Filling Line Improvements to avoid the Defect of Product on the Stopper for Sterile Syringes

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Abstract

This research aims to optimize the syringes filling line at the facility to not exceed the action limits because of the defect of syringes with product on the stopper. The product or liquid on the stopper of the syringe is one of the defects that can be encountered in sterile solutions for subcutaneous administration. This defect is classified as major, and the established control limit is not more than (NMT) 1.0%.

The project implementation will reduce the defect of syringes with product on the stopper to ensure the manufacturing of the product according to the quality standards and lowest customer risk. Furthermore, will reduce re-inspection lots, the product cost, and Quality Events.

Key Terms — Product on the stopper, sterile solutions, sterile solutions filling line, syringe defect.

Introduction

On June 2022, the control limit of not more than (NMT) 1.0% was exceeded for the total major defects because of high incidences of syringes with product on the stopper.

This research includes recommendations for filling line optimizations to avoid the defect of syringes with product on the stopper. Optimizing the filling line will decrease the defect of syringes with product on the stopper to ensure the product's manufacturing according to the quality standards and lowest customer risk.

Background

Filled syringes contain a sterile solution for subcutaneous administration.

The product on the stopper defect is illustrated in Figure 1.

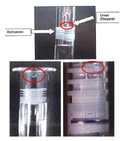

Figure 1
Product on the Stopper Defect

Product on the stopper is a condition that originates during the filling process. The most common causes for this defect are:

- Air bubble size (below the criteria of 2.00 mm)
- Air bubbles in the filling hoses during filling
- Dried product at the filling needles' tip
- The stopper position is too low because of air bubble size is below the criteria of 2.00 mm
- Misalignment of the filling needles

Problem

The control limit of not more than (NMT) 1.0% was exceeded for the total major defects because of high incidences of syringes with product on the stopper.

The project implementation will reduce the defect of syringes with product on the stopper to ensure the manufacturing of the product according to the quality standards and lowest customer risk. Furthermore, will reduce re-inspection lots, the product cost, and Quality Events.

Methodology

The filling manufacturing process of the sterile solutions for subcutaneous administration (syringes) was evaluated to determine what conditions contribute to the product's defect or liquid on the stopper.

Data was gathered from six (6) manufacturing lots that exceeded the control limit of 1.0% because of product or liquid on the stopper, including:

. Atypical situations reported during the manufacturing activities.
. Start-up air bubble size
. In-process air bubbles in the filling hoses during filling
. Filling needles work orders (e.g., misalignment, clogged)
. Work orders because of the malfunction of the insertion rods
. Work orders for the stoppering system

The DMAIC methodology will be followed for the data analysis.

Define

In the define phase was described the defect of product on the stopper on the pre-filled syringes. Also, was included a process flow map with the process steps for the pre-filled syringes manufacturing.

Measure

In the measure phase was included the data gathered related to the identified lots that exceeded 1.0 % of pre-filled syringes with the defect of the product on the stopper. In addition, historical data of pre-filled syringes inspection results (% defects of product on the stopper).

Gathered data includes evaluating the filling sets, work orders, and batch records.

Analyze

A surrogate run assessment was executed to assess the filling process and identify any area of improvement to avoid product on/over the stopper.

The data from inspected lots from 01/01/22 to 08/01/22 was assessed to determine if the process was in control. The I-MR control chart was generated to identify if the process demonstrates control regarding the defective units because of product on the stopper inspected.

A one-sample-t-test was performed at a significance level of 0.05 to determine if the % of defects because of product on the stopper seems to be less than 1.

Improve

The filling line was improved based on the analyzed data, implementing controls to avoid product or liquid on the stopper for the pre-filled syringes.

Control

The control phase includes the monitoring of the inspection results of the pre-filled lots manufactured after the implementation of controls to avoid product or liquid on the stopper for the pre-filled syringes.

Implementing the process controls will minimize the risk of adversely impacting the quality attributes of sterile solutions for subcutaneous administration because of product or liquid on the stopper. The manufacturing process was monitored for three (3) consecutive lots to assess the effectiveness of the implemented controls to not exceed the action limits because of the defect of syringes with product on the stopper. In addition, statistical analysis was performed with the inspection results of the pre-filled syringes after the implementation of control in the manufacturing process.

Results and Discussion

The stopper setting parameter has an impact on the Air Bubble size of the syringe. Stopper setting parameter has a relation with the ABS, if the value changes, the Air Bubble will change. If the stopper setting parameter is higher, the air bubble will be higher and if the stopper setting is lower, the ABS will be lower. An adjustment to the parameter more negative side can result in the insertion tube getting more introduced on the syringe, reaching the product and leaving product on stopper during the insertion tube retraction causing the defect of product on the stopper.

In-Process ABS values below 2.00 mm throughout the filling process can create the defect of product on stopper by inserting the insertion tube deeper that needed to place the stopper, causing it to reach the product. If the insertion tube reaches the product, the stopper will "clean" the walls of the insertion tubes and the stopper will have product on the ribs when placed on the syringe.

There were 4 corrections made to the filler:

1. The insertion tube holder from set #2 was replaced with a new one.
2. Syringes X/Y table slide plate stop mechanism was adjusted so that the syringes have less movement without creating damage to the syringes.
3. Fine-tuned the tub transfer positions for stoppering, checking to make sure that the insertion tubes will not rub on the inside of the syringes when stoppering.
4. Changed the stopper plunger home position from -4.5 to -4.9 and insertion tube home position from -2.7 to -2.9 in order to place the stoppers higher in the syringes during startup with a -33mm stopper position. (https://myplace.bms.com/personal/emeris_rivas_bms_com/Documents/Emeris/Personal/Manufacturing%20Competitiveness/Design%20Project%20Fall%202022/Project%20Presentation/Mechanical_stoppering_%20standard%20Video.avi)

The three lots filled after the implementation of the improvements were monitored to assess the inspection results. The three monitored lots complied with the control limit of product on the stopper defects less than 1.0%.

The improvements to avoid the product on the stopper were implemented on 08/03/22 at the Filling line. It is observed in the time series plot (Figure 2) that the lots manufactured from 08/05/22 to 08/12/22 complied with the control limit of less than 1.0% of defects because of product on the stopper.

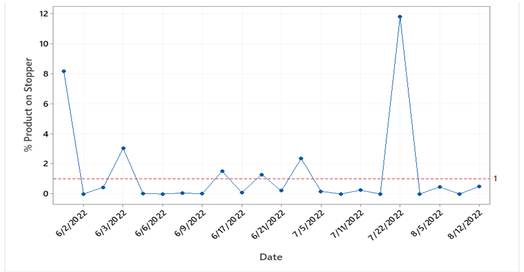

Figure 2
Time Series Plot of % Product on Stopper

It was demonstrated that there was a shift in the mechanical reference of the insertion tubes and insertion rods axis. This in turn caused the value of -33mm to not represent the same position as previously set. This shift was corrected by adjusting the stoppering system home position to place the stopper higher on the syringes during the initial startup position.

The cost per unit is of approximately $1,250.00. The total units rejected because of product on the stopper from June 2022 to July 2022 (prior improvements) was of 17,025 ($21,281,250). The total units rejected because of product on the stopper on August 2022 (after improvements) was of 524 ($655,000). When the costs of rejected units prior the improvements and after the improvements are compared, there is a financial benefit of $20,626,250.

Conclusions

The lots manufactured after these findings/corrections were monitored and complied with the alert control limit requirement of not more than 1.0% of units with the defect of product on the stopper. Based on the satisfactory results, it is concluded that the root cause of the events included in this report was identified as a combination of the described elements.

The data of % of product on the stopper per lot was analyzed in stages per month from 06/01/22 to 08/12/22 (Refer to Figure 3). After the implementation of the improvements in the filling line (August 2022), it is observed that the control limits are significantly closer and the center line (individual value/moving range) reduced significantly, closer to the control limit of NMT 1.0%.

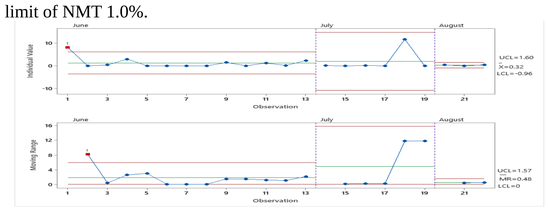

Figure 3
I-MR Chart of % Product on Stopper by Month

Future Work

Stoppers dimensions can affect the insertion of it on the syringe, creating a probability of over insertion. As part of the vendor feedback, Beckton Dickinson (BD) acknowledge the "Barrel to Barrel and Barrel to Machine Contact" during the syringe forming, printing, and assembly process step as potential cause for syringe breakage.

Based on the information provided by BD, it is understood that the additional printing process that undergoes syringe material could reduce the strength of the barrel making the syringes prone to breakages during the handling at the filling process. For future research, it is recommended to assess the printed syringe barrel process and identify opportunities for improvement.

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