USP Standards to Support Gene Therapy Product Development and Manufacturing

Biologics Stakeholder Forum
February 22, 2024

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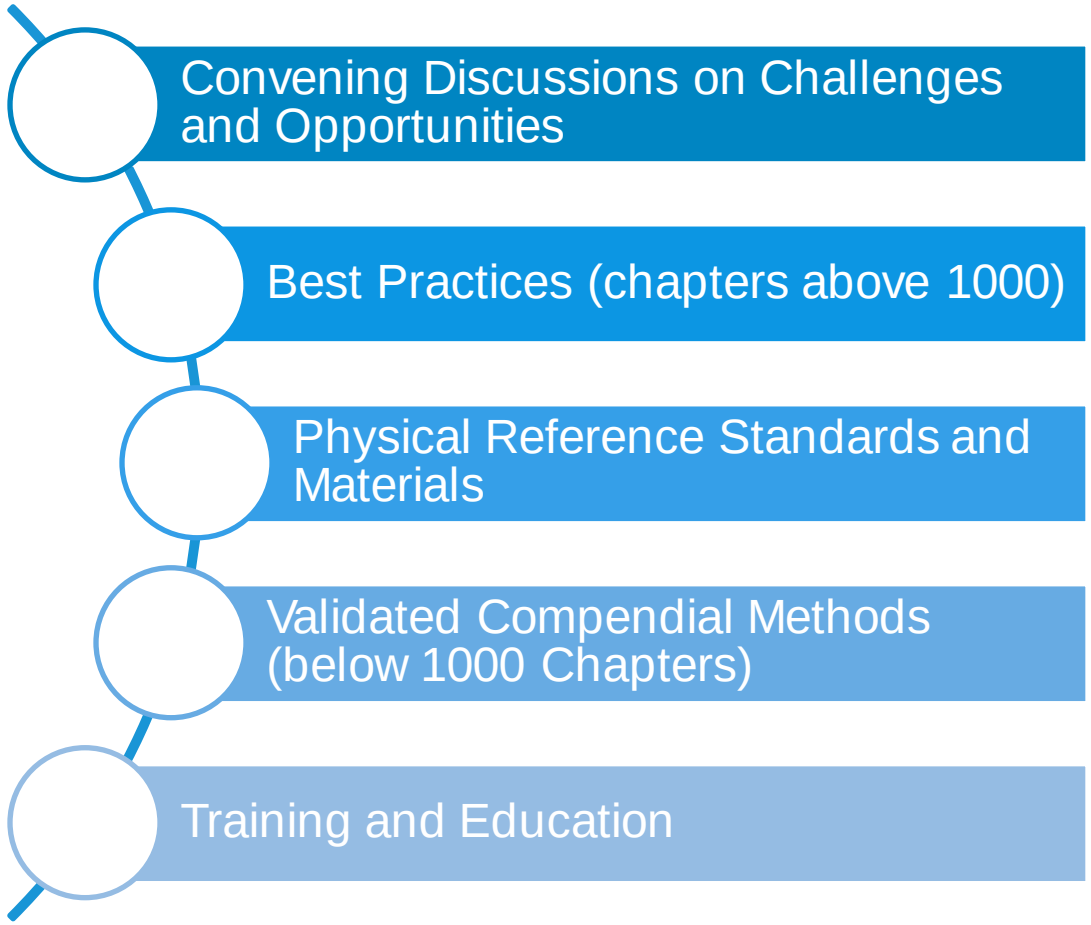
200 usp
The standard of trust

Outline

- The role of USP and standards
- USP standards for gene therapy

Supporting Quality and Consistency of Emerging Modalities

- 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

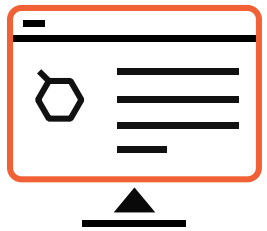
- <111> Design and Analysis of Biological Assays
- <1032> Design and Development of Biological Assays
- <1033> Biological Assay Validation
- <1034> Analysis of Biological Assays

Compendial methods

Assay Name	USP Chapter
Appearance	<790>
Color	<631>
Clarity	<1>
pH	<791>
Osmolality	<785>

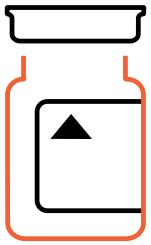
Assay Name	USP Chapter
Particulates	<788>
Bioburden	<61>
Mycoplasma	<63>
Endotoxin	<85>
Sterility	<71>

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* ***NEW***
- *<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
- *<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*



Reference Standards

- CD34+ Enumeration System Suitability (freeze-dried cells)
- Fetal Bovine Serum
- Albumin (bovine and recombinant human)
- Trypsin (bovine and recombinant porcine)
- Collagenase I and collagenase II

USP Chapters Supporting Manufacturing and Quality Control of Gene Therapies

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

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

<1047> *Gene Therapy Products*

(under revision)

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

Chapter for Plasmid DNA Best Practices

- 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

⟨1040⟩ Quality Considerations of Plasmid DNA as a Starting Material for Cell and Gene Therapies

Webinar: https://www.regmednet.com/webinars/quality-considerations-for-plasmid-dna-as-a-starting-material-for-cell-and-gene-therapies/

CHAPTER OUTLINE

Manufacturing Considerations
- Master Cell Bank
- Facility Design

Quality Management
- Phase Appropriate Quality Systems and Facilities

DNA Starting Material Quality
- Quality Attributes
- Stability Testing
- Performance Testing
- Plasmid to Plasmid Cross-Contamination
- Receipt Testing
- General Acceptance Criteria and Manufacturing Considerations

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**

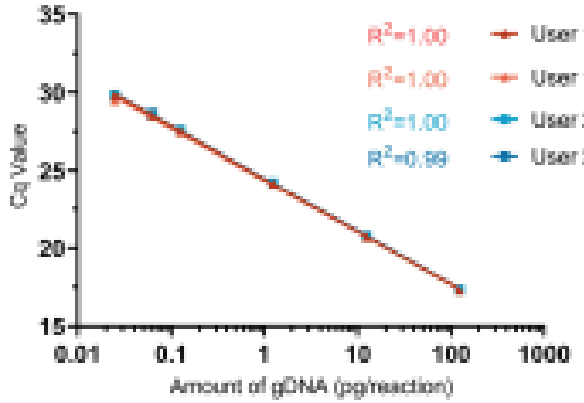
Lentivirus for Gene Therapy Chapter Outline
(as of February 2024)

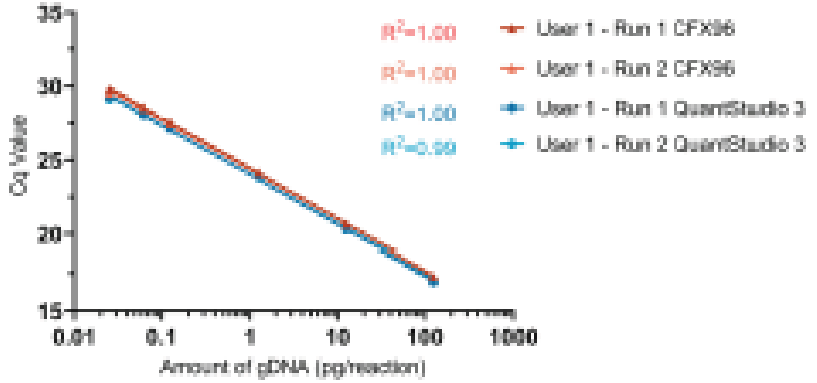
- **Construct Design**
- **Critical Raw Materials**
- **Starting Materials**
- **Production**
- **Characterization and Release Testing**
- **Formulation**
- **Stability**
- **Comparability**

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



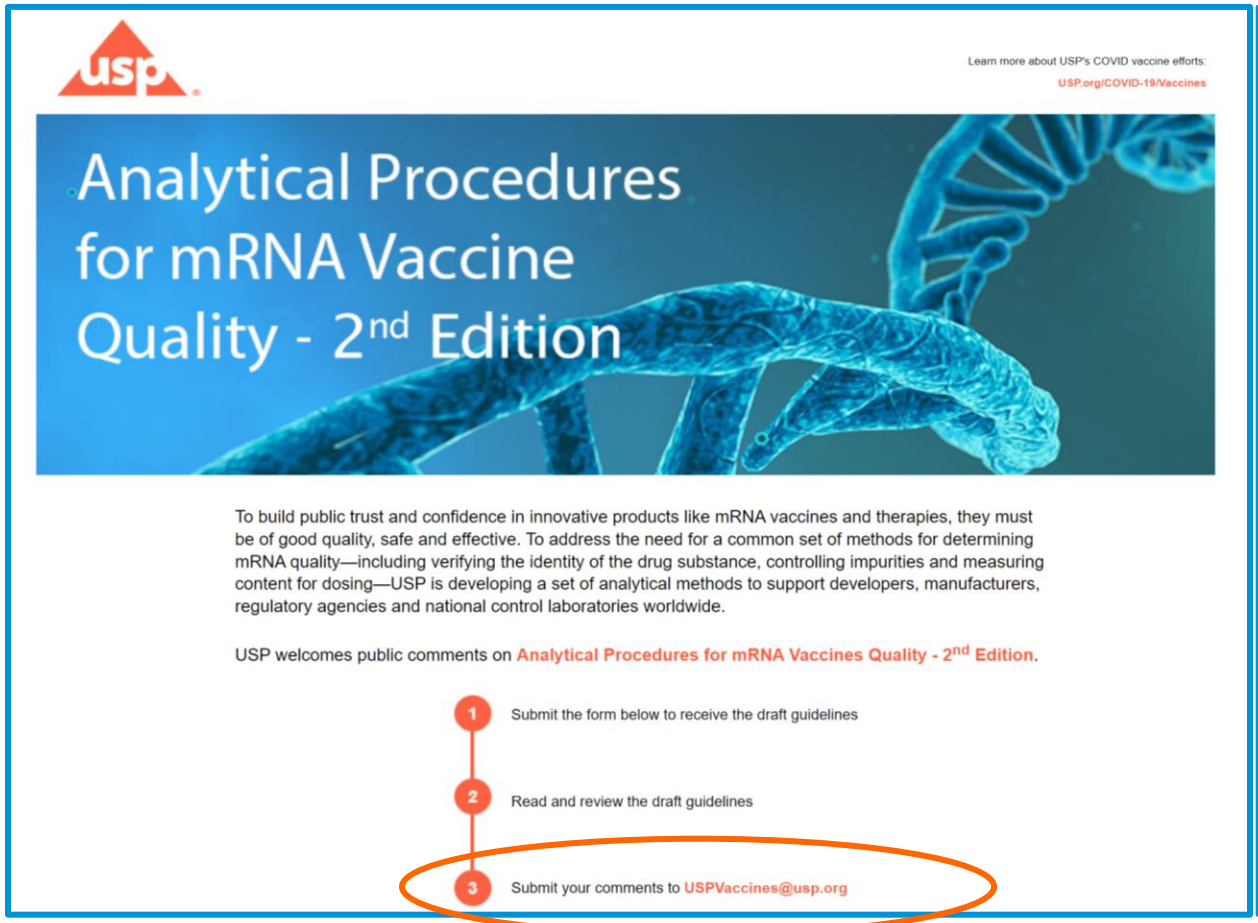


Physical Reference Materials in Development

- 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

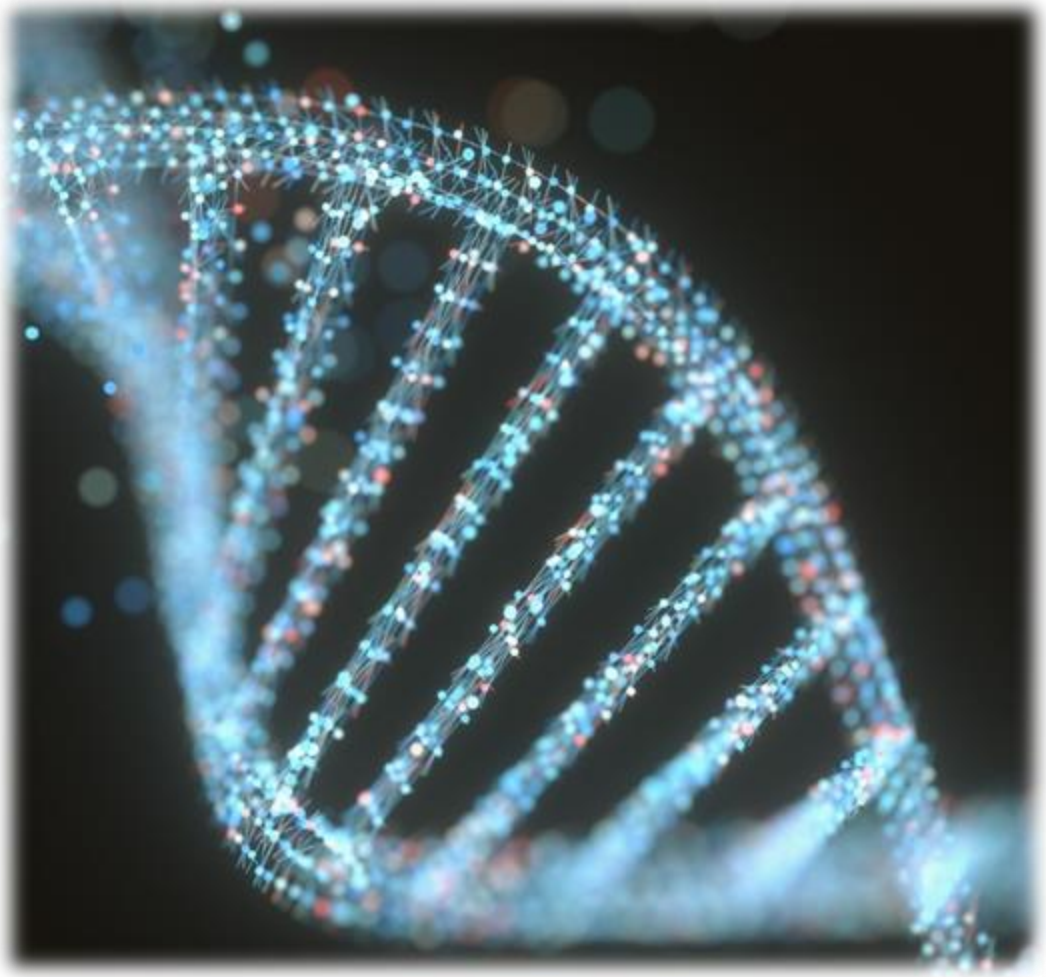


Available Online at: www.usp.org/mrna-quality

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