RELEASE BY EXCEPTION PROJECT DESING OPTIMIZATION

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Abstract

Pharmaceutical companies are trying to improve the adverse effects that technology brings with the change in documentation. Going from a paper record to an electronic record is a new challenge that must be absorbed and implemented as a growth projection.
The objective of this study is to implement the Release by Exception, analyzing, and obtaining only the critical steps of the process that must be complied according to regulation requirements. At the same time, this study contemplates improving other areas that guaranteeing the release of as many batches as possible. In other words, optimize the process to make it more efficient and effective without forgetting critical details. The research question is the following: What improvement strategy can be achieved under the implementation? In this context, the use of the Lean manufacturing principles and DMAIC methodology through the analysis of a representative sample of 30 manufacturing lots provides the way to achieves the objectives.
The implementation of this project indicates that, under a redistribution of the certified assigned personnel, the determination and justification of the critical steps and the reduction of open exceptions, reflects that a single batch of Adalimumab currently takes between 51 to 58 days from manufacture to final approval by Quality department as expected.
Key Terms - DMAIC, Electronic Record, Release by Exception, Quality department.

Introduction

The audit and compliance process are a guarantee that the product complies with the specifications and regulations required by the 21 CFR Part 210 and 211. Given the complexity of the process, certified experts are required to guarantee the above to be approved and authorized to market. The time of the resource, experience, education, effort invested in the process and documentation required is a complex one, therefore it takes time, but this time cannot be excessive that creates an impact on the industry. In a normal process, in a pharmaceutical industry that works parenteral biological can approve and release between 3 and 4 batches per month with all its process and phases completed. It was estimated that the audit process per record require between 400 to 550 man-hours with an Electronic Batch Record process implemented [4]. To achieve this goal Release by Exception is the main factor to reduce cycle time in audit process.

Background

The implementation process of the EBR's brings benefits such as automation, configuration validation, error reduction, and even provides the opportunity to view and work in line according to the flow of the process.
There are many benefits to using a properly designed EBR for example, documentation errors will be reduced, missing entries will be removed, and adverse results will be reported immediately [1]. Manual data entry errors occur in one in 100 entries, and a batch record in a single batch can contain multiple errors. These inputs can be as high as 47% of 100%, and studies indicate that the causes of this are 40% equipment-based, 40% operator-based, and 20% caused by other problems. Therefore, two out of five batches are due to operator errors. Electronic Batch Recording System (EBR) can reduce manual data entry times by at least 60% and create a larger flow for the layout of a record (Figure 1) [3]. The Food and Drug Administration (FDA) regulation has as a requirement that all exceptions to the process must be investigated signed and closed before the batch is arranged the sale to the market [2].

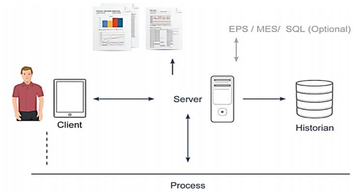
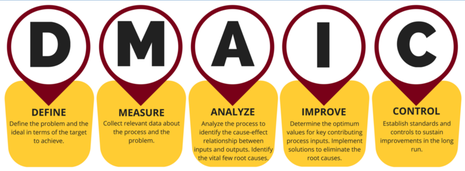


Figure 1: Data consolidation process in Electronic Batch Records [1].

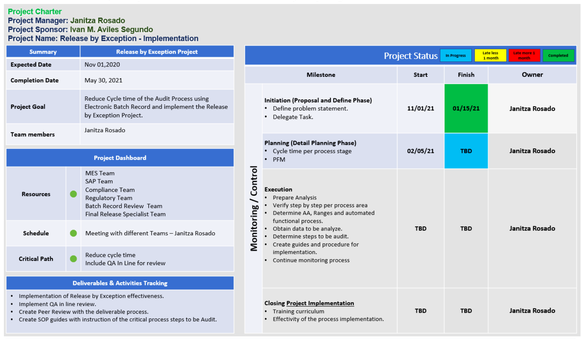
Problem

- Reduce and improve audit process cycle time.
- Create and implement guides of critical steps per process validation ensuring compliance.
  Increase the batch release process throughput from 1 to 4 per month.
- Identify improvement in the department, resources, tasks development to create an organization strategy for optimizing the audit process.

Methodology



The Design Project will focus on the type of observational and experimental research that will collect the greatest amount of primary and critical information of the Bulk Drug Substance for Adalimumab process in the parenteral manufacturing industry
The design project will use the DMAIC principles methodology that provides a structure and organization through a series of stages from which we can extract the key elements of analysis to establish improvement. To monitor manufacturing phases for one manufacturing lot of Adalimumab (Inoculum, Fermentation, Capture and Purification) a project charter was created.


Project Charter
Project Manager: Janitza Rosado
Project Sponsor: Ivan M. Avilés Segundo
Project Name: Release by Exception - Implementation

Summary	Release by Exception Project
Expected Date	Nov 01,2020
Completion Date	May 30, 2021
Project Goal	Reduce Cycle time of the Audit Process using Electronic Batch Record and implement the Release by Exception Project.
Team members	Janitza Rosado

Project Dashboard	
Resources	MES Team SAP Team Compliance Team Regulatory Team Batch Record Review Team Final Release Specialist Team
Schedule	Meeting with different Teams – Janitza Rosado
Critical Path	Reduce cycle time Include QA In Line for review

Deliverables & Activities Tracking
- Implementation of Release by Exception effectiveness.
- Implement QA in line review.
- Create Peer Review with the deliverable process.
- Create SOP guides with instruction of the critical process steps to be Audit.

Project Status — In Progress | Late less 1 month | Late More 1 month | Completed

	Milestone	Start	Finish	Owner
Monitoring / Control	Initiation (Proposal and Define Phase) • Define problem statement. • Delegate Task.	11/01/21	01/15/21	Janitza Rosado
	Planning (Detail Planning Phase) • Cycle time per process stage • PFM	02/05/21	TBD	Janitza Rosado
	Execution • Prepare Analysis • Verify step by step per process area • Determine AA, Ranges and automated functional process. • Obtain data to be analyze. • Determine steps to be audit. • Create guides and procedure for implementation. • Continue monitoring process	TBD	TBD	Janitza Rosado
	Closing Project Implementation • Training curriculum • Effectivity of the process implementation.	TBD	TBD	Janitza Rosado

Results and Discussion

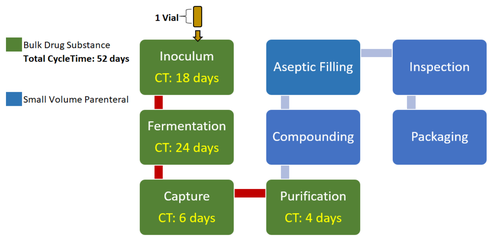


Figure 2: Aseptic/Parenteral Manufacturing Process for Adalimumab

The pharmaceutical manufacturing process of Adalimumab begins with the bulk drug substance process. It comprises 4 phases, starting with adding one vial of protein to the first bioreactor, where it will begin its growth in the inoculation process. After 18 days of inoculation, it continues to the fermentation phase, where the protein content will exponentially increase for 24 days and passes through valves to a viral inactivation in the third phase capture, leaving the protein completely free of viruses and bacteria to finally passes to the purification phase collecting the clean protein used in the syringe filling process known as Small Volume Parenteral (Figure 2).

Each instruction in the EBR of the manufacturing process was evaluated, analyzing the consumption of audit time by both department and, at the same time, the information retrieved from 30 batches was analyzed for the different errors found "exceptions". The exceptions are automatically generated if the system evaluates that within the instruction some established parameter was not met.

	Batch Number	Investigation	Deviation	Exception	Cycle Time days	Process Steps on EBR	Process Steps for Audit	Audit Process Time by MFG & QA hr.	Working days Resources	Total Time days Invested
Inoculum	99842133	0	9	13	18	354	354	42	6	24
Fermentation	99842134	0	14	15	24	2205	2205	56	8	32
Capture	99842135	0	3	10	6	1449	1449	28	4	10
Purification	99842136	0	8	18	4	2949	2949	42	6	10
Total		0	34	56	52	6957	6957	168	24	76

Table 3: Single Batch Record analysis and evaluation per manufacturing process

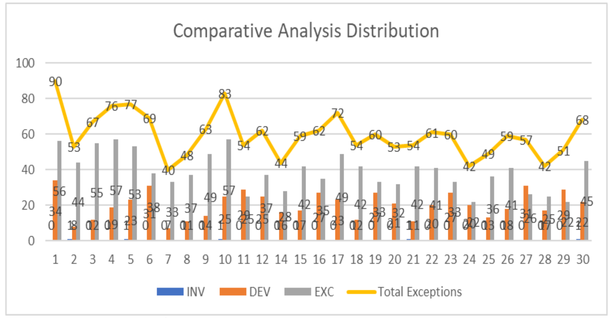


Figure 3: Comparative analysis distribution in a representative sample

The data shows that the amount of EXC generated in a population of 30 lots was higher compared to DEV and INV (Figure 3). The generation of EXC type exceptions was confirmed to be due to data correction errors, input or selection errors, and some notes included as part of the batch.

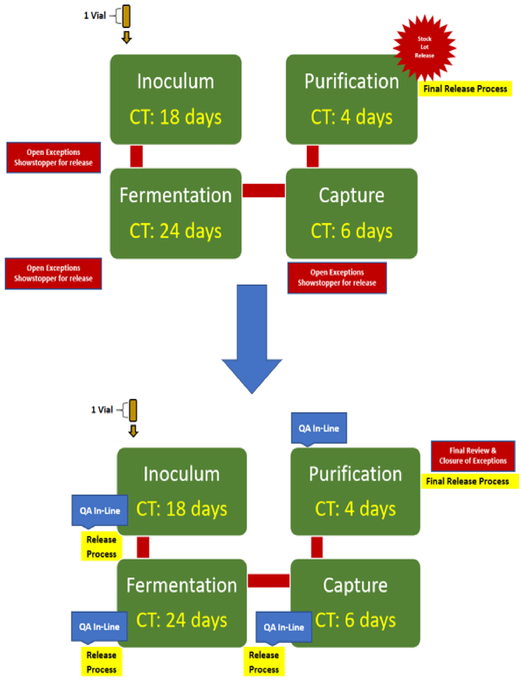


Figure 4: From – To of Bulk Drug Substance Process Flow

QA's In-Line by shifts guarantee that all operations will flow optimally and at the same time, work on all the exceptions or as many of them so that the group in charge of releasing batches the QA Dispositioner's receive them approved, shortening the audit time and consumption of days for the final release (Figure 3).

		Batch Number	INV	DEV	EXC	Total Exceptions	Cycle Time days	Process Steps on EBR	Process Steps for Audit	Audit Process Time by MFG & QA hr.	Working days Resources	Total Time days Invested
1	Previous Audit Process & Release											
	Inoculum	99842133	0	9	13	22	18	354	354	42	6	24
	Fermentation	99842134	0	14	15	29	24	2205	2205	56	8	32
	Capture	99842135	0	3	10	13	6	1449	1449	28	4	10
	Purification	99842136	0	8	18	26	4	2949	2949	42	6	10
	Total		0	34	56	90	52	6957	6957	168	24	76
2	Current Audit Process & Release - Release by Exception											
	Inoculum	99862989	0	2	4	6	18	354	47	2.5	0.36	18.36
	Fermentation	99862990	0	5	6	11	24	2205	239	6.5	1	25
	Capture	99862991	0	2	3	5	6	1449	118	5	0.71	6.71
	Purification	99862992	0	6	7	13	4	2949	327	7	1	5
	Total		0	15	20	35	52	6957	731	21	3.07	55.07

Table 2: Comparative results from previous with actual audit process after implementation of RbE.

All the steps with critical instructions in the Bulk Pharmaceutical Substance process were determined under a risk assessment to define a guide for each phase. A new curriculum and SOP were prepared for the employee to follow the specific instructions of the audit process and release by exception of the process, in addition, a certification structure was carried out for new personnel of the Quality department. The release by exception implementation was executed reducing audit time, redistribution of personal resolution and exceptions on time. Actions were documented under peer review 92637608 (Release by Exceptions Traceability Actions) to trace all analysis process. Implementation of RbE were documented under protocol ALTD-BA089562-2017 with approved training certification guidelines forms created with the critical step evaluation QA-05674-17.
The data shows the effectiveness of staff distribution with a significant reduction in the generation of exceptions and that the 76 days invested in the execution, formulation, review and release of a single batch of Adalimumab was reduced to 55 days with the new structure of RbE. An estimate cost avoidance per single batch of Adalimumab were 12,565.56 of time invested per resources.(Table 2).

Conclusions

Through the analysis performed as part of the strategy to reduce audit time for the release of a batch, it was possible to implement this release structure by exception in each phase of the parenteral process, determining the critical steps to be audited, in turn, incorporating the new structure of the Quality personnel to attend on time the opportunities in the live process, enabling personnel by shift and phase of the process, making the final release process more versatile, arriving on time with the exceptions approved and ready for the final verification and disposition.
The time reduction in auditing a complete batch of the parenteral manufacturing process for Adalimumab was reduced to the following: Inoculation phase from 42 hours spent between 2 resources was reduced to 2.5 hours of verification and release phase. Regarding the fermentation phase of 56 hours spent between 2 dedicated resources, it was reduced to 6.5 hours of verification and release. The Capture phase, from 28 hours invested with 2 dedicated resources, was reduced to 5 hours of verification and release and, finally, the Purification process, from 42 hours invested with 2 dedicated resources, was reduced to 7 hours of verification and compilation of final documentation for final disposition of the batch. With the previous process, a total audit of 168 hours was dedicated with the limitation of releasing a greater number of lots per month and stagnation of lots to be audited, so that up to 2 lots per month were released. Compared to the new structure and implementation of changes, only 21 hours are invested by the audit, releasing up to 4 lots per month. A structure of 8 resources, 4 of which changed from MFG auditors to In-line QA and the other 4 resources dedicated exclusively to batch release and other tasks relevant to final disposition as QA dispositioners enabled the ability to streamline the process. This represents a total reduction of 147 hours, an improvement in process and an organizational structure in the Quality department capable of meeting other business needs. Project optimization was recognized and awarded at plant level along with all the people involved for the completion of such effort with the Excellence Award.

Acknowledgements

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