USP's Global Biologics Summit: Virtual Edition-Executive Summary

On June 11th, 2020, USP assembled a panel of subject matter experts from various backgrounds for the first USP Global Biologics Summit. The panel included participants from industry, academia, government and other global organizations. Participants met to discuss the challenges facing the development and manufacturing of biologics and how to foster alliances to ensure the global availability of these drugs. The goal of this first in a series of events was to identify specific topics and opportunities for collaboration among participants for future roundtables and workshops. After a robust discussion, the panelists agreed on several important issues that will require leadership from key stakeholders, including standards-setting organizations, to ensure the widespread adoption and availability of biological medicines.

There was a consensus among the panelists that both providers and patients have high expectations for the quality of every dose of medication prescribed. The industry has a global responsibility not only to meet that high standard, but to exceed it in every market it serves. The realities of drug manufacturing, however, require acceptance of some variability in drug specification acceptance criteria as long as they remain in a range that is both safe and effective. Determining this range can be difficult in general, but especially for biologics. Because biologics are large molecules that result from complex manufacturing processes, they are inherently more variable. Also, the increase in complexity makes it more difficult to determine both the type and number of critical quality attributes (CQAs) that are necessary to ensure a product's quality. Defining CQAs depends on being able to link structural attributes to clinical performance. Bioassays can play a role in this linkage in the context of a risk assessment. The acceptable range of attributes that matter to patients is also important, and this may be complicated by the analytical method variability, which for biological methods is often higher than corresponding small molecule methods. A lack of understanding about which CQAs are clinically relevant for a biologically-derived drug creates a significant burden for manufacturers who must replicate these complicated processes and variable analytical methods when developing a biosimilar.

The debate around the type and number of CQAs for biologics determines what investments should be made to assure quality. In turn, the amount of investments impact costs that control both access and affordability. The panelists agreed that it is essential to understand which CQAs matter most to the patient, much earlier during biologic drug development. Currently, risk assessments, that consider prior knowledge, bioassays and available clinical data, are generated by each sponsor. *In vitro* and *in vivo* assays to support the identification of CQAs and biological characterization could speed development. In addition to drug product attributes evaluated based on potential clinical impact and patient outcomes, non-clinical methods can support this assessment. The consensus view is that the use of analytics to ensure quality should add value to patient outcomes and not necessarily be an accumulation of what is possible with available resources. Defining a set of shared CQAs for a class of products would be of value and reduce duplicative development and assessment efforts.

Once the product's quality attributes are defined, a wide variety of analytical tools can be used to assess quality of these products. In the case of biologics for which a potential biosimilar can be produced, the choice of the analytical methods to demonstrate a molecule is highly similar to the originator drug is one of the most critical elements for successful development. This approach can be expensive and time-consuming and may create a barrier to innovation and access because of the costs and constraints of conventional analytical

technologies. Validated analytical methods, and well-characterized performance standards that can be used in qualifying and validating assays for biological products, would be of high value to both developers and regulators.

For some product attributes, especially across a class of products, method standards may be of value in evaluating testing lab capabilities and understanding inherent method variability. Method standards would also provide substantial value to testing laboratories that are less experienced in the analysis of well-characterized biological products by providing certified materials for proficiency training on current technologies. They could also be highly useful in developing innovative new analytical methods for evaluating product attributes by demonstrating the technology's performance using a known reference material. Ideally, such method performance standards would be globally developed and harmonized to support emerging entities with biological drug development and assessment.

Developing the right standards for biological products is further complicated by the multiparameter approach necessary to ensure process control and product quality. For biologically-derived drugs, *the process is the product*, because even slight changes in the production process can impact the quality of the product. The safety of biological products also depends upon stringent adherence to GMP quality and compliance requirements for biologic production facilities, e.g., aseptic environmental controls. There are many dimensions of process control and product quality that would not be resolved by reducing quality to a final product testing strategy or a simple checkbox set of expectations that would apply to every sponsor. The challenge may differ based on a company's experience and prior knowledge with similar product types, and their GMP compliance status.

Furthermore, the path to quality taken by developers can be made unnecessarily burdensome by challenges unique to their operations. For established biologic manufacturers, creating a culture of quality is often influenced by the risk aversion inherent in regulatory approaches, or by a varied set of requirements from global health authorities. Some sponsors fail to use all of the available quality tools, like quality target product profiles, as guiding documents during drug development to align themselves with quality issues. Finally, some of the new entrants into the industry have no established prior-knowledge base for biological products or lack a culture of quality based on the current expectations for GMP compliance. The diverse needs of all these companies affect their approach to quality; however, their strategies should all be aligned to focus on patient needs and the application of the principles of Quality Risk Management.

The panelists recommended greater collaboration across the entire biopharmaceutical ecosystem to identify biological product CQAs and to address a lack of understanding of how they affect clinical outcomes. These issues are universal barriers across the industry that could be addressed by the partnerships mediated by consortia. Such partnerships could help create a common language around the work needed to correlate assays with clinical outcomes to determine the essential attributes. Collaboration can also help smaller organizations avoid some of the more common quality mistakes that are made during development. Consortia would also provide a trusted pathway for sharing information, which remains a challenge even though most companies are not competing on their manufacturing platforms.

Other forward-looking solutions include:

- Training and education programs for students or emerging companies entering the biologics development field can be used to promote standards and methods to align manufacturers around shared quality management systems and quality elements. Also, a short primer on the essential elements of quality, e.g., cGMP principles and aseptic processing, could help newer companies understand the unmet need in terms of the in-process controls for quality manufacturing of biologics and how to avoid common pitfalls. Some panelists even suggested the creation of certification schemes for individuals on key quality elements in biologics manufacturing and testing.

- Methodological guidance, combined with physical product reference standards, can be a powerful tool. However, because the identification and development of standards for biologics are in flux, it may be helpful to develop a series of non-compendial product reference standards, with the exploration of new business models, and the understanding that not all of them will be universally adopted. Any standard reference materials that become widely used by the industry can serve as a template on which to build the next generation of standards, whatever form they take.

- Numerous types of biomolecular and bioassay method performance standards, which are very well characterized in orthogonal methodologies, would be highly useful to calibrate analytical methods and potency assays, train laboratory personnel, and evaluate new more sensitive, more specific analytical technologies that could provide critical data sets for correlating product attributes to clinical outcomes.

- There are gaps in both communication and trust between industry and end-users of biosimilar medications that must be overcome. The lack of provider and patient confidence, based on concern over the quality and consistency of biosimilars, threatens their adoption in medical practice. The industry must be able to explain what differences exist between originator drugs and biosimilars, and when they may or may not matter to the safety and efficacy of the products. These assurances must be followed-up with appropriate pharmacovigilance over the entire life-cycle of a biologic product. The experiences of the panelists demonstrate that biosimilars are adopted at very high rates once providers and patients trust their quality.

- There are growing concerns over the security and integrity of global supply chains. Many of the raw materials and reagents required for production, testing, and distribution of biologics are sourced among international manufacturers. Developing and harmonizing global quality standards could provide useful tools for supporting surveillance testing efforts against counterfeiting and adulteration.

Conclusion

This first in a planned series of discussions on quality of biologics was meant to lay the foundation for continuing discussions with this group and beyond. The group supported future efforts to engage multiple stakeholders to discuss how to streamline technology innovations and advancements, and to share experiences around creating a culture focused on quality. Roundtables and workshops would be valuable to bring different stakeholders together so that they can learn from each other. Open discussions, sharing of information, training programs,

and guidance documents are all required to create an ecosystem focused on quality within the industry. In turn, a healthy ecosystem will foster the development of a variety of products, physical standards and method standards that don't depend on one particular path to enforceability.

To accomplish this, manufacturers, regulators, pharmacopeias, providers, and patients must rely on each other to build a community that creates tools that ensure safety and efficacy without wasted effort and resources. Creating a culture focused on product quality in an organization requires focused and sustained effort. Compliance can be an initial driver for establishing quality, but a sustainable culture of quality must go beyond compliance. A culture is defined by its shared norms; therefore, a culture of quality needs to be about shared ideas of what constitutes the necessary and sufficient measures of quality. Convening key stakeholders in biological product development is important for creating a culture of quality. Facilitated discussions allow participants to align regulatory expectations so that manufacturers can deploy innovations in quality within many countries at the same time. It is expected that fostering discussion among a diverse group of subject matter experts can lead to a consensus that will be beneficial to the industry, accelerate innovation, and enhance access to high-quality biologic drugs worldwide.

Summit Panelists	
Murray Aitkin	IQVIA
Sameer Awsare	Permanente Medicine
Naren Chirmule	SymphonyTech Biologics
Emer Cooke	World Health Organization (WHO)
Elizabeth Jex	Federal Trade Commission (FTC)
Steven Kozlowski	Food and Drug Administration (FDA)
Kelvin Lee	University of Delaware/ National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL)
Thomas Perrone	Lonza Biologics, Inc.
Nadine Ritter	Global Biotech Experts, LLC
Christian Schneider	National Institute for Biological Standards and Control (NIBSC)
Michael Tarlov	National Institute of Standards and Technology (NIST)
Marta Wosinska	Duke Margolis Center for Health Policy
Gillian Woollett	Avalere Health
Sarah Yim	Food and Drug Administration (FDA)
Fouad Atouf	United States Pharmacopeia (USP)

- Panelists appeared in their individual capacity as subject matter experts