as a possible root cause.

- Method: All manufacturing documents related to the Drug collar manufacturing and bonding process were reviewed to confirm there was not a change that could impact the elution rate. It was confirmed that no changes were made related to the process.

Drug Collars for the product been investigated is a drug collar part number with the same manufacturing process of a Legacy drug collar. The difference between the collars part numbers is the lot acceptance and stability testing requirements of each part number. Legacy drug collar part number includes dose testing as a lot acceptance while the new drug collar part number includes other testing required in order to comply with CDER requirements. The elution testing for the legacy drug collar is a process monitoring testing performed to demonstrate that the drug collar eluted. The new drug collar has a lot acceptance testing for Elution with the following time points (1hr, 24hrs and 72hrs). The specifications for Elution testing of the new drug collars were developed without making any change to the drug collar manufacturing process. All the data available for the lots manufactured during 2011 and 2012 was added to the development data in order to perform a complete evaluation of the behavior of the Elution results for the new drug collars, see Figure 11.

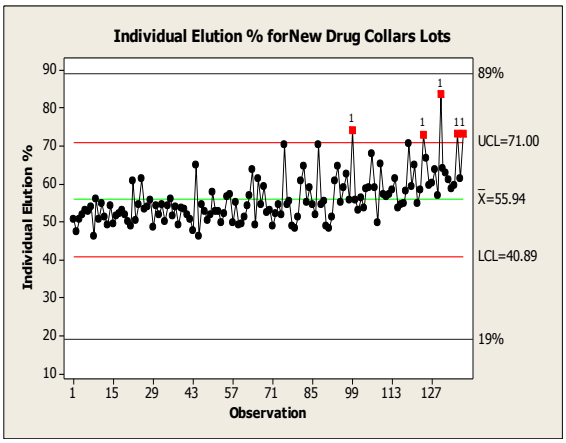

Figure 11
Individual Elution % For Fineline PU Configuration

Based on the data available, the elution results started being out of control around point 99 which corresponds to the first lot manufactured on 2011. Also, starting at that point, a shift to the upper side is observed. A verification of changes related to the shift was evaluated. There was a change during the same timeframe related to an evaluation performed to drug collars that were overlapping the tubing. In order to evaluate the change, related to the overlapping the PU tubing, it was observed that the drug collar bonding process of the leads manufacturing included a rework that allowed to cut the tubing in order to avoid overlapping. However, the sample preparation instructions did not contain the rework allowance at that time.

As a result of the evaluation performed, the rework step was added to the instructions of the samples preparation. Since there is not a standard cutting process established for the rework, there is a high possibility that the implementation of the rework (cutting the tubing) provides a higher gap between the drug collars and the tubing which could result in higher elution values.

- According the bonding process instructions, the drug collar bonding process allows a gap at any side of the drug collars. In order to characterize the elution results versus the variation of the collar position and gap area between drug collar and mannitol or tubing, a special test was done to compare elution values at different scenarios. Some of these scenarios included the requirement of filling the gap with a smooth transition of Medical adhesive (MA). A total of 6 group of testing were required as follows:
  - Group A - Collar assembly and bond flush to the mannitol bullet
  - Group B - Collar assembly and bond flush to tubing
  - Group C - Collar assembly and bond at center of collar groove
  - Group D – Collar assembly and bond flush to mannitol bullet with MA Transition
  - Group E - Collar assembly and bond flush to tubing with MA transition
  - Group F - Collar assembly and bond at center of collar groove with MA transition

Figure 12 includes the pictures of the three groups that did not had MA and Figure 13 include the pictures with the three groups with MA applied.

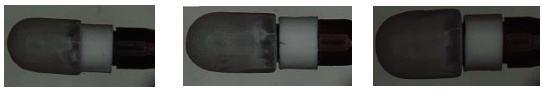

Figure 12
Groups A, B and C – No MA was applied

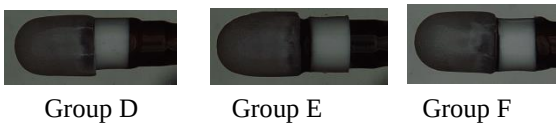

Figure 13
Groups D, E and F – MA was applied

Figures 14 and 15 contains the elution rates obtained for each group tested for individual and mean values. It can be observed in Figures 14 and 15 an obvious practical difference on elution between the samples without the MA transition (Groups A, B and C) and the samples that included the MA smooth

transition (Groups D, E and F). As expected, the groups that had an MA transition to fill the gaps between the drug collar and the mannitol or tubing had lower elution rate results than the data of the groups that did not require the MA transition. Proving a process to standardizing the gap between the drug collars and the mannitol or tubing could reduce the variability previously observed between operators.

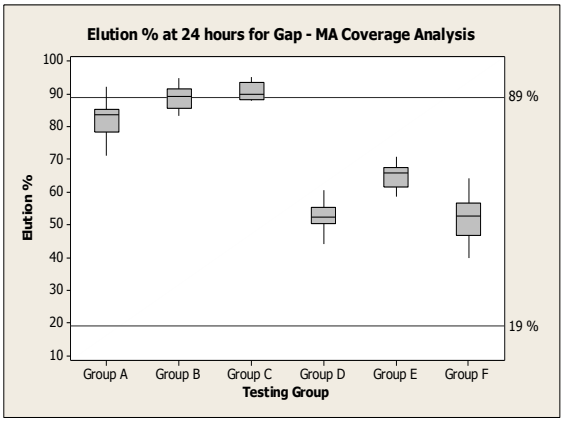

Figure 14
Boxplot of Individual Elution % at 24hrs for Gap – MA Coverage Evaluation

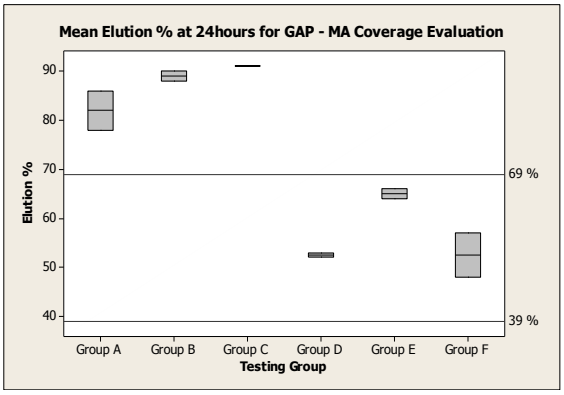

Figure 15
Boxplot of Mean Elution % at 24hrs for Gap – MA Coverage Evaluation

Based on the data presented for the bonding process evaluation, it can be concluded that the variability during the bonding process could be the most probable cause for the variability observed and the shift in elution results. Since there is not a standard way to place the drug collar, different product builders will perform the process by placing the drug collar without considering the impact in elution rate. Also, since the gaps between the drug collar and the mannitol or tubing is exposed, there will be a difference in elution rate caused by the different exposures during testing. Therefore, as an enhancement to the bonding process, a standardization of the location of the drug collar and a new process of filling the gap with MA is recommended to minimize variability of bonding process.

Improve

The improve phase includes an evaluation of the root cause determine and the recommendations for reducing the variability in elution results and therefore minimizing the possibility of failures. As documented in the Analyze phase, the most probable root cause is variability during the bonding process related to the drug collar placement and gap allowed between the drug collar and tubing or mannitol area. This variability of bonding process allows for different exposure areas of the drug collar during the elution testing. Therefore, it is recommended to standardize the location of the drug collar flush to the mannitol and fill the gap with medical adhesive since this group (Group D), provided the best elution results.

The implementation of this change is considered a process change and therefore will require the following:

- Process Characterization and specifications verification or adjustment.
- Bonding process validation
- Drug collar stability testing for at least 6 months.
- Submission to regulatory agencies.

The following timeline (Figure 16) is suggested for the propose change: The implementation of this change will ensure that variability between drug collar elution results is minimize therefore reduce the possibility of any failure that could jeopardize the patience trust and compliance with federal regulations.

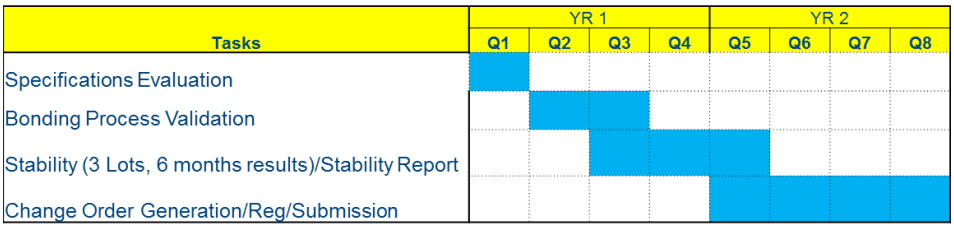

Figure 16
Timeline to Implement Bonding Process Standardization

Control

The control phase will include the certification of the product builders that will be performing the bonding process. The standardization of the process is critical to ensure that changes implemented are conducted in accordance with manufacturing instructions. Also, it is required to implement control monitor to elution testing results to ensure lot to lot variation and to be able to identify any change in the process.

CONCLUSION

This project used the DMAIC methodology as a problem solving technic to reduce the variability of elution results on drug collar lots of a medical device company.

The DMAIC (Define, Measure, Analyze, Improve, Control) methodology is an essential tool for ensuring that an adequate evaluation of an identified problem or opportunity is done. Each step is critical and needs to be done in order to identify inputs, outputs and determine the root cause for a problem.

Based on the assessment performed, it is concluded that implementing the change in the bonding process will standardize the way that the product builders are performing the bonding. As a result, the variability of elution results will decrease minimizing any possibility of failure.

The implementation of the propose change will ensure compliance with regulatory agencies and will reduce the possibility of scrap therefore avoid cost to the company.

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