VISUAL INSPECTIONS OF STERILE PRODUCTS

IPA QUALITY FORUM SUBGROUPS 2020-21
SUB GROUP 4

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TEAM INTRODUCTION

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In 2020-21, the QF focused on one of the key priority areas: Visual Inspection of Injections for Visible Particles. It took upon itself the challenge of establishing robust and seamless visual inspection and process, and release a comprehensive set of guidelines in 2021. The QF reflects the long-term commitment made by the IPA to address key issues facing the industry and develop a series of best practices."
2. INTRODUCTION

Purpose and Scope

- Applicable for the visual inspection activities carried out for different sterile dosage forms, i.e., injectable, ophthalmic products, lyophilized products, suspensions, and media fill containers.

Inspection Process Capability

- Zero defects
- 100% inspection
- Detection is a cumulative function of visible attributes

Background

Patient Risk

Safety considerations related to particulate matter in injections must be assessed for each drug product, intended patient population, and method of administration.
3. Inspection Process Flow

- **100% Inspection**
  - Filling: 100% inspection
    - Accepted unit
    - Rejected unit
  - Analysis and Trend Rejects
  - Acceptance Sampling and Testing
  - Packaging

- **AQL Sampling and Testing**
  - ANSI/ASQ Z1.4, ISO 2859, JIS Z9015

- **Remediation and Alternative Practices**

**Defect Category**

<table>
<thead>
<tr>
<th>Defect Category</th>
<th>AQL Range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical</td>
<td>0.010–0.10</td>
</tr>
<tr>
<td>Major</td>
<td>0.10–0.65</td>
</tr>
<tr>
<td>Minor</td>
<td>1.0–4.0</td>
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</tbody>
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**REINSPECTION**

repeating the 100% inspection followed by acceptance sampling inspection if the initial 100% inspection is not successful

**TWO-STAGE INSPECTION**

In cases where an assignable cause, such as formation of air bubbles or specific container or closure variation, results in a high false-rejection rate (rejection of acceptable units), the use of a second inspection step may be considered.
4. INSPECTION LIFECYCLE

Extrinsic: Foreign particles to the manufacturing process

Intrinsic, Inherent or Inherent Particles

- A continuous process verification program with statistical evaluation against pre-established alert and action limit of each batch prior to release of the batches
- 100% and AQL inspection data should also be analyzed for adverse trends on a periodic basis, typically at least annually

Trending of Visual Inspection process

Intrinsic: particles within the process intended to be associated with specific product formulations

Control and Prevention of Particulates

Particulate Removal by Component Washing

Common sources of intrinsic particulates

Glass Containers

Elastomeric Closures-RTU, silicone

Glass Handlings for Depyrogenation Process

Equipment Preparation for Sterilization Process

Filling Line

Packaging Components

Robust Design during Development

Formulation Components
5. Interpretation of Visual Inspection Results

- **Critical Defects:**
  Serious adverse reaction or death of the patient

- **Major defects:**
  Defect causes impairment to the use of the product

- **Minor defects:**
  No Impact, cosmetic in nature, affecting only product appearance or pharmaceutical elegance

### Unique Products and Containers Considerations

- Lyophilized Product
- Powder Product
- Emulsion and Suspension Product
- Amber Containers
- Translucent Plastic Containers
- Large Volume Containers
- Combination Products

### Alternate Inspection Strategies for Supplemental Testing

- Transfer
- Filtration
- Clarification
- Sieving
6. Inspection Methods and Technologies

Manual Visual Inspection (MVI)

• viewing filled and sealed containers under controlled conditions.
• The quality decision, to either accept or reject the container, is made by a trained person

Critical Process Parameters

- **Light intensity**
  - Light levels NLT of 2,000 – 3,750 lux
  - Light levels as high as 10,000 lux for amber glass

- **Background and contrast**
  - Increased contrast improves detection
  - White/black backgrounds provide good contrast

- **Inspection rate**
  - 10 second per container
  - 5 second each against both black and white backgrounds

- **Container handling and movement**
  - Careful swirl or inversion of the liquid product within the container

- **Magnification**
  - Magnification can be helpful for critical examination of a small number of units

Inspector Fatigue and Ergonomic Considerations

It is recommended that inspectors be given a break from performing inspection at least every hour. This break should allow time to rest the eyes and mind, and may be achieved with a short rest (e.g., 10 min/hour) or a longer meal break.
6. Inspection Methods and Technologies

**Semi Automatic Visual Inspection (SAVI)**

Semi-automated visual inspection combines automated material handling of the containers to be inspected with human vision and judgment to make the decision to accept or reject.

### Critical Process Parameters

- **Light intensity**
  - Light levels NLT of 2,000 – 3,750 lux
  - Light levels as high as 10,000 lux for amber glass

- **Spin speed**
  - Rotation rate of containers to ensure full rotation of vials in the inspection zone

- **Inspection rate**
  - Controlled by the speed of the infeed conveyor/rollers to produce an acceptable detection rate for defects of interest

The contrast of foreign particle is intensively enhanced under the strong light beam and the container can be inspected very quickly.
6. Inspection Methods and Technologies

**Automated Visual Inspection (AVI)**
Automated Visual Inspection (AVI) machine acquires a sequence of images of product appearance by electronic sensing, processes them according to parameter setting of recipe (pre-programmed acceptance criteria), and provides inspected results as 'accepted' or 'rejected' automatically.

**Light Obscuration Methods** (static division detection)

**Imaging Methods (camera inspection detection)**

The digital raster images acquired by the digital camera have a finite set of pixels which are the smallest individual element in an image, holding quantized values that represent the brightness of a given color at any specific point. The pixels contain fixed numbers of rows and columns.
Focus detection for Glass, metallic and rubber particles in Powder and Lyophilized Product
7  PREPARATION AND MAINTAINANCE OF CHALLENGE KIT FOR QUALIFICATION

**PREPARATION**

- Kit creation under controlled environment.
- Select naturally occurring particulates and physical or cosmetic production rejects removed from product lots.
- Containers must be absolutely free of visible particles. One container must have only one defect.
- Defined expiry date based on shelf life of product.
- Good samples and rejection from routine batch
- One rejection for each category available
- Maximum number of containers which can be inspected in one hour.
- Defect distribution from 5% to 15%, including critical, major and minor defects
- Particles size used for standard rejected containers should be between 100 µm to 250 µm (500 – 2,000 µm for fibers).

**MAINTAINANCE**

- Establish procedures for maintenance, issuance, retrieval and periodic replacement of the visual inspection kit.
- A master list of the qualification kit with details of defective/good container and respective allotted numbers should be prepared and approved.
- The constructed used for initially qualification & periodically for requalification.
- Storage under controlled secured conditions with identification label.
- If container in qualified kit being impaired with defect of container-closure or content, it shall be replaced with pre-qualified back-up containers.
- If there is gross physical damages as well as changes in content of containers in kit, the kit shall be discarded.
- A documented procedure shall be followed for the disposal of such kit and shall be pre-approved by Quality unit at site.
VISUAL INSPECTOR QUALIFICATION

Phase I
- Work experience
- Eye sight testing
- Training (cGMP, general SOPs and job specific SOPs)

Phase II
- Demonstration of visual inspection library
- Demonstration of the album for the defective container
- Demonstration of visual inspection process

Phase III
- Final qualification by giving a set of characterized containers having both good as well as defective containers

Parameter
- Distance criteria
  - 200 mm to 400 mm
  - 200 mm to 300 mm
- Holding of containers against the white and black background
- Total time for visual inspection
- Light lux requirements
- Bracketing approach
- Environment control
9. VISUAL INSPECTION OF MEDIAFILL CONTAINERS

- Inspection performed by Qualified inspector same as product. Focus on turbid container.
- Visual inspection Kit and media fill library preserved from previous mediafill/Trial Run.
- Expiry periods for good container defined based on risk assessment.
- Utilize Color Indicating media Powder for Media fills to easily defects contaminant by change in color medium.
- Qualification should be carried out with a quantity of physical rejection, containers inoculated with microorganisms.
10. Inspection of Retain/Control Samples

- Inspection in predefined frequency (annually)
- Criteria as per Manual visual inspection
- Adequate reconciliation and documentation
- Inspection by Qualified inspector
- Destructive testing for Lyo, powder, suspension products
11. Investigation Considerations for Visible particles

- Evaluation of following parameters is recommended to considered for Investigation of higher Visual inspection rejection:
  - Personnel training and qualification
  - Inspection booth/machine qualification/performance
  - Inspection process
  - Rejection pattern, e.g., entire lot or portion of lot
  - Type of defects
  - Type of dosage form
  - Raw materials assessment
  - Packing material assessment
  - Manufacturing process assessment (compounding to final stage of process)
  - Products rejection trends
  - Filling line rejection trends
  - Breakdown history of filling line
  - Preventive maintenance of filling line
  - Environment controls
  - Supplement testing
  - Over all rejection trends
  - Identification of defects (morphology, IR, SEM, X-Ray analysis and elemental analysis)
  - Source of defects
  - Vendor assessment
  - Risk assessment for visual defects
  - HHE evaluation for visual defects
  - Root cause analysis
  - Corrective actions
  - Preventive actions
THANK YOU