Release by Exception Project Design 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 guarantee 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 Release by Exception with DMAIC method indicates that, under a redistribution of the certified assigned personnel, the determination and justification of the critical steps and the reduction of open exceptions, 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.*

PROBLEM STATEMENT

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 [1]. To achieve this goal Release by Exception is the proposed strategy to reduce cycle time in audit process.

Research Description

The Quality Assurance Department is responsible for releasing the batches processed in the pharmaceutical and medical device industries. An important part of the batch release process is the audit of the production batch records following the 21 CFR Sec. 820.80 Receiving, in-process, and finished device acceptance. The batch record audit process consists of verification of process parameters, acceptance activities, inspection of the process and data collection.

This Design Project will be performed in a Biological Pharmaceutical industry plant located in Puerto Rico since 1969. The batch record audit process originally consisted of a paper-based system, averaging a total of 1,950 pages per batch record. Due to the high number of pages and the complexity of the task performed, the audit process required many man-hours to complete.

During 2014, an initiative to automate this process was implemented which consisted of configuration and validation of Manufacturing

Execution System (MES) avoiding the paper batch record execution from operator and document control. This implementation was successfully established and complete for the manufacturing process.

With the MES system new systematic implementation arises the concern and a problem that the required in the time, resources, and money is greater than expected, impacting then the operational costs and delivery. The Quality Assurance Batch Records group consists of 8 dedicated employees and processes an average of 1 or 2 batch record's release per month. However, the Batch Records area receives an average of 4 to 6 batches per months, which creates a bottleneck, delaying the availability of the lots and incrementing the need for overtime to increase the throughput of the area.

Research Objectives

- 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.

Research Contributions

This design project supports the overall goal of the Quality Operational Excellence Company with zero customer complaints and federal drug administration (FDA) observations/warning letters/field alerts related to insufficient final pharmaceutical device release documentation or observations found in the process. By automating audit verifications, reducing time, and freeing up more batches in the company is what ensures the efficiency, security, and compliance requirements, therefore, brings customer reliability and profit from it.

The main contributions of this project will be to improve the total audit cycle time, optimization of quality controls, increase batch release throughput from 1 to 4 per month, and to create new procedures to implement under Quality System. The objectives of this project are reducing the process time to complete final release only verifying critical steps under guides implemented avoiding evaluation of full batch record. Automated electronic system, validated and assure properly configured acceptability ranges, eliminating redundance verification. Optimizing and implementing Release by Exception project reduce time, costs, unnecessary resources and increase in profits to the company, product duplication and increased inventory with the ability to generate more future products.

LITERATURE REVIEW

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.

The content of an electronic system is dictated by regulation, in this case pharmaceutical industry governed by the federal regulatory code 21 CFR Part 210 and 211 seeks to incorporate all traceability data collection to are attached within the EBR as retention including the signature of the people who execute, approve, and revise 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 [2]. 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. On the other hand, the average review for batch record is 48 hours depending on the process and its complexity and some entities have reported that a full batch record review takes up to 500 hours, approximately 71 days. An 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]. This combination of having an electronic system incorporating in line auditing by quality personnel and with release by exception helps reduce the risk of non-compliance to the company the efficiency will improve by eliminating paper batch records, reducing review data and duplicity in reviews reduce costs, reduce cycle time and increase product performance, thus improving performance. Finally, the batch will reach the end of the process with almost no exception open to allow faster release of the final product. The goal is reducing the number of exceptions that arrive open at the end of the final phase to release due to 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 [4].

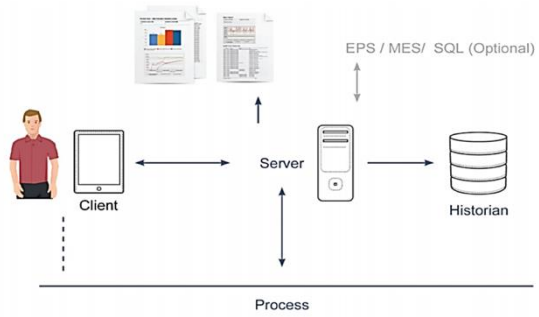

Figure 1
Data Consolidation Process in Electronic Batch Records [2]

The implementation of Release by Exception is the way to achieve the final improvement to the audit process for cycle time reduction and efficiency. Release by Exception arises from the need to shorten the disposition and audit time of the process by its complexity, so the company need to capture those necessary and critical steps of auditing through the configuration performed in the Electronic Batch Record (EBR) such as data integrity steps. Release by Exception implies that the exceptions can be reviewed and addressed in real-time, not after the fact, which is typical for paper-based workflows. By moving to a paperless workflow, the number of exceptions can be reduced as the manufacturing rules are enforced in real-time optimizing the audit process as in line review.

The total cycle time of a single batch of Adalimumab for release is currently between 71-78 days with 8 resources dedicated to each part of the process. An average of 1 or 2 lots are released per month. As shown in the Table 1 current process has a duplicity in audit efforts by MFG and QA.

Table 1
Current Manufacturing Process of the Product: 1 Single Batch of 4 Phases

Process	Cycle time in MFG	Audit days revision in MFG	Audit days in Quality	Total of days for Disposition	Cycle time in MFG
Inoculum	18	3	3	24	18
Fermentation	21-25	4	4	29-33	21-25
Capture	5-7	2	2	9-11	5-7
Purification	3-4	3	3	9-10	3-4

As shown in table 2, the project proposes eliminate the audit process by manufacturing area as per process flow. With the implementation of Release by Exception the layout of a batch is estimated to be approximately 51-58 days, that with 4 resources dedicated to each part of the process, approximately released between 3 to 4 lots per month. This can be possible incorporating audit and in line verification by the quality department for exception resolution and compliance verification according to the guidelines that will be established and eliminating the duplicity in reviews.

Table 2
Proposed Manufacturing Process of the Product:1 Single Batch of 4 Phases

Process	Cycle time in MFG	Audit days revision in MFG	Audit days in Quality	Total of days for Disposition
Inoculum	18	3	1	19
Fermentation	21-25	4	1	22-26
Capture	5-7	2	1	6-8
Purification	3-4	3	1	4-5

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. All the steps of the process will be evaluated with an analysis of the systematic evaluation to determine which steps per

manufacturing area (Inoculum, Fermentation, Capture and Purification) it is necessary to evaluate in order to eliminate audit process redundance and cycle time implementing Release by Exception. The design project will use the DMAIC method (Define, Measure, Analyze, Improve and Control) a tool that provides a structure and organization through a series of stages from which we can extract the key elements of analysis to establish improvement.

Define Phase

- Interview to Quality Control, Compliance, Regulatory, Quality System personnel to understand problem.
- Confirm Scope and Problem Statement with team members from Production, Batch Record Review, MES and SAP Electronic system and Final Release personnel.
- Delegate task per functional area of the process.

Measure Phase

- Measure current process cycle time for the Audit process.
- Measure process steps of the Inoculum, Fermentation, Capture and Purification process EBR's.
- Verify systematic configuration process per process steps with MES team.
- Complete Process Flow per process stage Inoculum, Fermentation, Capture and Purification process.
- Evaluate the elements of the Final Disposition process requirements.

Analyze Phase

- Analyze data obtaining per process stage.
- Analyze each element of the EBR steps, determining the critical step to be audit.
- Complete risk assessment for the steps to be audit with rational and justification.
- Generate solution ideas and implementation requirements to reduce cycle time.
- Evaluate different ways to audit in line by Quality Department.
- Define and execute implementation plan for Release by Exception process.
- Discuss solutions with the core team.

Improve & Control Phase

- Implement Release by Exception process per manufacturing area.
- Eliminate redundant audit process from manufacturing area.
- Create Peer Review explaining project goals and expectation completed.
- Create Training Curriculum to Quality personnel with the specific steps to be audit per manufacturing area Inoculum, Fermentation, Capture and Purification process.
- Document and train personnel before effectiveness.
- Discuss final improvements and resolution with project implementation.

RESULTS AND DISCUSSION

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. These processes can vary since they depend on the composition and pH added during production and processing. Once the fermentation phase formulation is completed, it passes through valves to a viral inactivation in the third phase known as capture, leaving the protein completely free of viruses and bacteria. Once the viral inactivation is finished for three days, it finally passes to the purification phase, a process in charge of collecting any remaining virus or bacteria with special smaller porosity filters that trap all waste, leaving the collected protein clean and clear to be used in the syringe filling process known as Small Volume Parenteral (Figure 2).

This parenteral process, and all manufacturing steps, are captured and was documented on a paper

batch records, which consumed process time in production. With the need for an improvement in documentation and in the manufacturing process time of a batch, the resources of the MES (Manufacturing Execution Systems) area created the structure to implement electronic batch records for each phase (Inoculum, Fermentation, Capture, Purification) of a single batch of Adalimumab, capturing all manufacturing instructions and requirement of the process as part of the system configuration to proceed with the generation of the EBR. This implementation provided a significant improvement capability of producing more batches in manufacturing causing a batch stagnation in the audit area in the quality department.

The implementation process of the electronic batch record and all manufacturing step instructions were evaluated in the Bulk Drug Substance area. As part of the systems evaluation, a duplicity of efforts between Manufacturing and Quality was identified. This duplicity adds more cycle time to the manufacturing lot and at the same time backlog in audit and release process. As part of the analysis, the process was evaluated to identify opportunities to reduce the duplicate audit time that prevents the release of more monthly batches and, therefore, a backlog in the plant for the flow of operations. Each instruction of the manufacturing process was evaluated in the electronic batch record, analyzing the consumption of audit time for each phase of the process by both department and, in turn, the information obtained from 30 batches was analyzed for the different errors found called exceptions. The exceptions are automatically generated if the system evaluates that within the instruction some established parameter was not met. These exceptions arrive open without resolution in the audit area, which requires additional time for resolution and finally approving the release of the final batch.

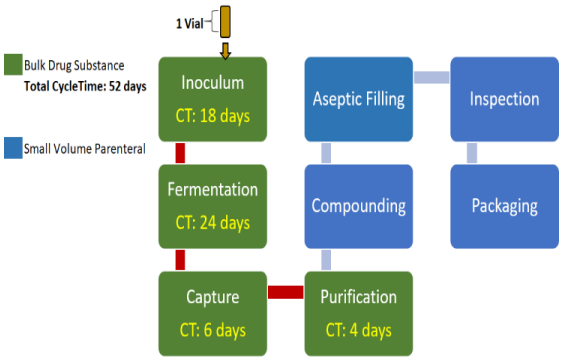

Figure 2
Aseptic/Parenteral Manufacturing Process for Adalimumab

As shown in Table 3, the single batch record of the manufacturing process of Adalimumab is composed of 4 manufacturing phases (Inoculum, Fermentation, Capture, Purification) with the cycle time consuming, process. For traceability, each phase has lot numbers associated with the manufacturing order that has one final lot number for release purpose. All manufacturing process has exceptions that must be close and approve before final release and that will be evaluated to find where the 4 resources that oversaw auditing and completing the documentation related to the batch as part of the production process helped determine the restructuring of the personnel.

Table 3
Single Batch Record Analysis and Evaluation per Manufacturing Process

	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**

These 4 resources were evaluated on their level of education, experience, and time in position to be absorbed by the Quality department in new improvement in the resolution. The quantity of process steps in the EBR's per phases was collected and, at the same time, the sum of the audit process time invested by both departments. The data show that the cycle time of manufacturing process take 52 days to be formulated. Also, audit process steps of the EBR's in one single lot of Adalimumab takes 168 working hrs. equal to 24 days. This elapsed time represent 76 days of total time invested in one single lot of manufacturing process to be released.

During the evaluation, a lack of personnel was found in the Quality department since there was only one resource per phase of the process in charge of auditing, at the same time that it completed open exceptions and investigations related to the batch in order to finally release the phase in addition of among other tasks and responsibilities. On the other hand, an excess of personnel was observed in the production area positions created bases business needs. These positions 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).

Once the audit and formulation consumption times were defined, all the steps and instructions of each process were systematically evaluated through MES to certify that the established parameters are defined according to the validation of the process and at the same time evaluate each step to determine the regulation and its requirements, which steps are defined as critical to audit, seeking a reduction in the time invested in the verification of records.

During the evaluation of the process it was learned that the generation of exceptions is determined in three types: EXC, INV, DEV where the EXC represent all the corrections and incorrect entries or some additional monitoring notes that need to be included in the record. The INV are exceptions that only appear if some control parameter went out of specification or that some process was executed improperly. Finally, the DEVs that are exceptions that are generated if there is a change in process, special instructions or alarms that arise out of range.

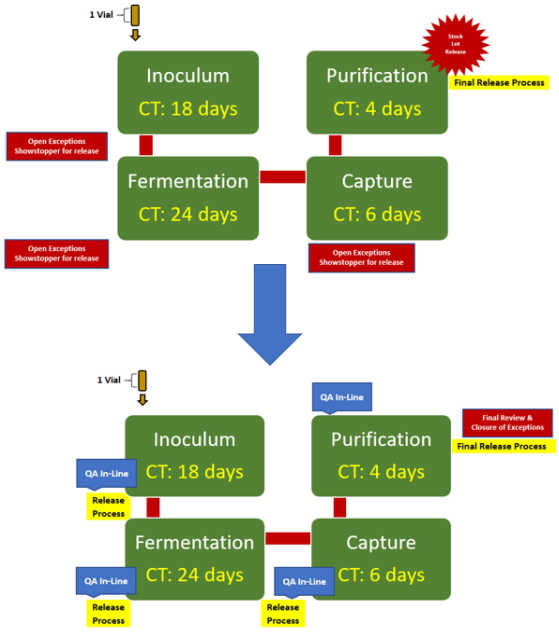

Figure 3
From – To of Bulk Drug Substance Process Flow

A representative sample of 30 batches with all their phases was taken to evaluate and observe trends. The data shows that the amount of EXC generated in a population of 30 lots was higher compared to DEV and INV (Table 4). 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. With the data collected and analyzed, it was established that these exceptions could be completed at the moment by the new personnel designated QA In-Line during the manufacturing process, guaranteed less time of consumption in the disposal area to release more final batches per month. With the data collected, a distribution analysis by category EXC, DEV, INV was obtained, and was confirm that the generation of the mayor exceptions that can be worked on and approved during the process without having to wait for resolution are type EXC. The comparative data shows that human errors are the top offender of the process, for this reason it is more efficient to correcting error at moment (Figures 4, 5).

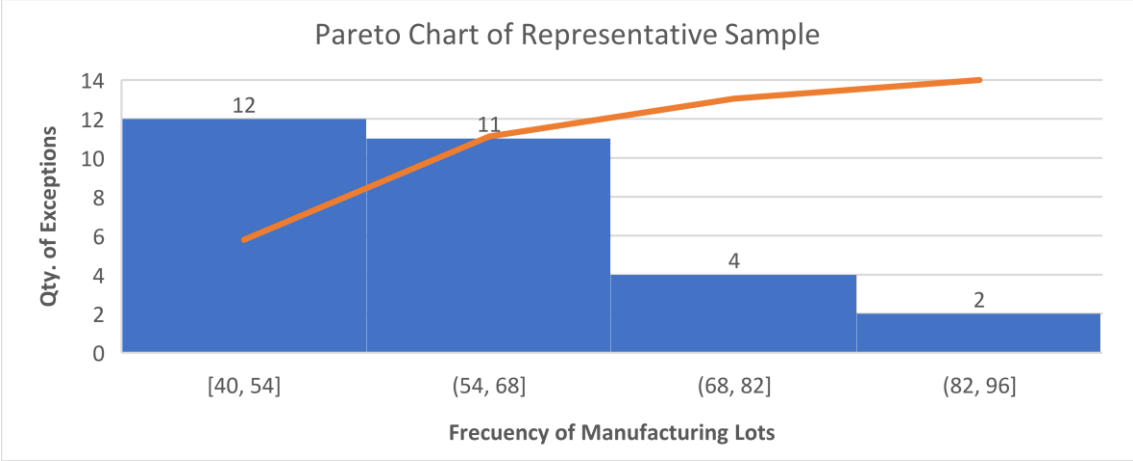

Figure 4

Pareto Chart of Representative Sampling

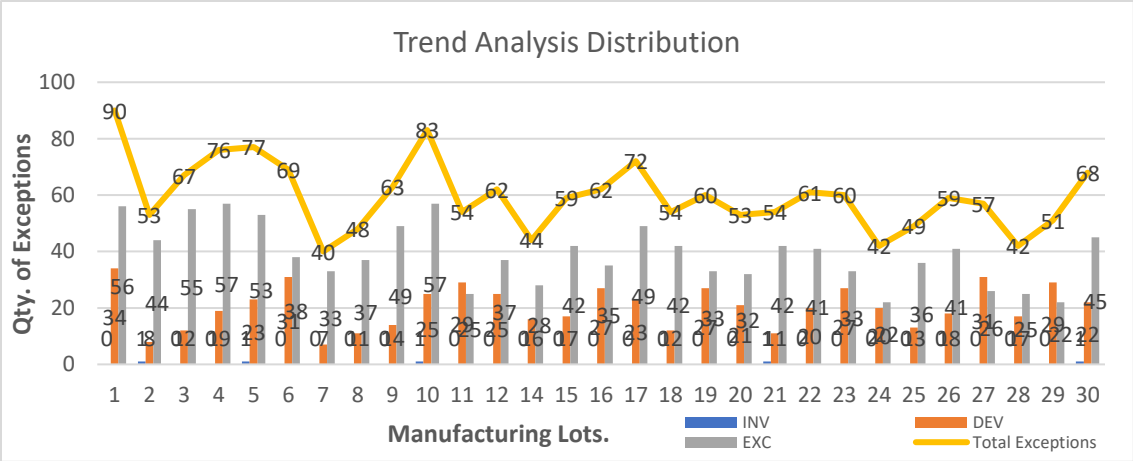

Figure 5

Trend Analysis Distribution in a Representative Sample

All the steps with critical instructions in the Bulk Pharmaceutical Substance process were determined with the execution of a risk assessment to define a guide for each phase of the process where each step and instruction was evaluated, and it was justified why it should or should not be reviewed. This guide is included as part of the documentation and training process. 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 comparison of the previous process with the implementation of the changes was made to see the versatility and effectiveness of the change to determine the time reduction of a batch to be released. 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 implementation of RbE and reduction of audits by releasing a greater number of batches per month to the Small Volume Parenteral area for the syringe filling process, with an estimate cost avoidance per single batch of Adalimumab of $12,565.56 invested on resources calculated with the remanent 21 days reduction and the working hours that represent an estimate of $452,360.16 annually (Table 5).

Table 4
Pareto Analysis - Representative Sample of 30 Manufactured Batches

Lot	INV	DEV	EXC	Total
1	0	34	56	90
2	1	8	44	53
3	0	12	55	67
4	0	19	57	76
5	1	23	53	77
6	0	31	38	69
7	0	7	33	40
8	0	11	37	48
9	0	14	49	63
10	1	25	57	83
11	0	29	25	54
12	0	25	37	62
14	0	16	28	44
15	0	17	42	59
16	0	27	35	62
17	0	23	49	72
18	0	12	42	54
19	0	27	33	60
20	0	21	32	53
21	1	11	42	54
22	0	20	41	61
23	0	27	33	60
24	0	20	22	42
Total	5	589	1135	1729
Average	0.172	20.310	39.138	59.621

CONCLUSION

The implementation of electronic batch records provides the benefit of making fewer entries during the execution of the process, making the manufacturing formulation efficient, reducing time, and providing a clear and continuous aspect of everything that occurs in the process. 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.
- 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.

Table 5
Comparative Results from Previous with Actual Audit Process After Implementation of RbE

	Previous Audit Process & Release											
		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	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**
	Current Audit Process & Release - Release by Exception											
		Batch Number	INV	DEV	EXC	Total Exceptions	Cycle Time days	Process Steps on EBR	Process Steps to Audit	Audit Process Time by QA hr.	Working days Resources	Total Time days Invested
2	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**

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.Finally, as defined by the project, the activities were successfully completed and implemented. Given the prosperous process flow with the implementation of Release by Exception. 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, being spokespersons for the incorporation of such process in sister plants.

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