Workflow Management in the Batch Record Review Process

Michelle Velázquez Vázquez
Master in Manufacturing Competitiveness
Advisor: Maria M. García Sandoval, Ph.D.
Industrial and Systems Engineering Department
Polytechnic University of Puerto Rico

Abstract *— The review of Batch Records creates a story of the materials, manufacturing, and packaging involved in the production of biopharmaceuticals. The Master Batch Record details who, when, where, and how each process stage is carried out and how much of a product is produced. Most pharmaceutical companies need help to check batch data in time to provide medications to clients. However, a prolonged process time affects how quickly goods must be made available to the public. As a result, reviewing batch records is a laborious process that mainly occurs afterward. For the manufacturing purification processes of a chromatography column, viral inactivation filtration, viral filtration, ultrafiltration, diafiltration, and bulk filling for a high cholesterol drug, this project assesses the viability of an incremental batch record review in real time. The DMAIC technique was used in this project's study to show how the queue time is decreased. The value-added time is increased, and other advantages.*

Key Terms *— Batch Record Review, Lead Times, Process Improvement, Workflow.*

INTRODUCTION

There are various reasons why process improvement activities are launched. Efficiency has traditionally been the main objective. A company can operate with fewer efforts, thanks to increased productivity or efficiency. The system of batch record review must be improved by the pharmaceutical sector. Supervisors need to be aware of options and resources that the business can use to boost productivity and cut costs.

A batch record review is an essential tool for ensuring the quality of a pharmaceutical process. This subject is covered in many rules and standards for the pharmaceutical business, and it is a crucial stage before a Qualified Person may release a product. However, over the years, documentation has become more and more extensive, and the review can be very time-consuming.

Description

The research aims to standardize the document review process so that documentation is clear, accurate, and concise. With this, there can be a reduction of steps and resources in the document review process, safeguarding the quality of the process.

Objective

The main goal of this project was to speed up the delivery of the product onto the market by reducing the review and disposition times for batch records. The goal was to minimize batch record review from one month to seven days or less. This implemented the reduction of steps for the completion of batch record review. Another factor was to simplify the workflow cycle for the batch record review working together with all functional areas to reduce overworking the process of reviewing a batch record. This occurred by implementing controls to establish the completion of the steps in the batch record review process.

Contribution

The study's contribution was based on two principal factors: reducing the batch record review completion cycle time by working together with QA, the Manufacturing Associate, and all other functional areas involved in manufacturing a product.

OVERVIEW OF THE BATCH RECORD REVIEW

Batch record review and release is an essential responsibility in any company and should not be

taken lightly [1]. An electronic batch record, whether input electronically or manually, demonstrates that a company effectively manages and records each crucial step in creating a product batch. This file contains information about the workers, the production process, the tools, the materials, and the supplies. Additionally, data from enterprise resource planning (ERP), process control systems (PCS), laboratory information management systems (LIMS), and other sources may be included.

Any company must take its critical role in batch record review seriously and release. The most straightforward approach to picture a batch record is to imagine it as a collection of images that, when arranged in the proper order and against a suitable backdrop, tell a story about the applicability and quality of the product [1].

Electronic batch records offer multiple benefits. These benefits are [2]: improve accuracy and consistency, increase productivity, reduce cycle times, reduce compliance costs, reduce operating costs, increase the ability to scale rapidly, and improve decision-making.

- Improve Accuracy and Consistency: An automatic Electronic Batch Record system will always perform a preprogrammed task similarly.
- Increase Productivity: People are the most significant factor in a company's ability to succeed in the marketplace. Companies may set the stage for higher productivity by giving employees a familiar interface that connects internal personnel - and even external business partners - to the relevant information and tools to work faster and wiser. Additionally, EBRs eliminates the time-consuming and error-prone data re-entry that comes from using several unrelated and paper-based systems.
- Reduce Cycle Times: The typical cycle time for pharmaceutical manufacturers is between 30 to 90 days, with batch releases requiring up to 60 days. In nonconformance situations, these cycle times generally double. Electronic batch records ensure that manufacturing processes are carried out consistently while giving a detailed, real-time view of process and deviation data. The time needed to identify, track, address, fix, and document manufacturing process abnormalities in numerous paper documents are essentially removed.
- Reduce Compliance Costs: To comply, information must be accurately collected, organized, retained, and subjected to speedy analysis and presentation. This necessitates processes and procedures that are a natural extension of a company's business model. Systems for electronic batch records assist businesses in the life sciences industry in operating and producing goods consistently and legally.
- Reduce Operating Costs: People are the manual processes' main expense. Carrying out processes that may and ought to be automated and optimized by technology costs businesses time. Automated systems also lessen the possibility of human errors, which may lead to extra work, the same steps, or even audits. Additionally, EBRs do away with the high expenditures of printing, reviewing, storing, and retrieving paper documents.
- Increase Ability to Scale Rapidly: Today, we talk to pharmaceutical businesses about lean muscle growth. Your company processes change as you expand because of the increased volume of customers, orders, products, suppliers, etc., flowing through them. Paper-based business systems have a much higher risk of disarray, making them prohibitive for a business that is expanding quickly.
- Improve Decision Making: Data is disconnectedly stored and hard to access in manual and paper-based operations. When data from these manual procedures is needed for decision-making, it can take time to convert it into a consistent and helpful format. And because collecting the data is expensive, many businesses choose to operate without it, which results in less-than-optimal and frequently delayed judgments.

METHODOLOGY

The research was carried out concerning the best batch record documentation review. The DMAIC technique was used in this project's study to show how the queue time is decreased. The value-added time is increased, and other advantages.

DMAIC, which stands for "define, measure, analyze, improve, and control," is a process analysis method used in Lean Six Sigma [3]. To comprehend the DMAIC methodology, one must first understand the history of Lean and Six Sigma. The term "lean" production derives from the Toyota Production System, introduced in Japan by Taiichi Ohno [3]. Lean principles are intended to permeate all aspects of an organization, including company culture and philosophy, leadership, technology, teamwork, and task standardization [3].

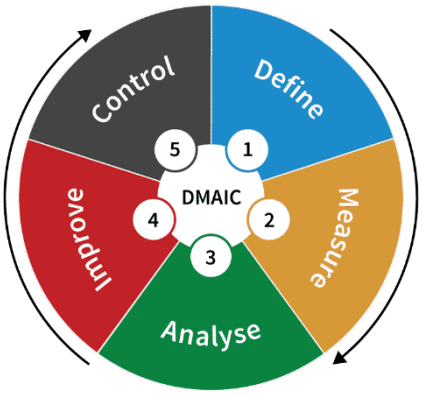

Figure 1
DMAIC Methodology

Define Phase

Manufacturing is highly regulated, and creating and checking batch records takes time and work. Batch records take up a significant amount of time for the operator, the supervisor, and the devoted reviewer. Despite this, lengthy lead times for batch documentation clearance and poor Right First-Time performance are typical. Currently, batch record review takes up to a month to complete. This is due to poor Process Engineer involvement, exceptions not being made during operations, corrections not being made on time, etc. Additionally, there is frequently a large cottage industry developed around error rectification. An Electronic Batch Record (EBR) has been used by some businesses to address these problems, but for many, the expense and complexity associated make this alternative unworkable.

For this project, the main focus was reducing the batch record review completion cycle time by working with QA, Manufacturing Associate, and all other functional areas involved in manufacturing a product. This would implement the reduction of steps for the completion of batch record review. Another factor was to simplify the workflow cycle for the batch record review working together with all functional areas to reduce overworking the process of reviewing a batch record. This would occur by implementing controls to establish the completion of the steps in the batch record review process.

Measure Phase

The measurement takes place throughout the project's life, but a key question to answer in the Measure Phase centers on how the batch record review currently performs. The following was Measured during this project:

- Alarm Assessments.
- Comments on BOM during execution.
- Data was acquired incorrectly in EBR.
- Data not obtained in EBR.
- Functional areas personnel not available.
- Communication problems between functional areas.
- Binders for supplementary documentation are only partially prepared.
- Right, First Time.
- Real-Time Review.
- Open Investigations.
- Open Work Orders.

As part of the measure phase, a workflow was created to help simplify the Batch Record Review process. The so-called workflows are logical sequences of routine execution to automate and facilitate operations. The workflow covers a series of tasks performed sequentially and periodically by the company. The purpose of the workflow is to improve communication between the areas involved in the various processes and guarantee the fulfillment of the tasks since there is a logical "movement" of execution and monitoring [4]. Also, a Batch Record

Review Checklist was made to let us look at the things done in Batch Record Review. The purpose of checklists is to keep track of tasks or projects and ensure nothing crucial is overlooked while they are being carried out. In this manner, you provide that nothing is left out that might affect your outcomes. They also make sure that tasks are carried out in a systematic, orderly fashion. This would work as a guide to performing Batch Record reviews [5].

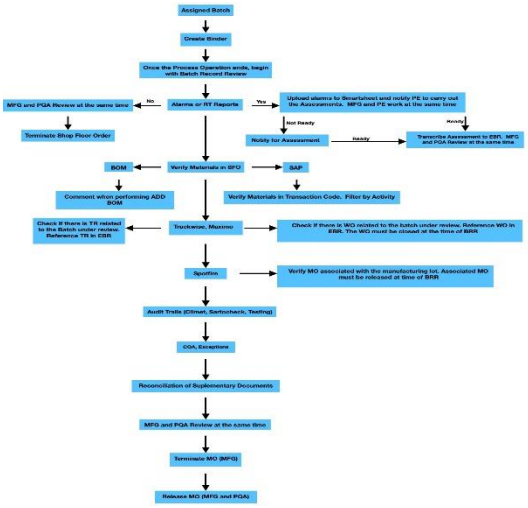

Figure 2

Batch Record Review Workflow

Product:		Batch #:	BR ID:
SOP-		FORM-	
Start Date:		End Date:	
Batch Record Review Checklist			
Task	Duration	Done	Comments
Create Binder	30 mns	☐	
Alarms in Smartsheet	1 hr	☐	
Alarm Assessments	1 hr	☐	
RT Report	15 mns	☐	
Audit Trail (Climet, Sartocheck, Solo VPE)	1 hr	☐	
Materials (Comment BOM)	10 mns	☐	
Trackwise, Maximo and Sportfire (Reference in SFO)	10 mns	☐	
Supplementary Documents	5 mns	☐	
MFG and PQA Review	5 mns	☐	
Circulate and Released	5 mns	☐	

Figure 3

Batch Record Review Checklist

Analysis Phase

- Evaluate different ways to perform batch record reviews.
- Perform batch record review following workflow and checklist.
- Analyze data obtained.
- Reduce cycle time by generating solution ideas and implementation requirements.

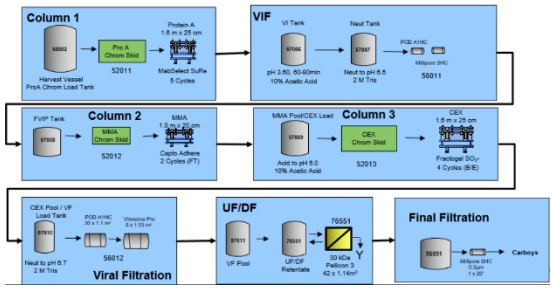

Figure 4

High Cholesterol Drug Purification Process

Improve & Control Phase

- Implement a simple and easy-to-execute batch record review system.
- Before effectiveness, document, and train personnel.
- With project implementation, discuss final improvements and resolution.

RESULTS AND DISCUSSION

The high-cholesterol drug purification process starts with the neutralized harvest filtrate. The neutralized harvested cell culture fluid is purified by protein A affinity chromatography. The protein A pool is viral inactivated utilizing a low pH hold, followed by a two-stage filtration step. The filtered viral inactivated pool is loaded onto the Capto adhere mixed-mode anion exchange (MMA) column, operated in flow-through mode. The pooled eluate from the MMA column is conditioned and then loaded onto a Fractogel SO3- cation exchange (CEX) column, used in a bind and elute mode with a gradient of increasing ionic strength. The CEX pool is conditioned and virus-filtered through Millipore Viresolve Pro or Virosart HF parvovirus-retentive filters before ultrafiltration/diafiltration (UF/DF). The UF/DF process concentrates and buffer-exchanges evolocumab into the diafiltration buffer by tangential flow filtration. 1% PS-80 is added to the UF/DF pool to target a PS-80 concentration of 0.01%, and the pool is filtered through a 0.2 pm filter to yield the Drug Substance (DS). The DS is filled into 10 L carboys and frozen at -30°C [4].

To perform this project, there needed to be assigned a manufacturing lot. Once the manufacturing lot was set, binders were created

where all supplementary documentation of that manufacturing lot was attached. Once that manufacturing process is finished, the Batch Record Review begins.

This Batch Record Review process includes two main functional areas: Quality and Process Engineer. The manufacturing process generates alarms. Once these alarms are generated, Process Engineer comes into the picture. These alarms need assessments, and Process Engineer provides these assessments. Once these assessments were available, they were transcribed to EBR, and Quality proceeded to acknowledge those exceptions created with these assessments. Some of these manufacturing stations do not generate any alarms. If this happens, supervisors will continue with the Batch Record Review. Also, as part of the Batch Record Review, the materials used for that manufacturing process were verified. These materials were verified in SAP and confirmed in the Electronic Batch Record.

When there was a BOM in the EBR, a comment was made explaining why that BOM was generated. Once this verification of materials was done, Trackwise and Maximo were verified to see if there were any Non-conformance or Work orders. If any of these were opened, an exception was made to the TR or WO. The associated MOs were also verified. To release a manufacturing order, these associated MOs must be removed. As part of the Batch Record Review process, an audit trail of the testing equipment was performed. Once the audit trail was made, the CQA and exceptions were acknowledged by PQA personnel. Supplementary documents were reconciled. After all, this was reconciled, MFG and PQA signed the corresponding reviews and proceeded to terminate the manufacturing order. Once all this was terminated, the MO was circulated and released.

During the execution of this project, four manufacturing process lots were used. These manufacturing process lots are listed in Table 1. These batches belong to the manufacture of High Cholesterol Drugs. This drug is used in adults with cardiovascular disease to reduce the risk of heart attack, stroke, and certain types of heart surgery. Before the company can release these batches to patients in need, supervisors conduct batch record reviews to ensure that these batches are manufactured to the highest quality and in compliance with regulations and standards. This batch record review is a vital part of the product's manufacturing. Everything that has to do with the manufacture of a lot has to be documented. For this, we use good documentation practices. Good documentation practices are techniques for writing and correcting records and information to ensure traceability, credibility, and validity.

Table 1
High Cholesterol Drug Lots Used for Project Execution

High Cholesterol Drug Lots Manufactured
10650610
10650611
10652132
10650613

The method used to carry out this batch record review was documentation, interviews, and direct observation. During the review, the researcher realized it took a long time to get the batches out and release them. This is due to different factors such as lack of assessments of the alarms generated in the manufacturing processes by the process engineer, comments on why the bill of material (BOM) was generated in the manufacturing batches, data that the EBR did not acquire or was incorrectly acquired, functional areas that are directly related to the batch record review not available, communication problems, binders for the reconciliation of supplementary documentation with the batch under review not fully prepared, associated manufacturing orders not released, right first time, real-time review, open investigations and open work orders. Another factor that influenced the batch record review that caused it to be inefficient had personnel needing proper training and experience doing the review.

All manufacturing processes generate alarms. These alarms are alerts the system produces if it finds something unsuitable during the manufacturing process. For this, there is the process engineer group.

Process engineers are dedicated to designing, implementing, and optimizing operations. The process engineer assesses these alarms to verify that everything runs under control and that validations establish the parameters. Due to other situations during the shift, these assessments take time to complete because no process engineer is available. This caused the assessments to be pending for up to three weeks, preventing batches from being released in a maximum of seven days. On other occasions, if the evaluations were carried out on time, having an effective batch record review.

For manufacturing processes, there is a list of materials that will be used to manufacture a product. These materials are taken out to deduct the material used from the system. A BOM is made when a material is not found in the order. A bill of material, or BOM, is a structured list of all the components and their quantities that make up an assembly. These BOMs are made a comment justifying why that BOM was made at the time of creating it. During the batch record review process, it was observed that most of these BOMs needed the proper justifications. These justifications were made during the batch record review process.

There is a bigger problem regarding the process of batch records. This problem is that the EBRs are not acquiring the correct data or do not acquire the corresponding data, and the step remains in transition. This problem is critical since, based on the data it receives, the EBR performs some calculations. If this data is correct, the calculations are correct. If this happens, an assessment must be carried out. MES specialists carry out these assessments. This problem can cause batches not to be released in a short time. For example, during the review of batch 10652132, some data was acquired that did not belong to that batch. An assessment had to be made, and corrections were made with the correct data. All this caused the lot to be released two days before the disposition due date. This could be done thanks to the efforts of manufacturing personnel, EBR leads, process owners, and QA.

The creation of binders for the manufacturing lots needed to be completed. These binders consist of a folder with a cover. They are divided by station or manufacturing process, which is understood as chromatography column, viral inactivation filtration, ultrafiltration, diafiltration, and bulk fill. According to the checklist, the time established for creating this binder is 30 minutes, so this binder complied with this established time.

Batch record reviewers must have all key people available to release a batch. Sometimes these key people are unavailable, affecting the time a batch is released. This lack of availability may be due to factors such as absent personnel, personnel undergoing training, personnel solving other situations, etc. As part of our batch record review, there are some associated manufacturing orders. To release a process batch, those associated manufacturing orders must be released. This also affects the release time of a batch process. In process batches, the right first time often needs better documented. This causes us to have to find who executed the step so that they can make the corrections. If a manufacturing order has investigations or open work orders, these must be closed and referenced in the process manufacturing orders. Real-Time Review significantly affects the batch record review. This can lead to a pile-up of batches to be reviewed. So, it affects the due release date of the batches.

As part of the project, a checklist and a workflow were created as a guide in the batch record review. To measure how practical these guidelines can be, two resources from the manufacturing area were used to carry out a batch record review following the checklist and the workflow. One of these manufacturing resources didn’t have much experience performing batch record reviews. With this, we wanted to test how practical these guides could be for a person with limited experience doing batch record reviews. The manufacturing resource argued that it could perform batch record reviews effectively by performing batch record reviews with these guidelines. The help was unaware of some terms in the batch record review. Once he had an overview of the batch record review process, he could run the review without significant issues. During this batch record review process, a total of

six resources were used: two from manufacturing, two from QA, and two from the process owner.

CONCLUSION

One of the most crucial tasks at a pharmaceutical company is records review. These reviewers ensured that the batch was produced correctly and followed the protocol and legal standards. Reviewers must pay close attention to detail, be self-sufficient, and be well-versed in the manufacturing process they are evaluating. Reviewers should be conscious of the criticality of their work.

QA and operations can find mistakes by analyzing the batch record before making the product available to the general audience. The corporation can avoid paying thousands of dollars in fines and preserve regulatory compliance by doing these assessments. According to best practices, the BR must be error-proofed using a precise technique to ensure that the human and document interface is error-free. The way needs are presented and organized should follow a clear pattern that is helpful to the user. The BR should also reflect the operator's task order. The BR shouldn't require many transcriptions or mental calculations. Only the necessary details should be entered. Parameters that are crucial or license-related must be emphasized to ensure the operator understands them. For parameter outputs, the difference between the target and the required should be clear. Additionally, a statement of policy and concept is required to prevent the BR's simplicity and effectiveness from deteriorating over time due to extra declarations, checks, and signatures resulting from improperly designed corrective action and preventative action improvements.

An improvement opportunity was identified during the process of batch record review. According to all the analysis established in the results and discussion section, some of the batches used to execute this project had no problem releasing it in just 72 hours, following the due procedure and noting that there were no significant problems when making batch record reviews. On the other hand, it was observed that there was a batch in which the review took approximately 504 hours to complete because a real-time review needed to be carried out. The real-time review helps us identify the problem early in the batch record review process and be able to solve it quickly. In this case, this did not happen, being released forty-eight hours before the disposition due date. This delay can cause the product not to reach the patients who need it on time for treatment.

As initiatives to improve working with the Batch Record Review, a Sr. Associate Manufacturing created a Visual Aid to generate exceptions and a Flowchart to work with the Batch Record Review during the shift.

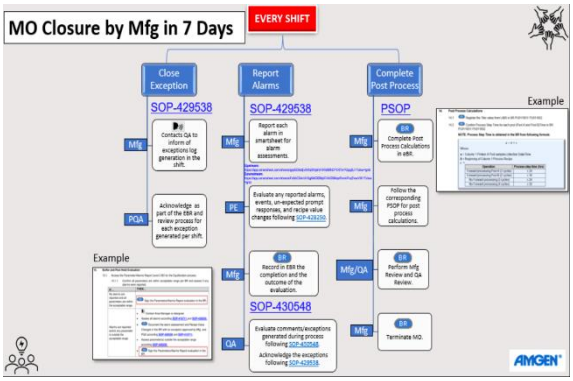

Figure 5
Visual Aid for Batch Record Review

REFERENCES

[1] S. Schniepp, "A Look at Batch Record Review," *Pharmaceutical Technology*, Vol. 41 No. 8, pp. 65-66, August 2, 2017. [Online]. Available: https://www.pharmtech.com/view/look-batch-record-review. [Accessed: October 10, 2022].

[2] Solutions, M. *Top 7 Benefits of Electronic Batch Records (EBRs)*. Merit Solutions - Empowering Growth & FDA Compliance, June 30, 2022 [Online]. Available: https://meritsolutions.com/top-7-benefits-of-electronic-batch-records-ebrs/. [Accessed: October 10, 2022].

[3] L. M. Monday, "Define, Measure, Analyze, Improve, Control (DMAIC) Methodology as a Roadmap in Quality Improvement," *Global Journal on Quality and Safety in Healthcare*, Vol. 5, No. 2, pp. 44–46, 2022. [Online]. Available: https://meridian.allenpress.com/innovations journals . [Accessed: October 10, 2022].

[4] SYDLE. *¿Qué es el workflow y cómo puede aumentar la productividad?* [Online]. Available: https://www.sydle .com/. [Accessed: October 10, 2022].

[5] PTD-400625: Evolocumab (AMG 145) HMP Purification Process Transfer Document for Commercial Manufacturing.