Strategies & Qualification methodologies for Visual Inspection

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07 June 2018
Strategies & Qualification methodologies for Visual Inspection

1. Introduction: Defect categories & definitions
2. Qualification methodologies for automated inspection: Strategies and Mindsets
3. Quality Control testing of difficult to inspect products
1. Defect categories & definitions

• Critical
  • may cause a lack of sterility, container integrity or cause serious (life threatening) harm to patients
  • e.g. cracks in the container

• Major
  • may alter the content or the function of the product or might possibly cause non-life threatening harm to patients
  • e.g. particles

• Minor
  • (Cosmetic) defects that are unlikely to affect patient health or product functionality
  • e.g. scratches
2. Qualification Methodologies for Automated Visual Inspection: Strategies and Mindsets

Overview

- **URS**: User Requirements
- **RA EQ**: Risk Assessment for the equipment
- **DQ**: Design Qualification / Design review
- **FAT**: Factory Acceptance Testing, including inspection performance testing
- **SAT**: Site Acceptance Testing, including vision installation and acceptance testing
2. Qualification Methodologies for Automated Visual Inspection: Strategies and Mindsets

Overview

- **IQ**: Installation Qualification: correct installation of GMP critical components, ...
- **OQ**: Operational qualification: SOPs, mechanical runs, alarms, fail safe, user mgt, ...
- **RA def.**: Risk Assessment for defects
- **PQ/PV**: Performance Qualification
  - Process validation
2. Qualification Methodologies for Automated Visual Inspection: Strategies and Mindsets

Risk Assessment for defects

- What is it used for?:
  - Recipe parameter development:
    - Which defect do we tune the machine for?
  - Input for qualification/validation:
    - Which defect do we qualify?
  - Deviations / CAPA’s:
    - In case of deviations during qualification are they acceptable or not?
    - Do we have to implement extra control strategies?
2. Qualification Methodologies for Automated Visual Inspection: Strategies and Mindsets

Risk Assessment for defects

• Based on:
  • the **severity** (classification) of the defect;
  • the **occurrence**;
  • the **detectability**, this includes all control strategies: QC, AQL and (expected) inspection performance of the AI process

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PERFORMANCE QUALIFICATION / PROCESS VALIDATION

DIFFERENT COMBINATIONS ARE POSSIBLE

**STEP 1**
- Fixed Acceptance Criteria
- Comparison 1 testlot contaminated with defects: AI versus MVI

**STEP 2**
- 3 lots with loss trending and AQL SSNIL 3
- Comparison with MVI of 3 test lots contaminated with defects

**STEP 3**
- Comparison 3 production lots with MVI
- Fixed AC & Comparison MVI (typically Knapp test for particles)
2. Qualification Methodologies for Automated Visual Inspection: Strategies and Mindsets

**Knapp test**

- a method which has been developed to evaluate the inspection efficiency of an inspection process/system (semi-automatic or automatic) with a reference inspection method (in most cases manual visual inspection)

**Basics:**
- All containers which are rejected $\geq 70\%$ by manual visual inspection are considered defects
- Acceptance criteria:
  - The overall inspection efficiency for these defects of automatic visual inspection has to be equal or greater than the inspection efficiency of manual inspection for these defects

- Initially developed for particles. Is and can be used for other defects.
2. Qualification Methodologies for Automated Visual Inspection: Strategies and Mindsets

**Performance qualification / Process Validation – recommendations**

- Regulatory expectation: compare *every defect category* to Manual Visual Inspection (gold standard)

- Use bracketing approach during PQ/PV for defining which lots should be inspected, based on:
  - Container type (e.g. 2 ml vial)
  - Fill level / strength, e.g. lowest and highest fill level
  - Product type (suspension, solution, freeze dry, ...)

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*eye-tec*
2. Qualification Methodologies for Automated Visual Inspection: Strategies and Mindsets

TEST SETS

• What should be in?:
  - All defects which can be inspected by AI
  - Existing products: based on historical data / defect library
  - New products: based on upstream processes or historical data of similar products

• Composition: based on historical data and criticality

• Assembly:
  - OPTION 1: Real production defects
  - OPTION 2: Artificially and characterized defects
  - For test sets which are compared with MVI:
    • Use invisible ink to mark (UV)
    • Not more than 10% defects

• Use a logbook for each test set
2. Qualification Methodologies for Automated Visual Inspection: Strategies and Mindsets

**Control strategies**

- **Routine operation:**
  - Functional test set: clear defects, use to check functionality of machine
  - Reject trending & control limits: for automated inspection, overall reject, per reject station, per camera station and/or area of inspection (e.g. side wall)
  - AQL sampling (ANSI/ASQ Z1.4, ISO2859-1):
    - Critical 0.01 – 0.1
    - Major 0.1 – 0.65
    - Minor 1.0 – 4.0

- **Requalification / Revalidation**
  - Periodic review of production data, change controls, CAPA’s
  - Every 3 to 5 years product specific?
3. Quality Control testing of difficult to inspect products

Introduction
Visual Inspection may have limited adequacy to detect visible particulate matter, due to
- Product characteristics (non-transparent)
- Container characteristics

Guidance Documents
- PDA TR79 Particulate Matter Control in Difficult to Inspect Parenterals
- USP <1790> Visual Inspection of Injections
- USP <1> Injections
3. USP <1790>

“Supplemental testing is required when the nature of the product or container limits visual inspection of the contents…”

- 3.1. 100% Inspection

Different particulate matter types:
- Extrinsic
- Intrinsic
- Inherent
  - Typical aspect of the (biological) product
  - Emulsions / Suspensions

- 5.1.1. EXTRINSIC, INTRINSIC, OR INHERENT PARTICLES
### 3. USP <1790>

<table>
<thead>
<tr>
<th>Section</th>
<th>DIP type</th>
<th>Sampling</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.2.1.</td>
<td>Lyophilised product</td>
<td>ANSI/AQS Z1.4 S-3 and S-4</td>
<td>Reconstitution after 100% inspection of cake</td>
</tr>
<tr>
<td>5.2.2.</td>
<td>Powder product</td>
<td>ANSI/AQS Z1.4 S-3 and S-4</td>
<td>Reconstitution after 100% inspection of powder</td>
</tr>
<tr>
<td>5.2.3.</td>
<td>Amber Containers</td>
<td>N/A (100%)</td>
<td>Increased light intensity Directional lighting from behind (transfer to clear container)</td>
</tr>
<tr>
<td>5.2.4.</td>
<td>Translucent Plastic Containers</td>
<td>N/A (100%)</td>
<td>Increased light intensity Directional lighting from behind</td>
</tr>
<tr>
<td>5.2.5.</td>
<td>Large Volume Containers</td>
<td>N/A (100%)</td>
<td>Increased inspection time Increased light intensity Directional lighting from behind</td>
</tr>
<tr>
<td>5.2.6.</td>
<td>Combination Products</td>
<td>N/A (100%)</td>
<td>Inspection prior assembly Second inspection post assembly if needed</td>
</tr>
</tbody>
</table>
3. PDA Technical Report No. 79

PDA Survey on DIP (3.1)

- All companies do 100% inspection
- Only half of companies perform supplemental destructive testing
- Only 1/3 apply AQL limits <0.1% for DIP
- Sampling plans based on
  - ISO 2859
  - ANSI/ASQ Z1.4
  - Fixed sample sizes
3. PDA Technical Report No. 79

Supplemental (Destructive) Acceptance Sampling and Testing (4.4)

- Only required under USP <790>; not in other pharmacopoeia
- In addition to AQL sampling
- Inspection of contents that is
  - Constituted (dried)
    - Withdrawn (transferred to another container)
- Filtration / Sieving / Panning
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Inspection Approaches for DIP Products / Containers / Devices (5.0)

• Non-destructive (100% inspection with modifications) (5.1)
  • Increased light intensity
  • Increased inspection dwell time
  • Illumination variations
  • Magnification
  • Mechanical fixtures
  • And other
3. PDA Technical Report No. 79

Inspection Approaches for DIP Products / Containers / Devices (5.0)

- Destructive (supplemental, based on sampling plan) (5.2)

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
<th>Product</th>
<th>Remarks / Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method 1</td>
<td>Reconstitution</td>
<td>Lyo &amp; powder</td>
<td>Diluent purity (filtered) MVI for clear solutions</td>
</tr>
<tr>
<td>Method 2</td>
<td>Filtration</td>
<td>Reconstituted p. liquids</td>
<td>USP &lt;788-2&gt; 0,8 micron Bigger pore size</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Only visible particles inspection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Viscous product</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Inherent particles to pass</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adapted membrane materials for spectroscopic analysis</td>
</tr>
</tbody>
</table>
3. PDA Technical Report No. 79

- Destructive (supplemental, based on sampling plan) (5.2) - continued

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
<th>Product</th>
<th>Remarks / Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method 3</td>
<td>Clarification</td>
<td>Emulsion Suspension Solid excipient</td>
<td>Solvent, acid or base (filtered) MVI for clear solutions or filtration</td>
</tr>
<tr>
<td>Method 4</td>
<td>Transfer / Diluent</td>
<td>Coloured solution Opaque container</td>
<td>Transfer to clear container / dilution ! : exclusion by needle ! : generation of stopper particles MVI for clear solutions or filtration</td>
</tr>
<tr>
<td>Method 5</td>
<td>Sieve / Mesh</td>
<td>Suspensions (known part size)</td>
<td>Microscopy of retain material 5 – 30 micron sieve (+ part size data)</td>
</tr>
<tr>
<td>Method 6</td>
<td>Panning</td>
<td>Suspensions (broad distr)</td>
<td>Transfer to clean petri dish + microscopy</td>
</tr>
</tbody>
</table>
3. PDA Technical Report No. 79

- Destructive (supplemental, based on sampling plan) (5.2) - continued

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<thead>
<tr>
<th>Description</th>
<th>Product</th>
<th>Remarks / Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method 7</td>
<td>Rinse / Flush + filtration</td>
<td>Implantable devices&lt;br&gt;Empty containers&lt;br&gt;Infusion tubing</td>
</tr>
</tbody>
</table>
Thank you for listening
### Back-up slide: Risk Assessment Defects

<table>
<thead>
<tr>
<th>CQA</th>
<th>Defect</th>
<th>Current control strategy</th>
<th>Proposed control strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product identity / safety</td>
<td>No wrong product in correct ampoule</td>
<td>C 10 1 No strategy in inspection is used to detect this defect</td>
<td>10 200</td>
</tr>
<tr>
<td></td>
<td>No wrong ampoule (different size)</td>
<td>C 10 1 AQL sampling</td>
<td>1 30</td>
</tr>
<tr>
<td></td>
<td>No wrong color ring (with same size)</td>
<td>C 10 1 OPTION 1 Visual inspection when feeding ampoules at infeed, triaging ampoules at outfeed. AQL sampling</td>
<td>1 70</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C 10 1 OPTION 2 100% automatic inspection of color ring and rejection if number of rings or ring color is wrong. AQL sampling</td>
<td>1 10</td>
</tr>
<tr>
<td>Extractable volume</td>
<td>Too low or too high filling volume according to PPS specifications</td>
<td>C 5 5 No inspection control strategy is used to control this requirement. SPC (IPC) is used in the filling department to control this.</td>
<td>20 290</td>
</tr>
<tr>
<td></td>
<td>Too low or too high filling volume (outside ± 20% in height, not volume)</td>
<td>C 5 5 100% automatic inspection of filling volume AQL sampling</td>
<td>1 35</td>
</tr>
<tr>
<td></td>
<td>No empty containers</td>
<td>M 5 100% automatic inspection of filling volume AQL sampling</td>
<td>1 35</td>
</tr>
</tbody>
</table>