Managing Particulates in Cellular Therapy

ISCT Process and Product Development Sub-committee

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Particulates

- What are particulates
- What risks do particulates pose
- What guidances currently exist to monitor particulates
- Where do they originate in the process
- What test methods exist
- What are the next steps for cell therapy
Cell Therapy and Particulates

Cell Therapy

Blood Transfusion

Pharma

No specific guidance

Numerous guidances

?
What are particulates

- Particulate
  - Discrete undissolved object or foreign material found in a solution that is unintentionally present in final product
  - Viable as opposed to Non-viable
  - Visible, Sub-visible, Submicron

- Based on the nature of the product itself—**a cell is a particulate**
- In cell therapy—the cell is the active ingredient in the product

*Challenge—What is inadvertently added during cell therapy processing may be difficult to remove at the end*
Associated Risks to Particulate Matter

• Patient safety
  - Anecdotal studies
    - Formation of emboli and granulomas most common result from IV solutions
    - Subvisible particulate often trapped in liver, lungs and spleen
    - Larger (visible) particulate generally don’t migrate far from injection site
  - Route of administration will need to be considered for each product

• Product performance
  - Particulate could potentially interfere with biological efficacy of cell therapy
Particulate Beads Dendritic Cell Red Cells

nm – mm

50 - 250µm 20 - 40µm 6 - 8µm
Particulate Origination/Accumulation

• Raw Materials/Disposables
  - Type of product and starting material
  - Manufacturing quality systems and controls
    - Materials designated for “R&D Use” or “Non GMP Grade”
    - Pharmaceutical or clinical grade material

• Cell Therapy Manufacturing Process
  - Quality of starting raw materials
    - Cells/biological material
    - Disposables, equipment, etc.
  - Inherent to the actual production process
    - Manufacturing quality systems and controls
    - Number and complexity of processing steps
# Commonly Observed Particulates and Sources

<table>
<thead>
<tr>
<th>Source</th>
<th>Raw Material</th>
<th>Disposable</th>
<th>Final Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture media</td>
<td>Flasks/tubes</td>
<td>Biological (from original</td>
<td></td>
</tr>
<tr>
<td>Storage media</td>
<td>Plates/Dishes</td>
<td>cellular starting material)</td>
<td></td>
</tr>
<tr>
<td>Serum</td>
<td>Bags/vials</td>
<td>Raw materials</td>
<td></td>
</tr>
<tr>
<td>Buffer solution</td>
<td>Tubing sets</td>
<td>Process disposables</td>
<td></td>
</tr>
<tr>
<td>Reagents, etc.</td>
<td>Filters</td>
<td>Operators</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pipettes</td>
<td>Primary Containers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Syringes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sterile gloves</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Beads</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stoppers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type</td>
<td>Protein aggregates</td>
<td>Cell (aggregates)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minerals (salts)</td>
<td>DNA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Organic Fibers</td>
<td>ECM (extracellular matrix)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plastic fragments</td>
<td>Organic fibers</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plastic</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cellulose</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inorganic particles</td>
<td></td>
</tr>
</tbody>
</table>
Particulate Testing Methods

• Visual Inspection
  - Examination of product held against white or black background
  - 100% inspection
  - Useful for particulate >100µm

• USP<788> Testing Particulate Matter for Injection
  - Guidelines for sub-visible particulate testing and allowable limits
  - Refer also to
    - Ph.Eur. 2.9.19. Particulate Contamination: Sub-visible Particles
    - JP 6.07 Insoluble Particulate Matter Test for Injections

• New methods likely required as no specific method will apply to all products

* No current required testing/limits established for cell therapy
## Current USP<788> Testing Particulate Matter for Injection

<table>
<thead>
<tr>
<th>Volume</th>
<th>Particle Size Microscopic Limits:</th>
<th>Particle Number Microscopic Limits:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large Parenteral Volume (&gt; 100mL)</td>
<td>&gt;10 micron</td>
<td>12 per ml</td>
</tr>
<tr>
<td></td>
<td>&gt;25 micron</td>
<td>2 per ml</td>
</tr>
<tr>
<td>Small Parenteral Volume (&lt; 100mL)</td>
<td>&gt;10 micron</td>
<td>6000 per container</td>
</tr>
<tr>
<td></td>
<td>&gt;25 micron</td>
<td>600 per container</td>
</tr>
</tbody>
</table>
Points to Consider

- It is essential to determine a control strategy for particulate early in the product development lifecycle
  - Consider:
    - What composition, size and amount can be considered safe?
    - How will particulates inherent to respective process be monitored?
    - What will be acceptable and what test/s can be performed?
    - Can cell therapy product manufacturers be compliant with current requirements for particulates in injectables?
    - Minimally manipulated vs. Complex processes

- Some principles of current guidances can be considered, but certainly not in their entirety
Potential Strategy/Next Steps

• Start by determining product classification and consider compliance with current industry standards
  - Minimally manipulated manufacturing process
    - More closely resembling blood or blood component manufacturing activities
  - Complex, more than minimally manipulated process
    - More analogous to parenteral drug solutions in pharmaceutical industry

• Cell therapy developers, manufacturers and suppliers should all be working closely very early in the process
Potential Strategy/Next Steps

• Specific areas to consider:
  - Qualification/screening of raw materials, disposable process equipment and final product containers
  - Full assessment of manufacturing process (via FMEA) to identify ingress routes and establish controls
  - Periodic process validations
  - Collection of data to determine “expectable” particulate burden
  - Establish visual inspection process
    - Confirmation of effectiveness
    - Batch Accept/Reject rate
  - Filtration of solutions if/where possible
  - Delivery method/route for final product
  - Employ more clinical/pharmaceutical grade materials for manufacturing

* Characterizing particulate early in the manufacturing process is key
Summary

- The field of cellular therapy is presented with some obvious challenges with respect to particulates.
- One set of guidelines for product particulates does not apply equally well between cell therapy, blood products, and pharma products.
- No specific test or method for particulates will apply to all products.
- Guidance documents will be generated over time as more and more cell therapy products are approved.
- For cell therapy, the work needs to be done upstream making sure that adequate controls are in place to control the level of particulate matter.
- Ultimately, it will be important for members of the cell therapy community to define what is reasonable for the industry.
THANK YOU

Acknowledgements:
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ISCT Product and Process Development Committee
Particulate Project Team Members

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