Enhance Annual Product Review Process at Pharmaceutical Company in Puerto Rico

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Abstract *— Annual Product Review (APR) is a requirement from Good Manufacturing Practices (cGMP) under the FDA (Food and Drug Administration) and European Medicine Agency (EMEA). The EMEA refers to Annual Product Quality Review (APQR). The APR function is to assess the need for re-validation, and continue suitability and reproducibility of the manufacturing and control processes. The main objective of the study was to identify opportunities to reduce time to prepare the APR Analytical Section. The project methodology applied was DMAIC improvement strategy coming from Lean Six Sigma principles. After the analysis of the data collected, the opportunities identified could reduce the analytical section completion time by 43%. In addition, recommendations that will eliminate waste and standardize activities for QA (Quality Assurance) and QC (Quality Control) will eliminate another 36%. The proposed recommendations comply with procedures and corporate guidelines maintaining Company compliance, therefore project objective was successfully achieved.*

Key Terms *— Annual Product Review, Annual Product Quality Review, Code of Federal Regulations (CFR), Good Manufacturing Practice; DMAIC.*

PROJECT STATEMENT

Through the years, the data collection and reporting of the APR/APQR process for the Company has been considered complex and time-consuming. The Company creates APR/APQR for all different distribution markets such as: United States (USA), EU (Europe) and ROW (Rest of the World). All of these Product reviews require different sections as part of the final report. Corporate guidelines and Standard Operating Procedures (SOP) indicate which content should be included per market.

The complexity and time consuming activities of the product review affects the process cycle time which could result in none compliance with the internal Procedures and Regulatory agencies. As part of internal procedures, the Company has 90 days to complete and approve the Annual Product Quality Review (APR/APQR). During the past three years, the Company created an alternate system to maintain compliance with 90 days schedule using CAPA (Corrective /Preventive Actions) system. The QA compliance department generates a CAPA to each collaborator in order to follow up and document any action or delay. The Company is looking for a reduction in process cycle time by, but not limited to, re-distribution of tasks; standardization and eliminating repetitive tasks or none value added activities (waste) without harming the system compliance. In order to impact the Process cycle time, the areas subjected to evaluation will be Quality Compliance; Quality Control Laboratory and Technical Services tasks related to analytical data reporting and statistical analysis.

Research Description

This project has been outlined with the purpose of analyze and evaluate the current APR/APQR process to make it consistent, quick and simple, while maintaining compliance. Primarily, to standardize processes, reduce complexity and eliminate repetitive tasks performed during data collection and documentation of APR Analytical Report, section 6.0. This section is mostly completed manual and it is time-consuming.

Research Objectives

The main objective of this project is to identify opportunities to reduce the time required to prepare Analytical data section of the APR (Section 6.0) by re-distributing tasks and practices or processes standardization. If possible, eliminate manual process and utilize current systems such as: SAP, GLIMS, OCM, and Track wise; remove repetitive tasks or waste. All the improvements should mmaintain compliance with Standard operating procedures, corporate policies and regulatory agencies.

Research Contributions

The project implementation will reduce process time to complete the Analytical Section of the Annual product review; will reduce work load QA compliance; and will eliminate repetitive task or waste from the process. This assessment could be extend other areas of the Annual Product Review not evaluated as part of this project.

LITERATURE REVIEW

To guarantee Compliance of a Drug manufacturer with Good Manufacturing practices ("the Law'), it's necessary to complete an Annual Product Review or Annual Product Quality Review of each of the products manufactured in a yearly basis. The purpose of this document is to assess the need for revalidation and the continued suitability and reproducibility of the manufacturing and control processes; or alternatively to recommend any changes required to procedures, methods, or specifications. Therefore provides a mechanism to help highlight any requirements for changes and re-validation. The annual product review content structure is defined by the Company corporate guidelines and procedures. Such procedures provides guidance for data collection, analysis and reporting methods. [1] [2]

Annual Product Review and/ or Annual Product Quality review should contain the following parts: [3]

- Summary and Conclusions
- List of batches reviewed (approved /rejected)
- Reprocessed and reworked batches
- Review of the summaries of the latest available product reviews from bulk formulated products and drug products (for packaging site or finish product)
- Starting and Packaging materials (ROW requirements)
- Analytical data
- Changes
    - Test methods and/or Equipment
    - Manufacturing and/or packaging
    - Manufacturing/in process control equipment systems and facilities
    - Specifications
    - Marketing Authorizations (ROW requirement)
    - Post marketing commitments (ROW requirement)
- Stability Data
- Deviations
    - Out of specifications (OOS)
    - Deviations reports Level 1 and 2
- Complaints (Product Quality)
- Recalls, Stock Recoveries, Field Alerts
- Returned (Rest of world (ROW)/US requirement) and salvaged good (for US products)
- QA agreements (ROW requirements)
- Qualification status of relevant Equipment and Utilities (EU requirement)

Each site should decide which of those sections should be included in the Product review based on the Product market distribution. The Pharmaceutical Company currently produces four (4) different products. Its most produced product "Product X" is distributed to all markets: US, EU and ROW. Therefore, Product Review should include all the sections listed above. [2] [4]

The Annual Product Review currently is compiled following procedure LDMS _001_001175557, which details schedule, area of responsibility, APR sections to cover per product, steps of data to be included in each section.

The first step to initiate the requirement of an Annual Product Review for a product starts with an email notification from the Quality Compliance to the collaborator 15 days prior to the period end. The email is sent to all collaborators and contains: list of products manufactured with quality disposition (approve, rejected, conditional, and hold), template to report the data, and the time schedule for completion of the Product Review sections. The collaborators should complete their sections 15 days after the period end. The quality compliance collaborator, submit a second set of batches manufactured during the last 15 days not covered in the first request. Once all collaborators provides the summary of each area, the Quality compliance representative copy paste the summaries on the official template located in the share point. The Quality compliance representative generates the final summary and conclusions and the report is routed for approval. The approved APR is loaded to the share point and it's kept for maximum of three (3) years. The areas with more impact by current process are Quality Compliance, Quality Control and Technical Services which compiles most of the APR information (approximately 70%). [3]

The process evaluation will be conducted by collecting the necessary data, and analyze the "as is" process flow. Once the processes data is gathered, it must be validated before the execution of any change to ensure process and system compliance to make an effective change. These changes should standardize practices, reduce time and shall be completed with the required change documentation to prevent any observation by regulatory agencies.

In order to meet the proposed objectives, will be used Lean Six Sigma methodology. Lean Six Sigma is a type of method focused on business and process improvement. Lean Six Sigma is based on the combination of the concepts of Lean Manufacturing and Six Sigma principles, using DMAIC strategy (Yang, 2009). Lean Manufacturing is a philosophy derived from Toyota Production System that maintains a continuous flow of product, eliminate waste and improve customer satisfaction. There are seven types of waste which are in between these: overproduction, excess inventory, waiting, transportation, unnecessary motion, over-processing and defects. [5]

As a complement to the philosophy of Lean Manufacturing, Six Sigma pursues the decrease in variation and process improvement. This methodology began in the manufacturing industry and has expanded to other industries such as service, health care and banking (Yang 2009). Six Sigma was developed by Motorola in the mid-80 and known to the world in 1995 by Jack Welch, as it was used as a business strategy for the company General Electric (GE). Six Sigma used as strategy of process improvement the DMAIC project methodology, which is divided into five main processes: [6]

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

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

METHODOLOGY

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

- **Define Phase**: This phase consists in defining the scope, goals and project statement. It will use a project charter in order to describe the process and identify the possible opportunities of improvement.

- **Measure Phase**: The objective of this phase is the collection of the key aspects of current process and relevant data. As well as the identification of potential factors that may affect the process. It will use data collection, SIPOC and detailed process flow diagram.
- **Analyze Phase**: This phase consists on identifying causes with the objective of validate them with relevant data. The key components of this phase include a value- non value added analysis using a process flow diagram.
- **Improvement Phase:** The objective of this phase is optimizing the current process based on data analysis. Process improvements associated to the process should be approved by Pharmaceutical Company prior to implementation. This section will be completed after approval of the Company.
- **Control Phase**: This phase includes designing and documenting the new controls and procedures, in order to hold the gains. Key components to this phase are SOP's, periodic audit exercises and training process to monitor the success.

A schedule was generated as part of the initial phases of the project to monitor activities and completion of dates.

RESULTS AND DISCUSSION

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

Define Phase

Pharmaceutical company's compliance with the regulatory agencies it's critical to maintain healthy manufacturing operations. APR/APQR process not only guarantee Compliance of a Drug manufacturer with Good Manufacturing practices ("the Law") but also is a source to assess the need for revalidation and the continued suitability and reproducibility of the manufacturing and control processes; or alternatively to recommend any changes required to procedures, methods, or specifications. Therefore, provides a mechanism for continues improvement. APR process review has been considered for the past years a tedious, and time consuming process. The Pharmaceutical company is looking for a reduction in process cycle time by, but not limited to, re-distribution of resources; establishing clear processes to collect data; eliminate repetitive task , without harming the system compliance.

The project goal pursues to find opportunities to reduce time to complete the APR/APQR Analytical section (6.0) by 30% after project completion. The project scope includes process assessment for the following areas: Quality Compliance, Quality Control and Technical Services in reference to the Analytical data reporting. All other areas will be excluded from the analysis. This project implementation must not harm the process and system compliance with the Regulatory authorities and Company Corporate guidelines.

The project team members includes: QC Managers, QC Technicians, QC Managers and analyst, and TS Engineers. The role of the team members consists in recurrent problem discussion, the collection of information, progress meetings and decision making. These activities will be completed as part of the DMAIC measure phase. The measure phase has an expected duration from three week to a month, in order to complete the project goal of three months. Project Charter was created in order to define Project scope, agree on outcomes, goals and expectations. The Project Charter will be use as a guide for a timely completion of each milestone.

Measure Phase

In order to identify the relation between the suppliers, input product, process, output and customers a SIPOC Diagram was created. Refer to Figure 1 (SIPOC diagram).

- The process begins when the QA compliance alerts the APR collaborators that the APR for certain product will started. This notification is

done via email 15 days prior to finalize the APR year period for the product.

- E-mail submitted also contains due date for data collection and provide summary of each section (which is 15 days after period end) and list of manufactured batches with Quality disposition until that date. Once period ends a second list of batches is submitted to cover for 15 days period.
- All collaborators will collect data and will provide summary of each section to QA compliance 15 days after period ends.
- Once section summaries are received QA compliance copy paste date to official template on SharePoint. QA compliance prepares the final APR summary and collects the approvals. If there is any action resulted from the APR, QA compliance generates a CAPA.
- Once APR is approved, APR is download is added to the Share Point and a letter of acceptance is generated. If there is any change, QA compliance will generate an Addendum and route document for approvals.
- The direct customer is the Pharmaceutical Company site and indirect customers are the regulatory agencies.

It was identified the QA compliance, QC and TS as the areas of interest to perform process evaluation since those areas currently covers approximately 70% of the APR/APQR sections. The information collected as part of the investigation indicates that the TS, which is responsible of the analytical data statistical analysis, has more complex activities than any other area. In addition, a review of the CAPAs generated for the APR was conducted. Figure 2 confirms the information collected, the TS it's the only area that requested extensions during the last three years. In order to assess the steps and its complexity, process flow diagrams were generated and are shown in Figures 3 to 5. QA compliance flow diagram, shows all the steps the team completes, which are 11 sections of 14 sections required by the APR/APQR. Figures 4 and 5 shows all the steps followed by the QC and Technical Services areas to complete the Analytical Section of the APR, section 6.

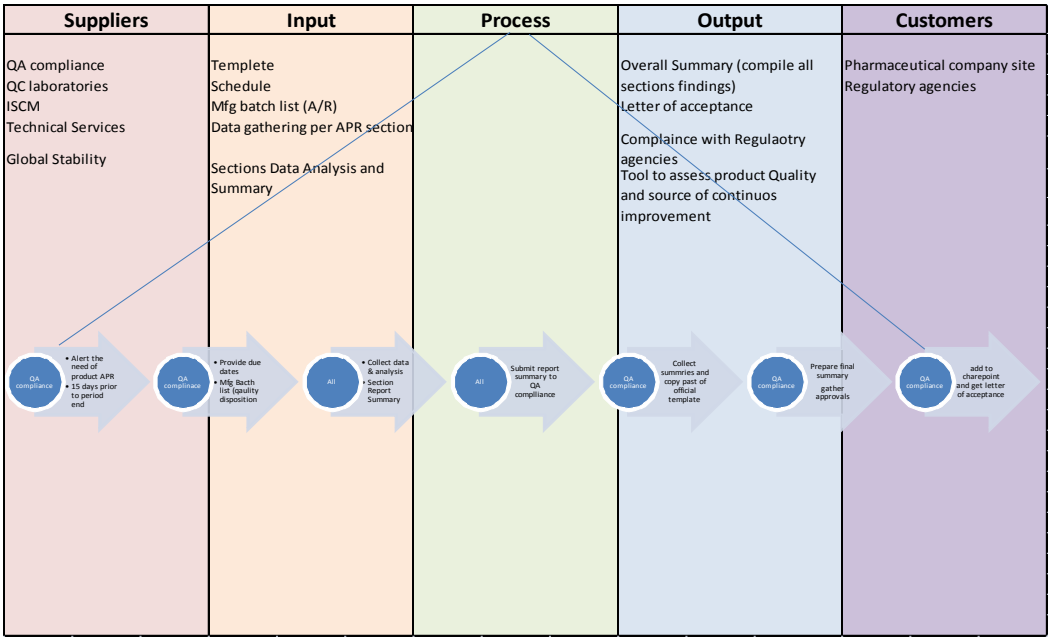

Figure 1
SIPOC Analysis

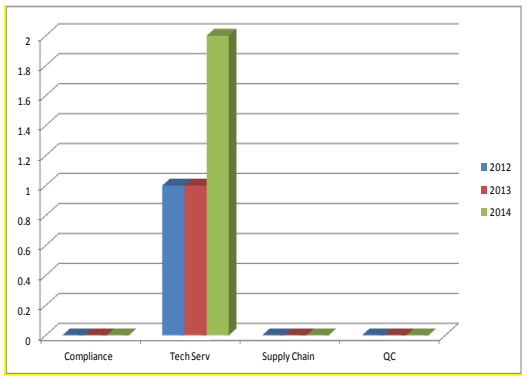

Figure 2
CAPA's Extensions

During the generation of the Process Flow Diagram, collaborators estimated the time required to complete each step. Table 1 shows the estimated cycle time for the each process.

Table 1
Process Cycle Time

ocess	Resources	Time (days)
QA Compliance	R1	15
	R2	9
	R3	6
QC Laboratory	No identification needed	19
Technical Services	No identification needed	37

Analyzed Phase

During this phase opportunities were found for improvement and standardization after reviewing the process flowchart, interviewing the Subject Matter Experts (SME), reviewing Standard Operating Procedures (SOP) and corporate policies. As presented in the measure phase, activities performed by the QA Compliance, QC and TS is about 70% of the sections required in the APR. Therefore, the data analysis was focused on those two areas.

Process flow charts were analyzed for the following: process time, value vs. none value added tasks, duplicity, and unnecessary tasks. The process time was analyzed based on lead times provided by the SME. The process found to have the longest lead time was the statistical analysis task. The major contributors to the lead time is the rearrangement of data once is downloaded from Glims (system used to enter products analytical results) in order to be used with statistical tool. Also, it is required to duplicate results in track wise or request investigations to United Kingdom (UK) (where products are tested) in order to be able to confirm it can be eliminated from the analysis. These two steps add to the process a total of 20 days.

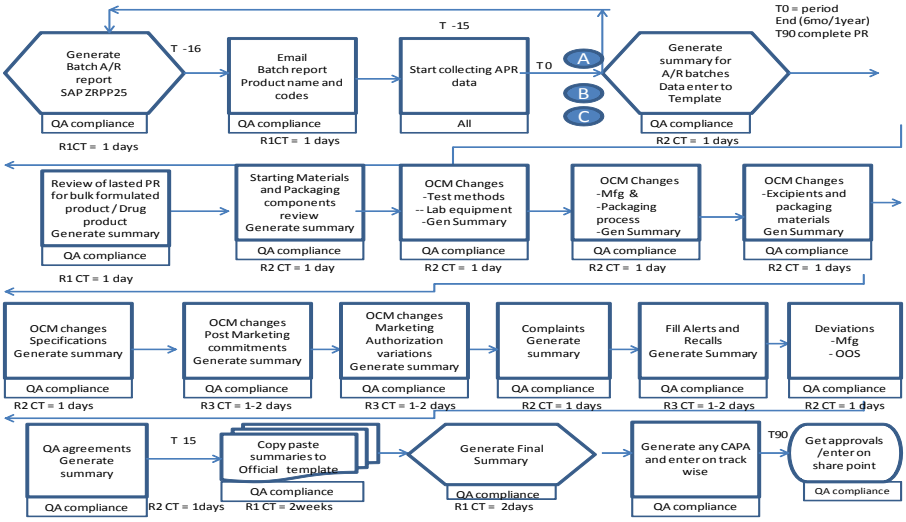

Figure 3
QA Compliance Process Diagram

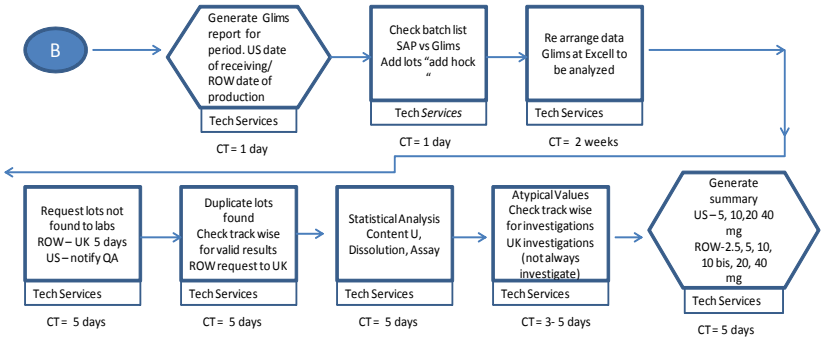

Figure 4
Technical Services Process Diagram

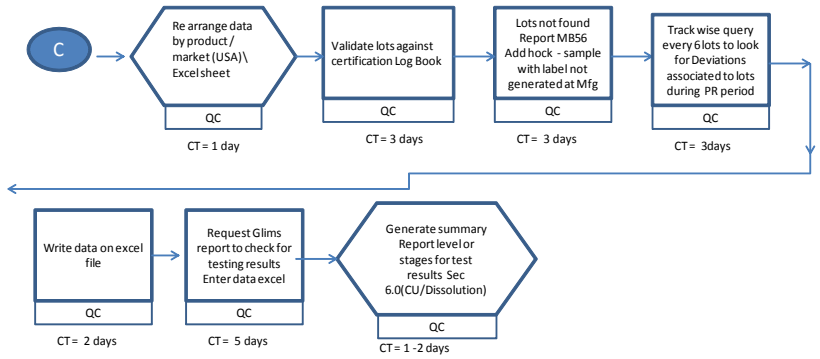

Figure 5
Quality Control Process Diagram

Value and none value added activities were analyzed between TS and QC in regards to completion of section 6 of the APR. Table 2 describes these activities.

Table 2
Value vs. None Value Added Activities

Area of responsibility	Value added activity	None value added activity	Comments
Technical Services / Quality Control Complete section 6: Analytical data	Perform statistical analysis of filed quality attributes of product and include analysis of trends, lows, highs and graphical representation	Review data from Glims manually and report levels or stages of test results.	Procedures requires to perform analysis of trends, lows, highs, and exploit data using capability trending
QA compliance / Quality Control Complete section 9: Deviations	Performs query in track wise to look for OOS during the period and compare it to the previous period and trend analysis	QC performs a review of deviations in track wise and reports number of deviating results per test it in section 6	Procedures requires reviewing level 1 and level 2 deviations and comparing it to previous period. Assess is there is any trending

Data collected shows that the activities currently performed by QC for the same section of the APR are already covered by the statistical analysis report generated by TS. During the process analysis, it was found that there were some tasks than can be classified as duplicates or unnecessary activities as follows:

QA compliance generates a report of approve and rejected batches 15 days prior to APR period ends and its submitted to the SME. Once the period ends, this report is re submitted to the SME with the lots not covered during the first 15 days. During interviews, SME indicated that having the report 15 days prior to period end is not necessary and work has to be done after they get the complete information. Therefore, generating the batch list twice is not necessary and does not contribute to the process. In addition, it was found that Technical Services and Quality Control performs a review of the batch list provided by QA compliance against the Glims batch list. This activity should not be necessary if the initial report contains only the batches manufactured with a final quality disposition. The batch list obtained from the

inventory system (SAP) should match with batches obtained from Glims.

It was also found, that once all the SME submit their data to QA Compliance, the data it's transcribed to the share point official template. This activity takes minimum of two (2) weeks. The transcription of data it's considered none value added an unnecessary activity that should be eliminated.

After the assessment was completed, a second verification was done in order to evaluate which activities performed by QA compliance can be assigned to Quality Control. It was found that two activities could be re-assign: section 9.1 (OOS deviations) and section 7.1 (changes to laboratory methods and equipment).

Improvement Phase

After reviewing and discussing findings with the Company team it was agree to recommend the following improvements to the process.

- Revise SOP LDMS_001_00117557 to indicate that the batch list report will be generated approximately 10 days once the period ends. This change will allow having lots manufactured at the end of the period with final disposition.
- APR schedule has to be revised according to the new instruction.
- Re evaluate the batch list information to include only batches manufactured with final disposition during the period. Corporate guidelines and FDA CFR indicates that the batches to be reported at the APR should have final disposition (approved/reject). This change will avoid the need of doing a review to the data vs. Glims. In order to standardize the batch list report generation form SAP its recommended to add step by step instructions on SOP LDMS_001_00117557.
- Provide access to each SME in order to enter the information directly to the share point. This change will avoid the need of entering data to the share point by QA compliance minimizing possible errors due to data transcription. Also, will standardize the process with Company sister sites which each SEM enters the data to share point.
- Evaluate alternatives to "tag" none valid analytical result when duplicates results are generated in Glims as part of a laboratory investigation. This change may provide the data re arrangement automatically and or use Glims statistical tools and will eliminate the need to do verification of data in Track Wise. This change may reduce the lead time from 37 days to 21 days.
- Enforce quality agreement with UK contract laboratories
- Revise SOP LDMS_001_00117557 to clarify requirements on section 6 of the APR template in order to eliminate none value added activities already performed by Quality Control.
- Re-distributes tasks to QC: Section 9.1 (OOS review); Section 7.1 (Changes to test method and/or equipment). Instructions in how to perform the OCM query should be added in the SPO in order standardize the process.

After analysis recommendations proposed, Table 3 presents the proposed reduction in time after implementation.

Table 3
Proposed Time Reduction

Process	Resources	Time (days)	New time (days)
QA Compliance	R1	15	5
	R2	9	8
	R3	6	6
QC Laboratory	No identification needed	19	9
Technical Services	No identification needed	37	21

Proposed flow charts are shown in Figures 6, 7 and 8.

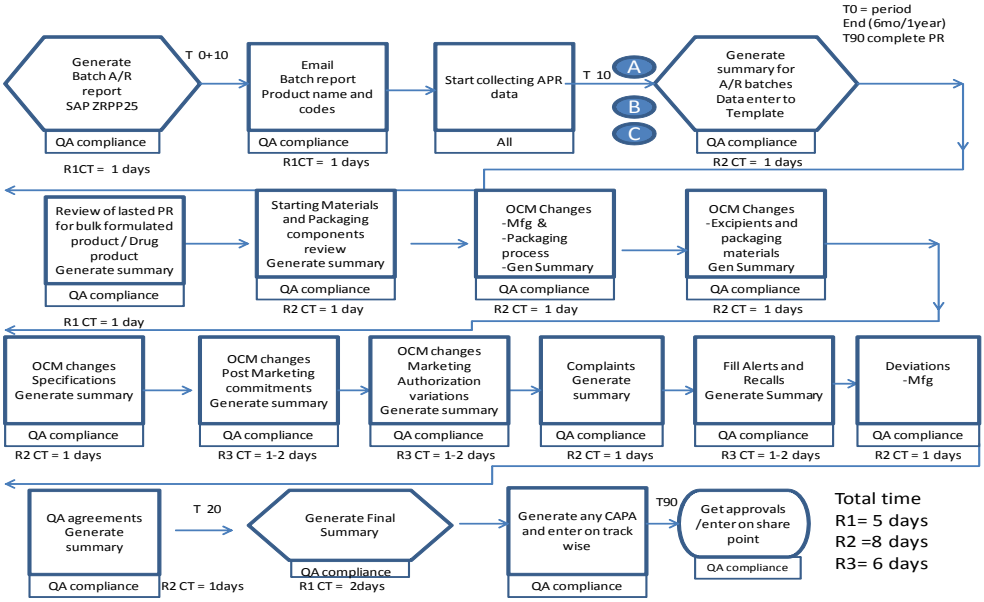

Figure 6
QA Compliance Proposed Process Diagram

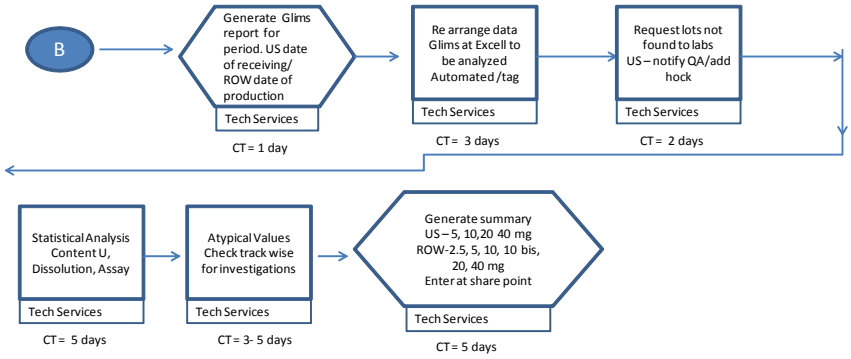

Figure 7
Technical Services Proposed Process Diagram

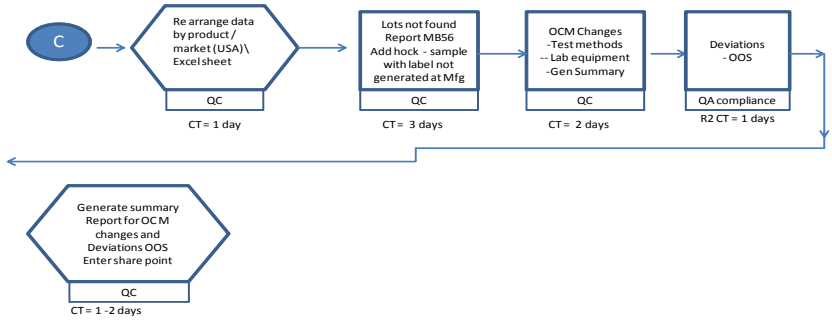

Figure 8
QC Proposed Process Diagram

CONCLUSIONS

Pharmaceutical company's compliance with the regulatory agencies it's critical to maintain healthy manufacturing operations. The Pharmaceutical Company identified the Annual product review process as an area of opportunity for improvement within the compliance organization. The main objective of the project was to identify opportunities to reduce the time required to prepare Analytical data section (Section 6.0) of the APR by 30%.

Opportunities identified could reduce the analytical section completion time from 37 days to 21 days which represents a 43%. Recommendations that will eliminate the waste and will standardize processes will add another 36% for QC and QA activities. The proposed recommendations comply with Pharmaceutical Company corporate guidelines and standard operating procedures maintaining the company compliance requirements. Therefore, project scope was successfully achieved.

In order to standardize process and maintain consistency, it's suggested the revision of the Standard Operating Procedures to incorporate recommendations and perform personnel training..

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