USP Standards to Support Gene Therapy Product Development and Manufacturing

Biologics Stakeholder Forum
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The role of USP and standards

USP standards for gene therapy
Benefits of Standards include:

- **Consistency** Help facilitate consistent and predictable manufacturing processes, product testing throughout lifecycle
- **Innovation** Foster innovation and adoption of new technologies, lower R&D costs by building on existing standards
- **Support** for meeting regulatory expectations, and facilitating market entry for safe and effective products, including products from emerging technologies

Remains challenging to define a standard that suits every developer’s needs

- Diverse range of product types
- Unique requirements for raw materials
- Lack of alignment on Product Quality Attributes and test methods
USP Standards for “The Basics”

Guidance on method verification, validation, and analytical procedures

- <1225> Validation of Compendial Procedures
- <1226> Verification of Compendial Procedures
- <1224> Transfer of Analytical Procedures
- <1220> Analytical Procedure Lifecycle

Guidance on developing robust bioassays

- <111> Design and Analysis of Biological Assays
- <1032> Design and Development of Biological Assays
- <1033> Biological Assay Validation
- <1034> Analysis of Biological Assays

### Compendial methods

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<th>USP Chapter</th>
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Existing USP Public Standards for Raw & Starting Materials

Documentary standards—General chapters

- <1044> Cryopreservation of Cells
- <1043> Ancillary Materials for Cell, Gene, and Tissue Engineered Products
- <1042> Cell Banking Practices for Recombinant Biologics
- <1027> Flow Cytometry
- <1024> Bovine Serum
- <1040> Quality Considerations of Plasmid DNA as a Starting Material for Cell and Gene Therapies
  PF closed January 31st, 2024

Reference Standards

- CD34+ Enumeration System Suitability (freeze-dried cells)
- Fetal Bovine Serum
- Albumin (bovine and recombinant human)
- <90> Fetal Bovine Serum--Quality Attributes and Functionality Tests
- <89> Enzymes Used as Ancillary Materials in Pharmaceutical Manufacturing
- <92> Growth Factors and Cytokines Used in Cell Therapy Manufacturing
- <127> Flow Cytometric Enumeration of CD34+ Cells
- Trypsin (bovine and recombinant porcine)
- Collagenase I and collagenase II
USP Chapters Supporting Manufacturing and Quality Control of Gene Therapies

- Ancillary raw material qualification
- Regulatory considerations
- Risk management and tiered assessment strategy
- Performance testing and residual testing

**<1043> Ancillary Materials for Cell, Gene, and Tissue-Engineered Products**

- Addresses both commercial and clinical trial materials
- Manufacturing and process development considerations
- Vector design, manufacturing and purification
- Analytical tests for Gene Therapy products

**<1047> Gene Therapy Products**
(under revision)
Stakeholder feedback indicated there was insufficient regulatory guidance for plasmid DNA used in the manufacturing of cell and gene therapy.

USP has recognized this gap and initiated efforts to define plasmid DNA best practices:

- USP Expert Panel for plasmid DNA was established to provide guidance.
- General Chapter was published in Pharmacopeial Forum on Nov 1, 2023.
  - Over 400 public comments during the 90-day comment period.

Aligning on Best Practices for AAV and Lentivirus

AAV Products Chapter Outline (as of February 2024)

- Materials
  - Raw and critical starting materials
- Vector Characteristics
  - Safety, transgene cassette, capsid
- Manufacturing
  - Drug Substance (Seed train to purification)
- Control Strategy
  - Microbial and viral testing
  - Reference Standards, Assay Controls, In-Process Controls
  - Drug Substance/Drug Product Quality
- Stability
  - Starting Materials, intermediates, DS, DP, other
- Comparability
  - Phase Appropriate Comparability Strategies
- Formulation & Final Presentation

Lentivirus for Gene Therapy Chapter Outline (as of February 2024)

- Construct Design
- Critical Raw Materials
- Starting Materials
- Production
- Characterization and Release Testing
- Formulation
- Stability
- Comparability
New Reference Materials for Residual DNA

Residual Host Cell DNA
- USP-ATCC Genomic DNA products
- Support quantitation of residual DNA by qPCR for common CGT cell lines
  - Residual HEK293 DNA
  - Residual Sf9 DNA

https://www.usp.org/biologics/atcc-usp-genomic-dnas
Physical Reference Materials in Development

- Vector genome titer for AAV
- Vector genome titer for LVV
- LVV integration copy number
- LVV integration site
- AAV Capsids
  - Empty: full ratio
  - Capsid protein analysis
  - Aggregation
- Plasmid DNA for residual analysis
Analytical Procedures to Support Quality Assessment of mRNA- & Viral Vector-based Vaccines

www.usp.org/vaccines

Available Online at: www.usp.org/mrna-quality

Available Online at: www.usp.org/viral-vectors
Future USP Standards for NGS-based Testing

- Stakeholder input prioritizes USP’s standards development for NGS-based testing
  - Non-compendial reference standards and reference materials
  - Analytical procedures guidelines

- USP needs expert volunteers to collaborate
  - Participate in working groups to develop chapters
  - Participate in roundtables

- USP needs companies to sponsor the development of compendial standards
  - Donate methods and/or material to support standard development
  - Participate in Round Robin and Collaborative Testing
Thank You

Empowering a healthy tomorrow