VISUAL INSPECTION

QP Forum 2016
Agenda

- Compendial References
- Submitted Questions & Answers
- Inspection Observations and Learnings
- Discussion & Questions
References

• EP
  o Parenteral Preparations (0502)
  o Particulate Contamination: Sub Visible Particulates (20.9.19)
  o Particulate Contamination: Visible Particulates (20.9.19)

• USP General Chapters
  o <1> Injections
  o <771> Ophthalmic Products
  o <787> Subvisible Particulate Matter in Therapeutic Protein Injections.
  o <788> Particulate Matter in Injections
  o <789> Particulate Matter in Ophthalmic Solutions
  o <790> Visible Particulates in Injections
References

• Informational Chapters
  o <1788> Methods for Determination of Particulate Matter in Injections and Ophthalmic Solutions
  o <1787> Measurement of Subvisible Particulate Matter in Therapeutic Protein Injections
  o <1790> Visual Inspection of Injectable Products for Particulates
    1. Scope
    2. Introduction
    3. Typical Inspection Process Flow
    4. Inspection Life-Cycle
    5. Interpretation of Results
    6. Inspection Methods and Technologies
    7. Qualification and Validation of Inspection Processes
    8. Products in Distribution
    9. Conclusions and Recommendations
   10. References

The draft document is available on the website of the USP Pharmacopeial Forum http://www.usp.org/usp-nf/pharmacopeial-forum. The deadline for comments is 31st Jan 2016
Q1: How are defect libraries generated and maintained?

Defect libraries record the type and nature of the individual defect.

Generally documents that contain pictures and description of defects identified.

Documents needs to be controlled

Review and Approval system

Maintained current

- For example they need to be updated with newly identified defects, deviation and change control process.

Used for Training Purposes

New Products?
Q2a: How are inspectors qualified for manual and or semi-automatic inspection?

- Inspector Selection
  - Visual Acuity 20/20, Colour Blindness
- Defect recognition training is generally carried out using the defect library and real examples.
- Phased approach if multiple products involved.
- Inspector needs to be qualified for each product type e.g syringes and vials.

- Inspector Challenge
  - Generate Test Set (Defect Standards)
  - Test Sets need to reflect the range of defects in your products.
  - Needs to reflect defect types, sizes, densities.
Q2b: How are inspectors qualified for manual and or semi-automatic inspection?

- Can use matrix approach.
  - Test conditions must reflect actual working inspection conditions (e.g. lighting, pace)
    - Breaks, Fatigue
    - Blind Trials

- Challenge Inspector with standards to generate probability of detection levels for the Inspector
  - Max limit for defects

(Control System for Defect Standards)
Q3: Assignment of criticality of defects found during visual inspection – what criteria should be used?

• Defects are generally categorised into three categories Critical, Major, Minor.

• Use QRM approach to define the defect categories

• QRM needs to take into account:
  o Type of product (e.g. Routes of Admin: IM IV)
  o Patient profile
  o Medical Impact
Q4: What level of glass defects or particles are companies happy to accept in final product?

- Level of particulates reflects your overall production process:
  - Materials, equipment capability and production process.

- Limits based on historical performance:
  - Have established categories for defects.
  - Assign limits based on historical data.

- Exceedance of limit requires an investigation:
  - May include additional inspection
  - May indicated loss of control

- Trending:
  - Need to have a trending process

- Process Improvement
Q5: Level of visual inspection acceptable following transportation of unlabelled product to a packaging site

• Options:
  1. Site A carries out 100% inspection and AQL inspection. Product is shipped to Site B. Site B labels and packs and distributes?
  2. Site A carries out 100% inspection and Site B carries out AQL inspection?
  3. Site B carries out 100% inspection and AQL inspection.

• Questions?
  o Transportation System – potential for damage
  o AQL performed on product from site B? Will this generate relevant comparable data?
FDA Observation 1

Quality oversight over visual inspection is deficient. For example,

• AQL inspections are conducted by personnel that also perform the 100% visual inspection.

• From September 2013 to September 2015, QA oversight over the 100% visual inspection operations has occurred six times.
Learning from Observation 1

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. This observation arose even though the company made sure that 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.
FDA Observation 2
The preventive maintenance program and the functionality testing program for the Seidenader semi-automatic visual inspection machines on Line N1 and N2 are deficient. The Seidenader equipment are used to perform 100% visual inspection of lyophilized vials, including (PRODUCT NAME) on Line N1. For example,

a. The light intensity of each unit is not verified during routine preventive maintenance and is not verified prior to use

b. The functionality test used to determine the reject function of the equipment is required before and after 100% visual inspection. The functionality test results for each equipment are not clearly documented as to the test results. Only the line clearance results are documented.

c. On DDMMYYYY, an operator on line N2 utilizing equipment #1234 was observed on two separate occasions pointing to one vial to be rejected, but causing the reject of two vials on both occasions.
Learning from Observation 2

a. The inspectors voiced a clear expectation that the light intensity of the unit would be checked **daily** before use, and that the check would be recorded. As a result of this observation, the company instituted a daily check for light intensity, and included in the 6-monthly replacement of bulbs that maintenance personnel do a light intensity check on the old bulbs before replacement as well as on the new bulbs after installation.

b. The functionality of the unit was checked at each line clearance by marking vials and confirming that they were rejected by the unit. The instruction on this was part of the line clearance SOP. However, this check was not recorded as a separate line item in the line clearance record. The success of the check was implied by the completion of the overall line clearance record. FDA voiced a clear expectation that this check should be a specific line item in the record.
Learning from Observation 2

c. This one was the subject of much discussion! The company was sure that the operator had in fact marked two vials, and the operator himself verified this, but that the inspector did not see that. The company did further demonstrations of the system but failed to convince the inspector. The company restated its position in its response to the observation, but also undertook to include this as a test in the qualification of future units added to the site.
FDA Observation 3

Qualification of operators for 100% visual inspection and AQL inspection is deficient as follows:

a. According to SOP-1234567, the test set library shall be largely covered with regards to existing (i.e. known) defects. No less than eight deviations for cracks on vial bottoms occurred since approximately DDMMYYYY, for example, deviation DR 6543210 for (PRODUCT NAME) Lot XXXXX. This defect type has not been added to the test set library.

b. Doc ABC-123 consists of defect library photos with descriptions and must be read and understood during training. However, operators are not required to demonstrate comprehension for qualification. Several of the defects in this document are not in the physical test set. Examples included (but are not limited to) wrong stopper form (malformed) and glass splinter visible on bottom of cake..
Learning from Observation 3

a. The management of the defect library is a dynamic process. Some defect samples change over time, and may become easier or harder to detect. New defects appear which should be added to the defect library. The FDA inspectors had a clear expectation that the defect library is subject to regular review, and updated as appropriate. They also made it clear that the changes to the defect library have to be done in a controlled way, though they did not express an opinion as to what form of change control, including approval processes, might be required. The process in place at the time was that the Subject Matter Expert for the visual inspection process would add or replace defects as he saw fit. He would also record the changes to the defect library. However, the process was not defined by SOP, and there was no review or approval of the changes. There was also no procedural requirement as to the frequency of review or the timeliness of updating the library. This observation resulted in a complete overhaul of the management of the defect library.
Learning from Observation 3

b. The initial training of operators was not a problem, in that the training included photographs and actual examples, as well as a competency check based on ability to find the defects in a test set of vials (a large number of vials containing good and defective units). The competency of each operator is also checked annually using the test set of vials. The practice at the time was that as new defect types were added to the defect library, those defects were communicated to operators, including through the use of photos and actual samples, but there was no check on the ability of the operator to detect the vials immediately following training. The operators’ ability would only be confirmed at the next annual competency check. The observation also mentions the new defects being added to the test set, so there is a clear expectation as to the sequence of activity when new defects are found.

- Update the library and test set in a controlled way
- Train the operators. Note that the use of photos rather than actual samples was not seen as a problem
- Check for competency using the updated test set of vials