Audit Process Optimization in the Manufacturing Area

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Abstract *— This project was developed to demonstrate a viable audit process optimization in the manufacturing area. The AbbVie site ubicated in Barceloneta, Puerto Rico, started with only one 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 the audit. The implementation of Release by exception will help mitigate the audit time and keep the production running as business needs. This project is a recommendation to accommodate the reality of the site. The use of a manufacturing execution system (MES) is expected 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 can improve the audit cycle time.*

Key Terms *—Audit, DMADV, MES, Release by Exception.*

PROBLEM STATEMENT

As the manufacturing requirements on ABL grew, the site needs to achieve a faster way to audit the lots. The release of batches is crucial to be completed on time. ABL is a 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, ABL only manufactured Adalimumab in our bulk drug facility, but now ABL 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 (QA) 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 is completed.

Research Description

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 (ABL) at Barceloneta, Puerto Rico.

Research Objectives

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 and eliminating any redundant data or documents.

Research Contributions

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 contributions are not limited to the release of the commercials running faster and the reduction of redundant material. 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 cost of storage of these documents or the generation of these documents will be reduced. The operators will be less susceptible to

generating errors in documentation. The QA team will be more available to do frontline audits on the manufacturing floor.

LITERATURE REVIEW

Manufacturing Execution System (MES)

"Manufacturing Execution Systems (MES) is a dynamic information system application that drives the execution of manufacturing operations. MES guides, triggers, and reports plant actions as events using current and correct data" [1]. The MES collection functions supervise production activities from the point of order release into manufacture to the end of the shipment. MES used as defined helps to communicate across any process control system. MES does not execute, but collects, analyzes, integrates, and presents the data generated by the operator leading to the predictivity of the process. Some of the benefits of having MES are:

- Supply chain optimization through better workflow controls better and real-time documentation steps.
- Improve data quality assessing process and products.
- Visibility and transparency throughout the entire production process: only deviations are to be analyzed.
- Reduction of storage cost for work-in-progress material due to decreased lead time.
- Reduction of administrative work for maintaining manufacturing documents.
- Better decision-making process through easy access to current data and information for all critical business cases.

Release by Exception

Release by exception is likely if the process is well characterized and important process parameters and quality features are well defined and understood. The product (or intermediate product) will be released automatically if there are no deviations in the manufacturing process.

This can be a hassle for many processes, but there are undoubtedly many tools that allow businesses to approach this goal. Previous posts, such as Implementing Process Analysis Technology (PAT) and Continuous Process Validation, focuses on some technologies and features that could support this effort. As a rule, manufacturers can achieve these goals with tools that eliminate process variability, enable error-free production for the first time, and enable real-time measurement of critical quality features. To reduce the risk in the implementation process, guidelines for MES design and implementation are as follows [2]:

- Level 4: Business Planning & Logistics (Production scheduling and Operational Management). Establishing the basic plant schedule, material use, delivery, and shipping. Time Frame: months, weeks, days.
- Level 3: Manufacturing Operations Management (Production, QA, Inventory Management). Workflow/recipe control to produce the desired end products. Maintaining records and optimizing the production process. Time Frame: days, shifts.
- Level 2: Workflow/recipe control to produce the desired end products. Maintaining records and optimizing the production process. Time Frame: days, shifts, hours, minutes, seconds.
- Level 1: Sensing the production process, manipulating the production process.
- Level 0: The actual production.

Electronic Batch Record, 21 CFR Part 11

The 21 CFR Part 11 (Code of Federal Regulations) describes the rules that industries must follow to change their paper files to electronic files and, by extension, the authorship of this through signatures. The 21 CFR Part 11 contains three subparts that define the rules to implement and comply with the FDA (Food and Drug Administration). The federal code includes minimum requirements for organizations to change their files from paper to electronic. The implementation of Part 11 seeks the industries' innovation while maintaining the integrity of the documented data. In August 1997, it was implemented and currently covers all electronic

documentation industries. The validation of computerized systems is a pillar within part 11 since it ensures that the data is not corrupted and remains intact, complying with the purpose of 21 CFR Part 11 [3].

Let's start defining what a batch record is. A batch record is a document that provides the complete manufacturing data or a pharmaceutical product. It aims to deliver what is considered a safety and quality of the product being offered. Provides instruction to the operator during the execution of a manufacturing process. Documents exactly how the manufacturing process is conducted.

In ABL manufacturing site auditors have the following documentation to execute a manufacturing process: Standard Operating Procedures (SOP), Process Control Record (PCR), and finally, the MES recipe. The MES recipe is redundant to the PCR; however, is treated as a different type of document. The EBR, as any document in the industry, must follow the ALCOA principles for data integrity, The POMS system complies with ALCOA [4] and data integrity stipulated by the FDA, as shown in Table 1.

Table 1
ALCOA

ALCOA	Paper Based Record	Electronic Record
Attributable	An operator signs off a data entry with his initials, signature, and a written timestamp. Device date must be copied manually.	An electronic signature is related to the operator or device identity and includes a precisely auto-generated timestamp.
Legible	Readability depends on handwriting, paper quality, and storage conditions. Accessibility of physical records is limited, and generating backups is tedious.	Data can be easily read; printed copies can be created. Data can be securely stored in multiple locations.
Contemporaneous	Often requires two operators; one who executes the process, while the other verifies the execution.	Similar, but data generated by a device can be linked to the record.
Original	The original record is the paper on which the data was first written.	Any data representation must be verified to be an exact copy of the data. *
Accurate	Every manual copy introduces a chance on mistakes taking a long time to audit	The digital system can check user input in real-time.

What is needed to release a Batch?

Biological products licensed under the Public Health Act are subjected to Subpart A of 21C.F.R. Part 610 (General Biologics Products Standards).

- 21 CFR §610.1 provides that "no lot of any licensed product shall be released by the manufacturer prior to the completion of tests for conformity with standards applicable to such product . . . " [5].
- 21 CFR §610.2(a) and (b) provide that "samples of any lot of any licensed product together with the protocols showing results of applicable tests, may at any time be required to be sent to the Director [of the Center for Biologics Evaluation and Research or the Center for Drug Evaluation and Research, as appropriate] . . . Upon notification by the Director . . . a manufacturer shall not distribute a lot of a . . . product until the lot is released by the Director . . . [5].

The site needs to submit the following prior to the release of the lot: protocols, results, and samples. The samples are for the agency perform a confirmatory testing of lot. Once the agency reviews all the data and concludes with an acceptable result, the agency will notify the company of the release of

the lot. It should be noted that the FDA does not have a timeframe for lot release. Nevertheless, the FDA agency strives to complete the review in 30 business days once they receive all the required information. On ABL, auditors have an audit cycle time of 45 days this goal is never achieved.

METHODOLOGY

As mentioned earlier, 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) [6], the researcher 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. One batch can take up to one month to be completed right after the process concluded; thus, it can take up two months. In addition, lowering the batch discrepancies percentages can improve the documentation practices, audit practices, and the operator intakes of the process.

The manufacturing execution system, POMS, has all the tools to accurately document each manufacturing process. Three types of recipes generate electronic batch records Main Recipes. These recipes are the ones that work directly on the product (Fermentation and Purification), and Formulations Recipes (Buffers and Media). The Miscellaneous Recipes are the ones that are used to document Clean in Place, Sterilizations, or any process that is required to be completed before any operation. Buffer and Media, Tank Wash, and Miscellaneous recipes belong to Central Services. POMS can record, if well configured, all sorts of data. However, some documents are redundant with the information already stored on the system.

Thus, all batch records must be configured on POMS; this would simplify the audit of a manufacturing run. This will directly impact the audit of batch records by only evaluating the inputs documented in the electronic batch record exclusively. There will be no errors of legibility as wrong dates, smear ink, missing information. This data will be attributable to every step of the process. The tracking of step in process could be verified within minutes instead of searching in archives.

The elimination of the duplicity of documentation, and a complete gasp assessment will ensure all the data is collected as usual. The designing of new recipes templates that integrate systems such as SAP, LIMS, PCS. Outline a strategy of reducing discrepancies and improve or design a timeline to approve the discrepancies within five days of being generated on the manufacturing floor or during an audit.

Define: In the define phase, ABL used SIPOC and a VOC to establish the rage of what it's intended to accomplish in this project. Defining the business case: EBR capabilities are not maximized to optimize the EBR Audit Process. Suggest an improved EBR Audit Process (Release by exception). The scope is to Optimize EBR Audit Process at ABL Site, included an assessment to maximize electronic recipe coverage. Out of Scope Redundant EBR and paper batch record; potential new project for SAP Material Master Data Simplification; frontline BRR; and other variables that impacted release cycle time. Implementation of the proposal will be covered in future projects. Operational Benefit of the project Optimize and Streamline EBR Audit Process (Release by Exception) and agile Batch Record Review process. Recourses required to complete and implement: the Key players / SMEs from Management, BTS, BRR, MQA, MFG, Validation, Technical Area, among others, are needed to assess the current EBR Audit Process and support implementation. Voice of the Customers, a discussion with employees and the managers what they commented on release by exception in the site.

Measure: The data was collected as the following: For this project, the researcher used 11 manufacturing runs to compare the start and release of the lot through SAP. This information will be used later as a metric to identify expectations of the release of the lot.

In the analyze phase data from the manufacturing's runs was acquired to compare the complete audit time of 10 manufacturing runs. This data was analyzed in a scatter plot to see a correlation in data.

It's essential to also verify the audit cycle time entries in the logbooks. The audit time will drop if it is only based on what can be tracked on PCS and only keeping the logbooks of the data that cannot be withdrawn through any system. A histogram with a batch record review data:

- Products in Manufacturing
- Manufacturing Runs
- Batches Release
- Cycle Time Target
- Non-Conformance Reports
- Audit Working Time
- EBR Coverage to Date
- Recipe Executions

Analyze: In analyze all the data collected and the survey results will be classified per categories. As this project seeks to improve the audit process a team proposal will be summited to implement the project in the future. Also, new application and/or technologies need to be evaluated to have full electronic recipes. Evaluate data to provide a proposal for short-term and long-term implementation.

Design: An action plan was presented on how the project should move to achieve the reduce the audit time and the reduction of redundant data in a lot, using people as primary resources as subject matter experts.

Verify: In verify, a control plant was designed to aid and minimize the variability during the time the project is executed by the team. This action plan needs to include recipe configuration if needed. The generation of what the QA must audit prior to the lot release. Validation of the new design.

RESULTS AND DISCUSSION

Define**:** a SIPOC was established. This form process mapping trace and shows how the project needs to be executed.

Voice of the Customer: As part of the define process, the researcher interviewed on the topic to visualize the customers expectations from this project: QA Analyst, Biological Operators and Management. This project impacts operators, QA analysts, supervisors, IT employees. The following is the intake of those interviews and how Design infrastructure supports and sustains this effort (lifecycle). Ex. Templates, validation, so on.

- EBR audit process focuses on manual steps and exceptions.
- QA to start BRR Audit while ongoing in MFG area.
- Data in paper that cannot be in the EBR.
- All products are to be electronically documented.
- Essential to define the sequence of activities and timing during execution.

Some deficiencies can delay the process beyond the use of duplicity of documents. As some employees expressed, the QA needs to start while the manufacturing process is ongoing. This can delay the lot release process or even the discontinuation of a manufacturing batch in later stages of production. All the products that need to be electronically is part of the business requirements. The validation of recipes could take months; the PCR documents are faster to generate than a full recipe on MES, thus convenient to the management. Data in paper or PCR cannot be in EBR, as the redundancy of some steps. Some steps need to be verified on MES to be transcribed in paper. This transcription of data could lead to a documentation error. Essential to define the sequence of activities and timing during execution refers to steps that could have potential impact in the process be verified prior to the end of the manufacturing process and even more if the process is through paper.

Table 2
SIPOC

Supplier	Input	Process	Output	Customer
System	SAP (Order / Batch / BOM / Insp Lot) POMSnet – MES (Recipe, Equipment Log) LIMS (QC results) PCS (alarms, controls, recipes, formula) PI PLC Maximo	QA Batch Record Review	Revised recipe by QA Recipe disposition in SAP Certificates	Material Management
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 Batch Record and package			
Quality Control	Results, Environmental Monitoring			
Validation	Protocols Closure			
MQA QA BRR	Discrepancies resolution Alarms Certification			

Analyze: Maximize Electronic Coverage, an assessment of the list of manual components (paper) not in electronic to evaluate innovative technologies/application / electronic solutions. 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, in the end, need to be audited. For example, adding a scale standardization in the main recipe, would eliminate the need to create manual logbooks of critical actions before the execution. Configuration of electronic batch record to reduce manual entries with a set of pre-selected values. Simplify the recipe to avoid unnecessary steps. The manual entries are the major offenders on the manufacturing floor. For example, SAP could retrieve an expiration date and portray that data on the EBR. Create Worksheets to eliminate logbooks or manual entries. Ex. WFI flush, link status in EBR. Maximize systems interactions.

Table 3
LogBooks in the Manufacturing Area

Logbook Tittle	Frequency	Completed Reviewed
WFI Flush Logbook	Monthly	2 Months
pH Logbook Two Points	Monthly	3 Months
Scales Logbook	Monthly	3 Months

The audit of the logbooks in the manufacturing area is not aligned with the review of the EBR's. When a deviation is generated, the logbooks are not verified to compare the event. This case only demonstrates that there is redundant data to the process, or the use of SAP, LIMS, and others can resolve the discrepancies.

Release by Exception

Before implementing "Release by Exception," the manufacturing team must perform a critical steps gap assessment on data acquisition. This assessment will confirm if the recipe is ready for "Release by Exception." Maximize system capacities to work for us, POMS system at ABL site has an annual cost of $20 million. A system so expensive should be molded to the requirements of the business. Integrate audit checklist in POMs with auto-close if no discrepancies. This tool would move the process faster and reduce the working hours. Frontline from office, real-time audit, or closer.

Develop Templates

To minimize errors and exceptions, new recipes models for the integration systems such as SAP, LIMS, PCS, POMS with templates per area for new recipes should be created. All designs should have a structure/template. This would facilitate the audit for newcomers or cross-departmental training of personnel. These models minimize manual entries that lead to human errors. Manual entries or critical steps should always have a verifier in POMS/MES. Complement instructions with guidelines to reduce EBR information.

Improve Discrepancies Resolution

Training all personnel that works directly or indirectly with the batch records, to engage in discrepancy documentation, should work on that so he/she could improve discrepancies resolution. Training QA approvers in the process to expedite discrepancies resolution. Regular communication to share major offenders to prevent errors across the manufacturing related areas in a non-negative environment. The focus should be on how to stop and approach the event. The assessment evaluates errors (ERs, MES exceptions, manual entries) to improve the recipe and reduce errors. Evaluate recipes with the highest number of exceptions and configuration errors to improve it. 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 open MES exceptions per run 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.

Measure: On site, there are three manufacturing products. Each product has a variation of each one; thus, the QA team must audit six products (Regular Formulation, Concentrate Formulation). Yearly on AbbVie have over 60 manufacturing runs. In the second quarter of the year, the site has only released 12 batches. There are approximately 20,000 hours in audit yearly. Yearly in operations, the operators open a whole 34,750 electronic batches. Table 4 shows how long it takes after the manufacturing run ended.

Table 4

Manufacturing Lot Release

Manufacturing Runs	Manufacturing Run Start	Manufacturing Run Ended	Release Ready
20.18	10/9/2020	11/11/2020	70
20.19	10/4/2020	11/16/2020	99
20.20	10/20/2020	11/23/2020	111
20.21	10/25/2020	11/30/2020	113
20.22	10/30/2020	12/5/2020	109
20.23	11/4/2020	12/7/2020	96
20.24	11/9/2020	12/14/2020	198
20.25	11/14/2020	12/17/2020	195
20.26	11/19/2020	12/21/2020	190
20.27	11/24/2020	1/4/2021	190
20.28	11/29/2020	12/31/2020	182

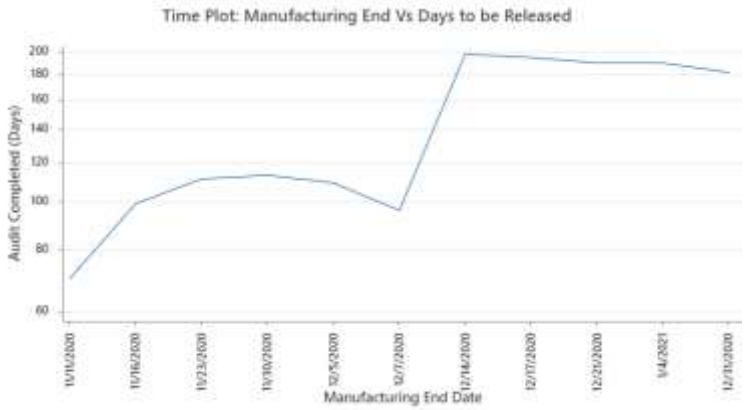

Figure 1
Graph: Time Plot, Manufacturing End Date VS Days to Be released

The data collected on table 4 shows an average of 141.18 days from one lot to be completed and released.

Design: A focus group with subject matter experts to move forward with the project. There should be six focus groups with their experts.

- Enhance Discrepancies Resolution
- Template Creations and Modeling
- Frontline Audit
- Electronic Coverage
- Release Cycle Time

The researcher advised five phases to ensure all the gaps will be covered. Communication across teams will be crucial to completing the process.

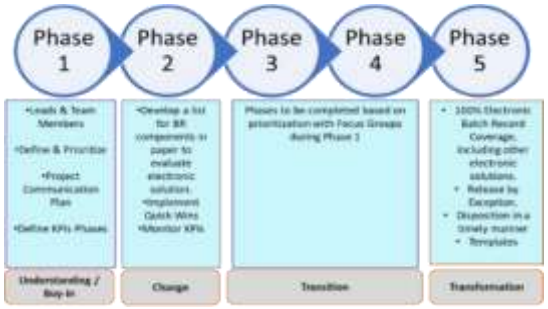

Figure 2
Road to Implementation

Table 4 shows how long the lot takes to be released after the manufacturing run ends. The site has 45 days after the manufacturing run ends to complete the audit of all EBR's and logbooks associated with the run.

Verify: Table 5 clarified how the process needs to be performed to be completed. The four primary manufacturing areas (Inoculum, Fermentation, Capture, and Purification) will evaluate the recipe or EBR to streamline the release by exception process. Not all the exceptions generated in each area are the same. Each area must use historical data through QA to determine the significant offenders in exceptions, deviations, or non-conformance results.

Table 5

Task Path

ID	Task Name	Duration	Predecessors
1	Recipe Evaluation and Revision	275 days	
2	Inoculum	185 days	
3	Discrepancy and MES Exception Evaluation	45 days	
4	Validation/Recipe Configuration Evaluation	45 days	3
5	Recipe Changes	95 days	
6	Generate Change documentation and batch record review plan	21 days	4
7	Make recipe changes	60 days	6
8	Complete Validation Documentation	14 days	7
9	Fermentation	200 days	
10	Discrepancy and MES Exception Evaluation	60 days	
11	Validation/Recipe Configuration Evaluation	45 days	10
12	Recipe Changes	95 days	
13	Generate Change documentation and batch record review plan	21 days	11
14	Make recipe changes	60 days	13
15	Complete Validation Documentation	14 days	14
16	Capture	265 days	
17	Discrepancy and MES Exception Evlaution	40 days	
18	Validation/Recipe Configuration Evaluation	45 days	
19	Recipe Changes	96 days	
20	Generate Change documentation and batch record review plan	21 days	18
21	Make recipe changes	60 days	
22	Complete Validation Documentation	14 days	21
23	Purification	195 days	
24	Discrepancy and MES Exception Evaluation	40 days	
25	Validation/Recipe Configuration Evaluation	45 days	
26	Recipe Changes	95 days	
27	Generate Change documentation and batch record review plan	21 days	25
28	Make recipe changes	60 days	27
29	Complete Validation Documentation	14 days	28
30	Central Services Group 1 (Weight and Dispense)	190 days	
31	Discrepancy and MES Exception Evaluation	50 days	
32	Validation/Recipe Configuration Evaluation	45 days	31
33	Recipe Changes	95 days	
34	Generate Change documentation and batch record review plan	21 days	32
35	Make recipe changes	60 days	34
36	Complete Validation Documentation	14 days	35
37	Central Services Group (Buffer and Media Preparation)	190 days	
38	Discrepancy and MES Exception Evaluation	50 days	
39	Validation/Recipe Configuration Evaluation	45 days	38
40	Recipe Changes	95 days	
41	Generate Change documentation and batch record review plan	21 days	39
42	Make recipe changes	60 days	41
43	Complete Validation Documentation	14 days	42
44	Central Services Group (Glasswash and Autoclave Area)	190 days	

45	Discrepancy and MES Exception Evaluation	50 days	
46	Validation/Recipe Configuration Evaluation	45 days	45
47	Recipe Changes	95 days	
48	Generate Change documentation and batch record review plan	21 days	46
49	Make recipe changes	60 days	48
50	Complete Validation Documentation	14 days	49
51	Complete Risk Assessment	44 days	

CONCLUSION

The use of MES, POMS tool in the case of ABL site is not exploited to benefit the QA team and the operators on the site. The risk assessment was not 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. 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. 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.

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