Qualification of a Manual Inspection Process for a new Fill Finish Facility

Fiona Byrne and Caroline Devery
MSD Ireland (Carlow)
Employ over 2,000 people at sites in Dublin, Carlow, Cork, Tipperary and Wicklow.

Invested over €2.2bn in Ireland over the last five decades

In 2011 spent in excess of €400 million on goods and services in Ireland, supporting many other businesses and jobs in the Irish economy

In 2012 we contributed €2.3m in support of medical education for healthcare professionals, for local Irish charities, community and patient groups, and in our work towards environmental sustainability
MSD Ireland (Carlow)

- Capital expenditure is in excess of $227MM
- 200,000 ft²
- MSD’s first vaccine and biologics investment outside the U.S. which is needed to allow MSD to fully realise its pipeline of new products
- 2013 received a licence from the Irish Medicines Board (IMB)
- 2014 go-live for commercial manufacturing.
• MSD Ireland (Carlow) – Site Overview

- Production Building (77,000 sq ft)
- Production Support & warehousing (95,000 sq ft)
- Energy Centre (11,000 sq ft)
- Admin building (17,000 sq ft)
Manufacturing Technology

- Vaccine and Biologics manufacture
- High Speed Syringe and Vial Filling lines
- Grade A Isolator - Fill
- Utilising Disposable technology.
- Automatic and Manual Inspection Capability
Outline

• Part 1:
  – Outline the qualification strategy for manual inspection at MSD Carlow.
    • Fiona Byrne (Technical Operations - Process)

• Part 2:
  – Implementation and management of manual inspection at MSD Carlow.
    • Caroline Devery (IPT - Operations)
Qualification strategy for manual inspection at MSD Carlow
Content

• Manual Inspection

• Strategy Overview

• Training

• Sensitivity Studies

• Knapp Manual Baseline

• Manual Inspector Qualification
Manual Inspection

• As a new site implementing Automatic Inspection in the vial and syringe suites

• Manual inspection is the traditional approach applied when 100% visual inspection is required

• This involves appropriately trained & qualified Operators visually checking each vial / syringe to ensure it is not defective

• The vial / syringe is manually handled and evaluated for acceptance and defective product is separated from acceptable product
Manual Inspection

• The key to establishing a consistent and repeatable manual visual inspection process is standardisation of approach

• The following are some of the critical considerations:
  – Candidate Eye Testing
  – Proceduralized & Documented Training
  – Candidate Qualification Assessment
  – Standardized Inspection Environment
  – Controlled Lighting
  – Repeatable Inspection Durations & Pacing
Manual Inspection Qualification Strategy

• **Objective:**
  – To outline the qualification strategy for inspection at MSD Carlow.

• **Input & Background:**
  – Eudralex Annex 1 Manufacture of Sterile Medicinal Products
  – European Pharmacopoeia
  – USP 32 General Requirements <1> Injections
  – MSD Network Core Requirements and Guidelines
  – MSD Inspection SME across the network
  – MSD Carlow Inspection SME
  – Knapp Papers - Published Journals & Literature
  – Industry Practices within (HPRA) jurisdiction
Phase 1: Training

• **Purpose:** To create a team of trained Manual Inspectors to allow Defect Selection and Manual Baseline studies to proceed

• **Consists Of:**
  – Workshop on manual inspection
  – 20/20 vision test
  – Vision colour acuity and depth perception test
  – Read & Understand - Procedures and Work Instructions
  – Defect Set Test:
    • 80% good product; 20% defective product
    • Approx. 120 containers
    • 1 gross example of each categorized defect type
    • Inspector must catch 100% of defective product
    • Inspector must not false reject more than 5% of good product
Phase 2: Sensitivity Study

- **Purpose:** To establish the min size value that is repeatedly detectable by manual inspection for range type defects

- **Consists Of:**
  - Defect set:
    - Those identified during RA (risk assessment) with varying ranges
    - Excludes single presentation defects e.g. missing stopper
    - Approx. 1,500 Samples (20%:80% ratio)
  - Raw data will be analyzed to determine min size value (based on reject zone > 70%)
  - Based on analysis of group statistics (min. 10 inspectors)

Rick Watson and Joe Straub (Merck), Manual Inspection Capability to Detect Particulate in Parenterals: PDA Visual Inspection Forum, 7-8 Oct 2013, Bethesda, MD
Phase 3: Knapp Manual Baseline

• **Purpose:** To obtain a manual baseline % RZE (reject zone efficiency) result which will allow both the machine and inspectors to be challenged against

• **Consists Of:**
  – All defect categories:
    • Defect ranges determined by Phase 2 Sensitivity Study
    • All single presentation defects e.g. missing stopper
  – Approx. 1,500 Samples (20%:80% ratio)
  – Data compilation
    • Determine manual inspection Baseline Reject Zone Efficiency i.e. RZE$_M$
  – Inspected by multiple trained inspectors as a blind study to determine inspector efficiency & effectiveness (RZE value)
  – Based on analysis of group statistics (min. 10 inspectors)
Phase 4b: Manual Inspector Qualification / Requalification

**Purpose:** To successfully qualify / re-qualify manual inspectors to release them for manual inspection of finished product

**Consists Of:**
- Defect set:
  - Same accepts, defect types, ranges, sizes and presentation as those used in the Phase 3 Manual Baseline
- Compilation of new manual inspector efficiency $RZE_{ni}$
  - (Reject Zone Efficiency new inspector)
- Acceptance Criteria:
  - $RZE_{ni}$ within 3-sigma of baseline
  - False Reject$_{ni}$ within 3-sigma of baseline
- Requalification on annual basis
Matrix / Leveraging Approach

• Above strategy will be completed for first products announced for Carlow.

• As new products are announced a Risk Assessment will take place to determine if new baseline will need to be completed.

• Baseline Qualification:
  – If Risk Assessment of new product shows:
    • Equivalency to current product – no new baseline will be needed
    • Gaps to current product – gap analysis completed to determine requirements
    • Difference to current product - new baseline required
## GAP ANALYSIS AGAINST 2R SOLUTION PRODUCT GLASS VIAL BASELINE

<table>
<thead>
<tr>
<th>Defect Type</th>
<th>Categorisation</th>
<th>Compare</th>
<th>Impact</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missing Stopper</td>
<td>Critical</td>
<td>Identical</td>
<td>No</td>
<td>Same size and from the same supplier.</td>
</tr>
<tr>
<td>Missing Flip Off Cap</td>
<td>Major</td>
<td>Identical</td>
<td>No</td>
<td>Same size and from the same supplier. The cap is the same component but will differ in colour</td>
</tr>
</tbody>
</table>
| Dirty Container              | Minor          | Identical | No     | The dirt on the side of the vial is localised and the overall size of the container does not effect the manual inspectors detection ability.
Summary

• Qualification of manual inspectors at MSD Carlow is completed via a four phase process

• Qualification set is equivalent to a shift duration to challenge fatigue

• Blind studies are used to determine inspector efficiency and effectiveness (RZE value)

• Based on statistical analysis
Implementation and management of manual Inspection at MSD Carlow
Requirements for Manual inspection at Carlow

• Routine 100% visual inspection of sterile injectable.

• Visual inspection of the statistical sample of accepted material post 100% inspection.

• Manual re-inspection of product due to a deviation.

• Creation of a baseline to support qualification of automated inspection processes.

• Provision of contingency in the event of operational failure of automated inspection processes.

• Process Simulation Inspection.

5 Vial Images

2 Syringe Images
Material Flow

- Fill
- Auto Inspection
- Cold Store
- Manual Inspect
- Cold Store
Manual Inspection Area & Equipment

Manual Inspection Room

- 8 Inspection Booth’s
  - Eisai-Bosch, MIH-DX Inspection Hood
  - 2000-3750 Lux, Daily Check
- Separate room for AQL
- Lean Process Flow
- Multiple Concurrent Inspections
Control and Record of Manual Inspection

- Work Station
- Werum PAS-X MES
Inspection Technique – Standard Work

Standard Work Instruction

<table>
<thead>
<tr>
<th>Step</th>
<th>Alert</th>
<th>Operator Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td></td>
<td>While against white background, grasp the vial at the body and check the vial flip cap and seal for any defects including seal crimp. Ensure cap type and colour is correct.</td>
</tr>
</tbody>
</table>

- Check vial stopper is present; the correct type of stopper has been inserted and is free from any defect. Verify fill level is correct.
- While rotating the vial inspect the overall container for any cosmetic defects in the glass, including neck, heel ad body.
- Ensure Product colour is correct.
- Inspection should be performed for approximately 5 seconds against the white background and 5 seconds against the black background to enhance the detection of particulate matter against each background.

Associated Graphic/Photo Aid

- Seal
- Stopper
- Shoulder
- Fill Level
- Heel
- Vial Body
- Flip Cap
- Crimp
Categorisation of Rejects

**Syringe Qualified Defects - 26**

**Defect Name**
- Particulate Stainless Steel
- Particulate Glass
- Particulate Fiber
- Particulate Hair
- Particulate Rubber Stopper
- Plunger Stopper Molding Defect
- Incorrect Plunger Orientation
- Missing Plunger Stopper
- Cracked Container Defect
- Incorrect Plunger Stopper Defect
- Incorrect Container Defect
- Overfill Syringe Defect
- Underfill Syringe Defect
- Missing Tip Cap
- Discoloured Product Defect
- Foreign Product Defect
- Inverted Plunger Stopper
- Liquid in Plunger Stopper Rib Defect
- Incorrect Plunger Stopper Position
- Cracked/Broken Flange Defect
- Empty Syringe Defect
- Material Embedded in Glass Defect
- Material Embedded in Plunger Stopper Defect
- Broken Container Defect
- Dirty Container Defect
- Scratched Container Defect

**Vial Qualified Defects - 29**

**Defect Name**
- Particulate Stainless Steel
- Particulate Glass
- Particulate Fiber
- Particulate Hair
- Particulate Rubber Stopper
- Loose Seal Defect
- Missing/Uncrimped Seal/Cap
- Missing Vial Stopper
- Incorrect Stopper General Defect
- Incorrect Stopper Short
- Incorrect Stopper Long
- Cracked Container Side
- Cracked Container Bottom
- Protruding Stopper Defect
- Incorrect Colour Flip Cap
- Gross underfill Defect
- Discoloured Product Defect
- Foreign Product Defect
- Incorrect Container Defect
- Missing Flip off Cap
- Incomplete Crimp on Seal
- Empty Container Defect
- Broken Container Defect
- Material Embedded in Stopper Defect
- Material Embedded in Glass Defect
- Scratched Container Defect
- Dirty Container Defect
- Damaged Aluminium Seal
- Gross overfill Defect

- Observance of uncategorised rejects are SME assessed using a Risk Assessment methodology.

- Unclassified rejects are monitored for line performance and investigations and are periodically assessed for qualification.
Development & Control of Defect Library

- Defect set’s are physically built (using standard methodology) on-site representing production presentations.

- Stored in controlled laboratory conditions – logbook control.

- Dedicated trained Operations SME responsible for building, maintaining, monitoring for performance and training.

- Same set’s used for training, functionality tests and qualification.

- Representative format sizes used in set’s based on assessed equivalency.
Sampling and Reject Trend Monitoring

• **AQL – Final Accepted Vials**
  - ANSI Z1.4 2008 is used for determining samples size and acceptance criteria
  - Beginning, Middle, end of batch. Separate area & Personnel.
  - Failures investigated as per site deviation process.

<table>
<thead>
<tr>
<th>Defect Criticality</th>
<th>AQL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical</td>
<td>None Allowed</td>
</tr>
<tr>
<td>Major</td>
<td>0.4%</td>
</tr>
<tr>
<td>Minor</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

• **PCL – Early stage – Dynamic PCL: \( \mu + 3\delta \)**

• **Reject Trending**
  - 1.5 to 1% reject rate manual inspection
Start-up Challenges

- Material Logistics & Management of Product TOR
- Eye break management
- Inspector Training & categorisation of rejects
- Large pool of non-dedicated personnel, building competency and experience
- Multiple images across 2 formats
- Implementation of Electronic batch records.

*Implementation of Standard work*

*and lean process flow*