Engineering and Procedural Improvements to Avoid Cracks on Syringes During the Packaging Process

Rossana M. Colón Rosado
Advisor: Dr. Héctor J. Cruzado
Master of Engineering Management Program

Abstract

One cracked syringe was found during the device functionality tests performed to a lot manufactured by XYZ biopharmaceutical company. A cracked syringe is categorized as a critical defect since it represents a risk to product quality and to patient safety. Strength testing and fracture analysis technology were used to determine the cause of the cracked syringe. It was found that the root cause of this defect was the design of the syringe-labeling equipment, which produced a lateral force on the syringe when passing through the outfeed vibratory rail. Labeler equipment modifications and packaging procedural improvements were implemented to eliminate the root cause and to avoid the breakage of syringes during the packaging process.

Introduction

XYZ is a biopharmaceutical company that manufactures parenteral treatments (prefilled syringe injections and vial injections) for catastrophic diseases. During the glide force testing of a syringe packaging lot from XYZ company, one cracked syringe was found. With this critical defect identified, the lot failed its quality inspection, and it was not allowed to be released for market distribution. Defective unit analysis and syringe packaging process evaluation confirmed that the syringe broke as result of a force applied to the mid-barrel area sometime after application of the label.

Background

Over 20 pharmaceutical companies use prefilled syringes as preferred delivery method because they allow a quicker administration of injections, assure accurate dosages and self-medication, increase medication life span, and allow for the assembly of anti-needlestick accessories for safer administration [1]. The material used for the manufacturing of syringe barrels (bodies) is glass. Prefilled syringes lots must undergo 100% inspection and are submitted to integrity testing to ensure that the product is particle-free, sterile and safe [2]. Syringe defects are classified as critical, major and minor, based on their potential impact to quality and safety and their detectability. The acceptance criteria for the inspection is based on acceptance quality limits (AQL), as per American National Standards Institute/American Society for Quality Controls (ANSI/ASQC) Z1.4-2008, Sampling Procedures and Tables for Inspection and Attributes [3]. Body cracks on syringes are classified as critical defects, with an accept/reject criteria of 0/1, since they can compromise the syringe integrity and sterility of the product [4]. Pharmaceutical companies apply methods of strength testing and fracture analysis (fractography) to determine the root cause and corrective actions for glass defects [5].

Problem

There was a cause of cracked syringes during the packaging process at XYZ pharmaceutical company. Due to the cracked-syringe event, the impacted lot failed its quality inspection and the three lots previously packaged in the Syringe Packaging Line were compromised. Line production was stopped until the cause of the cracked syringe was identified and resolved.

Methodology

Cracked Syringe Root Cause Analysis
To find the root cause of the cracked syringe, techniques in **Table 1** were applied.

Table 1: Root Cause Analysis Techniques

Step	Method	Discovery
1st	Computerized Tomography (CT) Scanning of the fully assembled device	No indication of improper assembly was identified for any of the device components. The safety syringe unit completely activated, and drug product was fully dispensed with no atypical behavior.
2nd	Syringe Forensic Analysis	The syringe was removed from its device and its label was partially removed. The syringe barrel was cracked under the label and the location of the crack was approximately 28-33mm from the flange, as shown in **Figure 1.**
3rd	Fracture Analysis Techniques	Optical Stereo Microscopy (OSM) and Scanning Electron Microscopy-Energy Dispersive Spectrometry (SEM-EDS) techniques were used. There was no evidence of uneven glass wall thickness. The data confirmed that the syringe broke because of a force that was applied to the mid-barrel area. This force was likely applied after application of the label on the syringe, as the label held the syringe together.
4th	Labeling Process Evaluation	A syringe drone was run through the labeling process to measure and record applied forces, spinning, tilting, and impact to the syringe drone by the equipment. The maximum pressure the labeler machine applied to the syringe drone was 25 psi. However, data gathered from previous technical runs demonstrate that a pressure of 25 psi is not strong enough to break the syringe during normal operating conditions.
5th	Post-labeling process evaluation	The outfeed conveyor of the labeler machine is a vibratory rail. After multiple runs, creating different inward force conditions, a cracked syringe was replicated and had a crack origin in the same area syringe barrel (approximately 28-33mm from the flange). A temporary misalignment between the stainless-steel vibratory rail and the black plastic rail at the outfeed of the conveyor produced a lateral force, that cracked the syringe.

Root cause
The post-labeling process evaluation confirmed that the root cause of the cracked syringe was a misalignment at vibratory rail of the labeler machine.

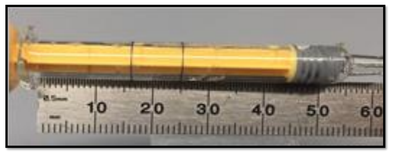

Figure 1: Cracked Syringe

Equipment and Process Improvements
With the root cause identified, the following equipment modification, inspection and procedural updates were performed to eliminate the cause of cracked syringes during the packaging process:

- Installation of a support mechanism in the Vibratory Rail system to prevent misalignment of the rails.
- An additional acceptance quality limit (AQL) inspection was performed to the first 25 lots packaged at the Syringe Packaging Line after the Vibratory Rail support installation. The objective of this inspection was an effectiveness check to demonstrate zero cracked syringes.
- Revision of the labeler machine and syringe packaging line procedures to specify syringe verification instructions after labeling.

Results and Discussion

Support Mechanism Functionality
Support mechanism shown in **Figure 2** was installed at the Vibratory Rail System to prevent misalignment with the transfer guide towards the manual assembly station. This custom-made support device allows adjusting and setting the Vibratory Rail to a fixed position, preventing it from moving due to equipment vibration and safeguarding its alignment with the plastic rail at the outfeed of the conveyor throughout the entire packaging process.

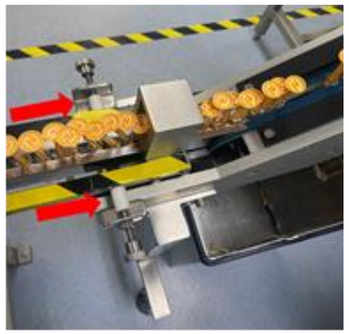

Figure 2: Vibratory Rail Support Mechanism

AQL Inspection Results
After the installation of the support mechanism at the Vibratory Rail System, an additional AQL inspection for cracks in syringes was completed for the first 25 lots packaged in the Syringe Packaging Line. For each of the 25 lots, a sample size of 50 syringes was inspected; refer to **Table 2** for the sampling plan used. Sampling plan in **Table 2** was indicative of the following:

- Less than 5% risk of rejecting the lot with a true defective rate of <0.1% (<0.10253%)
- Less than 10% of risk of accepting the lot with a true defective rate >4.5% (>4.5007%)

Table 2: AQL Inspection Sampling Plan

Lot Size	Sample Size	Accept / Reject	AQL* (0.95)	LTPD* (0.10)
≥ 150	50	0 / 1	0.10253%	4.5007%.

*AQL stands for Acceptance Quality Limit. LTPD stands for Lot Tolerance Percent Defective.

For this inspection, samples were segregated in beginning, middle and end portions for each lot. The label was removed from each syringe to check for cracks underneath the label. The AQL inspection was successfully completed and met the acceptance criteria for the 25 lots inspected. No (zero) crack defects were observed for each of the 25 lots.

Packaging Procedures Revision and Training
With the effectivity of the support mechanism confirmed and proved by the AQL results, labeler machine and syringe packaging line procedure and batch record were updated to include an instruction for syringe verification after labeling.

The station after the syringe-labeling process is for manual assembly. Operators were instructed and trained to perform a 100% inspection of the syringes before transferring the units to the manual assembly station. The inspection consists of verifying the integrity of each syringe body and that each syringe assembly contains all its components (label, plunger rod, needle shield and flange extender). This additional inspection acts as a fail-safe system to detect and record any defective unit produced up to labeling process station.

Conclusions

By integrating quality acceptance standards with strength testing and fracture analysis technology for glass containers, XYZ biopharmaceutical determined that the cause of cracked syringes was the labeler equipment design. Along with labeler equipment modifications performed, packaging procedural improvements were also essential for root cause elimination, as the packaging process of syringes at XYZ site is a semi-automatic one that requires frequent human intervention. This finding established a new failure mode and additional control requirements for the current Vibratory Rail System and Outfeed Conveyor of the Labeler equipment.

Future Work

A further evaluation for the redesign or replacement of the Labeler machine already started. Through this evaluation, new packaging technology alternatives are under consideration to optimize in terms of output, efficiency, and quality the syringe labeling process at XYZ biopharmaceutical company.

Acknowledgements

The collaboration, knowledge, time and commitment of Packaging Technology, Investigations, Engineering, Quality Assurance and Operations teams from XYZ company were key in the completion of this project.

Special thanks to Héctor J. Cruzado for his guidance and feedback throughout the development of thi project.

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