USP Biologics
Strategic Updates

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VP, Global Biologics

Biologics Stakeholders Forum
January 10, 2020
Biologics

- Evolution of USP biologics compendial standards
- Implementation of the USP Biologics strategy
- Path forward for biologics standards and stakeholder engagement
200 Years of building trust

1820: a single “recipe book”

2020: Procedures and acceptance criteria to support medicinal articles in the market place

**Heparin Sodium**

**DEFINITION**

Heparin Sodium is the sodium salt of sulfated glycosaminoglycans present as a mixture of heterogeneous molecules varying in molecular weights that retains a combination of activities against different factors of the blood clotting cascade.

**IDENTIFICATION**

- A. 1H NMR SPECTRUM
- B. CHROMATOGRAPHIC IDENTIFICATION
- C. ANTI-FACTOR Xa TO ANTI-FACTOR IIa RATIO
- D. MOLECULAR WEIGHT DETERMINATIONS
- E. A solution of Heparin Sodium imparts an intense yellow color to a nonluminous flame.

**Filgrastim**

**DEFINITION**

Filgrastim is a recombinant form of human granulocyte colony-stimulating factor (r-metHuG-CSF). It is a single chain, 175 amino acid nonglycosylated polypeptide produced by *Escherichia coli* bacteria transfected with a gene encoding a methionyl human granulocyte colony-stimulating factor.

**IDENTIFICATION**

- A. It meets the requirements in the Assay.
- B. The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained as directed in the test for Organic Impurities, Related Compounds.
- C. PEPTIDE MAPPING
  (See Biotechnology-Derived Articles—Peptide Mapping (1055).)
<table>
<thead>
<tr>
<th>Nonproprietary Name</th>
<th>Brand</th>
<th>Indication</th>
<th>Applicable USP Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin Human</td>
<td>Several</td>
<td>Diabetes mellitus</td>
<td>Monographs</td>
</tr>
<tr>
<td>Somatropin</td>
<td>Several</td>
<td>Growth hormone deficiency and others</td>
<td>Monographs</td>
</tr>
<tr>
<td>Filgrastim, Filgrastim-</td>
<td>Neupogen, Granix, Zarxio</td>
<td>Febrile neutropenia</td>
<td>Monograph</td>
</tr>
<tr>
<td>sndz, tbo-Filgrastim</td>
<td></td>
<td></td>
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<tr>
<td>Interferon beta-1a</td>
<td>Avonex, Rebif</td>
<td>Multiple sclerosis</td>
<td>Monographs, Published for comment</td>
</tr>
<tr>
<td>Monoclonal Antibodies</td>
<td>Several</td>
<td>Lymphomas, Arthritis, other</td>
<td>Procedures and broadly applicable</td>
</tr>
<tr>
<td>CD34+ Stem Cells</td>
<td>Products under development</td>
<td>Several applications and clinical trials</td>
<td>standards</td>
</tr>
</tbody>
</table>
USP Performance standards and applications to monoclonal antibodies

Included in USP chapter <129>
- Size exclusion chromatography
- Purity: Capillary Electrophoresis-size separation (CE-SDS)
- Oligosaccharide assays (for N-linked oligosaccharides and sialic acid)
Standards for method performance - USP chapter <127> Enumeration of CD34+ stem cells - Flow Cytometry

USP CD34+ Cell Enumeration System Suitability Reference Standard is used to calibrate instruments, assess reagents and ensure correct gating for data acquisition and analysis.

USP CD34+ Cell Enumeration System Suitability Reference Standard is made from mobilized peripheral blood collected by apheresis from a G-CSF mobilized donor. The reference standard contains human leukocytes, erythrocytes and CD34+ cells that have been fixed and lyophilized.

Store USP CD34+ Cell Enumeration System Suitability Reference Standard in a freezer. Allow the vial to warm up to room temperature. Reconstitute the entire contents of the vial with 500 µL of water, use immediately as a system suitability standard as described in <127> Flow Cytometric Enumeration of CD34+ Cells. After reconstitution in 500 µL of water, the concentration range is 16-34 CD34+ cells/µL.

Additional Information:

USP CD34+ Cell Enumeration System Suitability Reference Standard is made from mobilized peripheral blood collected by apheresis from a G-CSF mobilized donor. The reference standard contains human leukocytes, erythrocytes and CD34+ cells that have been fixed and lyophilized.

Store USP CD34+ Cell Enumeration System Suitability Reference Standard in a freezer. Allow the vial to warm up to room temperature. Reconstitute the entire contents of the vial with 500 µL of water, use immediately as a system suitability standard as described in <127> Flow Cytometric Enumeration of CD34+ Cells. After reconstitution in 500 µL of water, the concentration range is 16-34 CD34+ cells/µL.
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USP Biologics standards

2015–2020

USP Convention Resolution VI: Standards for Biological Medicines

USP will promote alignment with stakeholders to develop quality standards for biological medicines, ensuring that innovation and availability are facilitated and complemented.

Biologics Approach

Develop new standards for biologics based on broad understanding of public health as well as regulatory and technology impact

- Continue to modernize standards for legacy biological products
- Prioritize development of performance standards, with broad applicability to classes and families of products
- Develop standards to support emerging therapies based on novel technologies
USP Standards: dedicated to biologics development throughout the lifecycle

- Focused on expanding the portfolio of standards which support biologics analytical testing
- Used to ensure and demonstrate methods and process performance, system suitability and assays
- Focused on assays and technologies used in biopharmaceutical analysis
- Supported by comprehensive data packages
Expanding our focus beyond specific product classes

Evaluate standards for technologies and assays with broad application and impact

Examples:

<table>
<thead>
<tr>
<th>Technology</th>
<th>Assays</th>
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<tbody>
<tr>
<td>LC, HPLC</td>
<td>Protein characterization</td>
</tr>
<tr>
<td>Electrophoresis</td>
<td>Potency (Bioassays)</td>
</tr>
<tr>
<td>MS</td>
<td>Residual HCP, HC DNA</td>
</tr>
<tr>
<td>NMR</td>
<td>Contaminants viral, microbial</td>
</tr>
<tr>
<td>Flow cytometry</td>
<td>Particulates, metals</td>
</tr>
<tr>
<td>Immunoassays</td>
<td>Sequencing: deletion/insertion</td>
</tr>
<tr>
<td>PCR</td>
<td>Algorithms, software</td>
</tr>
<tr>
<td>Genomics</td>
<td></td>
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</tbody>
</table>
Collaborative approach to standards development

- Early engagement of stakeholders (industry, regulators, academia other pharmacopeias)
- Industry roundtables to discuss needs, challenges, potential standards, next steps
- Ongoing engagement with global partners, e.g.
  - APEC Regulatory Harmonization Steering Committee and associated centres of excellence
- Collaboration with other industry groups, e.g.
  - BioPhorum
  - Alliance for Regenerative Medicine
  - Standards Coordinating Body
  - National Institute for Innovation in Manufacturing Biopharmaceuticals
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Standards development for biologics and commitment to stakeholders engagement

* Even if no USP standard is developed, scientific information gathered could be made available as a best-practice document.

** USP will not publish as official new monograph standards for specific biologics products unless supported by FDA and stakeholders.
USP’s Biologics path forward

- Global leader in biologics quality
  - Defining and enhancing quality from R&D through manufacturing and distribution
  - Anticipating and tackling critical quality issues
- Engagement and scientific connectivity with biologics stakeholders
- Reference standards, with an initial focus on performance and raw material standards
- Documentary standards targeted at advancing quality topics broadly
- Adjacencies such as education, training
- Technical collaborations and partnerships
Wide variety of applications for new standards
Therapeutic Proteins

Analytical Characterization
- cIEF Standards (pI standards)
- Peptide Mapping
- IgG MW Standards
- PENNY peptide for quantitation

Raw Materials
- Cell Culture Media
- Media supplements
- PEGs
- Standards for column qualification
- Polysorbate

Impurities
- Host Cell Protein (HCP)
- Host Cell DNA
- Protein A
- Metals
- Antifoam

Post-translational Modifications
- Deamidation
- Oxidation
- O-linked glycans

Assay Standards
- FcRn Receptor Assay
- ADCC Activity Assay
- TNF as a target

Applicable to MAM workflows
Other Standards under Development

- **Standards for column qualification**
  - Roundtable in November 2018
  - Preliminary lab work in progress to evaluate mAb materials for CEX and SEC

- **Trace metals in media**
  - Collaboration with BioPhorum
  - Roundtable held June 2019

- **Visible particles**
  - Roundtable held November 2018
  - Dialog with industry

- **Higher order structure**
  - Initial focus on CD and FTIR
  - First step: spiking study with peptide or protein standards to establish ability to detect changes
Potential standards for cell and gene therapy

- Vector Copy Number Standard
  - Jurkat T cells transduced with a lentiviral vector containing 1, 2, 3 and 4 integrated proviruses per cell
  - Parental cells used for 0 copies/cell

- Standards for mRNA
  - Roundtable held in November 2018
  - Potential standards
    - Standard for T7 RNA polymerase activity
    - mRNA size standards

- Standards for AAV
  - Roundtable held in March 2019 cosponsored with NIH-NINDS and NCATS
  - Potential reference standards
    - AAV9 vector as a new standard
    - AAV empty capsids
    - AAV plasmid standards with multiple AAV specific targets as a broad PCR standard
    - Raw materials
  - Documentary standards outlining best practices
USP Workshop on CMC for Gene Therapy

Regulations, Standards, & Quality

February 18-19, 2020 | USP Meeting Center, Rockville, MD

usp.org/biologics
Opportunities for Collaboration

- Roundtables and working groups
- Expert committees and expert panels
- Material characterization
- Method development
- Development of standards
  - Material selection
  - Proof of concept and round robin studies
  - Collaborative testing

Diagram:
- Qualification of material and sample testing
- Bulk Material
- Characterization, fill finish and multi-lab studies
- Collaborative Study Design and Testing
- Data Review/Value Assignment & Report
- Approval by Biologics Expert Committee
- Release to Inventory
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Visit: usp.org/trustneedschampions

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Empowering a healthy tomorrow