Particulate Matter and Visual Inspection: Industry Trends 2015

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Agenda

- FDA Recalls and 483 Observations
- Industry Benchmarking Survey
- USP <790> and <1790>
- Observations and Conclusions
- Q&A
FDA Recalls and 483 Observations
FDA Sterile Injectable Drug Recalls 2008-2012

- Lack of Sterility Assurance: 22%
- Visible Particles: 9%
- Impurities/Degradation: 47%
- Other*: 22%

* Incl. crystallization, discoloration, failed pH, impurities/degradation products and storage temp excursions.

Steven Lynn, FDA Office of Manufacturing and Product Quality, March, 14, 2013
Visible Particulate Recall Events

CDER Office of Drug Security, Integrity and Response, compiled by Stephen Langille
Recent FDA Recalls

• 7-17-2015 … Baxter Initiates Voluntary Recall of Two Lots of IV Solutions due to the Potential Presence of Particulate Matter
  – Insect
• 6-8-2015 … Mylan is Expanding its Voluntary Nationwide Recall of Select Lots of Injectable Products due to the Presence of Particulate Matter
  – Visible foreign particulate matter
• 7-29-2014 … Hospira Announces Voluntary Nationwide Recall of One Lot of Lidocaine HCl Injection, USP, 2%, 20 mg per mL … Due To Particulate Matter
  – Visible particles in solution and embedded in vial neck
• 6-2-2014 … Alexion Initiates Voluntary Nationwide Recall of Certain Lots of Soliris® (eculizumab) … Due to the Presence of Visible Particulate Matter in a Single Lot
  – Visible proteinaceous particles
US FDA 483 Themes

• Must establish a maximum allowable reject rate.
• Must control reinspection of product, including when appropriate, inspection conditions and number of reinspections permitted.
• Inspectors must be trained and training documented.
• Inspectors must be periodically recertified.
• Training and certification conditions must align with routine 100% inspection conditions.
• Address inspection fatigue during qualification.
US FDA 483 Themes

• Must conduct thorough investigations. Identify particulate matter when performing investigations.

• Must use statistically sound sampling plan(s) for AQL inspection.
Industry Benchmarking Survey
Survey Format and Participation

• Objective:

• On-line survey with multiple choice questions
• 77 questions, responses blinded
• Open to PDA members and non-members
• Response requested by site, so may have multiple entries for the same company
• 151 Responses from Aug to Sept 2014
Please keep in mind …

• The same population (PDA Members) was sampled for each survey, but the specific companies and manufacturing sites that responded each year are different. This limits to some degree the identification of trends.

• The survey documents current industry practice, but does not indicate if these are good or bad practices.
Topics

- General Information
- Manual Inspection
- Automated Inspection
- Inspection Results
- Acceptance Sampling and Inspection Strategies
- Future Direction
Summary and Conclusions

• Good geographic representation in plant location with NA (49%), EU (28%) and Japan + A/P (21%).

• Good geographic representation of markets supplied with NA (80%), EU (73%), Japan (59%), A/P (56%) and SA (54%).

• Good representation of small (<1M units/year) to large (>100M units/year) manufacturing sites.
What is the approximate total number of injectable units produced at this facility?

- 15% <1
- 20% 1-10
- 26% 11-30
- 11% 31-60
- 5% 61-100
- 22% >100

Millions
Summary and Conclusions

- The majority of surveyed products inspected are for human use (76%) and include a significant amount (57%) of biological/biotech products.
- The majority of surveyed products inspected are aqueous solutions (84%) or lyophilized powders (63%).
- These products are mostly packaged in tubing (70%) and molded (55%) glass vials, with a significant, but lesser number in glass syringes (42%) and ampoules (28%).
Summary and Conclusions

• Manual inspection continues to be the most used method for both particles (46%) and container/closure (50%).
• Continued interest in using automated inspection with 49% of firms having plans to implement systems in the next two years. Similar results observed in previous surveys.
• Automated systems are validated with production defects (83%) to be equivalent to manual inspection (51%).
Summary and Conclusions

- Most firms (69%) control manual inspection time and do not use magnification or polarized light.
- The median inspection time response was 6-10 sec which agrees with the current EP and USP inspection conditions.
- Illumination intensity is typically 2,000-4,000 lux (59%) which agrees with the current EP and USP inspection conditions with some (28%) using higher values.
What is the average inspection time for this container type?

![Graph showing inspection time for different container types.](image)

- **Molded Glass Vial (≤10mL)**
- **Molded Glass Vial (11-100mL)**
- **Tubing Glass Vial (≤10mL)**
- **Tubing Glass Vial (11-100mL)**
- **Glass Vial/Bottle (>100mL)**
- **Glass Ampule**
What is the average illumination intensity at the container during manual inspection?

- <1,000 lux: 2%
- 1,000 - 1,999 lux: 13%
- 2,000 - 2,999 lux: 33%
- 3,000 - 3,999 lux: 26%
- 4,000 - 5,000 lux: 13%
- >5,000 lux: 15%
Summary and Conclusions

• Inspection continues to be performed most often (79%) off-line, but a significant amount (60%) is also performed in-line with packaging.

• Training (94%), a test of visual acuity (92%) and inspection performance (90%) are part of the typical inspector qualification process.

• Annual requalification (79%) continues to be the typical time interval used for human inspectors.
Summary and Conclusions

- Test sets with 100-300 units (52%) with a defect rate of 5-10% (34%) are used most often for inspector qualification.
- Inspectors are given a break every 60 minutes / 1 hour (49%) or every 30 minutes (27%).
- Most firms use the same inspection conditions for different regions (81%), veterinary products (82%) or clinical supplies (87%).
The composition of test kits used to qualify inspectors.

Total Units in Test Kit:
- 100-300: 52%
- 301-500: 17%
- 501-750: 4%
- 751-1,000: 8%
- >1,000: 7%
- <100: 12%

Defect Rate in Test Kit:
- 5-10%: 34%
- 11-15%: 17%
- 16-20%: 21%
- >20%: 10%
- >5%: 18%
Summary and Conclusions

• The typical total reject rate is 1-2% for aqueous solutions and <1% for lyophilized powders.
• Differences in typical rejects rates are likely due to detection ability rather than underlying quality.
• Particles and specifically lint/fibers continue to be the most common defect.
What is the average reject rate for this product formulation?
What are the most common defects found during visual inspection? (Rank order with 1 most frequent)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Particles</td>
<td>1</td>
<td>1</td>
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</tr>
<tr>
<td>Scratches</td>
<td>2</td>
<td>2</td>
<td>4</td>
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<tr>
<td>Crimp Seal</td>
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<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Cracks/Chips</td>
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<td>5</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Cap</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Hi/Lo Fill</td>
<td>6</td>
<td>4</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Stopper/Plug</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Cake</td>
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<tr>
<td>Leaks</td>
<td>9</td>
<td>7</td>
<td>8</td>
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</tbody>
</table>
What are the most common types of particles found during visual inspection? (Rank order with 1 most frequent.)

<table>
<thead>
<tr>
<th>Type</th>
<th>2014</th>
<th>2008</th>
<th>2003</th>
<th>1996</th>
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<tr>
<td>Lint / Fiber</td>
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<td>Glass</td>
<td>2</td>
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<tr>
<td>Product Related</td>
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<td>4</td>
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<tr>
<td>Metal</td>
<td>4</td>
<td>5</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Rubber</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>
Summary and Conclusions

• After 100% inspection, lots are routinely (92%) audited most often (70%) by QA per equivalent standards ANSI/ASQ Z1.4, ISO 2859 or JIS Z9015.

• The median values for AQL’s used with these plans are 0.065% for Critical, 0.65% for Major and 2.5% for Minor.

• There is a shift in the median AQL value used for Critical defects from 0.10% to 0.065% and for Minor defects from 4.0% to 2.5% between 2008 and 2014.
What AQL value (in %) do you use for acceptance sampling of these defect categories?

48% use patient risk to set AQL values.
Summary and Conclusions

- More firms (60%) classify glass particles as Critical.
- There has been a shift to a Critical classification for particles likely due to regulatory pressure but this is not consistent with the new USP <790>.
- Firms have established alert/action limits based on 100% inspection results (87%) and investigate (88%) and/or reinspect (69%) when these limits are exceeded.
Regulatory Experience and Future Expectations

- 45% have been challenged by a regulatory inspector on their inspection method or acceptance criteria in the last two years.
  - Various
- 40% expect changes in customer expectations in the next five years.
  - Tighter particle limits
- 68% expect changes in regulatory expectations in the next five years.
  - Tighter particle limits
USP <790>
and <1790>
USP <790> Visible Particulates in Injections

• Inspection conditions defined
  – Harmonized with EP
  – 2,000-3,750 lux
  – Black and white backgrounds
  – No magnification
  – 5 sec viewing against each background
  – Swirl and/or invert sample

• Applies to *Extrinsic* and *Intrinsic* particles

• *Inherent* particles addressed in individual monographs or approved regulatory filings
USP <790> Acceptance Criteria

• At Time of Batch Release
  – 100% inspection followed by acceptance sampling
  – ANSI/ASQ Z1.4-2003 or ISO 2859
  – AQL= 0.65%, UQL= 2.3-3.3% typical
  – Alternate and equivalent plans acceptable

• For Product in Distribution
  – n = 20, a = 0
  – AQL= 0.26%, UQL= 10.9%
USP <790> Supplemental Testing

- Required when the nature of the product or package limits effective inspection
- Sample size based on ANSI/ASQ Z1.4 Special Sampling Plans
  - S-3 or S-4 plans recommended in draft USP <1790>
- Opaque Products
  - Reconstitute powders or lyo products
  - Inspect samples prior to lyophilization
  - Dissolve suspensions
  - Dilute strongly colored solutions
- Colored, Translucent or Opaque Containers
  - Transfer product to clear container
USP <790> Status and Final Revisions/Clarifications

- Published in USP 37 1\textsuperscript{st} Supplement
  - Official August 1, 2014
- Clarifications added:
  - A smaller sample (such as the Special sampling plans in the standards) is appropriate for destructive testing of powders and suspensions
  - Now states that this chapter does not add a new requirement for stability testing
  - Alternative light sources such as LED’s are acceptable
  - The light intensity range stated is intended to establish a lower limit of 2,000 lux, but that it may be appropriate to inspect at levels above 3,750 lux
Citizen Petition

• By: Hogan Lovells US, LLC, Washington, DC
  – Meredith Manning, Partner
• Submitted to Docket: April 13, 2015
• Action Requested:

  “Promptly issue guidance for agency staff and regulated industry acknowledging the “essentially free” standard published in USP <790> as current good manufacturing practice and an applicable standard for visible particulate matter in parenteral drug products. This can be accomplished through an addition to the IOM (see … Proposed Amendment to Investigations Operations Manual) or a related guidance document.”
Citizen Petition

• Parenteral Drug Products and Visible Particulates
  – References PDA *Industry Perspective on the Medical Risk of Visible Particles in Injectable Drug Products*

• USP’s “Essentially Free” Standard for Visible Particulates
  – Summarizes rationale for USP <790>
  – Probabilistic nature of visual inspection

• The USP’s “Essentially Free” Standard is cGMP

• FDA Guidance Must Incorporate the USP Standard
USP <1790> Visual Inspection of Injections

• <1790> Visual Inspection of Injections
  – Draft Information Chapter
    • Published for comment in PF 41(1) January 2015
  – Contents
    • Patient Risk
    • Typical Inspection Process Flow
    • Elements of a good inspection process
    • Inspection Lifecycle / Continuous Improvement
    • Interpretation of Inspection Results
    • Inspection Methods and Technologies
    • Qualification and Validation of Inspection Processes
USP <1790> Scope

- **Scope**
  - Inspection for visible particles in filled, sealed containers
  - Applicable to detection and removal of other visible defects
    - e.g. container integrity
  - Primary focus is manual inspection methods, but semi-automated and automated methods are discussed
USP <1790> Typical Process Flow

1. Filling
2. 100% Inspection
   - Accepted Units
   - Rejected Units
   - Analyze and Trend Rejects
   - Supplemental Testing
3. Acceptance Sampling and Testing
4. Packaging
• Related Chapters
  – <1> Injections
  – <790> Visible Particulates in Injections
  – <787> Subvisible Particulate Matter in Therapeutic Protein Injections
  – <788> Particulate Matter in Injections
  – <789> Particulate Matter in Ophthalmic Solutions
  – <1787> Measurement of Subvisible Particulate Matter in Therapeutic Protein Injections
  – <1788> Methods for the Determination of Particulate Matter in Injections and Ophthalmic Solutions
Observations and Conclusions
Conclusions and Observations

- Current industry performance is generally at or beyond the limits of medical risk.
- Visual inspection is a probabilistic process. 100% detection and removal is not achieved for all particles, even with the best inspection technology/process.
- There is significant variation in industry inspection practices and results.
- Compendial guidance is ambiguous, but getting better.
Conclusions and Observations

• “Zero defects” is a valuable goal, but not a practical limit for particulate matter.
• Limits should be practical; based on patient risk and process capability.
Acknowledgements

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  - D. Scott Aldrich - Ultramikro
  - John Ayres - Eli Lilly
  - Roy Cherris - Bridge Associates International
  - Desmond Hunt - USP
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  - Janie Miller
Questions

Remember, everyone is an inspector …