Audit Process Optimization in the Manufacturing Area

Author: Alexander Ortiz Martinez
Advisor: Rafael Nieves Castro, PharmD.
Industrial Engineering Department

Abstract

This project was developed with the intent to demonstrate a viable audit process optimization in the manufacturing area. The AbbVie site ubicated in Barceloneta Puerto Rico started with only once product back in 2003, by the end of 2021 the site has become a multidrug facility with six products. This increase in production has a higher requirement in audit. Release by exception will help to mitigate the audit time and keep the production running as business need. This project is a recommendation to accommodate the reality of the site. The use of a manufacturing execution system (MES) is common in the pharmaceutical and biotechnological industries to perform the activities related to the manufacturing of a product. This tool, MES, have the potential to benefit the audit of the process reducing the time to achieve a faster lot release. Using the DMADV framework on this project improve the audit cycle time.

Introduction

As the manufacturing requirements keep increasing to comply with the customers and patients. The release of batches is crucial to be completed on time. Our biopharmaceutical industry relies upon the use of Manufacturing Execution System called POMS. This system has the capability to document the process and the execution of the operator in the process and communicate with other platforms like SAP, DeltaV.and POMS, a manufacturing execution system known as MES helps to record any deviation of the standard operating procedure through an exception. Before 2014, we only manufactured Adalimumab in our bulk drug facility, but now we have two additional products (Vedolizumab and Risankizumab). Each product has a regular formulation and high concentration formulation.

The MES system records all the exceptions, deviations, and Investigations generated. The Quality Assurance team evaluates and resolves the discrepancies. Once all the exceptions are resolved, the batch is released to the market. The resolution of the exceptions could take up to three to six months to release one batch once the execution of the batch.

Background

The purpose of this research is to help maximize the audit process through POMS to achieve the release by exception of the manufacturing runs through the review of Electronic Batch Records (EBR's) in AbbVie Biotechnology Ltd at Barceloneta Puerto Rico. In the ABL facility, the audit process could take up to six months to resolve all the exceptions related to one batch. There are opportunities across departments to streamline the process and take a reasonable time to complete the resolutions of the discrepancies. The MES has the capability to record any operation, equipment status, and EBR's. Redundant documents such as logbooks or process documents should be consolidated if the data is duplicated.. The QA team will be more available to do frontline audits on the manufacturing floor.

Problem

This research aims to find a viable way to reduce the audit time of each batch, increasing the release of commercial lots within the expected date. In addition, eliminating any redundant data or documents.

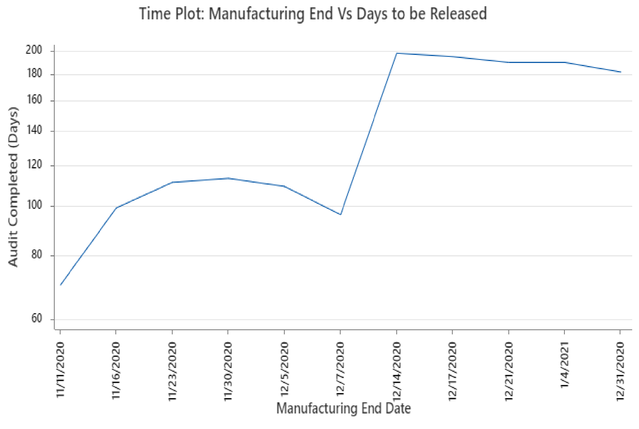
Methodology

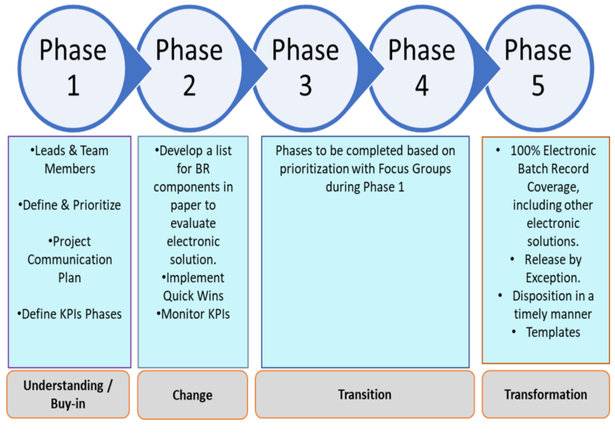
The purpose of this research is to reduce the time auditing the batches to streamline the release of the products. Although this project will use the DMADV (Define, Measure, Analyze, Design, Verify), I will be challenging the site's design process. The company will benefit from these changes if implemented because AbbVie has been certified by the FDA as a multiproduct facility. In DMADV, a business process is analyzed to find options that will help satisfy the customer's needs and specifications.

- **Define** — The define will be used SIPOC and a VOC to establish the rage of what it really intended to accomplish in this project
- **Measure** — The data will be collected the following. For this project, the purpose will be to use only 11 manufacturing runs to compare the start and release of the lot through SAP.
- **Analyze** — In analyze, all the data collected will be collected and the survey results will be classified per category. As this project seeks to improve the audit process a team proposal will be summited to implement the project in the future. Also, new applications or technologies need to be evaluated to have full electronic recipes . Therefore, evaluate data to provide a proposal for short-term and long-term implementation .
- **Design** — An action plan will be presented on how the project should move to reduce the audit time and reduce redundant data in a lot, using people as primary resources as subject matter experts.
- **Validate** — In verify, a control plant will be designed to aid and minimize the variability when the team executes the project. This action plan needs to include recipe configuration if required. The generation of what the QA must audit prior to the lot release. Validation of the new design.

Results and Discussion

Supplier	Input	Process	Output	Customer
System	SAP (Order / Batch / BOM / Insp Lot)	QA Batch Record Review	Revised recipe by QA	Material Management
	POMSnet – MES (Recipe, Equipment Log)		Recipe disposition in SAP	
	LIMS (QC results)		Certificates	
	PCS (alarms, controls, recipes, formula)			
	PI			
	PLC			
	Maximo			
Manufacturing	Executed BR			
	Logbooks			
	Supporting Data (i.e., Charts, attachment, autoclave, filler report, etc.)			
	Open MES Exception (during batch execution)			
	Worksheets			
	Equipment Cleaning Certification			
	MFG BR and package			
Quality Control	Results, Environmental Monitoring			
Validation	Protocols Closure			
MQA	Discrepancies resolution			
QA BRR	Alarms Certification			





Results and Discussion Cont.

The System Integration to the same electronic batch record: Delta V, SAP, LIMS, POMS, Maximo, PI. Ex. alarms, differential pressure, scale standardization, etc., could help reduce redundant worksheets or generation of EBR's that need to be audited in the end. For example, adding a scale standardization in the main recipe would eliminate the need to create manual logbooks of critical actions prior to the execution. Manual entries for potential configuration (Equipment log, status in EBR, etc.) Simplify the recipe to avoid unnecessary steps. Reduce manual entries; the manual entries are the primary offenders in the manufacturing floor. For example, SAP could retrieve an expiration date and portray that data on the EBR. Create WKs to eliminate logbooks or manual entries. Ex. WFI flush, link status in EBR. Maximize systems interactions. Before implementing "Release by Exception," the manufacturing team must perform a critical steps gap assessment on data acquisition. The system links one MES exception to several steps instead of having multiple exceptions related to the same event. Define target date to complete discrepancies, real-time or within days, if complex, will set the mark a window time to the release of the batch. Create Dashboard for visibility and tracking of open MES exceptions per run in MES to send notifications once MES exception is generated. Evaluate language barrier for instructions and documentation. QA support 24/7 is crucial to achieving the resolution of exceptions in time.

Conclusion and Future Work

The use of MES, POMS in the case of our site the tool is not exploited to benefit the QA team and the operators on the site. The risk assessment was not performed accordingly with the increase of manufacturing runs during the years. The site started with only 15 manufacturing runs, and now the site is expected to run 130 runs per year. This project will be a great tune-up of the system and move the plant to a Release by Exception Site. The electronic batch records will aid the operators to achieve great results while manufacturing the product and the QA team to audit faster each step in the manufacturing process. A task path was performed if followed the

Acknowledgements

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References

[1] "Guidance for industry," *U.S. Food and Drug*. [Online]. Available: https://www.fda.gov/files/vaccines,%20blood%20&%20biologics/published/Guidance-for-Industry--Considerations-for-Plasmid-DNA-Vaccines-for-Infectious-Disease-Indications.pdf. [Accessed: 12-Dec-2021].

[2] M. Naedele, H.-M. Chen, R. Kazman, Y. Cai, L. Xiao, and C. V. A. Silva, "Manufacturing Execution Systems: A Vision for managing software development," *Journal of Systems and Software*, 29-Nov-2014. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0164121214002532. [Accessed: 30-Oct-2021].

[3] "Part 11 electronic records electronic signatures scope and application," *U.S. Food and Drug Administration*, Sep-2003. [Online]. Available: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/part-11-electronic-records-electronic-signatures-scope-and-application. [Accessed: 01-Jan-2022].

[4] R. Majumbar and K. Selvi, "Six sigma-overview of DMAIC and DMADV," *Research Gate*, 05-Apr-2014. [Online]. Available: https://www.researchgate.net/publication/346081379_Six_Sigma-Overview_of_DMAIC_and_DMADV. [Accessed: 25-Nov-2021].

[5] T. Lambrechts, "7 key requirements for electronic batch records for GMP processes," *MyCellHub*, 10-May-2021. [Online]. Available: https://mycellhub.com/7-key-requirements-for-electronic-batch-records-for-gmp-processes/. [Accessed: 10-Dec-2021].