Handling and Managing of Vial Rejects

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Abstract *— A large accumulation of filled vial rejects generated in an aseptic filling line of a parenteral medication was identified to be in the custody of the Quality Assurance department indefinitely. Using the DMAIC methodology the current vial handling practices and the batch records from the lots manufactured from 2019 until August 2021 were evaluated. Two (2) root causes were identified for storing all rejected filled vials indefinitely: (1) vials were needed for the visual inspection qualification defect library and (2) no formal procedure was established for the handling and management of rejected vials. New procedures were designed and implemented providing guidance on how to evaluate and onboard rejected filled vials to the defect library, or to discard the vials per waste regulations. The new implemented procedure allows for a compliant, easy to manage vial inventory and it supports the continuous updating of the defect library.*

Key Terms *— DMAIC, Material Reclassification, Reject Management, Visual Inspection*

PROBLEM STATEMENT

A large accumulation of filled rejected vials was observed in the Quality Operations cage. These vials were generated from product lots filled from 2019 to the present, not discarded or repurposed after being collected. This research project will aim to identify the root cause of the accumulation of filled rejected vials. Upon identification of this issue, some members of the team justified the vial accumulation. This research project will challenge the justification provided for the vial accumulation (is it a true need?) and will develop a procedure for the handling and managing of the rejected vials.

BACKGROUND

This project's scope is limited to managing and handling the rejected vials of a parenteral biological product generated in an aseptic filling line. As defined by Ludwig [1], the term parenteral dosage refers to those formulations that are to be administered directly into body tissues (injected) rather than ingested via the digestive tract. The word parenteral "is derived from the Greek words para (beside) and enteron (the intestine) and most often refers to subcutaneous (S.C.), intramuscular (I.M.), or intravenous (I.V.) administration of drugs [1]." Aseptic techniques are crucial during the formulation and administration of parenteral products as poor techniques can be harmful to the patient. The minimum quality standards for pharmaceutical manufacturers are expressed in the Current Good Manufacturing Practices (cGMPs), which are constantly evolving as technology advances. In his work, Ludwig [1] states that "injectable products must be manufactured using the highest quality active drug substance and excipients. Parenteral products must be sterile, pyrogen free, and free from visible particulate matter and remain so throughout shelf life".

Engineering controls must be embedded in the manufacturing process to lower or eliminate the opportunities for errors during production. Errors in manufacturing can result in material to be rejected if it does not meet the established acceptance criteria. Several factors can contribute to the rejection of material. For example, improper or lack of training, improper use of the equipment, incorrect parameters used, to name a few. Rejected material can negatively impact the business if the

error cannot be re-worked, resulting in material loss.

The Filling Process

Raghavan [2] explains that "aseptic processing involves the interplay between several different processes, all of which must be designed, executed, and controlled in order to yield sterile products. In an aseptic process, the drug product, container, and closure are first subjected to sterilization methods separately, as appropriate, and then brought together." The environment in which these sterile components are to be assembled must be controlled, monitored, and adequate to the quality of the product being manufactured.

An interview was conducted with R. Fletcher, one of the Sr. Process Engineer of the aseptic filling line, to understand the aseptic filling process of vials and the functionalities of the filling machine. During the interview with Fletcher [3] it was described that the filling machine is equipped with an isolator. The isolator is an aseptic barrier integrated with the filling line to ensure separation between filling operations and the surrounding room for protection of the product.

After being washed, vials pass through a depyrogenation tunnel to achieve sterilization before entering the sterile filling isolator; sterility is achieved in the isolator through Vaporized Hydrogen Peroxide (VHP) [3]. The vials are filled with finished filtered product and transferred to the stoppering location via transport rake. After stoppering, the vials are transferred to the capping isolator to be capped. The vials then pass through the coding station where a print is applied on the crimping caps on the vials and exit the isolator via the passthrough for palletization.

Fletcher [3] also stated that the vial filler is equipped with scales in the filling station and has multiple sensors throughout the length of the filler to inspect the vials as they are being processed in the different stations. The filler has the ability to identify and reject vials with processing defects related to critical parameters. As defined by the Parenteral Drug Association (PDA) in [4], critical parameters are the values that are controlled and/or measured and are linked to safety and efficacy of a product or process. Failure to meet a critical parameter should result in rejection of the load. Fletcher states during the interview [3] some examples of processing defects that would result in the automatic rejection of a vial by the filler: over or under fill of product into the vial, missing cap, missing stopper, or improper stopper or cap placement. At the end of the fill, a reconciliation is performed, and all rejected vials are transferred from Manufacturing to Quality Assurance.

Visual Inspection of Parenteral Products

The inspection of parenteral products is driven by the need to minimize the introduction of unintended particulate matter to patients during the administration of injectable medications. Toler [5] describes that visual inspection also allows the opportunity to detect and reject other categories of nonconforming units. It is the expectation of the United States Pharmacopeia (USP) that "each final container of injection be subjected individually to a physical inspection, whenever the nature of the container permits, and that every container whose contents show evidence of contamination with visible foreign material be rejected [5]."

"The purpose of a visual inspection program is to satisfy the regulatory agencies and ensure the safety and quality of the drug product. Having an appropriate inspection program can aid an organization in avoiding a Form 483 or Warning Letter from the U.S. Food and Drug Administration (FDA) [5]." When designing the qualification for the inspection process the visible particles that come from the filling process and its predecessors shall be considered and incorporated in the program. Visual inspectors must demonstrate acumen in particle detection to ensure that containers holding visible particles are identified and rejected from the lot [5].

The manual inspection is considered the benchmark for all other particle inspection methods and devices. It is important to note that human inspectors must undergo appropriate training and

testing to become qualified for inspection [5]. The qualification is maintained through good supervision, proper procedures, and continued retraining. Proper inspector training is critical to a properly designed visual inspection program. The handling of the sample and the "calibration" of the inspector is vital to obtaining accurate and repeatable results. The rejection probability calibration curve is generated using a test set of containers, each with a single, durable, and accurately measured visible particle in a suspending fluid. Toler states in [5] that ideally "the test set should include samples that are representative of the entire particle contamination spectrum from clean to must-reject contamination. This test set can be applied to multiple inspectors at multiple sites, defining the test environment."

Qualification and Validation of Inspection Process- Test Sets

According to the U.S. Pharmacopeia [6], the development of inspection standards begins with a description of the defect types that will be represented in the test set(s). This information typically comes from the manufacturing area, where naturally occurring defective units can be identified from rejected product. Visual inspection standards may be identified from known production rejects or created manually with characterized particulate material.

These qualified defect standard units are assembled into test sets. These may be used to specifically challenge the particle detection technique of human inspectors, used as part of a defect test set (including container–closure defects) for human qualification, or for comparison during automated equipment qualification and validation.

METHODOLOGY

The DMAIC methodology will be used in this research project to understand the current state, implement solutions linked to underlying causes and establish best practices to make sure the solutions stay in place. As described in [7], DMAIC is a structured problem-solving methodology widely used in business. The letters are an acronym for the five (5) steps of Six Sigma improvement: Define, Measure, Analyze, Improve, Control. Several six sigma tools will be employed throughout the execution of the DMAIC methodology.

- **Define:** Problem statement to be determined. A process map will be completed to understand the current state.
- **Measure:** Data from the lots produced will be collected in a time series plot to understand the quantity over time of rejects produced by lot.
- **Analyze**: A brainstorm session will be conducted to complete a fishbone diagram followed by root cause identification using the 5-Whys method.
- **Improve**: Solutions will be identified in this step and will be valuated following the PICK chart tool.
- **Control**: The implemented solutions or processes will be monitored to ensure that the important elements are preformed consistently by using a control chart.

RESULTS AND DISCUSSION

A cross functional team was assembled, including the stakeholders and the personnel involved in executing the current established processes, to evaluate the problem.

Define

The problem to be addressed by this research project is the lack of a process for handling and managing the vial rejects generated in the aseptic filling line of a parenteral drug product. This problem is observed in every lot filled from January 2019 to the present. The lack of guidance and control could potentially impact the reject's accountability. The desired state is to have a defined process in the handling and managing of rejected vials.

The cross functional team met on August 16th, 2021 to complete the Define phase of the DMAIC.

To understand the problem, a process map, depicted in Figure 1, was created to clearly define the process inputs and outputs.

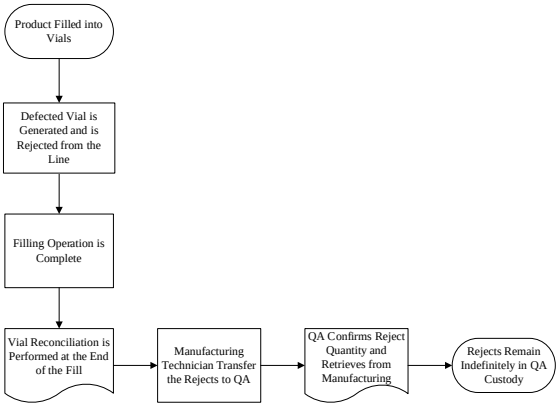

Figure 1
Process map- Current state

Measure

A total of ninety-three (93) lots were filled in 2019, one hundred and twenty-one (121) lots were filled in 2020, and, as of the project start date, ninety-six (96) lots have been filled in 2021. The batch record for each fill was reviewed to obtain the number of rejects generated under each lot. During this data review, it was observed that every lot produced empty vial rejects, but not every lot produced a filled vial reject.

A times series plot, shown in Figure 2, was created to show the quantity of rejected vials produced from 2019 until the start of this project on August 9th, 2021. This data was divided into filled vial rejects (blue) and empty vial rejects (orange).

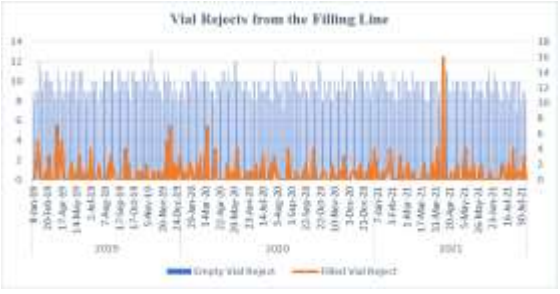

Figure 2
Rejected Vials from 2019 until the August 9th, 2021

The data gathered from the batch records was further analyzed to determine the minimum, the maximum, and the average quantity of rejected vials produced by the lots filled in a calendar year. Refer to Table 1. Although each lot will not produce the same amount of rejects each time, this information will help understand how many vials will be managed and will help determine storage needs.

Table 1
Statistics of Rejected Vials

	2019		2020		2021	
	Empty	Filled	Empty	Filled	Empty	Filled
Min	8	0	7	0	7	0
Max	13	7	12	7	11	16
Avg	9.77	0.86	9.66	0.59	9.47	0.75

Analyze

A fishbone or cause and effect diagram, depicted in Figure 3, was created with the cross functional team to summarize the potential root causes to the problem divided into categories (6Ms).

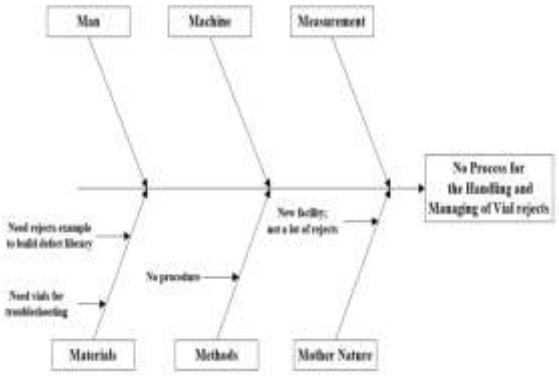

Figure 3
Fishbone Diagram

Once all the ideas were identified in the fishbone diagram, the potential root causes were valuated to determine if each of them was a contributing factor to the problem. Tables 2 and 3 summarizes the root cause analysis.

Improve

The analysis phase uncovered that the Visual Inspection Qualification QA team needed filled vial rejects for creating, updating, and backing up of the vial defect library. This defect library is used new visual inspector's training and re-qualification. This

need for vials for the defect library will be considered when developing improvements.

Table 2
Prioritized Potential Cause

Prioritized Causes from the Fishbone	Evidence to Confirm or Reject?	Cause Confirmed?
No procedure	Confirm no procedure exists	Yes
Vials needed for defect library	How many vials do we need to keep for defect library?	Yes
Vials needed for troubleshooting	Is engineering using these rejects for troubleshooting the equipment?	No

Table 3
5-Whys to Identify the Root Cause

		No procedure	Vials needed for defect library
01	Why?	Haven't needed to discard any vials yet	All rejected vials are being kept in QA custody
02	Why?	Did not identify the quantity needed for reject library	Until now there are not enough vials for training
03	Why?	New facility, still assessing needs of defect categories	Still assessing needs of defect categories
04	Why?		Planned to keep rejects for training
05	Why?		New facility still generating this library

After identifying the root causes to our problem several improvements were identified, as shown in Table 4.

Standard Operating Procedures (SOPs), job aids, and logbooks were developed and implemented for the Quality Assurance team to provide clear guidance on the steps to follow in handling and managing rejected vials from the filling line. A process map with the implemented changes was created, as depicted in Figure 4. Before the documents became effective, training was conducted with personnel affected by the new process to ensure acumen on the new requirements.

Table 4
Improvement Selection- PICK Chart

Prioritize Improvements	Select Improvements			
			Implement	Challenge
1. Create procedure for how to document the receipt of rejected vials and designate a location for them 2. Create procedure for how to evaluate rejects on if they should be kept and how to discard remaining vials	Benefit	High	#1 #2	
			Possible	Kill
		Low		
			Low	High
			Effort	

The filled vial rejects generated between 2019 and 2020 were discarded via hazardous waste. The filled vial rejects from 2021 were evaluated and were either onboarded to the defect library or rejected via hazardous waste. All empty vials were discarded.

Control

After the improvements were implemented, a total of twenty (20) days were used for monitoring in the Control phase, starting on September 6th, 2021, and ending on September 26th. Several empty and filled vials were produced during the control phase. To determine adherence to the new procedures, the batch records, the logbooks, and the ERP (enterprise resource planning) system were evaluated. During this evaluation it was confirmed that the empty vials were being discarded via nonhazardous waste. The filled vial rejects were kept in the designated quarantine area and evaluated for onboarding into the defect library or rejected via hazardous waste.

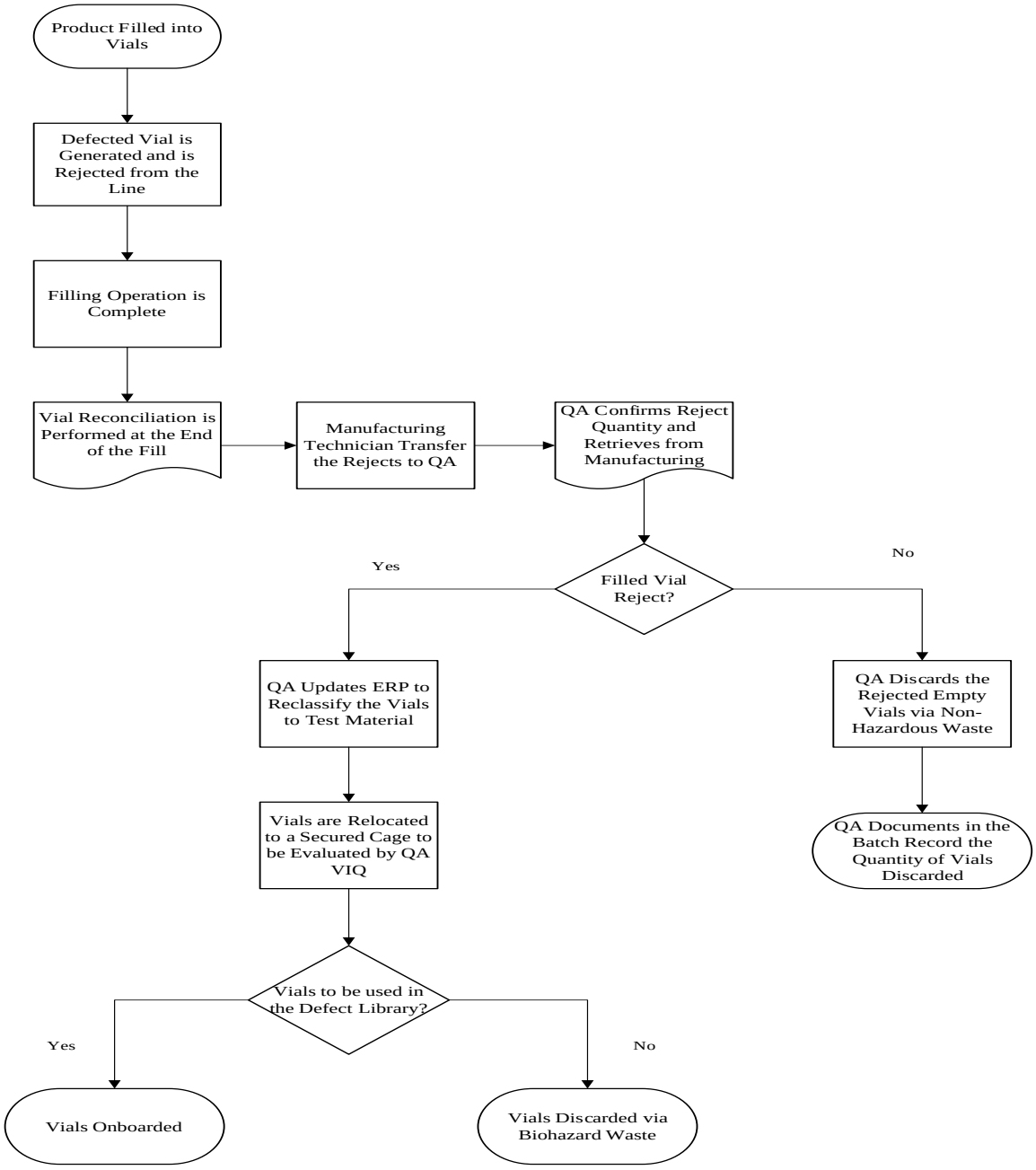

Figure 4
Process Map, Post-Improvement Implementations

CONCLUSIONS

The DMAIC methodology was completed to understand the problem of this research project. In the Define stage it was determined that no formal process for the managing and handling of rejected vials was in place. Data gathered in the Measure phase further supported this statement, where a large accumulation of rejected vials was observed dating back from 2019 to the present. Two (2) root causes were identified in the Analyze phase for the significant vial accumulation; (1) rejected vials were being kept, to be used in the defect library for the qualification of visual inspectors, (2) no procedure was established to dictate how to manage the rejected vials.

In the Improvement phase an SOP, two (2) job aids, and one (1) logbook were generated to provide

guidance on how to manage these vials and also to have the correct documentation of the process to remain compliant. Twenty (20) days were used for monitoring the Control phase process. During this time, it was observed that the empty rejected vials were being discarded and the filled vial rejects were being collected by Quality Assurance representatives. The filled rejected vials are now being kept in a designated locked cage that only QA personnel can access. Inventory records of these vials are generated to have visibility of the quantity, lot number, and location of vials. The inventory is further adjusted after the vials are either onboarded to the defect library or discarded via hazardous waste.

Summary of Contributions

The resolution of the problem for this project seemed obvious at first glance- discard all accumulated rejected vials and establish a process to continue to do so. It is when completing the different steps of the DMAIC, especially within the measure and analysis phases, that we understand this action will only solve the volume of vials, but it will not address the second root cause identified. The major contributions of this project are:

- In collaboration with a cross functional team, a new procedure was designed and implemented to manage the rejected vials generated in the aseptic filling line. This procedure was designed with the end user and their necessities at the center to avoid recurrences in the future.
- The QA representatives now have visibility on the inventory of these vials as the DMAIC provided a solution to include these vials in the ERP system for better tracking.
- Locations for storage were defined to keep the inventory organized and to provide control- only authorized personnel can access these vials.
- An estimated saving of $40,000 per defect set will be obtained once enough vials are onboarded to the library. Using these vials will ensure that the defects on the library are up to date with the particles being identified from the vial processing.
- A sense of unity was achieved at the end of the DMAIC exercise by the members that collaborated in the different sections. They felt valued because their needs and concerns were taken in consideration when designing improvements. The team has a better understanding of the process and values the importance of the safeguards implemented.

Future Research

The DMAIC used in this research project focused on the process after a rejected vial is retrieved by Quality Assurance representatives. Further evaluation in the visual inspection qualification area will be needed to determine if the improvements from this DMAIC are still valid. The assessment should include:

- Evaluation of storage capacity
- Efficiency in which the vials are being evaluated to be onboarded or discarded
- Digitalization of logbook
- Managing of the replacements of defects in a set
- Manual generation, in a controlled environment, of defected vials in the instance where an example is not obtained from the rejects coming from the filling line

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