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

Rossana M. Colón Rosado
Master in Engineering Management
Dr. Héctor J. Cruzado
Department of Civil & Environmental Engineering and Land Surveying
Polytechnic University of Puerto Rico

Abstract *— One cracked syringe was found during the device functionality tests of 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.*

Key Terms *— AQL inspection, glide force, strength testing and fracture analysis, syringe-labeling*

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.

Cracked syringes are categorized as a critical defect, since cracks represent a risk to product quality and to patient safety during drug administration. This paper describes the methods used for the root cause determination of the cracked syringe and the engineering and procedural improvements implemented in the packaging process at XYZ to avoid cracks in syringes.

LITERATURE REVIEW

Characteristics of Prefilled Syringes

Over 20 pharmaceutical companies use prefilled syringes as preferred delivery method for drugs due to the convenience, accuracy, sterility and safety they provide [1]. Prefilled syringes allow a quicker administration of injections, assure accurate dosages and self-medication, increase medication life span for up to three years, 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, “as it is non-reactive and stable during storage”, however, its main disadvantage is its fragility [1]. For this reason, prefilled syringes must undergo 100% inspection, either manual, semi-automated, or fully automated. Syringes that pass the inspection are then submitted to integrity testing to ensure that the product is particle-free and sterile [2].

Syringes Inspection

For syringes inspection, 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

since they can compromise the syringe integrity and sterility of the product [4]. The acceptance criteria (AQL) of critical defects is 0 accept / 1 reject; meaning that with at least one defective unit, the lot fails the quality inspection and it cannot be released to the market.

Pharmaceutical companies are encouraged to apply methods of strength testing and fracture analysis (fractography) to determine the root cause and corrective actions for glass defects [5].

ANALYSIS APPROACH

XYZ biopharmaceutical performs data analysis to an aleatory quantity of units of every syringe lot. During the glide force testing of one lot, an atypical graph was obtained for one of the syringes. "The glide force is the energy required for the plunger to continuously move through the barrel of the syringe" [2].

Cracked Syringe Root Cause Determination

To find the root cause of the atypical glide force graph, first, the syringe was sent for Computerized Tomography (CT) Scanning of the fully assembled device. During the evaluation, no indication of improper assembly was identified for any of the device components: plunger, flange extender and needle assembly. The safety syringe unit completely activated, and drug product was fully dispensed with no atypical behavior.

Next, a forensic analysis was performed to the syringe. The syringe was removed from its device and the syringe label was partially removed. It was observed that the syringe barrel was cracked under the label and that the location of the crack was approximately 28-33mm from the flange, as shown in Figure 1. The location of the crack coincided with the visually observable shift in the glide force graph.

The syringe then underwent Fracture Analysis Techniques including Optical Stereo Microscopy (OSM) and Scanning Electron Microscopy-Energy Dispersive Spectrometry (SEM-EDS). There was no evidence of uneven glass wall thickness or out-of-roundness in the barrel. The data obtained from the analysis confirmed that the syringe broke because of a force, either an impact or squeeze load, 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. A partially fractured syringe prior to labeling process would not have survived the stress caused by the labeler machine if unlabeled.

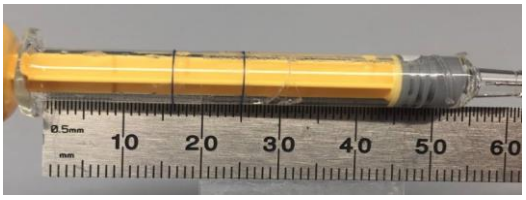

Figure 1
Cracked Syringe

The syringe labeling process was evaluated by the technical team to identify the stage at which the crack was caused. 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.

Packaging Technology team from XYZ pharmaceutical company performed multiple runs of the post-labeling process at the syringe packaging line. The outfeed conveyor of the labeler machine is a vibratory rail system where all syringe barrels are automatically aligned in the same direction (the syringe flange rests on the rail).

The syringe alignment is at a location of approximately 32-34mm from the flange, which is within the location where the lateral force that broke the syringe was applied (approximately 28-33mm from the flange). After multiple runs at the vibratory rail of the labeler machine, creating different inward force conditions, a cracked syringe was replicated and had a crack origin in the same area.

A temporary misalignment between the stainless-steel vibratory rail and the black plastic rail at the outfeed of the conveyor produced a lateral force, as shown in Figure 2, that cracked the syringe. This confirmed that the root cause of the cracked syringe was a misalignment at vibratory rail of the labeler machine.

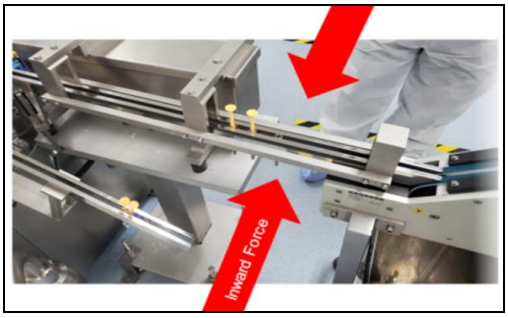

Figure 2
Vibratory Rail Inward Force

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 3 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.

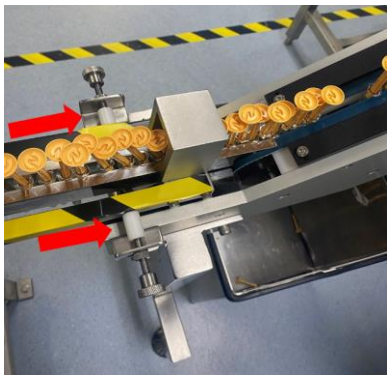

Figure 3
Vibratory Rail Support Mechanism

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 1 for the sampling plan used. Sampling plan in Table 1 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 1
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.

Quality Assurance personnel performed and documented the AQL inspection for cracks in syringes. 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 on 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.

As 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.

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