Recent 483's on "Injectable Visual inspection program"

Abstract:

The nature of visual inspection is probabilistic and the presence of trace levels of particles in parenteral products cannot be fully excluded, a holistic approach to minimizing the presence of visible particles in parenteral drug products is recommended. However a requirement of zero (or without) visible particles is overly stringent and practically not attainable. Particle controls are and should be one of the main formulation and process design criteria applied by the pharmaceutical industry. This continuous improvement objective being acknowledged across the industry.

1. Sequence of inspection:

Training is the important factor for manual inspection. Most of the firm are cited 483 due to inadequate procedure. Practical approaches and difficulties pertaining to the inspection process not fully demonstrated. As a result inspector will not able to meet the expectation.

For example, It was identified during an inspection that employee held one glass bottle against a white background and then black background instead of "slowly invert 2 bottles and hold against the white inspection light, move the bottle to the black inspection light and repeat inspection.

2. Time to inspect and documentation:

Sufficient time must be provided to allow for thorough inspection of each container; chapter <790> specifies a reference time of 10 s per container (5 s each against both black and white backgrounds). Larger or more complex containers may require additional time for inspecting all attributes.

Documented evidence required from Individual inspector which should include at least date of inspection, time of inspection, Batch/lot no., and tray number inspected by inspector. This will provide adequate traceability over an inspection process.

For example, one of the firm got an observation because they have mentioned "visual inspection happened during 12:35 pm – 1:00 pm but there is no documentation of how long each employee performs visual inspection.

3. Reserve sample inspection training requirement:

Separate training expected for reserve sample also. Most of the firm does not consider training for reserve sample inspection.

For example, During inspection one of the firm stated that no training requirement for employees performing visual inspection of reserve samples using "standard, office room light" as stated in SOP. As per the firm, the same employee performing packing line visual inspection also performs the reserve sample visual inspection.

4. Define re-inspection process:

Re-inspection or repeating the 100% inspection followed by acceptance sampling inspection may be appropriate if the initial 100% inspection is not successful. This includes instances when the established 100% inspection failure rate(s) and/or the accept/reject number(s) associated with the chosen AQL values have been exceeded.

Re-inspection should only be conducted using a procedure and should addresses key parameters such as

- The ***inspection conditions***, procedure should define whether same as primary inspection or modified to enhance detection of a specific defect type
- The ***number of times reinspection*** may be performed (this should be limited and justified),
- The ***acceptance criteria*** will be same as primary inspection or tightened.
- In case of ***frequent reinspection*** the consideration should be given to improving the sensitivity of the primary inspection process or of the manufacturing controls as determined by root cause analysis.

Due to inadequate inspection process or negligence by the inspector results several market complaints. Latter stage it will impact on the reputation and reliability of the firm.

For example, It was identified to reduce or avoid the reinspection inspectors are avoiding to report the failure. Even during AQL also people are not reported the critical defects. Majorly reported events are related to dent in cap, blemishes, minor scratches, spotting, brush marks, seams and external contamination. Apart from that number of firm reported with that major and minor defects are not evaluated nor trend to determine if corrective actions are required and there is no procedure available to performed AQL inspection on the lot that received a re-inspection.

5. Quality Oversight:

Number of inspection it was observed that Quality oversight over visual inspection is deficient. While the visual inspection is typically carried out by manufacturing personnel, the FDA has stated a clear expectation that the checks on the operation are done by people with no interest in the performance of the individual inspectors. The person who did the AQL sampling on each tray of vials could not be the same person who had inspected those vials. FDA was looking for a separate independent reporting line for the people carrying out the checks on the visual inspection operation

For example,

As a part of outcome of over site of quality following observation are given,

- *AQL inspections are conducted by personnel who already perform the 100% visual inspection for same batch.*
- *As per inspection database from September 2013 to September 2015, "QA oversight over the 100% visual inspection operations" has occurred six times.*

Conclusion:

Inspection process, inspector training, Kit preparation, process defect library maintain, source identification and failure investigation are the major key steps for robust visual inspection process. The pharmaceutical and biotechnology industries perform 100% inspection of containers filled with drug product to ensure that the container is free of container/closure defects and that the drug product in the container is free of particulate matter. Either type of defect can have harmful effects on the patient if missed. Container/closure defects can potentially lead to a breach in sterility. Particulate matter

in the drug product indicates potentially dangerous contamination introduced during the upstream process. Both types of defects are serious and USP chapter <1> injections, requires 100% inspection of sterile injectable products.

Good product development will lead to a stable product with a lower risk of particle formation. Identification of the type or types of particles found during product development and routine manufacturing is an important aid in source identification and reduction. Neither human manual inspection nor fully automated inspection systems can provide assurance of particulate-free products. Visual inspection is a probabilistic process, with detection probabilities less than 100%, especially for particles less than 200 μm in diameter. Visible particle testing is influenced by multiple, highly variable factors such as drug and container clarity, lighting, particle size, optical density, refractive index, colour, contrast, and operator or automated inspection sensitivity and reliability.

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