Visual Inspection Training and Qualification Test Sets - Ensuring Product Quality and Manufacturing Process Control

Introduction

The presence of visible particulates in injectable drug products may indicate manufacturing process failure, product instability or other quality issues and potentially may pose threat to patient safety. A holistic, risk-based approach to controlling visible particulates, which includes solid product development, suitable manufacturing process controls, compliant and suitable visual inspection method, a sound visual inspection training and qualification concept, well-developed particle characterization strategy and investigation approach, as well as suitable corrective/ preventive actions need to be established at a pharmaceutical manufacturer.

Inspection Methods

Manual inspection, controlled by statistical means, continues to be the golden standard for detecting visible particulate matter and other finished product defects. National pharmacopeias provide guidance on manual inspection (MVI) methodology, but detailed practical guidance on setting up the visual inspection process or strategy is lacking. Semi-automated visual inspection (SEVI) systems are also commonly used, but are typically installed off-line, as in-line inspection at high speeds is challenging. Fully automated inspection systems, which can perform both container/closure and particulate inspection in a single pass, are becoming more common and offer enhanced sensitivity and consistency compared to manual inspection. Recent advancements in artificial intelligence have further improved the performance and robustness of automated inspection systems.

Training and Qualification Test Sets

Regardless of the inspection method, training and qualification test sets are essential to establish the performance of the inspection process and ensure it aligns with product attributes. Training test sets are important tools for training inspectors and machine vision systems. These sets need to reflect the variety of real-life defects which may be encountered in the given manufacturing facility, providing an ample base for learning and familiarization with potential defects.

Qualification test sets enable adequate MVI/ SEVI/ AVI qualification/ requalification process, establishment of a manual performance baseline, accurate assessment of visual inspection process capability and provision of the required proof for inspector/machine vision system performance. The manual baseline supports the validation of alternative inspection methods, evaluation of process changes, and pre-production functionality testing of automated inspection systems.

The qualification test sets should contain a sufficient number of defect-free containers and a subset with known defects. Aqueous training kits should be manufactured using stable solutions in compatible containers to achieve a shelf life of 3 to 5 years.

Product-Specific Attributes and Defect Selection

The visible particle inspection process is significantly affected by product-specific attributes, which must be understood before designing training/ qualification test sets. For example, attributes such as viscosity, surface tension, turbidity landfill volume can affect particle detection. The container closure system type and configuration can significantly affect the ability to detect particles as well, with e.g. amber glass and opaque polymer containers requiring increased light intensity and enhanced camera settings to detect particles. Syringes typically have a smaller diameter size, providing less room to form a vortex during swirling/ spinning. In addition, new therapeutic modalities use less conventional primary packaging containers such as pouches and bags which feature specific challenges in regard to visual inspection. To compare differences in the probability of detection and other inspection variables with statistical confidence, a training/ qualification test set should be manufactured with each container size and fill volume, with designated particle sizes and types. After, the probability of detection for a specific defect type and size should be established.

To statistically compare differences in detection probability and other inspection variables, a qualification test set should include various container sizes, fill volumes, and designated particle and container defects' types and sizes. The probability of detection for specific particle types and sizes should be established.

Statistical Probability of Detection (POD)

In an approach developed and pioneered by Julius Knapp and coworkers in the 1980s and still used today, validation procedures involve repeated inspections by multiple inspectors in order to establish a statistically sound POD for each defect and container. The use of qualification test sets consisting of a sufficient number of containers that represent the range of defect types and sizes required to provide a statistical assessment of process capability is critical for validation. A typical qualification test set consists of 200 - 2'000 units. The selection of the particle type and size to manufacture the defect units of a training kit is of great importance. Whereas a 50 µm particle size (independent of particle morphology) was historically accepted as the threshold for a human inspector, it may add little value for routine qualification as it may only have a detection rate of 0-3%. In general, larger particle sizes must be used and other particle attributes including morphology, composition, color, contrast, density, etc. and particle behavior during the inspection must be considered. Studies also indicate that one particle size range for manual inspection may not be suitable for all product/container combinations as container type (e.g. vial vs. bag), size, and fill volume affect the probability of detection of a particle and must be considered when selecting particle sizes for testing. Also, data suggest that once a given size of a particle type is detected with approximately 90% reproducibility, there is little added value to further increasing particle size of that type.

Typically, a qualification test set is divided into three subsets based on the probability of detection. An acceptance subset which comprises approximately ⅔ of the training kit. Containers in the acceptance subset should have a rejection probability ranging from 0-0.3. The remaining ⅓ of the training kit is equally divided into a Grey Zone subset and a reject subset. The Grey Zone subset should have a rejection probability ranging from approximately 0.3-0.7. The Reject subset should

have a rejection probability ranging from approximately 0.7-1.0. The total number of rejects should be limited to 10%-20% to avoid positive reinforcement of human inspectors.

Bracketing Approaches

A bracketing approach can be used to reduce the time and cost of validating inspections for multiple drug products. Such approaches group products with similar physical properties, and a representative product is used to validate each group. Expert knowledge is required for classification, and product groups must have particles that behave similarly during inspection.

Re-qualification of training kits

The use of historical data is recommended to compare the current classification of containers in a training kit. Containers that show significant changes compared to the initial classification should be closely examined or removed. Periodic inspections of training kits are also recommended to identify microbial growth or product appearance changes. A predefined procedure that specifies requalification intervals and how to handle and document findings is necessary for consistent performance. Containers with unidentified particles should be sent for particle characterization.

Summary

A comprehensive, risk-based strategy is essential for controlling visible particulates in pharmaceutical manufacturing. While national pharmacopeias provide some guidance, practical advice on training programs, including training and qualification test sets, the impact of product-specific properties is lacking. Training & qualification test sets are crucial for ensuring a consistent and effective visual inspection process, promoting harmonization across a global manufacturing network.