Particle Detection Tool for Liquid Product Inspection Machines

Angie Ly García Duprey
Master of Engineering in Manufacturing Engineering
Advisor: Carlos González, PhD.
Industrial and Systems Engineering Department
Polytechnic University of Puerto Rico

Abstract *– Improvements opportunities were found during the inspection process of recent manufactured lots in new manufacturing single-use technology, which was validated due to expected increase in product demand. An increase in fiber particulate matter which are more difficult to detect by the current inspection tools due to the particle dynamic, morphology and appearance in the liquid product. The implementation of a polarized camera is under management evaluation to increase the detection of translucent particles, similar to the ones observed during the inspection process.*

Key Words – *Defects, Inspection, Particulate, Polarization.*

INTRODUCTION

As technology is continuously improving in all type of manufacturing industries, it is also improving in the pharmaceutical industry. Many pharmaceutical industries have adopted an innovative and transforming process known as Single-use Technology (SUT). The implementation of this new technology has been found to help industries in the compliance with regulatory requirements, while offering less costly facilities and operations [1].

Manufacturing industries have found that this technology offers many advantages, such as, little to no cleaning validation required, decrease process time, lower capital investment among others [2]. The primary disadvantages found regarding single-use technology is what Snyder calls “difficulty in efficiency producing in bulk”. One of the most noticeable difficulty during production is observed during the downstream process, meaning the inspection of the products.

Quality assurance is often part of every manufacturing process, where product is inspected or evaluated for multiple types of defects. Figure 1 shows an illustration on process flows [3]. Visual inspection processes used for the assurance of the product quality may be performed by qualified inspectors via manual or semi-automatic inspection or using an automatic inspection machine.

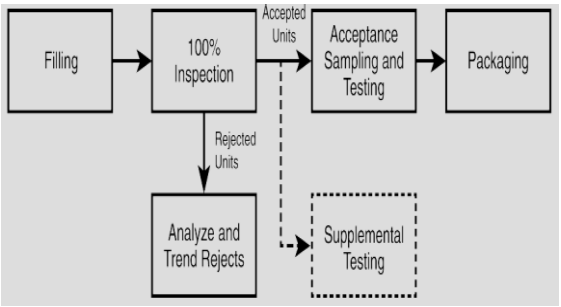

Figure 1
Simplified Process Flow

Defects may be categorized into either particulate and non-particulate or cosmetic defects. Regarding the disadvantage mentioned when implementing SUT, it is related to particulate defects found in the parenteral product after the filling process. The single-use technology uses plastic components, including but not limited to formulation bags, line tubing and connections, which are in direct contact with the drug solution.

PROBLEM STATEMENT

After the introduction of single-use technology to the manufacturing process of liquid vial product, the inspection process has been experiencing an increase in particulate matter in the final product. Intrinsic particles of the process such as plastic fiber materials. Detectability of these type of particulate is more difficult due to the dynamic and morphology of such. Fiber and plastic particulate

found during the inspection process may be describe as translucent and buoyant.

INVESTIGATION DESCRIPTION

This project will explore the introduction of a new polarization tool that will increase the detectability of translucent particles during the automatic inspection process of the liquid vials.

During the evaluation, the current particle rate, control limits and AQL failures will be taken in consideration and how these aspects of the process impact no only the quality of the product, but control specifications, scheduling, product complaints and production costs.

OBJECTIVE

Provide a complete and detailed evaluation of the improvements that may be observed after the implementation of a new tool in the automatic inspection machine. The tool will increase the detection of translucent particulate by introducing a polarized degree.

With the implementation of the polarized tool, the inspection process is expected to:

- Better detect translucent particles
- Reduce the mitigation time
- Reduce AQL failures due to translucent particles
- Reduce re-inspection processing

INVESTIGATION CONTRIBUTION

This project investigation will evaluate the process improvements that could be observed after the implementation of a tool to increase the detection of translucent particles observed from SUT manufacturing process.

In addition, the implementation of this tool is believed to improve product quality per regulatory specifications.

LITERATURE REVIEW

Visual inspection processes have always been present in all kinds of industries, whether product or service related. Focusing on product related quality, the number of defects per unit is directly related to the quality of the product. Quality may also be evaluated based on statistical evaluations on the number of returns or defect identification lead time [4].

Multiple inspection processes have been implemented preventively to ensure a lower rate of customer complaints by eliminating defective units while the product is still in the site.

Manual visual inspection is believed to be the oldest introduced as early as the 20th century [5]. While this process provided many advantages such as, low initial costs based on equipment and training and high flexibility, the disadvantages makes this process not suitable for large manufacturing industries. The disadvantages include:

- Higher labor cost for large production companies.
- Inspection time takes longer that automated and/or semi-automated processes.
- Fatigue factor must be taken in consideration as well as human concentration and emotional well-being of the operator which may impact the outcome.

In order to mitigate the disadvantages of the manual visual inspection, big companies such as Seidenader developed semi-automatic inspection machines (figure 2) to provide faster inspection times, better operators support, while preventing premature fatigue in the operators.

Figure 1
Seidenader Semi-Automatic Inspection Machine Illustration

This machine counts with an inspection station designed to provide suitable conditions for the detection of both particulate a non-particulate defects. Focusing on the detection of particulate defects, the machines are equipped with a concentrated beam of light, usually Tyndall light, which, in translucent liquids, is reflected by the particulate. To properly detect the vast variety of particulate defect that may be found in the product, that machine is also equipped with a background light containing a polarization filtering effect.

Polarization Background Properties

The polarized background consists on both a filter installed in the background light and a magnifying glass with adjustable polarized filter. The magnifying polarized filter counts with a lens used to adjust the polarization intensity between non and full polarization (usually from 0 to 90 degrees). By increasing the polarization angle, more background light is filtered, this results in a darker observation field, making feasible the detection of clear particles. However, the filter allows the adjustment of the polarization intensity by decreasing the polarization angle. By decreasing the polarization angle, less light is filtered resulting in a whiter observation field, stimulating the dark particle detection [6].

Polarization magnifying lens is required to be adjustable to assure both dark and translucent/white particles are properly removed by the operator during the inspection process. The higher the polarization degree, the operator will have better probability of detection for translucent/clear particulate.

Particle Detection in Automatic Inspection Machines

The particle detection tools usually consist on what is known as Static Division (SD) sensors. This technology was developed back in the 1970's by EISAI manufacturer [7]. The SD technology uses variations of electrical signals or voltage levels sense in terms of light interference as particles are detected in the product. Figure 3 provides a detailed explanation on the SD technology.

As this technology depends on the light interference by the particulate matter, translucent and/or clear particles have less detection probability than darker particles.

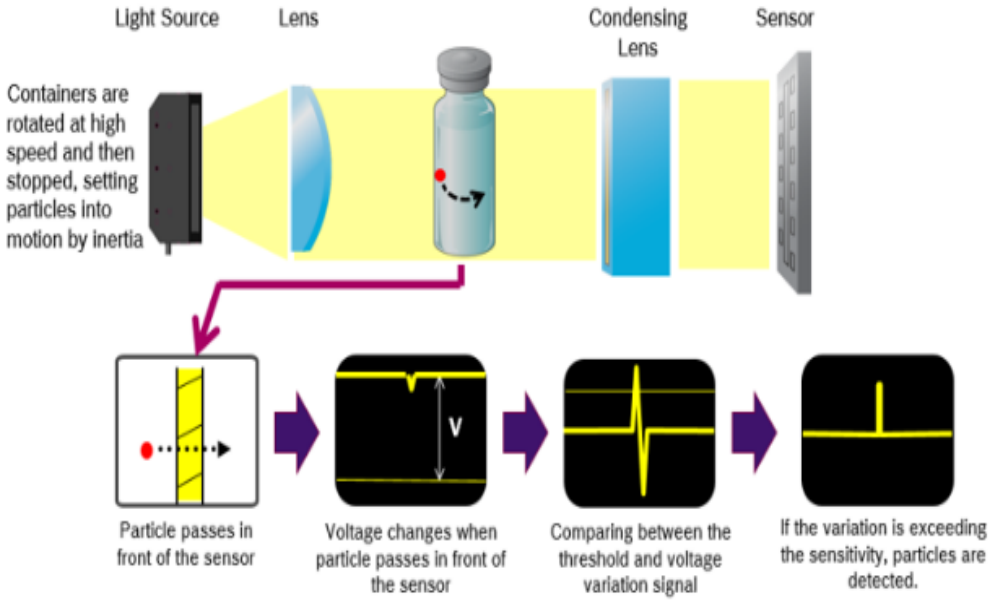

Figure 2
Static Division Technology Mechanism

METHODOLOGY

There are multiple improvements programs to attend different kinds of issues in the processes [8]. Each improvement program has different focuses, for different improvement opportunities. The improvements are Six Sigma, Lean thinking and the Theory of Constrains. Each one of these improvements programs focuses on different process issues. For example, six sigma, lean thinking and the theory of constraints focuses on the problem, the flow and the system constraints respectively. One very important point when an improvement wants to be made in a process is the understanding of what improvement program will properly attend the issue on hand. The first step to properly select the improvement program is to be clear what are the focuses, tools and methodology of each program [8].

The most suitable improvement programs for the solution of a problem or situation and how to reduce the process variations is the six-sigma tool. For years the six-sigma methodology has been described with five phases: DMAIC (define, measure, analyze, improve and control). These five phases represent all the necessary steps to properly solve a problem.

Phase 1: Define

In this phase we identify the situation in question. The situation or problem can be properly identified by understanding the problem or situation that needs to be attended. Voice of the customer, management requirement, can additionally influence the problem or situation defining phase.

Phase 2: Measure

This phase is about understanding the current states of the problem or situation. On this phase you measure current process parameters, and/or any parameter that may be causing the situation or problem.

Phase 3: Analyze

Collected data will not means anything until its analyzed. This step is usually related to the Measure phase. This phase will help us determine the causes of the problem or the situation.

Phase 4: Improve

This phase defines the measurements to be taken to fix the situation or problem. This phase is where the solutions for the problem are put in place to solve the issue.

Phase 5: Control

After solving the issue, this phase provides sustainability of the resolution. This phase ensures the problem solution is in place to prevent further situations.

RESULTS AND DISCUSSION

There is no question that one of the most important steps when performing improvements to any process is the management approval. The six-sigma business strategy will introduce the before explained six sigma methodology, while ensuring all the levels in the company from the administration to the operators are working towards the same goal, reduction of the process variability.

Definition

After the implementation of a new manufacturing suite consisting on single-use technology, the downstream process (inspection and packaging) experienced an increase of particulate load in the lots.

Particulate observed after the implementation of the single-use technology, was analyzed and concluded to be compatible with the polymer components found inside the plastic bags used for the formulation and filling process.

The American Chemistry Council describes the general attributes of most polymers:

- Polymers are very light in weight, meaning that, generally, polymers will float in liquid products.
- Polymers are materials that may be manufactured in countless characteristics and colors, including clear/translucent flexible films or fibers (figure 4) [9].

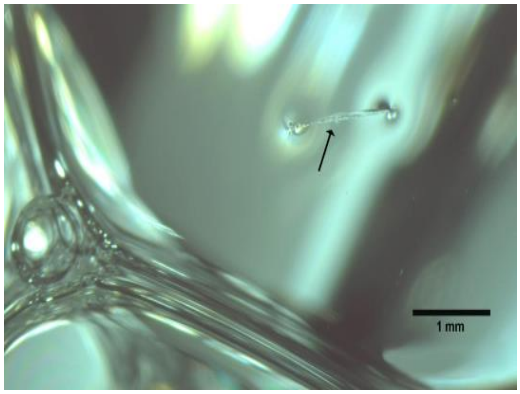

Figure 4
Fiber Particulate Example in an Injectable Vial

Based on the polymers' characteristics or attributes defined above, the static division technology used for the particle detection on automatic inspection machines would have a lower detection for this type of particulate.

Measure

The implementation of the new manufacturing suite with single-use technology, the particulate load was evaluated for both suites. The particulate load increased up to 167% if traditional technology is compared with single-use technology (figure 5).

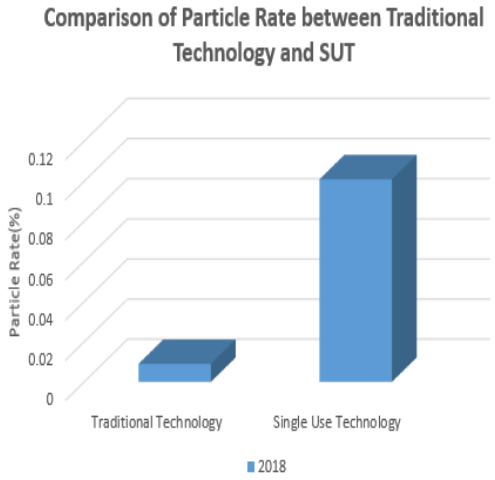

Figure 5
Traditional Technology and SUT Particulate Load Rate

Analyze

The analyze phase of the project, consisted on evaluating both the upstream and downstream processes improvements opportunities.

Upstream Improvements Opportunities

Possible improvements in the upstream processes include new quality agreements negotiations with single-use bags vendors. The particulate observed in the inspection process, compatible with the bags, could have been carried in the process from stages as early as the third-party manufacturing process of the bags. In addition, new single-use bag vendors could be considered.

Downstream Improvements Opportunities

Based on the fiber detection improvement opportunity in the automatic inspection machines, the implementation of a new fiber inspection tool is being considered.

Instead of relying the particulate detection to the static division tools installed in the automatic inspection machine, a polarized camera aiming for the detection of fiber particles will support the operation. Theoretically, the polarized camera will work similar to the polarization concept in semi-automatic inspection machines.

The polarized camera will capture an image of the container after the container is forced in a fast spin motion. This spin to the container will set particulates into motion inside the vial, allowing proper detection by the camera [10]. Figure 6 shows the difference between polarized and non-polarized camera captures in liquid product containers.

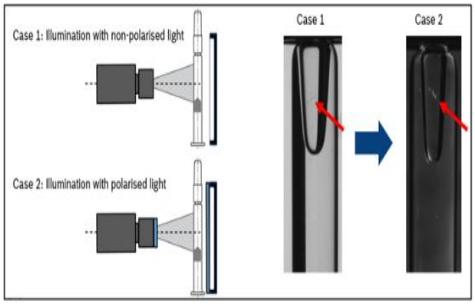

Figure 6
Non-polarized and Polarized Camera Captions for Inspection Processes

Improve

After management approval of the project, the implementation phase should be started. This phase

will include both upstream and downstream stages of the process.

Upstream Stage

Single-use technology vendors for bags and connections are under evaluation for the reduction of particulate load in the received equipment. Moreover, the current qualified vendor is revising the quality agreement and evaluating methods to reduce the particulate matter found in the ready to use bags used for the formulation and filling processes.

Downstream Stage

Upon implementation of the polarization camera tool to increase the detection of fiber-like particulate matter, a series of protocols and procedures must be revised to ensure the process remains in a validated status, meeting the process requirements.

Documentation such as Validation Plan and User Requirements Specifications must be generated at the beginning stage of the implementation phase. Factory Acceptance Testing and/or Site Acceptance Testing will also be required to ensure the tools meets the specifications required to the vendor.

Consequent to the approval and successful testing of the tools, qualification protocols will be required to qualify the tool installation, operation and performance.

Control

After all the other phases of the DMAIC system have been completed, the control phase begins to assure effective measures were taken in consideration to mitigate the problem.

Standard operational procedures will have to be revised to include any cleaning, handling and operation of the tool. Every operator, group leader, supervisor, mechanic and engineers that support the operations in the inspection area will be provided with an on the job training, given by both in site and external personnel. Inspection team technical services will be in charge of the documentation regarding on the job trainings and assurance that no personnel operate the equipment without proper training.

CONCLUSION

Quality assurance of the product manufactured in the industry is a work for every department. The effectiveness of a polarization camera that will increase the particle detection, thus assuring the customer gets the best quality of product the objective of customer driven improvement tool six-sigma.

Even though 100% removal of defects cannot be ensured by any of the inspection processes, improvements driven to the further reduction of defect in the manufactured lots is what makes a company reliable.

REFERENCES

[1] G. T. Frank, “Transformation of biomanufacuring by single-use systems and technology,” *Current Opinion in Chem. Eng.*, vol. 22, Dec. 2018, pp. 62-70. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S2211339818300297.

[2] Pharmaceutical Processing World. (2015, Nov. 9). *The downside to single-use technologies* [Online]. Available: https://www.rdmag.com/blog/2015/11/downside-single-use-technologies.

[3] United States Pharmacopeia. (2017, August). *USP <1790> Visual Inspection of Injections*, Rockville, MD, USA, pp. 8099–8119 [Online]. Available: https://www.pharmout.net/wp-content/uploads/2018/02/NGVF-2016-Visual-Inspections-of-Injection.pdf.

[4] J. D. Wisner, K. C. Tan and G. K. *Leong, Principles of Supply Chain Management: A Balanced Approach*, 3rd ed. Mason, OH, USA: South-Western, 2011.

[5] J. E. See et al., “The Role of Visual Inspection in the 21st Century,” proposed presentation at the *Human Factors and Ergonomics Soc. Annual Meeting*, Austin, TX, USA, Oct. 9-13, 2017. [Online]. Available: https://www.osti.gov/servlets/purl/1476816.

[6] *Seidenader V90-AVSB: Visual Inspection of Ampule, Vials, Infusion Bottles, Cartridges and Pre-filled Syringes.* Markt Schwaben, Germany. [Online]. Available: http://www.bickel-wolf.com/files/lieferanten/SEIDENADER/dokumente/SDM_V90_EN.pdf.

[7] Bosch Packaging Technology Pharma Blog. (2018, April 4). *A historical evaluation of inspection technology: 4th generation static division* [Online]. Available: https://boschpharma-blog.com/2018/04/04/evolution_sd/.

[8] D. Nave, "How to compare Six Sigma, lean and the theory of constraints," *Quality Progress*, pp. 73–78, March 2002. [Online]. Available: https://www.lean.org/Search/Documents/242.pdf.

[9] MVA Scientific Consultants. (2019). *Particulate analysis of injectable products* [Online]. Available: https://mvascientificconsultants.com/particulate-analysis. [Accessed: October 3, 2019].

[10] Bosch Packaging Technology. (2018, Nov. 15). *Applying camera technology in automated particle inspection* [Online]. Available: https://www.bioprocessonline.com/doc/applying-camera-technology-in-automated-particle-inspection-0001.