USP Workshop on Gene Therapy Chemistry, Manufacturing, and Controls: Regulations, Standards, and Quality
Executive Summary

Overview

Rockville, MD — The United States Pharmacopeial Convention (USP) held a two-day workshop on February 18–19, 2020. The workshop focused on quality considerations in support of gene therapies. The goal of this workshop was to bring together diverse stakeholders—including regulators, gene therapy developers, and vendors—to present and discuss recent advances in and regulatory expectations for gene therapies. By engaging with diverse stakeholders, USP aims to identify tools and solutions that may facilitate gene therapy development, thereby accelerating the delivery of these important therapies to patients. The venue also provided an opportunity for attendees to better understand USP's existing and forthcoming gene therapy standards.

The workshop was divided into four sessions. After each session, attendees had the opportunity to engage with presenters in a panel discussion. Examples of important points are highlighted in the summary below.

Session I: Regulatory and Raw Material Considerations

Attendees heard from Angela Whatley, Regulatory Scientist at FDA's CBER, who summarized important aspects of raw material selection, control, and qualification. She emphasized the importance of implementing a risk-based approach to assure raw material quality and product safety. Sponsors were urged to select the highest quality raw materials available, conduct vendor qualifications, and develop quality agreements to ensure that all materials are suitable for their intended use. FDA provides opportunities to manufacturers for early discussions on raw material qualification and testing strategies. Ultimately, manufacturers are responsible for demonstrating the quality of all raw materials and justifying their use. Heath Coates from Parexel covered regulatory considerations for gene therapies, including phase appropriate compliance, raw materials, management of CDMOs, and examples of 483 issues. Finally, James Brown of Aldevron discussed considerations for the manufacture and testing of materials such as plasmid DNA and gene editing enzymes.

Key Takeaways from the Panel Discussion

It is important to begin raw material selection with a risk assessment to identify which materials are critical for the manufacturing process and identify those that pose the greatest risk to safety and efficacy. There is also a need to harmonize the terminology used for raw materials (e.g. "starting" or "critical") in gene therapy as well as the value of different quality grades used by vendors that may or may not reflect suitability for a particular purpose.

Session II: Analytical and Control Strategies

Session II included several talks on the development of potency assays for adeno-associated virus (AAV)-based gene therapy products. Marina Feschenko, Director of Analytical Development at Biogen, presented Biogen's approach for exploring stability-indicating properties and potency assays for two different gene therapy programs. Attendees also heard from Lauren Drouin, Associate Director of Analytical Development at LogicBio, who presented on a qualitative potency assay that was developed to assess mRNA expression and determine relative potency. Additionally, Eric Yearley of BridgeBio discussed

phase appropriate analytical control strategies using case studies that included a process impurity and an in-vitro potency assay. Richard Snyder from ThermoFisher detailed virus manufacturing and control strategies appropriate for production of viral vectors. Finally, Frank Zhang from GSK discussed the unique challenges of developing control strategies for mRNA vaccines.

Key Takeaways from the Panel Discussion

Attendees discussed the difficulty in developing product-specific gene therapy standards. Standardization of polymerase chain reaction (PCR) methods could help reduce variability across laboratories during collaborative testing of reference standards. It is important to distinguish the stability of a virus from the capabilities of a stability-indicating assay and if product stability is really reflected in some of the forced degradation study designs that have been proposed.

Session III: Novel Approaches for Characterization

Six speakers representing both manufacturers and instrument vendors presented on a variety of novel approaches for characterization, including charge detection mass spectrometry (CD-MS), next-generation sequencing (NGS), and size-exclusion chromatography–multi-angle light scattering (SEC-MALS). The methodologies presented could be used for a variety of applications such as characterizing AAV capsids and encapsidated recombinant AAV genomes, resolving empty and full virus particles and partial genome packaging and identifying impurities.

Key Takeaways from the Panel Discussion

Attendees identified AAV capsids (full and empty) and system suitability standards as tools needed for the development of orthogonal analytical methods for AAV vectors.

Session IV: Standards to Facilitate Gene Therapy Product Development and Quality

In Session IV, attendees heard from Catherine Zander, Technical Program Manager at the Standards Coordinating Body (SCB), and Judith Arcidiacono, Regulatory Scientist at CBER, on the importance of collaboration across stakeholder groups and the value of establishing international partnerships and global harmonization. Yuan Zhao, Principal Scientist and Head of Gene Therapy at NIBSC, provided an overview on the international collaboration that led to the development of the first WHO International Standard for gene therapy.

Jim Richardson, USP's Senior Science and Standards Liaison in Science–Global Biologics, reviewed the need for gene therapy standards, summarized USP's existing standards and outlined USP's standards in development.

Extended Panel Discussion on Standards to Support Gene Therapy

Following the presentations, USP Biologic's Senior Scientific Fellow, Maura Kibbey, facilitated an extended discussion on standards to support gene therapy. Attendees identified the following key standardization areas:

- Developing broadly applicable standards and specifications to support the quality of raw materials
- Creating additional awareness and education around the existing standards applicable to gene therapy

- Implementing a standardized protocol, including the tests and procedures associated with materials, in order to have higher confidence in value assignments
- Facilitating global collaboration among organizations that develop standards, coordinating bodies, industry, and regulators

What's Next?

Collaborating with USP on Standards Development
USP is forming an Expert Panel dedicated to developing standards for plasmid DNA used in manufacturing of advanced therapies. The Expert Panel will focus on establishing best practices and considerations for sourcing, manufacturing, and testing plasmid DNA. The Expert Panel will also focus on analytical tools for detecting cross contamination.

During our 2020–2025 cycle, USP will form a new Expert Committee, Biologics Monographs 5–Advanced Therapies, that will focus on standards to support cell, gene, and tissue-based therapies. To find out more about volunteering to serve on a USP Expert Committee or Panel, please contact USPBiologics@usp.org or visit USP's Call for Candidates.

USP is committed to working with stakeholders to streamline and expedite the development and delivery of safe and effective GT. USP will offer a fellowship for standards development, providing financial assistance for up to two years. Stakeholders who have ideas for GT standards or are interested in a USP fellowship should reach out to jim.richardson@usp.org

Looking Ahead
On October 20–21, 2020, USP Biologics will host a Workshop on Raw Materials for Manufacturing of Biologics: Best Practices and Quality Standards. Check USP's workshop page for more information, including a Call for Speaker Abstracts.