Improvement of the Statistical Techniques Quality System Element in a Medical Device Industry

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Abstract *— This project is focused on reducing the compliance risk of a Medical Device Manufacturer by improving its Statistical Techniques Quality System Element. Lean Sigma Methodology was used to identify the inputs or major contributors to the compliance risk. The Methodology section explains further how the tools were used. By reducing the compliance risk, the organization expects to achieve zero observations related to Statistical Techniques on regulatory inspections performed by the Food and Drug Administration (FDA).*

Key Terms *— Compliance Risk, DMAIC, FDA, Statistical Techniques.*

INTRODUCTION

In the last decade, thousands of patients have been impacted by product recalls from different Medical Device Manufacturers. Those recalls have been either a voluntary decision of the manufacturer or a compulsory mandate from the FDA. Recalls are mostly driven by a potential safety hazard that the product poses on human life or by serious compliance deviations. In the most extreme cases, some products have cost patient deaths which concern everyone including FDA, Government, Manufactures, Patients and the whole population.

FDA regulates the Medical Device Manufacturers that sell product in the United States (U.S.) Territories according to the Code of Federal Regulation (CFR), specifically, 21 CFR Part 820. Periodical inspections or unplanned visits are conducted by FDA to ensure that manufacturers are in a state of compliance. Compliance discrepancies or observations are documented on a 483 form. This form is used to notify the company of objectionable conditions and is presented and discussed by FDA inspectors with the company's senior management with the goal of seeing changes made quickly. The company is encouraged to respond in writing with their corrective action plan and then implement that corrective action plan expeditiously.

If 483 observations are not adequately and timely corrected, the FDA could issue the manufacturer a warning letter. This letter is a correspondence that notifies the manufacturer about violations that FDA has documented during its inspections. Typically, a warning letter notifies a responsible individual or firm that the Agency considers one or more products, practices, processes, or other activities to be in violation of the Federal Food, Drug, and Cosmetic Act (the Act), its implementing regulations and other federal statutes. Warning Letters should only be issued for violations of regulatory significance, i.e., those that may actually lead to an enforcement action if the documented violations are not promptly and adequately corrected.

The increase on product recalls and safety hazards have caused FDA to be been under a lot of scrutiny and stress. As a consequence, the agency has increased their workforce in order to increase frequency of inspections and to assess compliance of more manufacturers. At the same time, the inspectors have raised the bar in terms of the rigor, thoroughness and questioning used during their audits. The end goal of this increase in scrutiny by the FDA is to ensure patients safety, which should be a common interest of any Medical Device Manufacturer desiring to survive in the industry.

A Medical Device Manufacturer based in Puerto Rico (P.R.) has had an excellent execution on FDA Inspections for more than 10 consecutive years. No 483 observations or warning letters had been issued to this manufacturer. Unfortunately, the trend came to an end on the last FDA inspections performed on 2010. FDA performed simultaneous inspections in all Manufacturer Sites based in P.R. as well as on the Headquarters based in U.S. The results of the inspections were not inspiring; the agency issued 483 Observations to all P.R. Sites as well as to the U.S. Headquarters. Management of the manufacturer timely answered all observations and sent them for FDA evaluation. The agency was not satisfied with some of the answers and therefore issued a warning letter. This warning letter did not allow approval for market release of any new product from the manufacturer. Definitely the manufacturer's revenue and market share were significantly impacted.

This latest fact caused management to conduct a deeper research to identify the causes of the undesired and unacceptable performance. The identified cause was that the organization had fell in what is typically called a "comfort zone". The confidence caused by not having any audit observation during the previous years placed an unconscious hold on the continuous improvement efforts and therefore, the quality systems of the company had not been reviewed.

Management conducted a Pareto of all audit findings or observations per Quality System Element. Some of the elements identified as major offenders were: CAPA, Process Validation, Handling of Non-Conforming Product and Statistical Techniques. The company decided then, that a major re-design of the Quality System was needed and that the identified Quality System elements would be prioritized. Individual improvement projects were conducted for each Quality System Element and the methodology used for the re-design was DMAIC. The project team were multi site and multi functional. Additionally, expert consultants from the industry were made available for the teams benefit. This project's charter is particularly chartered on improving the Statistical Techniques Quality System Element across the manufacturer sites based in P.R.

PROBLEM STATEMENT

After extensive review of the audit observations issued to the Medical Device Manufacturer the problems or failure modes related to Statistical Techniques are described as a combination of the following:

- Complex and not harmonized Statistical Techniques Process across the sites.
- Non-standard practices for process monitoring and sampling across the sites.
- Lack of procedure for establishing and/or revising process monitoring and sampling of manufacturing processes.

LITERATURE REVIEW

This project was executed using tools from the DMAIC methodology (DMAIC stands for Define, Measure, Analyze, Improve and Control). DMAIC is typically applied to reduce defects and variation on manufacturing processes. For the purpose of this project, specific tools were chosen from the DMAIC Toolset to fit with the primary goal of this project which is to improve the Statistical Techniques Quality System Element. These tools helped to identify the problem statement, determine the key contributors and to identify and implement the improvements that would help to reduce compliance risk. [1]

Each DMAIC phase has a list of questions and deliverables that help answer those questions robustly. Tools are then applied to achieve those deliverables, and selected based upon how much rigor is required to solve the problem at hand. Simple problems require fewer rigors.

A description of each of the phases follows:

- Define – The purpose of this phase is to define problem statement and project scope. The output of the phase is:

- A clear statement of the goal or intended improvement (the business case and team charter).

- Measure – The goal of this phase is to measure with actual data the magnitude of the problem. The output of the phase is:
  - Baseline data on current process performance
  - Data that pinpoints problem location or occurrence
  - A more focused problem statement.
  - Potential process factor or inputs for improvement.

  These outputs are needed for the next phase.
- Analyze – The goal of this phase is to identify a root cause (s) and confirm them with data. Lean Six Sigma tools will be used to filter the most likely factors from all the other factors identified in Measure phase. The output of this phase is:
  - Identification of the critical process factors / inputs which will be improved in the next phase.
- Improve – The goal of this phase is to implement solutions that address root causes. The output of this phase is:
  - Implementation of planned, tested actions that should eliminate or reduce the impact of the identified root causes.

  Knowledge, Experience, resources and Lean Six Sigma tools will help implement the improvements required to achieve the agreed goals.
- Control – The goal of this phase is to ensure that key inputs and improvements are controlled to sustain the gains permanently. This phase will focus in the sustainability of the actions completed. It one of the most important phases because if forgotten, all work could be loose. The identification of the controls and systems required to maintain the improvements over the time is key.

  The output of this phase is:
  - Final Process Capability
  - A monitoring system
  - Complete documentation of results

METHODOLOGY

As previously mentioned, DMAIC was the methodology used on this project. For the purpose of this project, given the regulatory gaps or observations issued to the manufacturing sites, management decided that a Remediate Phase would be included between the Define and Measure Phase. This phase was used to implement immediate remedial actions or corrections that helped to mitigate compliance risk. The implementation of remedial action helped the manufacturer to be ready in case of an unplanned inspection from the regulatory bodies.

The following is a summary of the tools completed on each of the D(R)MAIC Phases and their corresponding analysis:

- Define – The milestones completed on this phase were: definition of the problem statement, team composition, remediate and redesign goals. The problem statement was previously defined in the Problem Statement section. The goals of the project were defined as:
  - Remediate Goal: Close any gaps identified as part of the remediate phase within a thirty (30) days timeframe.
  - Redesign Goals: Implement a standardized, harmonized and compliant process at all sites by end of project. Obtain Zero audit observations related to the failure modes addressed in the project. Reduce the risk score by 65% (from 153 to 54) by end of project.
- Remediate – The milestones completed on this phase were:
  - Gap Analysis: Current practices from the manufacturer sites were evaluated against the regulation 820.250. Several areas were found with gaps, specifically the lack of a statistical rationale for sampling plans. An action was generated for each of the

process owners to document a statistical rationale.

- Documented rationales were submitted for evaluation of Compliance Experts and Statistical Consultants. Then the documents were optimized by implementing the feedback provided by those experts.
- The rationales were implemented within a thirty (30) days timeframe. This fast implementation was required in order to mitigate compliance risk for upcoming external audits or inspections

- Measure – The milestones completed on this phase were:
  - Process Maps were generated for the two major areas identified in the FDA regulation: process monitoring and sampling. These process maps helped to identify all potential inputs that can contribute to improve the use of statistical techniques in those two areas. Nine potential or most likely inputs were identified with these tools.
  - Current Process Capability was determined using a risk evaluation. This risk is a function of the effect of the failure modes identified in the audit observations and the frequency or probability of occurrence of each failure mode. The effect is multiplied by the frequency in order to determine the risk of each failure model. Then, all failure modes risks are added in order to determine the overall risk evaluation. The overall risk evaluation was 153.
  - Cause and Effect Diagrams (C&E) were used to determine or prioritize the most likely inputs that would be improved as a result of the project. All inputs identified in the Process Maps were included in the C &E. Then, each one of the inputs was evaluated against each of the failure mode and a correlation rating was assigned. As the rating increases, the correlation between the inputs and the failure modes is stronger.
- Analyze – The milestones completed on this phase were:
  - The C& E helped to identify the key inputs that needed to be improved in order to re-design the Statistical Techniques System. The key inputs were: incomplete procedures, procedure complexity and training level or knowledge of engineering personnel on statistical techniques.
    - Incomplete Procedures – The procedures were incomplete because they did not address all the requirements of the regulation, 820.250. They did not have sufficient description or instructions to guide people on how to conduct statistical tools. For example, they did not require engineers to revise the sampling plans when process had changes nor provided the methodology to perform the revision.
    - Procedure Complexity – The procedures were complex because they had a lot of wording which made difficult to understand the content. Additionally, there were no visual aids or flowcharts to ease the understanding of the reader.
    - Training level or knowledge of personnel on statistical tools – The analysis showed that the engineering personnel of the manufacturer sites were not trained on statistics and therefore did not have the knowledge needed to properly use the tools. Additionally new hires did not have in their training plan the requirement of being trained on statistical tools.
- Improve – In order to accomplish the project goal, countermeasures for each of the failure modes were identified. The following countermeasures were implemented:

- Harmonized and Standard Procedures that include: a statistical techniques policy, Statistical Process Control Work Instruction and Sampling Work Instruction. All procedures are complete aligned with the FDA regulation, 820.250. They include the requirement to revise sampling plans and methodology to do the revision.
- Flowcharts and Minitab Instructions to guide the engineers on the process of generating the statistical tool analysis.
- Inclusion of OC Curves Methodology to support rationale for sample sizes
- Implementation of a Standard Form to document sampling plans rationales
- Implementation of a Standard Form to investigate out of control points when performing Statistical Process Control.
- Generation of Training Modules
- Training Plans were revised to include the requirement for new hires to be trained on statistical tools.
- Revision of the Change Control form to ensure that sampling plans are reviewed when there are changes.

- Control – The milestones completed on this phase were:
  - Final Process Capability was determined using a risk evaluation. The overall final risk evaluation was 36.
  - In order to ensure sustainability of the improvements, the following actions were implemented:
    - Revision of internal audit system to ensure that Statistic Techniques is periodically audited.
    - All employees were trained including new hires.
    - Training Plans were updated to include the requirement for new hires to be trained on statistical techniques.
    - Management Review Procedure was updated to request the review of Statistical Process Control Investigations and Sampling Plans Effectiveness. This review would take place on a quarterly basis.
    - All engineers were required to take the Lean Sigma Greenbelt Training.
- Phase Reviews – These reviews were conducted with management to communicate project progress, tools used, results per phases and get alignment on proposed improvements. Management decided based on those reviews if the project could be promoted to the next D(R)MAIC phase.

RESULTS

After completion of the project the following results were obtained:

- All gaps identified as part of the remediate phase were closed in a timely fashion. This helped to mitigate regulatory risk for upcoming audits or inspections.
- Harmonized and standardized Statistical Techniques processes, procedures and templates were implemented across all manufacturer sites in P.R.
- An audit was performed by a third party auditor contracted by the manufacturer, and no observations related to Statistical Techniques were found.
- The compliance risk score was reduced to 36 which is equivalent to a 76% reduction which met the project goal of reducing the risk by 65%.

CONCLUSION AND RECOMMENDATIONS

The project's end goal was to improve the Statistical Techniques Quality System in the Medical Device Manufacturer Sites of P.R. This improvement was achieved by improving the identified inputs or contributors to reduction of compliance risk. The project is considered successful given that all project goals were accomplished as summarized below:

- Goal 1 – All gaps were closed within a 30 days timeframe.

- Goal 2 – Standardized, harmonized and compliant process and procedures were implemented across all manufacturer sites in P.R.
- Goal 3 – Zero observations were found during an audit performed on the manufacturer sites after implementation of the improvements.
- Goal 4 – The risk score was reduced by 76% (from 153 to 36)

Additionally as a result of the project the following recommendations were implemented by the manufacturer:

- Trained manufacturing and quality engineering on Statistical Techniques.
- Revised training matrices of manufacturing and quality engineers to ensure that new hires are trained or have background on Statistical Techniques.
- Revised the internal audit system of the manufacturer to ensure that the Statistical Techniques Quality System Element is periodically audited.
- Train manufacturing and quality engineers as Green Belts.

The implemented countermeasures and recommendations definitely helped to strengthen the manufacturer quality system by significantly reducing the risk of obtaining regulatory observations during the upcoming external audits. Most importantly than the outcome of the audits, is that the manufacturer is striving without reserve to achieve its mission of ensuring patient safety and device effectiveness.

REFERENCES

[1] Williams, M, A, et al, "Overview of DMAIC", *Six Sigma Pocket Guide*, Ninth Printing, June 2002, pp. 5