INDUSTRY PERSPECTIVE ON THE CONTROL OF VISIBLE PARTICLES

Tapan Das

Biologics Development, Bristol-Myers Squibb

European Biopharmaceutical Enterprises (EBE) satellite Session
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EBE Visible Particle group

Focus group comprised of members from EU/US Biopharma practitioners

Ongoing discussion topics include:

- Building awareness for visible particle specifications in DP
- Particle size range for visual inspection (visibility)
- Particle characterization – What techniques and what extent to mitigate risk
- Automated visual inspection
- Upcoming activities in networks, regulatory bodies - including EDQM, EBE
Topics Discussed Today

Key points from the EBE position paper on visible particles

- Without (zero) visible particles is an unrealistic requirement
- Major steps in visible particle control
- Perspectives on patient safety
- Conclusions from the position paper

Size Matters

Soluble Aggregates: Reversible? Covalent? Non-covalent?

The Submicron Gap: Detection and characterization difficulties in ~50 nm to ~1 μm range

Visible particle

1nm 50nm 100nm 1μm 100μm 1mm
Number Matters
(particle count)

A few particles

Thousands of particles

Millions of particles
Method Matters

Laser Diffraction Analyzers
- NTA, DLS
- SE-HPLC, AF4, AUC, EM
- SDS-PAGE

Visual
- Light Obscuration, Microscopy
- Dynamic Imaging, Coulter, FACS

0.001 μm to 600 μm

Fragment
Monomer
Submicron Gap
Key points from the EBE position paper on visible particles
Acknowledgments – EBE Visible Particle Position Paper

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Compendial & Regulatory Guides

- Ph. Eur. monograph 2031
  - Monoclonal Antibodies for Human Use
- Ph. Eur. monograph 2.9.20
  - Particulate contamination: Visible particles
- Ph. Eur. ‘Parenteral Preparations’
- USP <1>
  - Requires 100% visual inspection at line (defects)
- USP <790>
  - Guidance for 100% visual inspection
- USP <1787>
  - Guidance on distinguishing/ characterizing types of particles
- JP 6.06
  - 6.06 Foreign Insoluble Matter Test for Injections
- cGMP requirements
Monographs for ‘Parenteral Preparations’

- EP requires “Practically free” of visible particles
- USP requires “Essentially free” of visible particles
  - Both terms have been used interchangeably.
  - These definitions acknowledge the probabilistic nature of visual particle inspection.
- JP requires ‘free from readily detectable foreign insoluble matters’
Problem Statement


■ **Production:**
  - *In-process control for container (vial, syringe etc) and post-filling inspection to eliminate containers that contain visible particles.*
  - *During development, to demonstrate that either the process will not generate visible proteinaceous particles in the final lot or such particles are reduced to a low level as justified and authorised.*

■ **Definition:** Examined under suitable conditions of visibility, they are *practically free from particles.*

■ **Tests – Appearance:** They are *without visible particles*, unless otherwise justified and authorised.
Clarifications for 2031

- ‘Without Visible particles’ was intentionally kept to give clear guidance that the presence of visible particles is unwanted and the appropriate formulation studies should be performed during development to find an optimal formulation.

- Practically free could not be a pass/fail criteria in a test and that

- Visual inspection is not a quality control test, even though performed at the end of the production.

Explanatory notes from PHARMEUROPA Vol. 23, No. 3, July 2011 provided explanatory notes and summary of changes to the monograph 2031 to be published in Supplement 7.3.
HA Query examples

- According to the Ph. Eur. monograph on Monoclonal antibodies for human use (01/2012:2031), monoclonal preparations are “without visible particles, unless otherwise justified and authorized.” The applicant has not provided an appropriate justification ……..

- For the monoclonal antibody XXXXXX, …..the sponsor should change the specification for the DP for Particulate Matter (Visible Foreign) to meet the requirements of the Pharm. Eur. 2031……..
Detection is Probabilistic

- **Due to probabilistic nature of detecting particles** by visual inspection method, without (zero) visible particles is an unrealistic requirement for QC.

- **Even with significant development** work, the probability of a visible particle being present cannot be completely eliminated.

- There is **no single size cut-off** for a particle being visible to the human eye
  - < 50 μm, at ~1% probability of detection
  - ~200 μm, > 95% probability of detection
The Industry Position Paper

- In our view, ‘practically free from particles’ should be considered a suitable acceptance criterion for injectable biotech and small-molecule products, as long as appropriately defined.

- Furthermore, we argue that visual inspection is a suitable QC release test and that ‘practically free from particles’ is a suitable specification when adequately described.

Key Points in the position paper

Review best practices in the industry for:
- Visual inspection process and associated operator training
- QC sampling
- Testing and setting acceptance criteria corresponding to “practically free of visible particles”
- Providing considerations when visible proteinaceous particles are deemed unavoidable
- A brief overview of visible particle characterization
- Perspectives on patient safety
Steps in Particle Control

- The manufacturing processes and associated controls are designed to yield a product free from visible particles to the extent possible.
- Visual Inspection (100%) at the end of drug product manufacturing
- Followed by sampling inspection (AQL sampling)
Products that may Contain Proteinaceous Particles

- Biologics including mAb can have as an inherent propensity to self-associate and form proteinaceous particles, despite development work.

- The Notes to Ph. Eur. 2031 recognises that final product may contain proteinaceous visible particles that are intrinsic to the product:
  - Inspector training to ensure differentiation of proteinaceous from non-protein particles.
  - Development and mfg history needed to support overall control strategy and justification for low level protein particle at QC release.
Raman Imaging – Protein vs. non-Protein

Courtesy: Dr. Gurusamy Balakrishnan
Perspectives on Patient Safety

- Particles remain a Critical Quality Attribute
- Empirical observations from clinical data – anecdotal (for particles in drug product)
- Package Insert of many approved biologic products (US, EU and elsewhere) state “may contain particles”
  - “may”, emphasizing the unpredictable and probabilistic nature of these particles
- A small number of visible particles in parenteral products is unlikely to cause adverse impact on safety
- Use of in-line filter for some products

Conclusions from the position paper

- Visible particle assessments remain a challenge.
- A holistic approach to minimizing the presence of visible particles in injectable products is proposed.
- However, a requirement of zero (or without) visible particles is overly stringent and practically not attainable.
- Particle controls are and should be one of the main formulation and process design criteria applied by the biopharmaceutical industry.
- This position paper recommends to consider “practically free from visible particles unless otherwise justified and authorised” as a standard requirement.
We welcome your feedback
Questions?
Misconceptions about Particles

- ‘Loss of active product’
  - Less than 0.1% mass of protein is usually involved in formation of particles

- ‘Reliable detection is in place’
  - No Compendial method for semi-quantitative analysis of visible particles
  - No universal visible proteinaceous particle standards
  - No guidelines around how many visible particles are acceptable

- ‘Good products are particle-free’
  - All liquid protein solutions have particles, visible and/or sub-visible

Courtesy: Maryam Mazaheri, Medimmune
Backup Slides
Visible Particle Testing on Stability

- Particles may form over time with slow kinetics
- Monitoring particles over stability time points
- The detection of pre-existing particles in stability should be avoided since stability testing should focus on changes in the product over time.

- Semi-quantitative visual or instrument based methods are in development to evaluate the levels of proteinaceous particles in a product. If these can be validated, such methods could possibly be introduced into release/stability product testing.
Particle Identification and Characterization

- When atypical particles are found
Flow Chart for Usage of Containers for Particle Characterization

**Step 1:**
Non-destructive Tests (container as received, unopened)
Tests include visual inspection, enhanced visualization by magnification, lighting, contrast, and optical microscopy

Move to next step as appropriate

**Step 2:**
Destructive Tests (container opened, particles isolated)
Tests with isolated particle(s) include FTIR, Raman, optical microscopy, SEM-EDX, TOF-SIMS

Move to next step as appropriate

**Step 3:**
Destructive Tests (isolated particles treated, such as digestion, solubilization, sputter coating)
Tests with treated particle(s) include MALDI, CE-SDS or SDS-PAGE, SEM-EDX, peptide mapping etc.
## Examples of EU/US biotech products that may contain protein particles (from package insert)

<table>
<thead>
<tr>
<th>Generic name (route of administration)</th>
<th>Product name</th>
<th>Product Information EU or US</th>
<th>Section Text</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anakinra injection (sc)</strong></td>
<td>Kineret</td>
<td>US</td>
<td>2.4 Administration</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>There may be trace amounts of small, translucent-to-white amorphous particles of protein in the solution. If the number of translucent-to-white amorphous particles in a given syringe appears excessive, do not use this syringe.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>11 Description</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>The solution <strong>may</strong> contain trace amounts of small, translucent-to-white amorphous proteinaceous particles.</td>
</tr>
<tr>
<td><strong>Etanercept injection (sc)</strong></td>
<td>Enbrel</td>
<td>EU</td>
<td>6.6 Special precautions for disposal and other handling</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>The solution <strong>may</strong> contain trace amounts of small, translucent or white particles of protein.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. There <strong>may be small white particles</strong> of protein in the solution. This is not unusual for proteinaceous solutions. The solution should not be used if discolored or cloudy, or if foreign particulate matter is present.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.4 Preparation of Enbrel</td>
</tr>
<tr>
<td><strong>Denosumab injection (sc)</strong></td>
<td>Prolia</td>
<td>EU</td>
<td>6.6 Special precautions for disposal and other handling</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>The solution <strong>may contain</strong> trace amounts of translucent to white proteinaceous particles. Do not inject the solution if it is cloudy or discoloured</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.2 Preparation and Administration</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prolia is a clear, colorless to pale yellow solution that may contain trace amounts of translucent to</td>
</tr>
</tbody>
</table>
AQL Sampling

- Additional assurance is provided by a second inspection based on statistical sampling (e.g. AQL sampling based on predefined sampling plans, such as ANSI Z1.4, ISO 2859-1 or better or equivalent).

- This second inspection is performed by different inspectors to those performing 100% inspection.

- AQL = Acceptable Quality Level. Also referred to as Acceptance Sampling Plan (ASP).

- A PDA survey of both European and US based manufacturers established that the industry median maximum AQL for the major (level 2) defect category is 0.65%.

- The AQL maximum of 0.65% has been adopted in USP <790> and should be used as the criterion for the AQL test, unless otherwise justified.


AQL example

- An illustrative example of AQL testing:
  - Applying a Level II ANSI/ASQ Z1.4 plan for
  - Batch sizes of 10,001 to 35,000
  - Sample size 315 units
  - Considered to be ‘practically free of particles’ if no more than five (5) units are observed to contain one or more visible particles
QC Sample Testing

- AQL Testing May Replace End-product QC Testing
  - *AQL inspectors are trained at QC level for the detection of visible particles*

- Batch Release End-product QC Testing & Sampling Size
  - *If AQL result is not being used for Batch Release*
  - *Survey suggests 10-20 samples for QC release*