Parenterals Vial Manufacturing Filling Area Yield Improvement Project

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Abstract — *In the Parenterals Pharmaceutical industry a quality, financial and manufacturing measure of how the process is being operated and that measures the appropriate use of materials, excipients, and active product ingredients is the Yield. The Yield on a Parenterals vial manufacturing filling area equals to a percentage between the amount of formulated product versus the calculated amount of product filled by using the quantity of vials and the filled weight. Some of the frequent factors contributing to product loss in the filling process are product filtration losses, rejected vials and filling weight variations. A reduction of yield result in financial costs, can led to quality events or investigations, and have an impact on the efficiency of the process. The vial filling process for a Parenterals manufacturing pharmaceutical has a yield for a Lyophilized product of 96.6% which is considered high when compared to a similar area filling the same product of 98%. To look into the factors and establish a strategy to increase the yield at this area, this project was developed under the Lean Six Sigma principles and using DMAIC systematic five-step approach, in order to identify major factors influencing the yield reduction to enable the company to reduce unnecessary costs, gain efficiencies, as well as supplying high quality product to the patients.*

Key Terms *— DMAIC, Financial Costs, Lean Six Sigma, Product Loss, Quality Events, Yield.*

PROBLEM STATEMENT

Over last year, the filling process yield was not achieving its financial standard of 97% per batch in a Parenterals Vial filling Area, causing financial losses and a reduction in the quantity of vials filled through the process. At present, the vials filling process yield is on average 96.6%. This situation in which the yield differentiates from the budgeted amount has a significant financial cost impact of about $12,000 per batch. For the product under evaluation a total of approximately 40,000 vials could be filled assuming a 100% yield filling process. The company is looking for an improvement in the filling yield in order to mitigate the financial losses and increase the produced vials in the process without compromising the product quality and regulatory submission.

Research Description

The project has been outlined with the objective of evaluating current filling process product losses per lot in order to reduce the major contributors that aversively affect the vials filling process yield. Although the goal of the project is to reduce product losses, due to the regulatory requirements in a Parenterals Filling process by implementing high impact changes over a validated process and time constraints for implementation in an operational area, it will focus the efforts in the identified improvements that can be implemented in a short period of time during a shutdown window.

Research Objectives

The objectives of this project are the following:

- Cost avoidance by improving filling yield;
- Maintain compliance for the filling process;
- Never compromise the quality of the product;

Research Contribution

With the implementation of this project, the pharmaceutical Parenterals vials filling process will increase process efficiency by reducing product losses, avoid costs associate to financial budget plans and will be used as a business case in other similar manufacturing areas while maintaining the product quality and customer satisfaction.

The project will also contribute to the vials filling process area operators and supervisor's mindset in order to understand the impact of a rejected vials or product losses during this process by being part of the ideas and evaluation process of the project.

LITERATURE REVIEW

Parenteral Drug Products are pharmaceutically produced products that are administered directly into the bloodstream, bypassing the body's natural defenses. Therefore, the manufacturing of these products need to be performed at sterile conditions to avoid product contamination and avoid risk to patient's health. Due to these complex required environmental conditions, today's Parenterals filling pharmaceuticals are moving into a higher contained filling area using Isolators or Restricted Access Barriers (RABs) to fill and seal these products to minimize any risk to product contamination. To operate and handling of the process, the operators use gloves to access the system which maintains human contamination risk from the product while filling and sealing is performed. Another utilized environment to fill Parenterals products is the use of aseptic areas or clean rooms. These areas required higher cleaning and sanitization in order to maintain the environment away from microorganism and particles that may affect the product integrity and sterility. The primary microorganisms flora found in the clean rooms (80-90%) are associated to humans which require higher gowning to personnel entering such environments [1].

The area in which this project is developed is a Parenterals vials filling area under an isolator environment. A vial is a glass or plastic container with a rubber stopper between the product and the exterior and sealed via an aluminum seal that is filled with liquid product. The stopper is used to facilitate the draw up process of the product by introducing a syringe into the vial while maintain the sterile environment inside the vial. The vial products under analysis for this project are filled, partially stoppered and then loaded into a Freeze Dryer equipment to start a Lyophilization process [2]. The stoppers are placed on top of the vial, but not completely sealing the inside of the vial from the environment to permit the Freeze Drying process to interact with the product. The Lyophilization or Freeze Drying process is a thermodynamic process used to preserve the product by removing the humidity from the product. The process consists of several phases to remove the humidity inside the vials through sublimation to change the product from the liquid to the solid phase. The phases in which the equipment undergoes are Freezing, Primary Drying and Secondary Drying. In the freezing phase the product is cooled, the primary drying phase creates a vacuum inside the chamber and the temperature is then increased through the process as per validated parameters.

After the cycle completes, Freeze Dryer press the partially stoppered vials completely and then unloads the vials to the capping equipment. The capping equipment then seals the stopper and vial combination of each vial crimping an aluminum seal. The filling process ends by loading the vials into trays and pallets for refrigerated storage or inspection and packaging process.

The yield in a Parenterals vial filling area is a critical parameter in terms of quality compliance and has financial costs indicating inefficiencies in the process. The yield is a percentage value between the actual filled product and the formulated drug product entering the filling process.

To meet the objectives of the project, a Sigma DMAIC strategy will be developed and followed. The Six Sigma teams us a problem solving approach called DMAIC, sometime pronounced "duh-may-ick". The letters are acronym for the five phases of the Six Sigma improvements: Define-Measure-Analyze-Improve-Control. These phases lead a team to underlining causes, and establishing best practices to make sure the solutions stay in place after the implementation [3].

These phases and their definition are summarized below:

- *Define* Phase*:* Define the project goals and customer requirements.

- Measure Phase: Measure the process to assess its current performance.
- *Analyze* Phase: Analyze the process and determine root causes or variations and/or defects.
- *Improvement* Phase: Improve the process by reducing variations and defects.
- *Control* Phase: Control the future process performance by institutionalizing the improvements.

These are the basic steps in an improvement procedure intended for existing process that are currently operating at low sigma levels and need improvement. DMAIC provides the worker team with a systematic and data-driven approach to solve and identified problems [4].

METHODOLOGY

The selected method to be used in this project is the Define, Measure, Analyze, Improve and Control (DMAIC) strategy coming from the Lean Six Sigma principles. The DMAIC strategy is divided in the five phases and each phase contains a definition and different tools used to achieve the project's objectives.

The following is the summary of each step used tools and approach to be followed:

- Define: This phase will consist of confirming problem statement with the process owner and project sponsors. To do so, several feedback sessions to get the Voice of the Customer (VOC) will be held and a project charter will be developed with the information provided in order to assure feasible and clear goals are established form the beginning. A SIPOC (Supplier, Inputs, Process, Outputs and Customers) map to understand the different customers and process inputs-outputs will be performed as well. A kick off meeting with the team members will be held showing approved stakeholders roles and responsibilities, clarifying projects objectives, scope, communication plan and ground rules to be followed at all times through the project. In order to understand and mitigate any risk involved in the failure to reach the project's objective, a risk assessment will be developed with support of team members.
- Measure: The measuring phase will consist of developing and data collection plan and measuring all filling process rejects or product losses as part of every manufactured lot batch record documentation. It will also cover the evaluation of actual product losses during the filling process in order to confirm a normal distribution and that the process is currently in control. The data will be collected following the data collection plan and tabulated for the analysis phase.
- Analyze: During this phase, the filling process product losses data obtained will be categorized by each factor and using a Pareto Analysis the major contributors will be identified. For the major contributors several Cause and Effect sessions will be held with the team members to identify the potential causes for the product losses for these major contributors. Also, the data will be statistically evaluated to confirm normal distribution of the data.
- Improve: The improve phase will consist on creating a potential solutions list with their respective theoretical solutions impact based on subject matter experts information or confirmed data. Using a Benefit & Effort matrix, the solutions that present a higher impact with minimum amount of effort to implement them will be selected to be implemented. The solutions selected will be implemented and the data of product loss during the filling process from the manufacturing batch records will be evaluated in order to confirm improvements satisfied the objective of the project. The data obtained from the product loss will be statistically evaluated to confirm normal distribution and validate the improvements.
- Control: In the control phase the approach taken will be to evaluate all implemented improvements and perform modifications or strategies to sustain these improvements in a

way they are maintained in the status were the project was implemented. In a regulated industry such as the Parenterals manufacturing, the change management procedures are key in the modifications to validated equipment and procedures are in place to sustain the actual validated status of the equipment and systems. Therefore, most of the improvements that impact these manufacturing areas will need procedures and/or batch record documentation to be modified as well. Other tools such as visual management methods or other will be evaluated as part of the control phase in order to give the user a better controlling and monitoring tool.

RESULTS AND DISCUSSION

This section contains the problem statement analysis and approach to achieve the project objectives and their respective results using the DMAIC strategy.

Define Phase

To begin the project, a project charter was developed to summarize the project goals, team members, milestones and timeline. Refer to Figure 1 below.

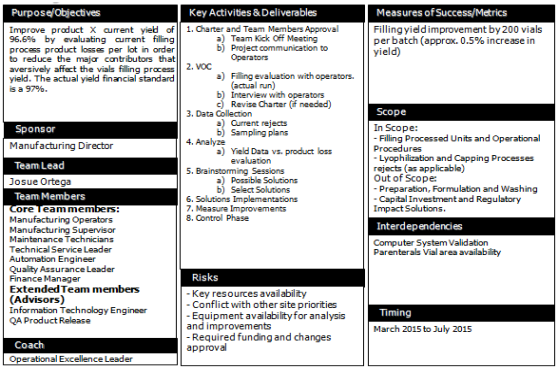

Figure 1
Project Charter

The project objective of yield improvement was agreed to be about 0.5% increase based on difference between the standard of 97% and the actual yield value of 96.6%. The communication plan for the project was developed, refer to Figure 2. This plan establishes the frequency, purpose and audience of each meeting as well as team members that shall be present.

Audience	Media	Purpose	Topics of Discussion/ Key Messages	Owner	Frequency	Notes/Status
Team Memebers	Meeting on a Conference	Follow up	- Measuring phase preliminary results - Previous meeting pending items - Feedback - Issues or Roadblocks - New Ideas	Project Leader	Weekly	
Project Leader, Sponsor and Area Owner	One on one	Follow up	- Status - Issues or Roadblocks - Risks	Project Leader	Monthly	

Figure 2
Communication Plan

The yield calculation formula and formulation process data was evaluated in order to review consistency and variations from the formulation process which is an input as presented on Appendix A - SIPOC diagram. The filling process yield calculation formula (1) is the following [5]:

$$Yield = \frac{good\ vials \times filling\ avg\ (g)}{formulated\ product\ (g)} \times 100\ \% \qquad (1)$$

Measure Phase

At the beginning of the measuring phase, the team members met and agree on the data collection plan for the project. The plan is included in Figure 3 below.

Performance Measure/Metric	Operational Definition	Sample Size	Source & Location	Collection Method	Who Will Collect Data	When Will Data be Collected
Manual Rejects	Obtain the number of manual rejects in the BR from the Buffer Accumulator and the Loading (needs to be breakdown)	Measuring: - Ten (10) Batches Validating Solutions: - Ten (10) Batches	Batch Records in documentation area.	From Batch Records and BCG group.	J. Ortega	Measuring: - During measuring phase. Validating Solutions: - When analyzing validating solutions.
Yield and Rejects	Obtain from finance department the Yield calculation from each Batch.	Measuring: - Ten (10) Batches Validating Solutions: - Ten (10) Batches	From SAP System	From Finance calculation.	J. Ortega	Measuring: - During measuring phase. Validating Solutions: - When analyzing validating solutions.
Machine Good Units and Rejects	Obtain from the OSI PI System the counters total for each batch ran at the machine (stoppers, good, bad	Measuring: - Ten (10) Batches Validating Solutions: - Ten (10) Batches	OSI PI Hisotrical Data (electronically)	From Filler Machine PLC Counters for each rejected or good vial.	J. Ortega	Measuring: - During measuring phase. Validating Solutions: - When analyzing validating solutions.
How will data be used? Identification of Largest Contributors Identifying if data is Normally Distributed Root Cause Analysis			How will data be displayed? Pareto Chart Control Chart Histogram Scatter Diagrams			

Figure 3
Data Collection Plan

A total of ten (10) batches were selected to analyze existing filling losses. The quantity of batches was also selected based on the amount of batches from this product that the area fills that can facilitate the confirmation of improvements with the same amount of batches. The filling losses were then

distributed among the equipment automatic rejects counters, the batch records losses as part of the process and any other manual reject in the line not captured by the machine's counters. All the product loss data will be presented in vials per batch units to be consistent and maintain the same unit for comparison between improvements.

Analyze Phase

To confirm that the data being evaluated follows a normal distribution and that the process is in control, a statistical probability plot with the yield value was performed. Also, the use of control charts will be utilized to evaluate for any outliers that may affect the data evaluation and to show improvements in a historical trend. After the data was obtain from the ten (10) filling batches established, the data was analyzed using a Pareto Chart in order to identify the major contributors to the filling losses which eventually affect the filling process yield.

The Pareto Chart is illustrated on Figure 4 below. The intention is to identify these major contributors to then evaluate the causes for each and perform root cause analysis with team members.

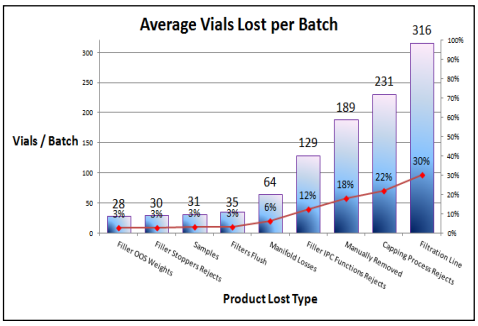

Figure 4
Product Loss Pareto Analysis

In summary, the following is a description of each contributor to product loss category:

- The filtration losses product loss category data was measured by the weight of product that remained on each filter upstream section or dirt section. This value is measured by weighing the filters before each lot and again at the end of each filling process. This weighing process is manually taken by the operators and documented in the batch records. The purpose of the filters is to guarantee sterile product during the filling process as part of Parenterals products requirements. The filters hold product that cannot be entirely filtered through them as they become more clogged while filtering.
- The capping rejects product loss category is caused by the vials inspection and sealing equipment after they are unloaded from the freeze dryers. The capping rejects data was taken from the capping machine rejects counters and batch records documentation.
- The manually removed product loss category is vials that were removed in the transportation system from the partially stoppering station to the freeze dryers and from there to the capping machine. These vials are counted manually by the operators at the end of the filling process and then documented in the batch records.
- The IPC (In Process Control) product loss category is vials that the filling machine automatically counts due to rejects in the filling system. This data was taken from the filling machine counters and batch records documentation.
- The filling manifold product loss category is the product that is left in a filling stainless steel manifold in which the filling needles are located. This data is taken manually by the operators by dispensing the remained product in the manifold at the end of the filling process and weighing the product in a floor scale to determine the product left in this section. This measured weight is then documented in the batch record.
- The filters flush product loss category is product that is lost during the filters flush process to remove any air in the filters at the beginning of each batch. Once the filters are full of product the operator closes the flush valve on top of the filter's cartridge. This product is then weighted to determine how much product was lost.
- The sampling product loss category is product that is taken during the filling process to guarantee the product is between established

and validated limits for sterility testing and for product purity and integrity samplings. These samples are used for product release purposes and laboratory analysis. The data is taken from the batch records documentation.

- The stoppers missing or misplaced product loss category is vials that the filling machine rejected due to misplaced or not placed stoppers sensed by a sensor inside the filling machine and counted by the filler machine. This data was obtained from the filling machine counters after each batch.
- Filling weights out of specification (OOS) limits product loss category is vials that did not met the filling weight specification during automatic weighing verification of the filling machine. This data was taken from the filling machine counters and the data historian server.

To determine the causes for these product losses and to identify potential solutions a root cause analysis brainstorming sessions were completed with the team members. Refer to diagram on Figure 5. The Fishbone Cause and Effects diagram tool was used and the different areas that may affect the product losses were identified. Several ideas that team members proposed during the brainstorming sessions were taken into considerations and evaluated as well. The figures below show the different outcomes of some of the sessions completed and the selected root causes.

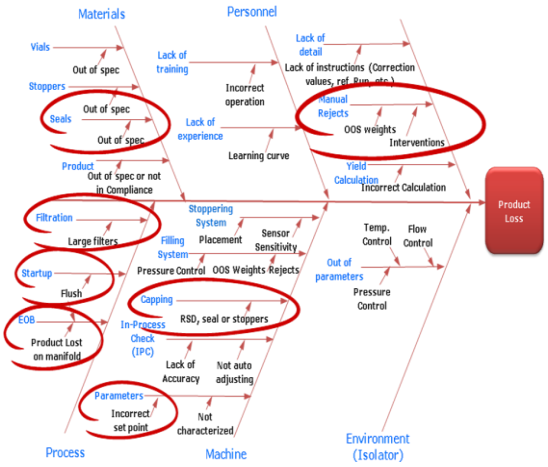

Figure 5
Product Loss Cause and Effects Diagram

Improvement Phase

From the brainstorming sessions and the identified root causes, the team members met in order to provide a solutions list for each root cause. The team also came with a preliminary duration for implementing each of the solutions taking into consideration each complexity, improvement impact and duration. On Table 1 below the list developed is presented.

Table 1
Potential Solutions List

Potential Solution	Effort (weeks)	Benefit (Vials)	Yield (%)
Modify SOP to reject only necessary	1	40	0.1
Improve Manifold Losses	2	64	0.16
Buffer Accumulator Rejects Identification	2	40	0.1
Avoid Flush in 100%IPC	1	40	0.1
Reduce Filtration area	> 8	150	0.38
Reduce fill weight target	> 8	145	0.36
Reduce samples	> 8	15	0.38
Perform dearation at startup	1	9	0.023
Relocate cap sensor in chute	1	50	0.125

To determine which of the solutions improvement the project will select, a Benefit vs. Effort matrix diagram was used in order to take into consideration the manufacturing windows available required to implement these solutions and that the project timeline is not impacted while achieving the project's goal. The different criteria area legends for the benefits and efforts were developed by the team members and approved by the project sponsor. Refer to Figure 6 below for Benefit and Effort Matrix diagram.

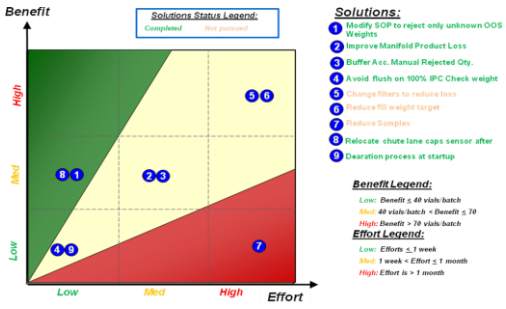

Figure 6
Benefit and Effort Matrix

As per results from the Benefits vs. Efforts matrix above, the solutions that belong to the green section will be implemented as part of the project. The solutions that belong to the red section in the diagram will not be pursued as part of the project and the solutions that are in the yellow section will be further evaluated in order to determine whether the project's goal can be achieved with the green section solutions.

The improvements selected were implemented during a manufacturing window (shutdown) and procedures impacted were revised. As part of the improvements phase, the amount of ten (10) filling batches were measured in order to validate the product loss improvements according to each expectation as per data collection plan established. The yield improvement as a result of these improvements was also measured against the previous ten (1) batches average in order to determine if the project goal of +0.4% yield average increase was obtained. A yield average improvement of 0.65% was achieved according to the data. This is a higher yield increase when compared to the project's goal of 0.4% yield increase per batch. Therefore, no other improvement was followed as part of the project. The yield values obtained were compared through a 2-sample t Test hypothesis test using Minitab software with an alpha of 0.05 to confirm improvement of yield. Refer to Figure 7 below for the summary results from the Minitab software. With a p-value of 0.030 (<0.05) confirmed that the average yield was higher after the improvements.

Control Phase

To assure the improvements implemented are sustained through the future use of the equipment and filling process, several controls were implemented. These controls included the revision of Standard Operating Procedures (SOPs) in order to address procedural changes during the filling process. These procedures included clear instructions, illustrations and photos to guide the manufacturing personnel in order to obtain the same results every time the filling process takes place. The batch records utilized by the manufacturing personnel to follow the filling process step by step were also modified. To give the manufacturing personnel visual and historical monitoring capabilities, a model in a web page was created so they can evaluate rejects counters from the filling and capping machines. Refer to example below on Figure 8.

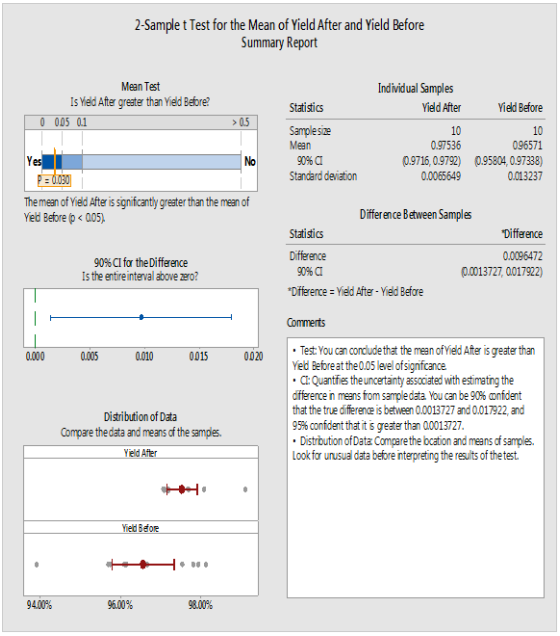

Figure 7
Minitab Hypothesis Testing Results Summary

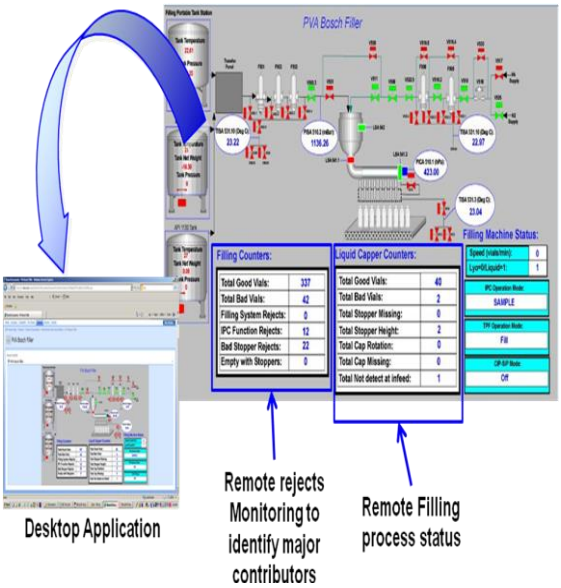

Figure 8
Monitoring Tool Developed

The process of implementing these changes also included training to manufacturing personnel and to all personnel involved in the filling process.

CONCLUSION

As part of this project the different phases were developed and implemented of the DMAIC methodology. As a result of the project, the yield average increase was around the 0.6% when compared to the 0.4% objective from this project. A summary of these improvements and their respective results is shown on Figure 9 below.

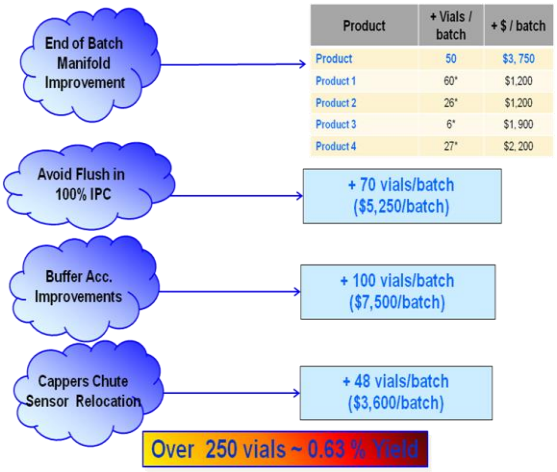

Figure 9
Improvements Results Summary

The project's results were validated using hypothesis statistical analysis testing to compare improvements before and after confirming the improvements on each category. Since the project to improve the filling yield was limited to a certain scope or goals, timeline and target objective, there were several improvements or areas of opportunities identified through the phases of the project that were not pursued. These improvements required higher complexity, effort or in some cases were on other manufacturing areas or not part of the filling process itself. These improvements were communicated on a closure and lessons learned meeting performed with team members and affected area owners. These areas of opportunities and improvements not pursued are summarized on Table 2 below.

Table 2
Improvements Not Pursued

Process Step	Description	Benefit (vials)	Effort (weeks)
Filling	Other products reject all vials before 100% IPC	12	4-6
Loading	Modify the Buffer Accumulator to identify each filling position to be rejected	93	6-8
Filtration	Improve filtration line product loss	150	> 12
Filling	Use a lower fill volume target during filling	TBD	> 12
Filling	Product 3 has recipe parameter to reject vials before 100% IPC active	TBD	2

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