Improving Steroid Out Of Specification (OOS) Trending on Pacemaker Lead

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Abstract *— The purpose of this project is to identify a roots cause and potential factors that influencing Steroid Out Of Specification Results (OOS) on pacemaker lead model XYZ. Project involves Define, Measure, Analyze, Improve and Control (DMAIC) problem solving methodology. The objective of the study is to decrease Failure Test Rate from 15% to 10%. The contribution will allow the optimization of the steroid application process, by control the potential factors that contribute the (OOS) results. This project might be used as benchmark to implement similar problem solving techniques around the manufacturing plant or as a model for other educational needs.*

Key Terms *— Combination Products, Out of Specification Trending, Pacemaker Lead, Steroid.*

PROBLEM STATEMENT

On pacemaker lead manufacturing plant, an investigation event was issued to address reported steroid results Out Of Specification Trending regards five-(5) lots of XYZ Lead Model. Accordingly, laboratory results were Out of Specifications (OOS) as per product specification.

Lead Model XYZ contains the steroid Beclomethasone Dipropionate (BDP) on the electrode tip. The function of BDP, per the technical manual, is to "suppress the inflammatory response beclomethasone dipropionate (BDP) that is believed to cause threshold rises typically associated with implanted pacing electrodes." BDP is applied by dipping the lead tip in steroid solution using Dipping Machines. Per specification, the target dose is between 22.5 µg to 37.5 µg.

Before leads may be released for United States (US)/Outside United States (OUS) distribution, they are tested to ensure that the steroid meets criteria described on products specification. Leads that fail the US criteria may be released for OUS use if they meet the criteria specified of OUS product.

Leads from five batches failed testing and did not met the requirements for specifications for US or OUS were disposed as scrap.

Research Description

XYZ lead model is experiencing Out of Specification (OOS) failures for Drug Content Uniformity (DCU), Assay and Elution testing. Several lots have been scrapped affecting the fill rate for United States (US) and Outside United States (OUS) markets. This corresponds to $365K of scrapped product and 15% of Failure Test Rate.

Research Objectives

The objective of the study is to decrease Failure Test Rate from 15% to 10%. This corresponds to a benefit of $105K yearly.

Research Contributions

The contribution will allow the optimization of the steroid application process, by control the potential factors that contribute the OOS results.

LITERATURE REVIEW

Before addressing the problem of having a variation in steroid application process I will explain the steroid application process and which are the different steroid analytical tests performed to pacemaker leads.

Pacemaker Leads

Leads are an important component of a pacemaker system. While commonly addressed simultaneously with electrodes, many lead design criteria differ from those of electrodes. Permanent pacemaker electrodes are designed to remain in a fixed position once implanted. The lead, however,

must be able to flex and possibly grow with the patient [1].

Leads are often threaded through vessels of the upper venous system into the heart to avoid open-heart procedures. They must therefore have diameters that do not occlude and be comprised of materials biocompatible with the cardiovascular system. Similar to electrodes, leads are usually intended to last the remainder of a patient's life [1]. See Figure 1 for Pacemaker illustration.

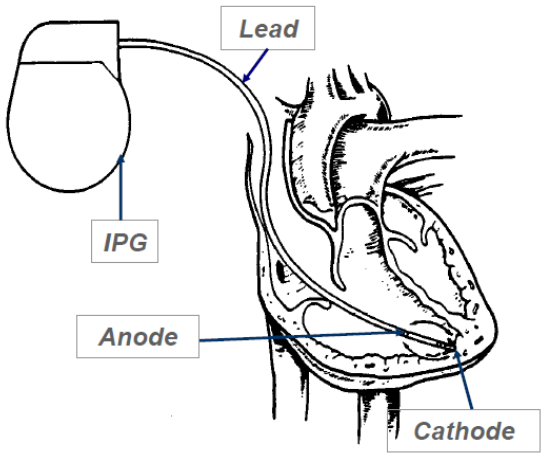

Figure 1
Pacemaker Illustration

XYZ lead model is characterized by a unique steroid application process. Lead is manually wash with alcohol and dry for 15 minutes minimum. The steroid Beclomethasone Dipropionate (BDP) solution is prepared the same day that the steroid is applied to the leads. Leads are processed on steroid dipping machine who controls the dunk depth of the lead in the steroid solution. The Steroid dipping machine for the XYZ lead model was developed to eliminate any risk associated with the manual dipping process performed by the operators. This machine is equipped with two (2) sensors: one sensor is able to detect the steroid level in the vial while the other one detects the lead electrode tip. This steroid dipping machine is only capable of dipping one (1) lead at the time. The parameters – rate of entry, lead tip dip time, rate of lead tip exit from the solution and the depth at which is dipped – are all PLC controlled and have been characterized to obtain the optimal settings. See Figure 2 for Dipping Machine Illustration.

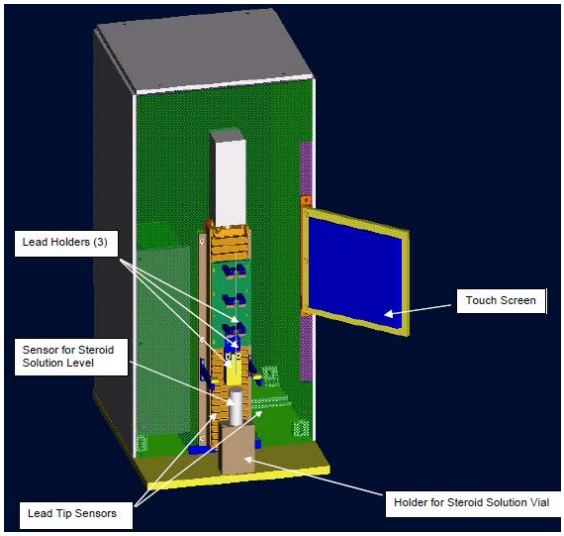

Figure 2
Dipping Machine illustration

After the leads are dipped, leads are dry in a clean bench for 15 minutes minimum. Leads are packaged in sterile pack then sterilized and final packaged with all product manuals.

Types of Steroid Analytical Tests

The critical steroid analytical tests performed to pacemaker leads are content Uniformity (CU), Assay and elution test.

Content Uniformity Test (CU) is a pharmaceutical analysis technique for the quality control of a specific drug product. [2] Multiple samples are selected at random and a suitable analytical method is applied to assay the individual content of the active ingredient in each sample.

Assay test is a pharmaceutical analysis technique to measure a property or the concentration of a component, one which needs to be measured with a high degree of accuracy and precision [2]. The component may be a major ingredient (~100%) as in an active pharmaceutical ingredient (API) or a minor ingredient (0.1%) as part of a drug product.

Elution test is a pharmaceutical analysis technique in which one material is extracted from another by washing with a solvent [2]. The amount of steroid eluted over time should be quantified.

METHODOLOGY

The Six Sigma DMAIC tool will be used to assess and perform the project. DMAIC is composed of five phases: Define, Measure, Analyze, Improve, and Control. Each phase will be discussed with specific tools.

ANALYSIS

Problem analysis was performed using DMAIC methodology. Define, Measure, Analyze, Improve and Control phases are described in the analysis.

Define

An investigation event was issued to address OOS Trending regards five-(5) lots of XYZ Lead Model. Accordingly, laboratory results were Out of Specifications (OOS) as per product specification.

Lead Model XYZ contains the steroid beclomethasone dipropionate (BDP) on the electrode tip. Per the XYZ product specification, the target dose is between 22.5 µg to 37.5 µg.

Before leads may be released for United States (US)/Outside United States (OUS) distribution, they are tested to ensure that the steroid meets criteria described the Specification of XYZ Lead Model. Leads that fail the US criteria may be released for OUS use if they meet the criteria specified of OUS product.

Leads from five batches failed testing either by not meeting the assay content, uniformity or the elution testing and did not met the requirements for specifications for US or OUS were disposed as scrap. Several lots have been scrapped affecting the fill rate for US and OUS markets ($365K scrap).

Measure

A multidisciplinary team was put together to evaluate the OOS trending event and to work with this project. The following have been the actions taken to collect data prior the root cause analysis:

- Review XYZ lead model Steroid Process and Reports
- Device History Record Review of affected lots
- Trending of Testing Results of Content Uniformity, Elution and Assay.
- Dipping Machines Evaluation of PM's and Calibration History
- Evaluation of Laboratory Method Validation
- Evaluate Events / CAPAs related to the issue described.

Measure Results

Review XYZ Lead Model Steroid Process and Reports:

- Validations documents were reviewed and no observations were found during the review process.

Device History Record Review of affected lots:

- A review of all batch record reports including Forms #ABC “XYZ model Production and Control Record” of the affected lots was performed. Evaluation performed concluded that all manufacturing processes were followed as specified and no deviations were found.

Trending of Testing Results of Content Uniformity, Elution and Assay:

- Trending was evaluated, a total of 17 lots results were received. Three lots have failed Elution test and identified as a Grade 2 (OUS product). Two lots have fail assay and content uniformity and one lot only content uniformity and all of them identified as Grade 3 (Scrap product). The remaining eleven lots have pass all testing and identified as Grade 1 (US product).

Denotable Highlights from the investigation were:

- Data is running on upper side of specification.
- Within Lot Variation (outliers fail)
- Lots that failed DCU, failed either Assay.
- Lots that failed elution, did not fail DCU or Assay
- Failures not related to change in BDP lot
- Lots failed due to outliers (high stdev).

Dipping Machines Evaluation of PM's and Calibration History:

- Evaluation of dipping machines was performed, all preventive maintenances and calibrations were performed on time and found to meet all required.

Evaluation of Laboratory Method Validation:

- Laboratory test methods were evaluated and they were found adequate.

Evaluate Events / CAPAs related to the issue described in this investigation event:

- Related events were identified and evaluated, it was identified a trend of dipping length dunk depth parameter out of tolerance as a roots cause for steroid OOS results.

Analyze

The trigger of the project was to avoid the steroid OOS results for XYZ lead model. As part of analyze phase it was determined to perform a cause and effect diagram to determine the factors to be study [3]. Refer to Figure 3 for Cause and Effect Diagram.

Material

BDP and Alcohol solvent components impacts directly lead steroid testing results. Lots history were verified for both components, no issues were reported.

Measurement

BDP weight and Alcohol volume measurements for steroid mix impacts directly lead steroid testing results. BDP and Alcohol components measurements were verified and no issues were reported.

Machine

Dipping machine set up evaluation was performed. No discrepancies were found during set-up and in-process execution. However, it is considered as a factor to be evaluated as part of the DOE execution in order to understand dipping length impact.

Dipping Machine Calibration and PM evaluation of dipping machines was performed to determine any equipment malfunction or a failure pattern. All preventive maintenances and calibrations were performed on time and found to meet all required.

Environment

Controlled Environment Area conditions were verified for discrepancies in regards of temperature and relative humidity room's requirements, no events were reported during the process.

Clean Bench CFM control was verified and Benches were calibrated as required. However, it is

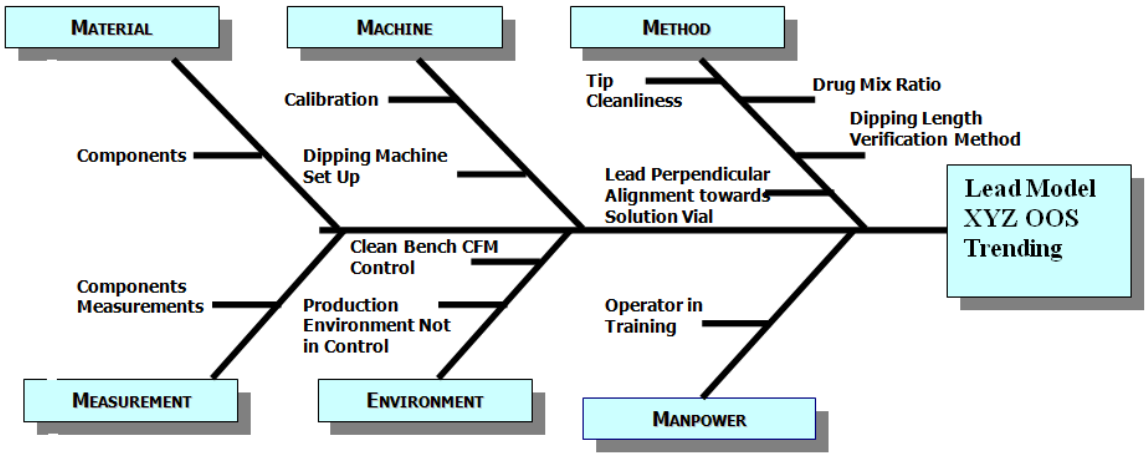

Figure 3

Cause and Effect Diagram (Fish Bone Diagram)

considered as a factor to be controlled as part of the DOE execution in order to minimize air flow variability that could impact the air dry process.

Manpower

Operator in Training criteria was verified. Steroid Batches Lot history was verified for operators track in / tracks out transaction. According to the results 2 certified employees and one trainee were working on Steroid Batch affected. However all steps were properly verified and are in accordance to specifications.

Method

Dipping Length Requirement Verification Methods were verified. Dipping dunk depth parameter setting in the dipping machine is verified during the set up and during process execution. This factor is considered part of contributor factor of variability of the process for this investigation.

Lead Perpendicular Alignment Towards Solution Vial factor was studied. XYZ lead model has a curvature in its distal area, which is required to be straighten with a tooling stylet prior steroid solution dipping. If the leads are not straight, it is possible that an incorrect amount of steroid will be adhered into them. Tooling stylets for lead dipping are changed when an obvious bent is seen. Stylets with This factor can affect the amount of steroid in the lead it will be considered as a contributor factor of variability of the process.

Steroid Mix Ratio factor was evaluated. BDP solution is prepared and transfer into vials. Process provides a steroid solution tolerance, solution concentration can vary from 14.58 mg/mL to 15.43 mg/mL. This factor is considered as a contributor factor of variability of the process.

Tip cleanliness factor was verified. Manufacturing Procedure states to clean entire lead assembly including tip area with IPA and clean room towel. During investigation phase it was emphasize lead cleaning method in order standardize it. It was observed a lower variability in the laboratory results since lead cleaning method standardization. This item will be considered as a contributor factor.

Design of Experiments and Confirmation Run

A Design of Experiment (DOE) was designed and executed to further understand key variables related to drug elution and content uniformity. From the previous analysis, it was concluded that the following variables need further investigation.

- Dipping machine
- Solution Concentration

A 2^2 matrix was created for the DOE as follows on Figure 4:

	Machine 1	Machine 2
Solution concentration 1 (LOW)	Run 3 / Run 4	Run 7 / Run 8
Solution concentration 2 (HIGH)	Run 1 / Run 2	Run 5 / Run 6

Figure 4
DOE Matrix

As part of the DOE design it was determined to fix some variables and perform some tasks in order to execute DOE. The actions that were performed prior to DOE execute on were:

- Clean bench re-layout was fixed to facilitate the handling of the leads.
- A work order was generated to calibrate the clean benches between 70-75 CFM (lower specification allowable) to fix the environment.
- New stylets were provided to manufacturing area to avoid the use of bent stylets.

An special build was performed to prepare two (2) BDP solutions to execute the DOE. One solution was prepared at High Concentration of BDP (3010 mg of BDP and 195 ml of IPA 100%) and the other solution was prepared at Low concentration of BDP (2990 mg of BDP and 205 ml of IPA 100%). Those solutions were used in two (2) available dipping machines. Two (2) duplications of 16 leads were performed per each

machine. A total of 8 lots were performed. Dipping lengths for each lead were measured using a microscope and caliper. Data was documented for future evaluation with the results of lab testing. As part of the DOE some variables were fixed to reduce noise during execution. The variables that were fixed during DOE execution were:

- One operator was fixed for Dipping process
- One operator was fixed to perform dipping dunk length measurements
- Same BDP lot was used during DOE execution
- Tip Cleaning standardization and lead positioning

DOE's leads were sterilized with one cycle of sterilization. Leads were sent to laboratory to perform testing for Drug content and Elution.

As part of DOE design it was determined to fix some variables during lab execution process:

- One Lab analyst processing all the testing runs
- Same equipment use for all the testing runs
- Same drug standard use for all testing runs
- Drug standard preparation by same operator for all testing runs

Results for DOE designed were analyzed in order to identify possible OOS trending roots causes. Several observations were identified for Drug Content Uniformity, Dipping Lead Length and Elution factors.

Drug Content Uniformity Analysis

Drug Content Uniformity was evaluated as part of the DOE analysis. A Main Effects Plot, Interaction Plot and Pareto Chart were created taking in consideration the solution concentration and machine factors. From the analysis several observations were identified.

- Higher Average DCU values were observed at Low concentration solution. (Figure 3)
- Higher Average DCU values were observed in Dipping Machine (MPR08040).
- Solution Concentration and machine were determined as contributor factors for DCU performance. However, Solution Concentration is a predominant factor compare to machine factor.

Dipping Lead Length Analysis

Dipping Lead Length was evaluated as part of the DOE analysis. As part of the evaluation several plots were created in order to understand the solution concentration and machine factors against Dipping Lead Length results. A Main Effects Plot and Pareto Chart were created taking in consideration the solution concentration and machine factors.

From the analysis several observations were identified.

- Higher Average Dipping Lead Length was observed at High concentration solution.
- Higher Average Dipping Lead Length was observed in Dipping Machine (MPR08040). This observation could explain the higher DCU value against machine factor.
- Machine and Solution Concentration / Machine interaction were determined as contributor factors for Dipping Lead Length performance. However, Machine is a predominant factor compare to Solution Concentration / Machine interaction machine factor.

Elution Analysis

Elution was evaluated as part of the DOE analysis. As part of the evaluation several plots were created in order to understand the solution concentration and machine factors against Elution results.

A Main Effects Plots for 1 hr and 48 hrs time of Elution and Average Elution plot between DOE runs were created taking in consideration the solution concentration and machine factors. From the analysis several observations were identified.

- Higher Elution rate was observed using Low Concentration Solution.
- Machine factor is not a considerable factor for elution rate performance.
- High concentration solution showed a lower elution rate performance.

- High concentration solutions failed Stage 1 at 24 and 48 hours periods. (Figure 14)
- Low concentration solutions passed Elution Stage 1 criteria. (Figure 14)

The standard deviation prior to the DOE was calculated. Prior to the DOE (including failures), the standard deviation was higher (4.65%) than after the DOE was executed emphasizing in blocking factors (1.46%).

DOE Conclusions

As part of DOE analysis it can be concluded:

- Blocked factors as (Clean Bench CFM Control, Lead Tip cleaning and lead positioning standardization, Visual inspection of dipping lead length to all leads and New stylets usage for dipping process) reduced DCU standard deviation from 4.65% to 1.46%.
- Solution Concentration and machine were determined as contributor factors for DCU performance. However, Solution Concentration is a predominant factor compare to machine factor
- Higher Average Dipping Lead Length was observed in Dipping Machine (MPR08040). This observation could explain the higher DCU value against machine factor.
- Machine is not a considerable factor for elution rate performance.
- Higher Elution rate was observed using Low Concentration Solution. This was an unexpected result since it was expected for high concentrations to have higher elution rates
- High Solution concentration yielded low DCU which is also opposite to expected results.

Since high concentration solution yielded results opposite to what it is expected, a confirmation run was performed to understand this variable further.

Confirmation Run

Confirmation run was designed taking into considerations the main contributing factors from DOE results. The main purpose of the confirmation is to understand solution concentration and to confirm an optimization scenario to achieve results closer to its target specification for DCU, Elution and Assay. Same DOE blocking factors were used which were: Clean Bench CFM Control, Lead Tip cleaning and lead positioning standardization, Visual inspection of dipping lead length to all leads and new stylets usage for dipping process.

The confirmation run for the DOE execution with the following configuration (Table 1):

Table 1
Confirmation Run Design

Configuration	Analytical Testing	Machine
High Concentration (3010 mg BDP, 195mL IPA) = 15.44 mg/Ml	DCU, Assay	MPR 08294
Low Concentration (2990 mg BDP, 205mL IPA = 14.6 mg/mL)	DCU, Assay	MPR 08294
Optimum DOE Scenario (2995 mg BDP, 202mL IPA = 14.82 mg/mL)	DCU, Assay, Elution	MPR 08294

The Optimum DOE scenario was chosen considering in order to optimize DCU at 100% based on product specification. Machine 08294 was chosen since DOE yielded DCU results closer to target (100%). DOE values at Low concentrations yielded results that may pass elution specification at all-time stages. Therefore, the optimum run was chosen with a concentration values closer to the low side to aim for acceptable elution results.

Drug Content Uniformity Analysis

The Drug Content Uniformity was calculated for High, Low and Optimum concentration runs. The average of the results was 104.5, 101.2 and 103.5 % respectively. The standard deviation was 1.9, 1.0 and 1.0% as well. The difference from low and high is 3.3%. Compared to the specification for all stages (75-125%), the values are close to target value of 100%.

The DOE and Confirmation Run results were analyzed on table below for results on machine MPR 08294 as summarized on table below (Table 2):

Table 2
DOE and Confirmation Run Results Comparison

Concentration	DOE DCU Ave / stdev	Conf. Run DCU Ave / Stdev
High	87.2% / 1.52%	104.5 / 1.9%
Low	104.8% / 2.27%	101.2 / 1.0%

Low concentration average and standard deviation values for DOE and confirmation runs had a difference of 3.6% and 1.27% respectively. The difference is relatively small considering the acceptable process specifications. The difference for high concentration average is 17.3%. Due to this difference several factors were evaluated. The root cause for the difference on high concentration results between the DOE and confirmation run cannot be determined. Initial DOE results suggested that for high concentration solution, DCU and Elution were lower than the Low concentration solution results. These results were not as expected. Nevertheless, confirmation run showed that for high concentration solution, DCU and Elution results were higher than low concentration solution. These results are more aligned with expected behavior of the process. Historical data did not run at high concentrations. However manufacturing lots have been running with low concentration parameters. Therefore the DOE (low concentration) and confirmation results are running at DCU values similar to the latest production historical data (Figure 5):

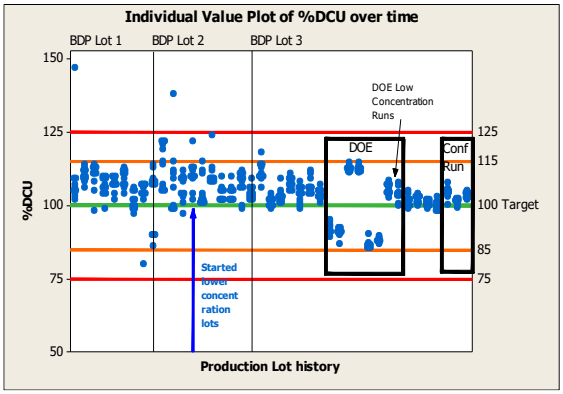

Figure 5
Production Historical Data Graph

Graph displays all XYZ model production, DOE and Confirmation run DCU results. DCU targets and specs were added as a reference. Vertical lines in black represent a change in BDP drug lot. A blue vertical line was added that indicates the date in which production lots started running with a lower (within specifications) concentration. DOE and Confirmation runs lots are delimited with a black box. The runs in the DOE that ran at lower concentration (similar to Confirmation run) are running at similar production lots values which also ran at low concentration solutions. A change in BDP lot did not represented a change or improvement in the data. The change in low solution concentration cannot clearly determine the elimination of outliers on data, however, no DCU, Assay or Elution failures have been reported either and a variability reduction can be observed. A standard deviation for DCU plot was developed to understand changes in time and improvements in production data. Graph below depicts an improvement in standard deviation once solution concentration is reduced and DOE blocking factors were emphasized (Figure 6).

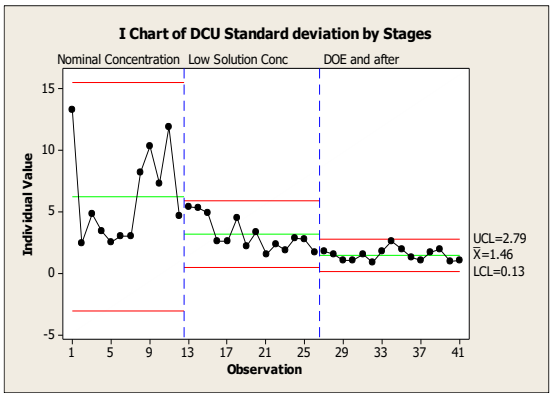

Figure 6
Standard Deviation for DCU

Drug Elution Analysis

Elution test was performed on Optimization Run. No outliers were found on results and all points were within specification. A comparison was performed to the DOE Results (below) and the confirmation run is running similar to the low concentration values on DOE (red upper line below). It is expected since optimum scenario solution concentration is running on the lower concentration side. DOE and Confirmation Results were compared to production historical data. DOE and confirmation results experienced a smaller gap when compared with the rest of the production lots. Items related to lead surface cleaning and drying conditions were controlled since they could contribute to the adhesion of the drug to the lead. Confirmation runs and DOE emphasized on the final wash of the leads, use of new stylets tools and low Clean Bench CFM settings.

Assay Analysis

Assay was only measured on confirmation run. Initial DOE focused only on DCU and Elution to minimize sample quantity and testing timing. It was determined that factors influencing DCU may relate to Assay behavior. The Assay values for the Confirmation Run were:

- High concentration = 102.7 %
- Low Concentration = 100.3 %
- Optimum Concentration = 101.7%

The values for the three runs were very close. Confirmation runs are running similar to the production lots at similar dates. Data is currently running at target (100%). (Figure 7)

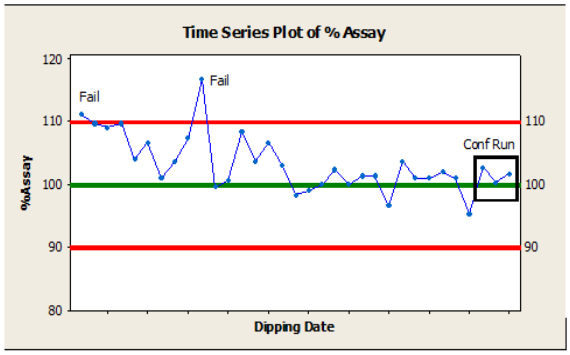

Figure 7
Standard Deviation for DCU

Dipping Dunk Depth Analysis

The Dipping Dunk Depth that was measured on both DOE and confirmation run was the BDP trace left on the lead. The length was measured with a caliper. According to process, the allowable trace length ranges from 0.475 to 0.525 inches. The dipping length on Machine 08294 was similar on both DOE and Confirmation Run.

DOE and Confirmation Run Conclusions

- High Concentration values yielding low DCU and Elution on initial DOE were not confirmed.
- Even that it cannot be fully explain the atypical result for the initial DOE high concentration setting, it has been shown through historical data and the Confirmation runs, that controlling multiple factors impacting the application process reduced the within lot variability.
- Technical Root Cause: Failures on Grade 1 results are due to outliers at either testing requirements (DCU, Assay and Elution).
- Process Root Cause: Not standard execution of multiple factors influencing the drug application process induces the generation of outliers. These factors are the final wash of the leads, the use of new stylets tools and low Clean Bench CFM settings. Additional contributing factors are Solution Concentration

ratio and Dipping Dunk Depth that induce shifting of the results.

Improve

As part of the Improve Phase an action plan was performed in order to improve the steroid dipping process. The following actions were performed:

- Manufacturing Procedures were revised in order to standardize process execution and for pictorial conversion.
- Implement and train MTM's in the use of the new reticule to inspect the leads after dipping process.
- Create a PM schedule for clean benches CFM verification and adjustment.

Control

As part of the control phase a plan was performed to determine the improve phase effectiveness.

Effectiveness Criteria

Since there is not a specific roots cause for the investigation event, outliers from laboratory testing could appear during the testing. Effectiveness check was specific to assure that:

- Yield Analysis: 90% of lot releases are released as grade 1 product.*
- Trending Analysis: No more than two consecutives lots are released as grade 2 or grade 3 products.

Effectiveness Assessment

Effectiveness assessment was performed to XYZ lead model releases after improve phase was completed. Effectiveness verification was performed to 14 released lots. A total of 13 lots were released as Grade 1 product and 1 lot was released as Grade 2 product. Data was collected from the jobs Device History Record. A calculated yield result is 93% (13 out of 14) which comply with acceptance criteria for effectiveness check of 90% or higher. No consecutive lots were released as grade 2 product on effectiveness sample taken. Therefore effectiveness results for yield and trending analysis complies with effectiveness plan criteria.

CONCLUSION

During the execution of DMAIC methodology for Steroid OOS Trending on XYZ lead model it can be concluded the following asseverations:

- Solution Concentration and machine were determined as contributor factors for DCU performance. However, Solution Concentration is a predominant factor compare to machine factor
- High Concentration values yielding low DCU and Elution on initial DOE were not confirmed.
- It has been shown through historical data and the Confirmation runs, that controlling multiple factors impacting the application process reduced the within lot variability.
- Technical Root Cause: Failures on Grade 1 results are due to outliers at either testing requirements (DCU, Assay and Elution).
- Process Root Cause: Not standard execution of multiple factors influencing the drug application process induces the generation of outliers. These factors are the final wash of the leads, the use of new stylets tools and low Clean Bench CFM settings. Additional contributing factors are Solution Concentration ratio and Dipping Dunk Depth that induce shifting of the results.

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