Enhancement of Batch Review Report for Annual Product Reviews in the Pharmaceutical Industry

Carol G. Rivera Ramos
Master in Manufacturing Competitiveness
Rafael Nieves, Pharm D
Industrial Engineering Department
Polytechnic University of Puerto Rico

Abstract *—The pharmaceutical industry is required to comply with various regulatory agencies which determine the industry capabilities for compliance and allow the marketing of their products. Regardless the regulatory agency one requirement that is common is the review of the batches that are manufactured and packaged, whether approved or rejected. The current process used to determine the batch status is delaying the process for the report submission. The project objectives were to reduce the cycle time along with an enhancement in the information provided within it. The Lean Six Sigma methodology, specifically the DMAIC tool, was used to accomplish these objectives. After a thorough review of the possible root causes it was determined that a new system to search the batches status was needed. Work instructions were developed and the personnel were trained. The project objectives were accomplished since the cycle time for the report preparation was reduced and the report accuracy was enhanced.*

Key Terms *—APRs, Batch Review Report, CFR Part 211, Cycle time.*

PROJECT STATEMENT

The Food and Drug Administration (FDA) requires the industry to provide a review of a representative number of batches that were approved or rejected. This requirement is stated in Title 21 Code of Federal Regulations (CFR) Part §211.80(e) (1) [1]. The industry generally records the batch review under the Annual Product Reviews (APRs), which are performed at least annually. In order to submit the batch review report, the planning department presents a report of the batches that were manufactured within a time frame. After this, the material disposition department performs the review of whether the batches were approved or rejected. This process is completed manually, one batch at a time, consuming in average a week or two of a full time employee (FTE) work.

RESEARCH DESCRIPTION

This project is intended to evaluate and implement a new and enhanced system on how to perform the batch review report. Along the enhancement it also projects the completion of the report within the provided timeframe. Since the completion of the report is so lengthy extensions are requested and reports are submitted from one week to one month after the due date. Some of the constraints that the material disposition department faces are the lack of personnel, voluminous auditing of batch records and the manual system that is currently in place. This report enhancement will reduce the time spent in performing the batch review report and improve the accuracy of it.

RESEARCH OBJECTIVES

The expected objectives are:

- Development and implementation of a new Batch Review Report;
- Improve accuracy of the report;
- Reduction of cycle time by 45%.

RESEARCH CONTRIBUTIONS

With this project the material disposition department will be able to improve the accuracy of the batch review report and reduce the cycle time of the report submission. In addition the employee efficiencies will improve by eliminating waste [2] (manual system and waiting time) and implementing the process improvements.

LITERATURE REVIEW

The pharmaceutical industry is regulated by various government agencies; among those is the Food and Drug Administration (FDA). Title 21 Code of Federal Regulations (CFR) Subpart J §211.80(e) (1), Records and Reports, requires the industry to review a representative number of batches, whether approved or rejected [1]. The responsibility of providing the information of whether a batch was approved or rejected belongs to the material disposition department. This department follows a series of Standard Operations Procedures (SOPs) in order to define the requirements for review and disposition of the documentation, in accordance with established procedures, company policies and cGMP requirements.

Prior the disposition of a batch a material disposition quality assurance representative will review the following items within the record:

- Materials used where within expiration date;
- Materials used were released prior to their use;
- Equipment used was correct and approved for use in the process;
- All steps were completed and the order of execution coincides with the instructions provided in the applicable SOP;
- Results are within the product specification ranges;
- Calculations are correct;
- All associated attachment were reviewed;
- In-process and analytical sampling were performed according to the instructions listed in the SOPs;
- The require pages and supporting documentation are attached.

Once all these items have been reviewed for accuracy and completeness the batch may be dispositioned. The final batch disposition is recorded through an electronic system called JD Edwards, which is the company inventory control system. JD Edwards is able to provide numerous kinds of reports that can be used for tracking the disposition status of a batch (approved, rejected, quarantine, hold, etc.). Currently, in order to prepare the batch review report the material disposition representatives are identifying the disposition status of each batch manually, instead of using the system in their favor.

A schedule is published with the assigned due date to submit the batch review report for each product. The timeframe for completing the batch review report averages between fifteen (15) to thirty (30) days. The timeframes varies depending on the amount of batches that are being reviewed. In the batch review report the material disposition department have to include a summary of the disposition of each batch; and if the batch was rejected the reason for the rejection. JD Edwards provides the user with a report that states the disposition of each batch within a preselected time period. This report could reduce the amount of time and labor that the material disposition department is spending in the preparation of the batch review report. Moreover, the accuracy of the report will increase.

In order to meet the project objectives the Lean Six Sigma methodology will be used. Lean Six Sigma is a methodology that focuses on improving the performance by removing waste, combining the Lean Manufacturing and Six Sigma techniques. The specific types of waste that are projected to be removed are: non-utilized talent, extra-processing and waiting.

METHODOLOGY

In this design project, DMAIC [3] will be used in order to accomplish and present the expected objectives.

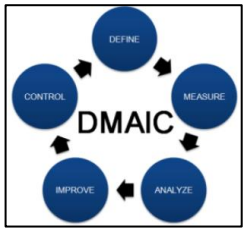

Figure 1
DMAIC Process

- **Define:** here the problem statement and project scope are defined. Also the process improvements are identified.
- **Measure:** is where the majority of evidence is collected, to establish an activity process map of the process performance.
- **Analyze:** the probable root causes are identified. The root cause is what makes the process performance to lack of flow and have poor deliverables. A Bonefish diagram is used to define the possible root causes.
- **Improve:** the potential solutions to the root causes are discussed, designed and implemented.
- **Control:** the objectives proposed at the define phase are expected to be completed and effective. The process improvement does not stop with the control phase since the objective of Lean Manufacturing is continuous improvement.

RESULTS AND DISCUSSION

The results of each stage are presented in the following sections.

Define Phase

This design project is intended to improve the completion and submission cycle time of the batch review reports. The Material Disposition (MD) department performs the batch review report manually instead of using the electronic inventory control system, JD Edwards. Due to this practice the reports are submitted from one week to one month after the due date. If the JD Edwards system is used by the MD department the cycle time would be reduced, the report submitted within the expected time frame and the report accuracy will increase.

The project pursues to accomplish the following objectives:

- Development and implementation of a new Batch Review Report;
- Improve accuracy of the report;
- Reduction of cycle time by 45%.

With the execution of this project the MD department employees will be able to submit the batch review report on time and in addition the department and employee efficiencies will improve.

Measure Phase

In order to have a better understanding of the process performed for the submission of the batch review report, figure 2 shows each stage. This flow chart comprises the current process used by each department involved, from the schedule publishing until the report submission.

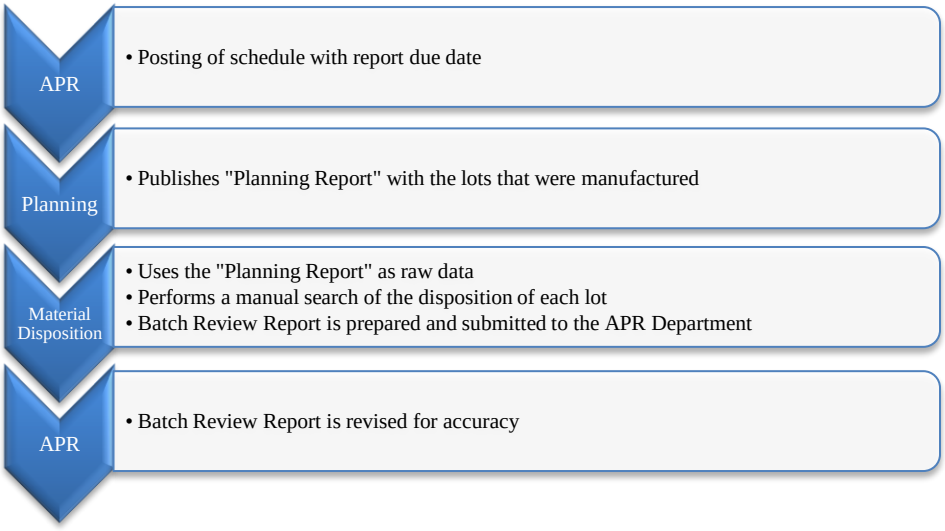

Figure 2
Current Process

The APR department publishes the schedule, which contains the information of the products, the date range for the query and the due date to submit the report. The schedule is published in a quarterly basis and each quarter is subdivided by three "buckets". Once the Planning department submits their report the Material Disposition (MD) department can prepare the batch review report. This report will contain the disposition status of each lot manufactured and/or packaged. Figure 3 illustrates the product distribution per quarter.

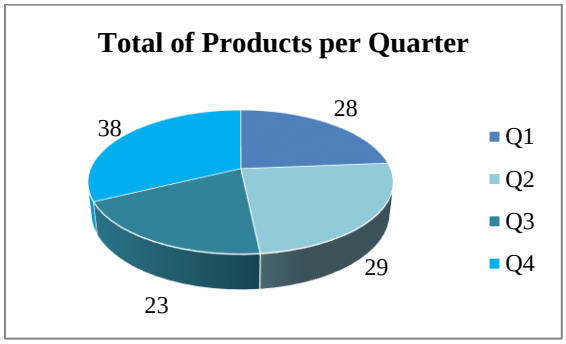

Figure 3
Products per Quarter

In order to find the disposition status, the QA-MD representative goes into JD Edwards and performs a manual search of the disposition conditions. The query is conducted using the "Lot Status Audit Report" (a PDF file). To perform a query using this report the QA-MD representative needs to provide the system with the product item number and the lot number. This process is performed for each lot individually. Once the "Lot Status Audit Report" is obtained the QA-MD representative creates an Excel spreadsheet with the lots information and the disposition status.

Other factors that the QA-MD representative needs to take into consideration are

- The date when the lot was released. If the date is outside the range that was provided in the schedule the lot will be considered pending for the next period.
- The status that is found in the "Lot Status Audit Report". If the status is other than "Release" or "Rejected", then a comment needs to be added of why the lot has not been released. The comments can be: "On Hold", "Quarantine", "Conditional Release", among others.
- The report accuracy. The lots information and quantity provided by the planning and MD department have to be equivalent.

Once the report is completed is then submitted to the APR Department for review. If no corrections are needed the process ends. If the report needs corrections it is returned to the MD department. When corrections are performed the MD department resubmits the report to the APR department.

The APR department needs two types of reports from MD department. These two reports are the batch review report for the manufacturing and packaging processes. The reports were divided due to the fact that the company serves as a global packager for products that are manufactured out of site. The current product distribution is the following: 58 manufactured products and 60 packaged products. The products are assigned by the MD supervisor to each QA-MD representative.

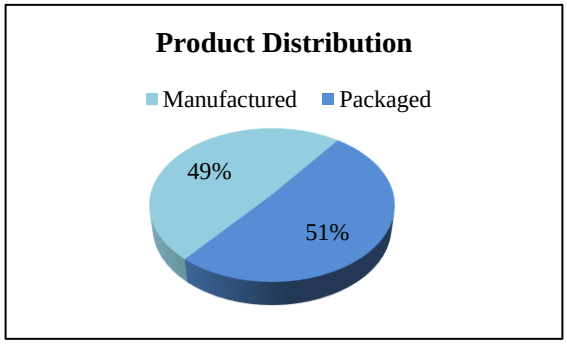

Figure 4
Products by Process

There are a total of 11 QA-MD representatives. The representatives are subdivided in teams: manufactured and packaged products (8 and 3 representatives, respectively). As seen in Figure 5 the manufactured products team gets in average seven products and the packaged products team gets twenty products. The distribution is proportional to the amount of lots that are included in the batch review report. The packaged products lot quantity is significantly minor compared to the manufactured products.

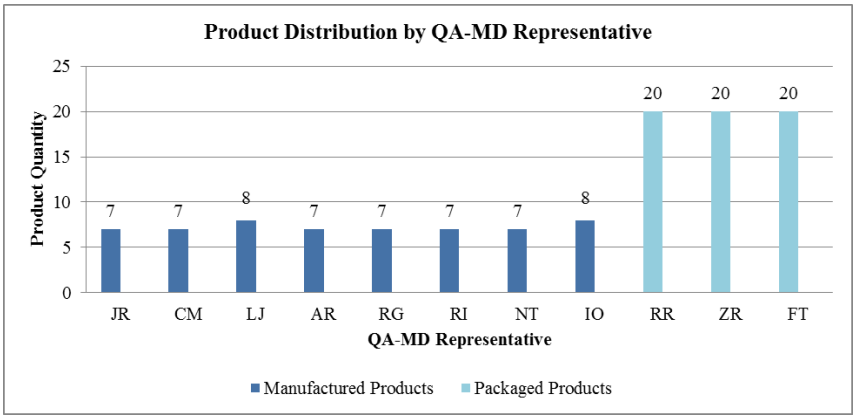

Figure 5
Product Assignment

Using the current process all the MD department reports are submitted after the due date that is provided in the schedule. As shown in Figure 6 the reports are submitted as follows: 49% after 5 days, 34% after 6-15 days, and 17% after more than 15 days.

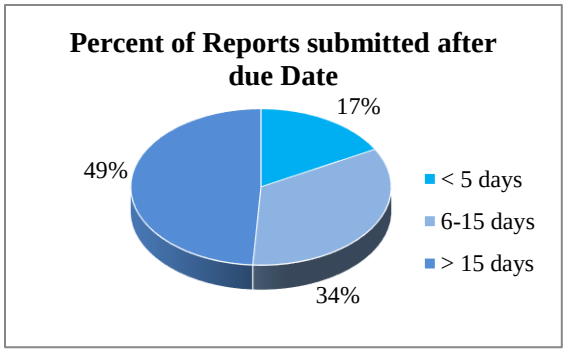

Figure 6
Distribution of Reports by Due Date

After the report submission the APR department proceeds with the report verification. About 15% of the submitted reports are returned to the MD department for corrections. Among the corrections needed are:

- Missing lots;
- Lots pending from the previous report not included in the current report;
- Rejected lots reported as released;
- Rejected lots without comments on rejection reason;
- Quantity of lots reported not equivalent to quantity of lots in planning report.

Analyze Phase

The main purpose of this phase is to identify the probable root causes of the delay in the batch review report submission. The data collected is analyzed to pursue the potential root causes for the poor deliverables in the process performance. A Fishbone diagram, presented in figure 7, was used to determine which components attributed more in affecting the cycle time.

Each component presented in figure 7 was analyzed. The components that are highlighted in the diagram were determined to be the major contributors in affecting the report creation and submission. These components need to be further analyzed to decide what magnitude each one of them has over the cycle time.

- JD Edwards: this is the company inventory control system. The "system owner" is the corporate division. Therefore, if any correction is needed in the system it would have to be authorized by the "system owner". The change control process to request an adjustment to the system is too lengthily and is out of the control of the site.
- Manual Query: the current practice performed by the MD representative is a manual query of each lot that is addressed in the report. The quantity of lots addressed can vary from five to over 1500 lots per report. The manual query is performed using three different sources of information: JD Edwards "Lot Status Audit

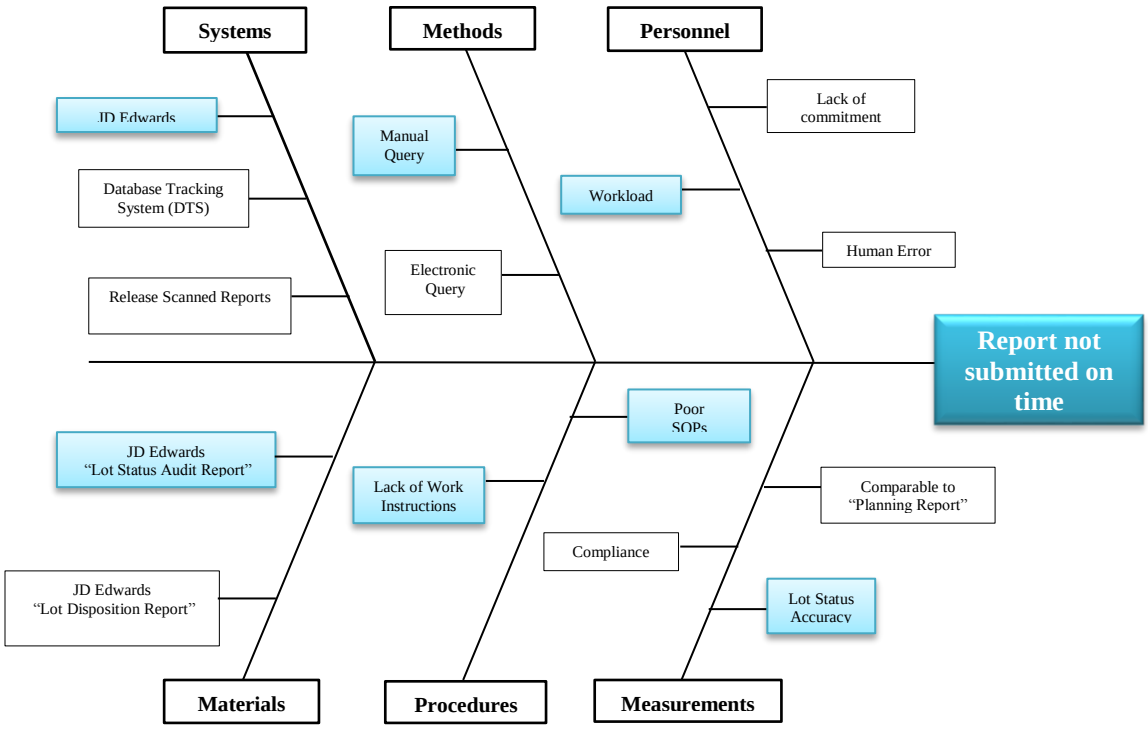

Figure 7
Fishbone Diagram

Report", DTS (Database Tracking System) and the folder "QAMD WIP and H2O Releases Scanned Reports". The MD representative uses these sources in the mentioned order to find the lot status. The main source of information is JD Edwards; however, if the lot information is not found in JD Edwards the MD representative will look for the lot status in the remaining sources.

- Workload: the MD representative performs several functions within its responsibilities. Some of the responsibilities are:
  - Prepare and issue Master Batch Records for Manufacturing and Packaging processes.
  - Conduct revision of executed Master Batch Records (manufacturing and packaging) and associated GMP documentation. Follow up with appropriate personnel to resolve discrepancies/deficiencies found (if any).
  - Conduct revision of miscellaneous documents associated with manufacturing, packaging and analytical testing of the pharmaceutical products.
  - Compile documentation associated with Annual Product Reviews and forward the information as per schedule.
  - Initiate Material Destruction Requests.
  - Revise documentation for incoming materials (raw materials, packaging components, labeling, etc.) to determine if the material will be released or rejected.
- Inconsistency in Data Entry: when using JD Edwards various inconsistencies in data entry were found.
  - Release date of the lot is entered in the "Approval Date" cell provided by the system.
  - "Approval Date" cell is left empty and the release date is recorded as a comment.
  - Lots with no data entered.
  - Lots status (quarantine, on hold, release, rejected, etc.) not entered by the MD

representative. Statuses are entered as comments.

- JD Edwards "Lot Status Audit Report": this report is a PDF file provided by JD Edwards. In order to obtain the lot status using this report the item and lot number need to be provided to the system. The disadvantage using this report is that the data is acquired one lot at a time. The report can be feasible for small queries; however, for big queries is a process that can take several weeks or even a month to complete.
- Poor SOPs: the Standard Operational Procedures that are currently in place are not detailed in the manner that the data entry should be performed. This is the main cause of data entry inconsistency. A revision of the procedure can be executed to add instructions on how to enter the data in JD Edwards. A procedure revision can take up to three months.
- Lack of Work Instructions: there are no work instructions, either as a separate document or as part of a SOP. Work instructions detailing the appropriate manner to enter the information in JD Edwards can help in the completion of the report on time since all the necessary data is in the system. Hence, the JD Edwards "Lot Status Audit Report" has to be used since this report provides a detailed summary of all the stages that the lot goes thru, including the specific dates. In addition, work instructions can replace the revision of a SOP.
- Lot Status Accuracy: due to the fact that the status of the lot is a manual search the accuracy can be compromised. For example, there have been cases were a rejected lot have been reported as released. With the use of the "Lot Status Audit Report" the data accuracy can be compromised even though the data is extracted from JD Edwards. The MD representatives have to go thru the report and manually look for the final status of the lot.

In order to determine which components are going to be targeted for improvement, the following categories will be use for the evaluation process:

- Low Impact – High Difficulty
- Low Impact – Low Difficulty
- High Impact – High Difficulty
- High Impact – Low Difficulty

The components categorization will depend in the effect in productivity, operation cost (if any), time for implementation and training, and effect on quality and compliance. After the data analysis the components were classified as follows:

	Low Impact	**High Impact**
High Difficulty	• Poor SOPs • JD Edwards	• Workload • Lot Status Accuracy
Low Difficulty	• "Lot Status Audit Report"	• Inconsistency in Data Entry • Manual query • Lack of Work Instructions

Figure 8
Component Categorization

After a thorough review in the assignment of the previous categories it was decided to target the High Impact – Low Difficulty components. The selection of these components was based in the fact that the creation of work instructions for data entry is going to:

- Eliminate inconsistencies in the data entry.
- Eliminate the manual query.
- Eliminate errors in the reported status of a lot.
- The report preparation time will reduce drastically.

Improvement Phase

The improvement phase uses all the data gathered and the analysis of it from the previous stages. The main goal is to design and implement systems that could resolve the root cause found in the analyze stage.

Based on the performed analysis it was determined that the manual query is the main contributor for the delay in the report submission. It was decided to create work instructions to train the MD personnel how to perform an electronic query. With the creation of the work instructions the query

can now be performed based on the date ranges of the batch review report instead of searching each lot individually (using the item and lot numbers provided by the planning report). This new search system will be displayed by the JD Edwards "Lot Disposition Report".

The "Lot Disposition Report" provides the MD representative with the correct lot status and the date of the displayed status. The information provided by the "Lot Disposition Report" is accurate since it is extracted directly from the system, with no human intervention. Some advantages of using the "Lot Disposition Report" are.

- Is an Excel file, which can be manipulated for final presentation.
- Data selection is based on: item number, work order type and specified period.
- Provides the current lot status with its applicable date.
- Can be used as supporting data for the Batch Review Report.
- Expedite the Batch Review Report preparation since all the information needed is within the report.

Control Phase

The control phase goal is to maintain standardization on the manner the MD representatives performs the batch review report electronic query. In order to obtain a control of this new system, work instructions were created with detailed orientation and snapshots of how to perform the query using JD Edwards. With these work instructions various sessions of training were executed with the Material Disposition department.

During these sessions the work instructions process was discussed with the personnel. Possible roadblocks that can be found while performing the electronic query were also considered and their solutions were presented. It was also informed that the final query can be presented as supporting data for the batch review report. The usage of the electronic query as supporting data was justified because the information is gathered from JD Edwards, the company inventory control system.

Once the new electronic query is implemented, cycle time data will be collected to determine if the electronic query was useful in the reduction of submission time of the batch review report. It is expected a reduction of 45% in cycle time due to the fact that the lot status search went from a manual to an electronic query. A comparison between the average completion times was performed. The manual query takes approximately one to five days to complete in contrast the electronic query can be completed in approximately four hours or less (depending in the amount of lots manufactured and packaged). The cycle time reduction will also depend in the commitment presented by the MD personnel.

CONCLUSION

The objective of this project was to decrease the cycle time in the submission of the Batch Review Report. This report compiles a review of a representative number of manufactured and packaged batches whether approved or rejected, during a specific time period. In order to accomplish the project objective the Lean Six Sigma methodology, specifically the DMAIC tool, was used. The define phase identified the final project objectives: develop and implement a new batch review report, improve accuracy of the report and achieve a cycle time reduction of 45%. In the measure phase the process streamline, product distribution, manpower quantity and current cycle time data was collected. After a thorough review the components that contributed to the report not being submitted in time were identified. Each component was discussed in order to recognize which were the major offenders.

Due to the fact that the most probable cause of the delay in the report submission was the manual query used to search the lot status it was confirmed that a new system was needed. The improvement phase consisted in the development of work instructions that displays the process of an electronic query using the company inventory control system, JD Edwards. These work instructions will help the

MD representative in eliminating the non-value added steps of a manual query. It will also improve the quality of the report and the performance of the personnel. It is expected that this process redesign will be a successful process improvement.

The criterion used to demonstrate that the improvement phase accomplished the project objective is the time needed to perform the query. Previously the manual query took about one to five days to be completed. In contrast the electronic query takes about four hours to be finalized. The time reduction will also depend in the MD personnel commitment in performing the report.

The Batch Review Report is used as a GMP document in the Annual Product Reviews. This report showcases a summary of the batches manufactured and packaged by the company. The presentation of this report is a mandatory requirement which is regulated by Title 21 Code of Federal Regulations (CFR) Part §211.80(e) (1). Since this new query complies with the CFR requirements it is considered that the project objectives were met.

REFERENCES

[1] *Food and Drug Administration, Code of Federal Regulations: 21 CFR Parts 210 and 211 cGMP in Manufacturing, Processing, Packing, or Holding of Drugs and Finished Pharmaceuticals*, FDA, 2014.

[2] H. Bevan, N. Westwood, R. Crowe & O'Connor, M. *Lean Six Sigma: Some Basic Concepts* [Online]. Available: http://www.northamptongeneral.nhs.uk/Downloads/OurServices/ServiceImprovement/Toolsforimprovement/LeanSixSigma.pdf.

[3] H. Fred Walker, "Statistical Quality Control for the Six Sigma Green Belt", Milwaukee, WI: ASQ Quality Press, 2007.