US Pharmacopeia Standards for Cell and Gene Therapy

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Background

US Pharmacopeia (USP) is a non-profit standards development organization with a 200 year history of providing standards to ensure the quality and safety of pharmaceutical products. USP is committed to working with regulators and developers of novel products to solve problems that can be addressed by standardization. Potential standards can be documentary, such as best practices and standardized methods, as well as physical reference materials for distribution to investigators.

Challenges:

Novel technologies like cell and gene therapies present several problems that are amenable to standardization approaches

- Complex and diverse products and production processes as compared to traditional biologics
- Lack of harmonization in methods usage
- Raw/starting materials that are not cGMP grade
- Fast moving environment
- Lack of consensus for dose-determining assays

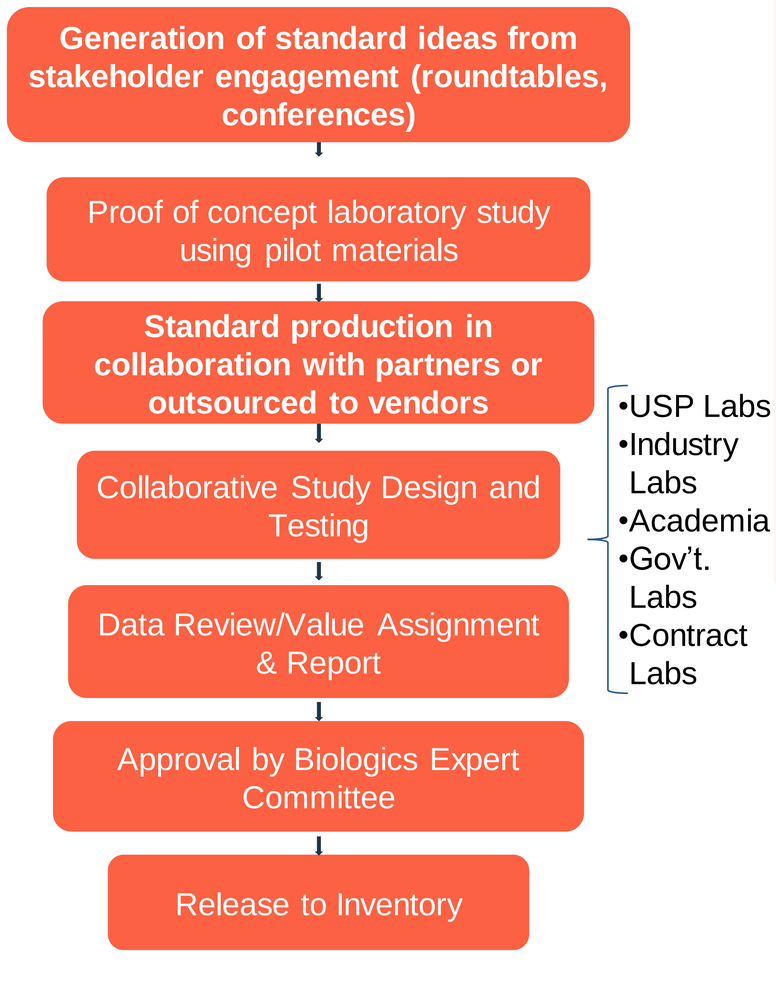
Potential solutions

- Documentary standards to harmonize best practices for:
  - Methods, release of raw materials, and use of standards
- Physical standards
  - Calibration of assay methods across industry
  - System suitability to monitor assay performance

New Paradigm for Performance Standard Development

- Standards will be voluntary but may be recommended for use if adopted industry-wide
- Standards will not be product specific but will cover broad classes of products or materials
  - Will require infrastructure for production and release of diverse materials, internally or by contract

New Standards Development



Existing Cell and Gene Therapy Standards

General Chapters providing "best practices" guidance:

- **USP Chapter <1046> Cellular and Tissue-based Products**
  - Covers Quality Systems, qualification of source materials and components, manufacturing, technology transfer, and analytical methods. Also provides guidance for clinical site preparation and administration of products along with guidance on stability, storage, shipping, and labeling of products.
- **USP <1047> Gene Therapy Products**
  - Guidance for development of gene therapy products, including vector design, characterization of cell and virus banks, manufacturing, purification and formulation. Best practices for analytical method development including in-process and release testing, setting specifications and validation. Also provides guidance for clinical site preparation and administration of products along with guidance on stability, storage, shipping, and labeling of products.
- **USP <1043> Ancillary Materials for Cell, Gene and Tissue-Engineered Products**
  - This chapter covers selection, characterization, vendor qualification, and QA/QC for ancillary materials used to produce cell and gene therapies. Details are provided for a tiered system of risk classification incorporating information about the material, the degree of characterization, and the point of use in the process. The chapter also covers suitability for use testing and ancillary material residual level assessment and removal.
  - Associated physical standards are available from USP for FBS and IL-4

Other Relevant Chapters

- **<127> Flow Cytometric Enumeration of CD34+ Cells**
- **<1024> Bovine serum, <90> FBS Quality Attributes**
- **<89> Enzymes used as ancillary materials**
- **<92> Cytokines and Growth Factors Quality Attributes**

Reference Standards

- **CD34+ Cell Enumeration System Suitability (1.24 x 10^4 CD34+ Cells)**

Current Priorities and Projects

mRNA Standards

- Standard for T7 RNA polymerase activity
  - Could be in "kit" with NTPs, template
  - Template choice (length, composition) up for discussion
- mRNA product in a vial at a defined concentration (1mg/mL) to standardize dose determining assays
- mRNA size standards across a range, e.g. 500, 1000, 2000, 3000, 5000, 7500, 1000, 12500, and 15000 nucleotides

AAV Gene Therapy Standards

- Round robin study of existing AAV2/AAV8 standards using modern and/or optimized methods
  - Use new technologies like droplet digital PCR in addition to qPCR
  - Standardize sample handling and prep, pipetting practices
  - Provide plasmid standards along with samples and methods
- Best practices for dose determining assays
- Plasmid DNA standards with multiple PCR targets
  - Used to calibrate assays across platforms, laboratories, and products

Lentiviral Vector Copy Number (VCN) Standard

- Genomic DNA from cells containing defined numbers of lentiviral sequences insertions
  - Used to calibrate VCN assays as well as processes for transduction

Get Involved

- Apply to join USP's new expert committee for Cell and Gene Therapies – applications for accepted up through May of 2020: https://callforcandidates.usp.org/node
- For questions contact Jim Richardson: jim.richardson@usp.org
- For additional information, attend presentation by Fouad Atouf, USP's VP Global Biologics, April 30, 8 am.