Drug Product Manufacturers and Packaging Suppliers Working Together to Enhance Drug Product Quality: Automated Vision Inspection for Parenteral Closures

Abstract:
The healthcare industry is challenged with meeting stringent quality requirements regarding the manufacturing of sterile drug products. Packaging materials are critical to this operation. Because of these requirements, each final container processed for parenteral preparation must be inspected thoroughly for the presence of visible particulates.

According to USP 32-NF 27, “Each final container of all parenteral preparations shall be inspected to the extent possible for the presence of observable foreign and particulate matter in its contents. The inspection process shall be designed and qualified to ensure that every lot of all parenteral preparations is essentially free from visible particulates.” A survey regarding industry practice related to visual inspections of injectable products was generated in 2008. Twenty-one companies responded and the survey results identified particulate as the most common defect found in parenteral finished products. Due to USP 35NF30 <1> requirements and the occurrence of particles at low frequencies and randomness, each finished injectable drug must be inspected.

Additional challenges facing the healthcare industry include reducing product and process variation, meeting Japanese defect-free quality expectations and minimising product rejection. According to Good Manufacturing Practices (GMP), “sterilized container/closures must be sterile as to not alter the purity of the drug product” - 211.67 and 211.113. Further direction regarding the manufacturing of sterile drug products, provided in Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing, recommends excluding particulate matter and container closure defects. Additionally, packaging suppliers can contribute to reducing particulate matter in finished drug products by supplying components virtually free of embedded and adhered particles. This practice will assist in reducing the risk of rejecting drug products caused by visible particulates. An attempt to proactively address these challenges in the healthcare industry would require all packaging components to be inspected for defects prior to shipment. This procedure would expedite the pharmaceutical industry process, while maintaining more stringent safety standards.

This article will examine the use of vision inspection systems to mitigate the risk for particulates and defects associated with container closure systems. Vision inspection systems used by elastomer closure suppliers are automated, program-controlled devices that inspect all sides of elastomeric stoppers and pistons. Vision inspection allows suppliers to develop standardised procedures for improving the component manufacturing process upstream. The ultimate goal is for suppliers to work with pharmaceutical companies to provide a finished product that meets the needs of the healthcare industry.

A quality drug product has been defined by Janet Woodcock of the FDA as a drug product free of contamination that delivers the therapeutic benefit promised in the label to the consumer. Particulate matter in finished drug products is a concern, since a product’s quality can be affected by the presence of various degradation materials, including particulate. The foreign particulate matter in parenterals comes from a combination of intrinsic and extrinsic sources. Extrinsic sources may include hair, cellulose, polyester, etc. Intrinsic sources are derived from processes and container contact surfaces such as rubber, silicone and glass. This article will explore regulatory expectations and methods for inspection of finished drug products. It will also examine the use of vision inspection systems to mitigate the risk for particulate and defects associated with container closure systems.

Visual Inspection of Foreign Particulate in Finished Drug Product

The particulate matter burden of an injectable product has been taken by some healthcare practitioners, academic investigators and regulatory personnel as an indicator of the overall finished drug product’s quality. Several regulatory guidance documents exist to inspect and control particulate in finished drug product. The manufacturing of sterile drug product requires visual inspection of the final drug product in filled, sealed containers. The inspection is intended to ensure the quality of the packaged drug product by rejecting any container that is defective or contains particulate. Filled containers of parenteral products should be inspected individually for extraneous contamination or other defects.

Inspection for visible particulate may take place when inspecting for other critical defects, including cracked or defective containers or seals. An inspection system can identify, isolate, trend and address particulate and other critical defects of container closure components, thus augmenting the quality expectations for sterile drug products. This type of preventative action will not only avoid nonconformance, but also will identify areas for improvement in component manufacturing, which results in higher...
quality packaging components.

Defects Associated with Container Closure Systems
Vision inspection by the manufacturer for embedded and adhered particulate in packaging components reduces the risk of finding particulate in finished drug product. In addition to inspecting for particulate, component vision systems also detect defects on closures. Defects may include trimming or molding defects, such as those seen in Figure 1. Any damaged or defective container closure systems should be detected and removed during the inspection of final product. Container or closure deficiencies can cause loss of container closure system integrity. In the event that a nonconformance is observed, the vision system shall be capable of detecting that defect category at a high level.

Vision Inspection Methods
Because of the various compendia and regulatory requirements and the implications to the safety and effectiveness of the drug, there are a variety of methods for inspecting parenteral finished drug products. The primary method is manual inspection, which can be subjective and relies on adequate training of human inspectors. Differences in visual acuity, personality and fatigue levels for each inspector may vary, and can lead to dissimilar levels of particulate detection. The subjectivity involved with manual inspection not only impacts effectiveness, but also may decrease the speed at which the inspection is completed. With regard to vision inspection, regulators expect improved methods to ensure better precision and consistent sensitivity. Because of the limits of manual inspection, automated inspection systems have been implemented for finished drug products. Currently, various light transmission and camera-based commercial systems that can be used to perform automated visual inspection of sterile drug products are available.

With regard to packaging components, automated vision inspection is preferred. Typically, component manufacturers who inspect manually will pull components based on a sampling plan. As a result, only a portion of the component is inspected, and specifications are set using Acceptable Quality Limit (AQLs). AQLs can be defined as the worst-case per cent defects that are allowable by the customer. If component manufacturers were to eliminate sampling plans and inspect each component manually, then the process would increase the amount of time humans come in contact with a packaging component. Automated vision inspection is preferred by packaging suppliers because it is capable of inspecting every component and reduces contamination from humans. Automated inspection systems can be qualified to assure that large volumes of products are consistently inspected, thus improving throughput and reproducibility.

Vision inspection machines (Figure 2) are currently used by some elastomer component manufacturers to inspect all sides of elastomeric stoppers and pistons. The machine is programmed to distinguish an acceptable component from a defective component. Each vision inspection machine consists of multiple cameras that use bright, dark and diffused illumination for the detection of defects. These defects include stains, marks, foreign matter and rubber inclusions embedded or protruding from the elastomer surface. Additional defects may be detected based on a specific component or customer specification. The end result is a quality component that is designed to meet or exceed the needs of the pharmaceutical manufacturer.

Automated Vision Inspection Process
Automatic vision inspection of rubber components occurs after the components are washed through a ready-for-sterilisation process. The end result is a washed product that meets specified limits for bacterial endotoxin, particulate matter and bioburden. After the ready-to-sterilise process, stoppers are unloaded from the washer in an ISO 5 clean room. The stoppers are passed from the ISO 5 clean room into a second ISO 5 clean room for vision inspection. The components are loaded into the vision inspection machine, inspected and packaged in sterilisable bags or rapid transfer port bags. Bags of product are removed from the vision inspection machine, sealed and labelled in the second ISO 5 clean room. Depending on customer requirements, the sealed and bagged products are either placed in final cartons or sent to be sterilised outside the ISO 5 environment.

To test the reliability of the vision inspection machines, a capability study is performed. For the purpose
of the study, a defect library is created to aid in the programming, debugging and testing of the device. The library can be populated based on extrinsic and intrinsic sources. The component supplier may create defect references, typically evidenced in the industry by dispersing defects throughout the rubber mix. Defects used to challenge a vision inspection machine include hair, fibre, loose particulate contamination, embedded and adhered foreign material, moulding defects, and cosmetic defects. The goal is to obtain one defect per component (Figure 4) to establish a representative defect reference. This assures that the vision inspection machine is consistently detecting the lone defect.

To perform capability testing, component sample sets from the defect library consisting of known good product and known rejected product are run through the vision inspection machine. The defects are used to optimise the vision software and challenge the vision system. Finally, the rates of acceptance and rejection are determined for each component.

After capability testing is performed, the defect library is used to verify that the vision inspection machine can detect the standard defects appropriately. Prior to production, a known set of components passes through the machine to verify that the machine meets requirements. The defect library has been found to be an acceptable method for challenging the vision inspection machine and assuring that defects are consistently detected.

Figure 4: Camera View of Foreign Matter
Strategies to Enhance Quality of Component Manufacturing

Creating a defect library advances manufacturers’ knowledge regarding reasons why component defects occur. To understand these causes further, all component defects are reviewed and trended. Statistically analysing each type of defect allows manufacturers to gain an enhanced understanding of the defects that occur during manufacturing. That knowledge can be used to improve processes throughout the manufacturing cycle and prevent recurrence of a particular defect. For example: process improvement may result from component rejection due to fibres found upon vision inspection. The outcome of the process improvement event requires manufacturing employees to wear new and enhanced gowning during closure moulding and trimming steps (Figure 5). The enhanced gowning further reduces the chance of hairs, fibres from clothing or other human-generated particulate from contaminating the product during manufacturing. Ultimately, the implementation of the new gowning requirements reduces particulate found during inspection and improves the overall quality of the components.

Component suppliers have been viewed as focusing on end control rather than preventing defects through process improvements. If properly utilised, vision inspection systems can not only detect defects, but also can analyse, determine the source of and prevent defects from recurring. As suppliers increase the amount of packaging components sent through vision inspection systems, they continue to drive toward better detection and understanding of defects occurring in the manufacturing process. Vision inspection can be used to assure that quality is built into component manufacturing that can meet and exceed the increasing standards of the healthcare industry.

Studies have been performed on vision inspected components to determine if healthcare industry needs have been satisfied. In one case study, a drug product manufacturer inspected finished drug product before and after the implementation of vision inspected packaging components. The goal of the study was to determine if the vision inspected components reduced reject rates. The results of the study demonstrated improvements in the overall quality of the finished product (Figure 6).

Conclusion

Currently, the pharmaceutical and biotechnology industries are challenged with meeting stringent quality requirements for parenteral products and maintaining integrity throughout the manufacturing process. Visual inspection of drug products is mandated, and includes performing 100% vision inspection of final product. Reducing product and process variation facilitates quality-by-design initiatives and minimises product rejects. Manufacturing efficiencies benefit suppliers and manufacturers, and ultimately help to ensure adequate supplies of needed drug products reach the market.

In an attempt to address the challenges of the healthcare industry, component manufacturers have introduced vision inspection for their products. Elastomeric closures for parenteral products, including serum stoppers, lyophilisation stoppers and syringe pistons, are vision inspected by automated machines designed to examine the external quality attributes of elastomer components.
of elastomer components. Knowledge gained from closure defects detected by vision inspection machines can be used to improve closure manufacturing quality. Automated vision inspection used in conjunction with continuous improvement techniques creates multiple opportunities for preventative action. Such action should be deployed when an inconsistency is identified from trending the inspection data. Manual inspection cannot achieve the same consistent high-quality results. In addition, manual inspection cannot catalogue data for improvement events.

Product offerings using automated vision technology can reduce the risk of defects and provide pharmaceutical manufacturers with improved compliance and risk mitigation. The ultimate goal for a component manufacturer is to build a relationship with the pharmaceutical manufacturer to provide a finished drug product that efficiently and effectively meets the needs of the patient.

References:

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