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

Emeris Rivas Rodríguez
Master in Manufacturing Competitiveness
José A. Morales, Ph.D.
Industrial and Systems Engineering
Polytechnic University of Puerto Rico

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.*

LITERATURE REVIEW

Syringes are one of the containers used in the biotechnology industry for the treatment of diseases and chronic conditions, such as multiple sclerosis and rheumatoid arthritis. The rise in parenteral drugs has required drug and packaging manufacturers to implement more sophisticated container closure and drug delivery systems. The pre-filled syringes (PFS) have multiple benefits for the patients, such as an easy injection process that simplify self-administration by the patient or caregiver, reduction of medical dosing errors, and decreased microbial contamination because of less manipulation before dosing. [1]

The syringes consist of a syringe barrel and a piston which may have an elastomer sealing ring and may fit a non-detachable needle. The barrel is clear to permit dosage reading and observation of the solution. The stopper is the elastomeric material component of the pre-filled syringe that, when depressed, pushes the liquid out through the needle into the patient [2]. The stopper at the end of the plunger must move smoothly in the barrel while preventing any leakage or contamination.

Sterility is the most important critical quality attribute of a parenteral/sterile drug product. The filled plastic syringes are sterile and pyrogen-free single-use medical devices for immediate administration of injectable preparations. Filled syringes contain a sterile solution for subcutaneous administration. After the formulation process, manufacturing personnel transfers the portable formulation tank to the filling room for the filling process.

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. The defect of product on the stopper is observed when liquid product is trapped between two plunger ribs or between the trim edge and first rib, that is, > 1mm in circumference. Single liquid droplet or cluster of droplets > 2mm above plunger stopper. The product on the stopper is classified as a major defect with a low likelihood of compromising product/container closure integrity. The product on the stopper defect is illustrated in Figure 1.

Syringes Filling Process

Before the start of the filling process, the fill weight start-up and air bubble size verification are performed. Air bubble size is the space between the stopper tip and the liquid meniscus. It is a process parameter that depends on the syringe's fill weight and stopper position. Manufacturing personnel verifies the air bubble size through the complete

filling process to ensure it is not more than (NMT) 4.0 mm. [3] The filling process starts after the fill weight and the air bubble size testing. The filling process is conducted under the Grade A (ISO 5) environment inside the filling isolator.

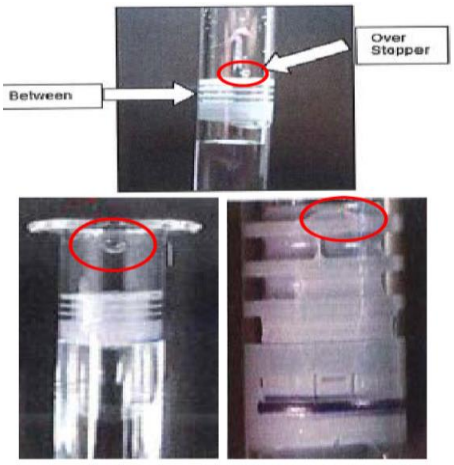


Figure 1
Product on the Stopper Defect

During the filling process, the filler and the stoppering machine dispense the filtered solution through the manifold that connects the Teflon product transfer hoses into the pre-sterilized syringes.

Once the syringes are filled with product, the filler and stoppering machine place the stoppers into the syringe barrel at the defined stopper position to achieve an air bubble size of NMT 4.4 mm. After stoppering, the filler and stoppering machine place the syringes in nested tubs.

After tub verification, manufacturing personnel closes each tub with flat lids. Nested tubs with pre-filled syringes are placed on carts and stored at a temperature of 2°C - 8°C until the visual inspection process.

Air Bubble System

Air bubble size is the space between the stopper tip and the liquid meniscus (Figure 2). It is a process parameter that depends on fill weight and stopper position. As part of the filling process, manufacturing personnel verifies the air bubble size to ensure it is NMT 4.4m. . During this process, the manufacturing area personnel visually verifies the area of the syringe that contains the stopper and the product meniscus. This is performed to confirm that the vision system is measuring the correct location between the product meniscus and the inferior stopper part.

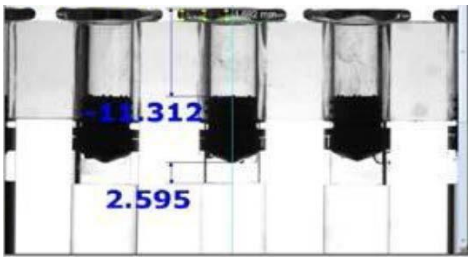


Figure 2
Picture of the Air Bubble Size Measurement

The Stopper Setting parameter determines the depth at the insertion tube to be introduced to the syringe to place the stopper. The Stopper Setting must be set to - 33 mm before starting the filling process. However, additional adjustments can be performed as required by the Air Bubble System (ABS).

Inspection Process

After the filling process, the prefilled syringes are subjected to 100% automated visual inspection.

After the 100% visual inspection, an AQL Single Normal Level II Sampling Plan inspection is performed. When re-inspection is required, the AQL follows a Single Tightened Level II Sampling Plan [4].

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

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. The stopper is the component of the prefilled syringe that, when depressed, pushes the liquid out

through the needle into the patient. The stopper at the end of the plunger must move smoothly in the barrel while preventing any leakage or contamination. Figure 3 illustrates the parts of a syringe, including the stopper.

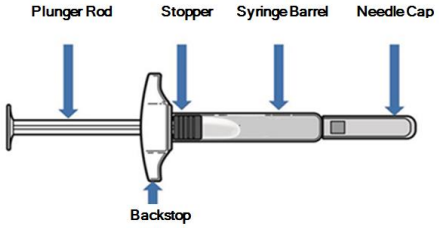


Figure 3
Syringes Parts

The product on the syringe stopper is classified as major, and the established control limit is not more than (NMT) 1.0%.

During the filling process, the filler and stoppering machine dispense the filtered solution through the manifold that connects the Teflon product transfer hoses into the pre-sterilized syringes. Once the syringes are filled with product, the filler and stoppering machines place the stoppers into the syringe barrel at the defined stopper position to achieve an air bubble size of NMT 4.4 mm. Nested tubs with pre-filled syringes are 100% visually inspected (manual or automatic).

Product on the stopper is a condition that originates during the filling process.

Filling parameters

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
- Malfunction of the insertion rods
- Stoppering system

Pre-filled syringes market is expected to grow at an annualized rate of 3.9% between 2016 and 2026. Most of the pre-filled syringes market is currently 35% from North America and 45% from the EU. In addition, it is expected that the pre-filled syringes market in Asia, Latin America, the Middle East, and Africa will likely grow faster than in developed regions. [1]

This research will be conducted following the DMAIC methodology and has three main contributions, which include evaluating the current state of control of critical process parameters, assessing the current operational state, and setting the expectation for future equipment modifications to ensure continuous improvement.

Define

The pre-filled syringes lots of inspection, and data available from February 2021 to August 2022, was evaluated. There were 20 lots inspected during this period that exceeded the 1% criteria for Liquid on/over stopper major defects, being "Liquid on Stopper" is the major contributor in all lots.

This research includes data from six (6) lots of pre-filled syringes that exceeded the Total Major Defects control limit of NMT 1.0% due to a high incidence of Product on the Stopper defects. The pre-filled syringes manufacturing process flow is described in Figure 4.

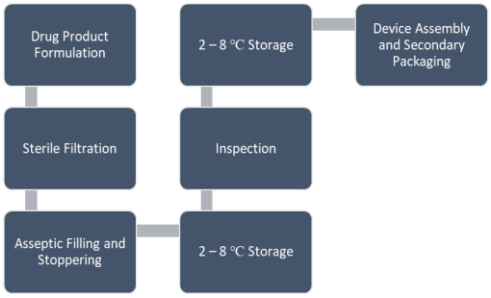


Figure 4
Pre-Filled Manufacturing Process Flow Diagram

Elements evaluated in this research are related to syringe filling, filler equipment, and the inspection process. The assessed data was from batch records, work orders, equipment performance, preventive maintenance, and instrument calibrations. Table 1 summarizes the product on stopper reported for lots manufactured from 04/23/22 to 06/23/22, the filling sets used for each lot, and information-related materials.

Table 1

Summary of Product on the Stopper Defect

Lot ID	Mfg Date	Syringes Inspected	Syringes with Product on Stopper	Product on the Stopper (%)	Total Major Defects % (NMT 1.0%)	Total Rejects % (NMT 3%)
A	04/23/22	54,876	4,476	8.2	8.4	9.0
B	04/08/22	54,284	827	1.5	1.5	2.0
C	05/16/22	20,635	626	3.0	3.3	3.4
D	06/12/22	53,076	687	1.3	1.6	2.4
E	06/01/22	49,628	1,174	2.4	2.4	2.9
F	06/23/22	49,322	5,813	11.8	11.8	12

Six (6) incidences were reported because the total major defects limit exceeded 1.0% for lots manufactured from 04/23/22 to 06/23/22. The main contributor was the product on the stopper defect.

MEASURE

In the measure phase were evaluated atypical conditions at the filling manufacturing process and the equipment filling components.

Filling Set Evaluation

Currently, there are two (2) filling sets for the manufacturing process of pre-filled syringes. The filling sets are composed of a filling component (Filling Needles, Orifices, Nuts, O-Rings, and Hose Connectors) and a stoppering component (Plungers, Plunger Holder, Insertion Tube Holder, Insertion Tubes, Insertion Rods (10 pins), Swivel Arm and Stopper Holder). Filling components from one set can be used with a stoppering component from another set. These components can be combined. Therefore, the filling sets do not contribute to the product on stopper defect.

The periodic inspection evaluation of the filling sets PM's showed no discrepancies that could contribute to the generation of the defect of product on the stopper in the impacted lots evaluated under this research.

Work Orders Evaluation

The work orders generated during the filling process for the six (6) lots were assessed in this research to identify any situation that could contribute to a high incidence of syringes with product on the stopper defects.

Batch Records Evaluation

The batch records for lots A, B, C, D, E, and F were reviewed to identify any situation that could contribute to the high incidence of syringes with product on the stopper defects. The review was focused on the alarms, air bubble size measurements, and situations reported during the filling process of the lots since these are the major elements in which a situation related to product on the stopper can be identified.

Based on the batch record and work order evaluation performed, the following was identified:

Syringe Breakage / Stoppages

Syringe breakages can create stoppages and cause air bubbles on the filling lines. If these bubbles burst before the syringe is stoppered, they can splash the wall of the syringe with product and fill the stopper walls with product. Also, stoppages could create product build-up on the filling needle tip that could affect the filling stroke by splashing product onto the syringe wall.

Low Air Bubble Size Readings During the Filling Process

The stopper setting parameter is responsible for moving the insertion tube and the insertion rod axis. If the mechanical zero (reference) for the insertion tubes and rods shifts, it would not represent the same position for the stopper setting parameter. This means that if there is a shift on either shaft, it will directly impact the stopper setting position by shifting it. If the parameter is -33mm, both shafts will move to the corresponding positions representing -33mm.

Also, the parameter impacts the air bubble size of the syringe. The stopper setting parameter is related to the ABS. If the value changes, the air bubble will change. If the stopper setting is higher, the air bubble will be higher, and if the stopper setting is lower, the ABS will be lower.

Although lots A, B, C, D, E, and F showed that the ABS results were within the established range, the lots reported ABS values below 2.00 mm during the filling process. If these values throughout the

filling process are below 2.0 mm, it can create the defect of the product on stopper by inserting the insertion tube deeper than 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 tubes, and the stopper will have product on the ribs when placed on the syringe.

Dripping Needle/Stoppages

Dripping needles can create stoppages and cause air bubbles on the filling lines. Stoppages during the filling process can create air bubbles on the filling lines. If these bubbles burst before the syringe is stoppered, they can splash the wall of the syringe with product and fill the stopper walls with product. This causes the defect of product on/over stopper. Another effect of the air of the line is that the filling stroke could cause spray that can create product droplets on the syringe walls. Ultimately, the insertion tubes can reach this droplet, get the product attached, and then transfer it to the stopper. Also, stoppages could create product build-up on the filling needle tip that could affect the filling stroke by splashing product onto the syringe wall.

Analyze

From the Moving Range chart (Figure 5), we can observe that the process variation is not in control, then the control limits on the I chart are not accurate. For example, red points indicate observations that fail at least one of the tests for special causes and are not in control.

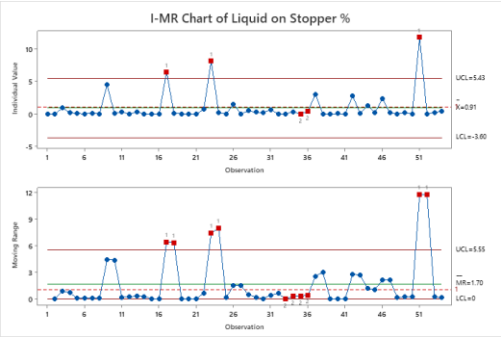


Figure 5
I-MR Chart of Product on the Stopper

In the t-test example, the test statistic is a function of the mean, and the p-value is 0.384. This indicates that 38% of the sample size 54, drawn from the population where μ = 1, will produce a mean that provides as strong (or stronger) evidence as the current sample that μ is equal to 1. The p-value of .384 indicates that the % of defects because of product on the stopper (not only the mean of the 54 samples) is probably equal to 1, not less than 1 (Refer to Table 2).

Table 2
Descriptive Statistics and One- Sample t Liquid on Stopper %

N	Mean	StDev	SE Mean	95% Upper Bound for μ
54	0.912	2.181	0.297	1.409

μ: population mean of Liquid on Stopper %

Null hypothesis	H_0: μ = 1
Alternative hypothesis	H_1: μ < 1

T-Value	P-Value
-0.30	0.384

At a significance level of 0.05, the % of defects because of product on the stopper seems to be not significantly less than 1. The syringes filling process requires improvements to have a process in control and to decrease the defects with product on the stopper % product on the stopper NMT 1.0%.

Surrogate Formulation

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 scope of this document is to identify areas of improvement to avoid the product on/over-stopper defect on the filler machine.

Inspection Process

Perform 100% inspection of the tubs in line. The I-MR control chart was generated to identify if the process demonstrates control. The data includes the inspection results and the defective units because the product on the stopper. Lots were inspected from 01/01/22 to 08/01/22.

PROJECT METHODOLOGY

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

Data will be 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 were 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 will be described the defect of product on the stopper on the pre-filled syringes. Also, will be included a process flow map with the process steps for the pre-filled syringes manufacturing.

Measure

In the measure phase will be 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 scope of this document is to identify areas of improvement to avoid the product on/over-stopper defect on the filler machine.

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 .05 to determine if the % of defects because of product on the stopper seems to be less than 1.

Improve

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

Control

The control phase will include monitoring 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. In addition, the manufacturing process will be 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 will be performed with the inspection results of the pre-filled syringes after the implementation of control in the manufacturing process.

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.

RESULTS AND DISCUSSION

The manufacturing data, from risk assessments, batch records, and work orders, was evaluated to identify causes that can produce the defect of the product on the stopper. A Cause and Effect Diagram was performed, and all the elements listed were thoroughly assessed and evaluated for each event.

Based on the evaluation performed, the potential causes that produce the product on the stopper during the syringes filling process are Syringe Breakages, Stoppages, Shift of the Mechanical Zero, ABS Low Measurement, Dripping Needle, IPC 12 Alignment, XY Table locked position, and IPC lifting device. Refer to Figure 6.

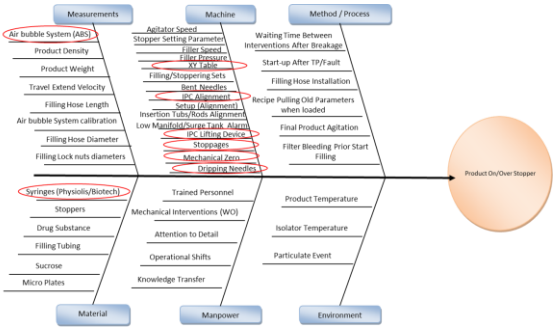


Figure 6

Cause and Effect Diagram (Fishbone)

Syringe breakages can create stoppages on the process and cause air bubbles on the filling lines. If these bubbles burst before the syringe is stoppered, it can splash the wall of the syringe with product and fill the stopper walls with product. Also, stoppages could create product build-up on the filling needle tip that could affect the filling stroke by splashing product onto the syringe wall.

The stopper setting parameter is responsible for moving the insertion tube and the insertion rod axis as a whole. The Stopper Setting parameter determines the depth the insertion tube will be introduced to the syringe to place the stopper. If the mechanical zero (reference) for the insertion tubes and rods shifts, it would not represent the same position for the stopper setting parameter (-33mm). This means that the if there is a shift on either shaft it will directly impact the stopper setting position by shifting it.

Also, 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 evaluated on this investigation.

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. Furthermore, if a low ABS value is reported and if the fill weight gets higher, the volume in the syringe will increase. Thus, having a smaller air gap and increasing the probability of creating the defect. These low air bubble measurements can be related to a shift in the reference of the stopper setting mechanical zero.

Dripping needles can create stoppages on the process and cause air bubbles on the filling lines. Stoppages during the filling process can create air bubbles on the filling lines. If these bubbles burst before the syringe is stoppered, it can splash the wall of the syringe with product and fill the stopper walls with product. This causes the defect of product on/over stopper. Another effect of air of the line is that the filling stroke could cause spray that can create product droplets on the syringe walls. Ultimately, the insertion tubes can reach this droplet, get the product attached and then transferred to the stopper. Also, stoppages could create product build up on the filling needle tip that could affect the filling stroke by splashing product onto the syringe wall. Product droplet could reach

the syringe wall creating the product on stopper defect.

Stoppers dimensions can affect the insertion of it on the syringe, creating a probability of over insertion. The evaluation of the incoming results was performed for the mentioned stopper lots and no atypical dimensional results were reported during the inspection process. Review of the incoming data showed that each syringe and stopper lot used complied with the Incoming Visual Inspection, Dimensional Testing and AQL inspection criteria.

As part of the vendor feedback, BD acknowledges the "Barrel to Barrel and Barrel to Machine Contact" during the syringe Forming, Printing, and Assembly Process Step as a potential cause for the condition reported by BMS. Based on the information provided by BD, it is understood that the additional printing process could reduce the strength of the barrel making the syringes prone to breakages during the handling at the filling process.

On 07/31/22, a testing run was performed at the Filling Manufacturing Process to identify areas of improvement for the reduction of product on/over the stopper defects. The filler machine technical support team observed operators setting up the machine to see if the setup could be causing any issues during filling. According to the filler machine technical support team the setup was adequate, operators setting up the machine were very experienced and per the established procedures.

On 08/03/22, after the completion of the surrogate run, there were 4 corrections made to the filler:

- The insertion tube holder from set #2 was replaced with a new one.
- Syringes X/Y table slide plate stop mechanism was adjusted so that the syringes have less movement without creating damage to the syringes.
- 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.
- Changed the stopper plunger home position (PL HOME POSITION) stopper plunger home position (PL HOME POSITION) from -4.5 to -4.9 and insertion tube home position (TU 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.

Changes were tested with Biotech and Physiolis (no lines) syringes to verify stopper position and reduced contact between stopper insertion tubes and syringes. No contact was observed between the insertion tubes and the syringes and the stopper insertion depth on the syringe was higher. After the adjustments the following lots were filled:

- Lot G was filled on 08/05/22 with Physiolis (no lines) syringes. During this lot, 53,439 syringes were filled, during Visual Inspection 249 syringes were found with product on stopper defect. This represents a 0.46% of major defect where the control limit is (NMT 1.0%).
- A second lot H was completed on 08/11/22, using Biotech syringes. During this lot, 52,670 syringes were filled, during Visual Inspection 0 syringes were found with product on stopper defect. This represents a 0.00% of major defect where the control limit is (NMT 1.0%) and is pending the inspection process.
- A third lot I was filled on 08/14/22. During this lot, 54,483 syringes were filled, during Visual Inspection 275 syringes were found with product on stopper defect. This represents a 0.50% of major defect where the control limit is (NMT 1.0%).

The mechanical zero tool "jig" parameters were adjusted accordingly. Changes were tested with Biotech and Physiolis (no lines) syringes to verify stopper position and reduced contact between stopper insertion tubes and syringes. No contact was observed between the insertion tubes and the syringes and the stopper insertion depth on the syringe was higher. This was to confirm that XY Table and mechanical zero adjustments were adequate.

Run report concluded that several observations that could contribute to the product on stopper defect were identified and addressed. It was

demonstrated that there was a shift in the mechanical reference of the insertion tubes and insertion rods axis. Other factors identified that could contribute to the creation of the defect is that the syringes in the X-Y table were loose when in the "locked position" and this could cause the insertion tubes to rub on the side of the syringe walls and the lifting device for IPC was very fast, this could cause the product to splash when returning into the X-Y table for stoppering.

The filling lines improvements were completed on 08/03/22. 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%. Refer to Table 3.

Table 3
Results of Lots Inspected after the Improvements Implementation

Lot ID	Syringes Inspected	Syringes Inspected w/Product on Stopper	Product on the Stopper (%)	Manufacturing Date
G	53439	249	0.46	08/05/2022
H	52670	0	0.00	08/11/2022
I	54483	275	0.50	08/12/2022

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 7) 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.

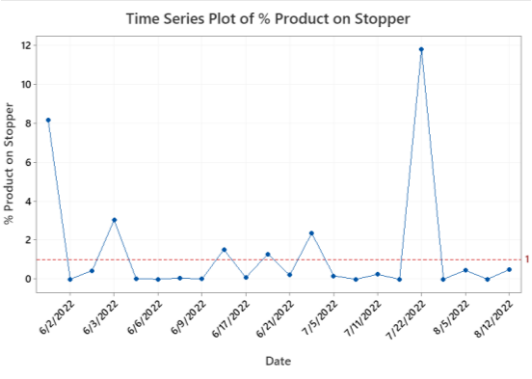


Figure 7
Time Series Plot of % Product on Stopper

CONCLUSIONS

Several observations that could contribute to the product on stopper defect were identified and addressed. 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. For the adjustments, changes were made to the stopper plunger home position (PL HOME POSITION) from -4.5 to -4.9 and insertion tube home position (TU HOME POSITION) from -2.7 to -2.9. Currently the mechanical zero jig is implemented for the appropriate adjustment of the insertion tubes / rods.

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 8). It is observed that the process was kept in control at every stage. The control limits in July were broader, and the center line (individual value and moving range) was higher when compared with June. After the implementation of the improvements in the filling line (on August), 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%. From July to August, the variation of the process, the area between the upper and lower control limits, decreased significantly over time.

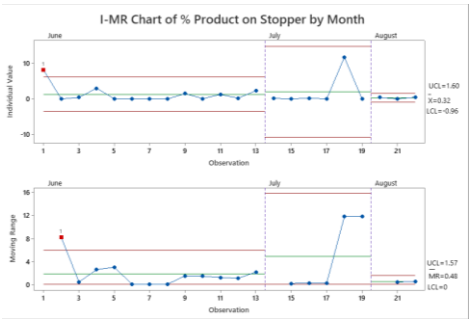


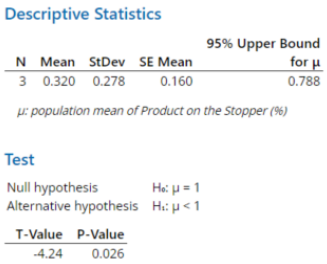
Figure 8
I-MR Chart of % Product on Stopper by Month

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. Prior to the filling line improvements (June to July), there were 32% of lots that exceeded the alert limit of NMT 1.0% because of product on the stopper. After the implementation of the filling line improvements, there were 0% of lots that exceeded the alert limit of NMT 1.0% because of product on the stopper. (Refer to Table 4).

Table 4
Results of Lots Inspected before and after the Improvements Implementation

June-July % Defects	August % Defect	Mean June-July	Mean August
8.1600	0.46	1.54844	0.32
0.0000	0.00		
0.4426	0.50		
3.0337	*		
0.0264	*		
0.0000	*		
0.0641	*		
0.0094	*		
1.5200	*		
0.0844	*		
1.2944	*		
0.2101	*		
2.3656	*		
0.1744	*		
0.0000	*		
0.2457	*		
0.0000	*		
11.7858	*		
0.0038	*		

In the one-sample t-test (Figure 9), the test statistic is a function of the mean, and the p-value is 0.026. This indicates that 2.6% of the sample size 3, drawn from the population where $\mu = 1$, will produce a mean that provides as strong (or stronger) evidence as the current sample that μ is not equal to 1. The p-value of 0.026 indicates that the % of defects because of product on the stopper (not only the mean of the 3 samples) is probably less than 1, in accordance with the product on the stopper's control limit.



Descriptive Statistics

N	Mean	StDev	SE Mean	95% Upper Bound for μ
3	0.320	0.278	0.160	0.788

μ: population mean of Product on the Stopper (%)

Test

Null hypothesis H_0: $\mu = 1$
Alternative hypothesis H_1: $\mu < 1$

T-Value	P-Value
-4.24	0.026

Figure 9
One-Sample T: Product on the Stopper (%)

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.

REFERENCES

[1] (2017). Prefilled Syringes Market 2016-2026. NEW YORK 4th: Edition., PR Newswire.

[2] ISO 11040. (2012). Plunger Stoppers for Injectables. Prefilled Syringes, Part 5.

[3] (2022). Parenteral Drug Product Visual Inspection Defect Harmonization, Classification and Risk Assessent . Puerto Rico.

[4] ASQ. (n.d.). ANSI Z