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Bioprocessing in a Post-COVID-19 World

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COVID-19 has compressed bioprocessing timelines, leaving no room for uncertainty in the characterization of raw materials and contaminants

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Bioprocessing has taken quite a remarkable journey over the last 30 years. In recent years, the demand for powerful and specific biopharmaceuticals has continued to increase, driven by monoclonal antibodies (mAbs), where the market can be expected to approach $140 billion by 2024.[1] Rising demand for biopharmaceuticals also reflects how biologics are expanding into new therapeutic areas, such as neurodegenerative and cardiovascular diseases. Finally, rising demand is being sustained by better geographic reach, label extensions, and the emergence of biosimilars.

Developments in molecular biology and clinical insight have also supported emerging modalities, such as cell and gene therapies, nucleic acid–based medicines, and new workflows in engineered vaccines. As part of this next frontier of medicine, cell and gene therapies will continue to provide novel ways to address chronic conditions and diseases.

The emergence of COVID-19, a pandemic unleashed by the SARS-CoV-2 virus, caused a rapid and unexpected evolution in the industry over the last year. As the industry has moved swiftly from research to production of new vaccines, the importance of system and raw material characterization has been magnified.

Accelerated timelines leave no room for uncertainty or unnecessary challenges related to documentation, stability, critical impurities, and other factors related to raw materials, quality, and consistency. No matter how much emphasis is placed on speed, it remains understood that no compromises to patient safety can be tolerated.

The past is prologue

We have become accustomed to well-characterized systems in mAb manufacturing, with baseline data supporting improvements in areas including process intensification, continuous manufacturing, single-use system adoption, failure mode and effects analysis, system digital twins, and modeling of release criteria. Quality-by-design approaches to manufacturing are based on the premise that product quality can be designed into product specifications. Clearly, this implies that the product developer has a comprehensive understanding of the variables affecting ultimate product quality.

For complex biological products manufactured in cell-based systems, that is not always the case. We continue to acknowledge the old adage that "the process is the product," and we still expect that every process should deliver product of the required safety and efficacy. But with cell-based systems, we face additional challenges. There is a lot that remains unknown about biological processes for cell and gene therapies that researchers will continue to uncover.

Understanding the multiple sources of process-related impurities, product-related im-

purities, and contamination is a significant enterprise, and the relationship between process parameters and quality attributes is not always well appreciated or understood during manufacturing scale-up and development. In the absence of a comprehensive understanding, it is critically important to have appropriate risk assessments, along with more robust data and analytics on raw materials and manufacturing, to yield future system improvements.

In some cases, the manufacturing process can also affect a product attribute and have clinical significance. Differences in trace metal concentrations in mAb-producing Chinese hamster ovary (CHO)fermentations were found to drive variability in protein glycosylation patterns, emphasizing the advantage of moving to better characterized, chemically defined media.[2] For autologous chimeric antigen receptor T-cell therapy, the $n = 1$ nature of the product makes it difficult to identify critical system variability above that already contributed by the patient. Even in allogeneic and bulk applications, challenges remain in these novel workflows.

The COVID-19 step change

The race to scale-up and deploy an effective, safe COVID-19 vaccine not only requires addressing vaccine manufacturing practices and challenges, it also demands moving at a pace not previously imagined. In such a situation, full system and raw material characterization becomes even more pivotal.

In addition to traditional attenuated virus COVID-19 vaccine initiatives, four novel modalities are progressing at unprecedented speed to the market.

GlaxoSmithKline (GSK)/Sanofi and Novavax, among others, are progressing a recombinant protein approach. This proven technology has long been used for commercial vaccines, but none has ever needed to be developed at this pace. It will be important to understand both the short- and long-term safety signals of these vaccines, given their expected uptake.

AstraZeneca/Oxford and Johnson & Johnson are some of the organizations exploring viral vector platforms for COVID-19 vaccine generation. Viral vector platforms offer an elegant means of introducing an antigenic signal for the development of an immune response, but the manufacturing systems are neither efficient nor fully understood at this time. These technologies have been successfully used for emerging gene therapy applications, but only two vaccines have been approved in this format.[3]

Clinical differences in vector performance have been observed from different manufacturing platforms.[4] Post-translational modification variability (glycosylation, acetylation, phosphorylation) and differences in genomic methylation are apparent from different manufacturing methods. In addition, differences in host cell protein post-translational modifications have also been observed. The effect of any such differences on efficacy or safety have yet to be quantified, but there is no doubt that there are a lot of opportunities to improve system characterization.

In addition to choices in viral vector manufacturing platforms, some raw materials central to these workflows have previously not been manufactured at commercial scale or to GMP specifications. As volumes scale and indications become more numerous, biopharmaceutical companies will need to work with their suppliers to validate and audit materials, and to ramp production schedules to meet this new demand.

Perhaps the most novel COVID-19 vaccine modalities—and the first to demonstrate efficacy[5]—are those based on nucleic acids. The mRNA process is unlike other traditional vaccine manufacturing work-

Before vials containing COVID-19 vaccine can move down the production line, multiple production issues must be addressed, including the elimination of process-related impurities, product-related impurities, and contamination. Andriy Onufriyenko/Getty Images

flows. No cellular systems are involved. Instead, enzyme-mediated transcription is followed by encapsulation by lipid nanoparticles. Plasmid DNA constructs are being developed by **Inovio** and others, and mRNA vaccine candidates are rapidly progressing with approvals: Moderna and Pfizer/BioNTech were both granted emergency use authorization by the United States FDA and approval for use in Europe by the European Commission.[6]

This novel approach necessitates a very different way of thinking about both the process and the input raw materials. For example, when CHO cells are used to produce mAbs, there is a keen appreciation of the necessity of understanding the impact of extractables and leachables on the manufacturing process, particularly in upstream operations. However, emerging workflows in nucleic acid processes use low-pH solutions and organic solvents. At this point, we may not fully understand the effects of these solutions and solvents on chemical compatibility and extractable and leachable profiles from, for example, single-use assemblies containing silicone.

Ramping up to nine billion doses

Let us consider the volume and scale required. The Global Vaccine Market Report that was issued by the World Health Organization in December 2019 estimated that the annual demand for vaccines in 2018 had reached three and a half billion doses.[7] With the emergence of COVID-19, the industry is expecting to produce approximately nine billion doses across different vaccine modalities by the end of 2021.[8] This sizable requirement further underscores the scale of the challenge ahead.

We will quickly see that mRNA and recombinant protein subunit vaccine workflows will require new and novel raw materials in manufacturing and formulation steps. More specifically, lipid nanoparticle and adjuvant constituents often include several novel functional lipids, sterols, and similar compounds (such as squalene and cholesterol). Such compounds were historically used in personal care and in lab-scale or preclinical studies as nonregulated process reagents; step-change improvements in scale, documentation, and characterization of potential impurities will now be required to use them in these new applications.

Traditional animal-derived sources will not be acceptable, and plant-derived sources that can meet consistent quality and impurity profiles (and qualify for use as excipients) have limited availability. These challenges are being addressed with plant-derived cholesterol in process scale-up to quickly meet order-of-magnitude demand signals while complying with exacting purity, endotoxin, and bioburden requirements.

Additionally, raw material inputs and single-use components for vaccine production are often shared with mAbs. Operational requirements for mAbs are already significant and time sensitive, with 13% of mAb revenue coming from orphan drug indications and greater than 38% from target oncology treatments.[9] Collectively, the biopharma industry and its suppliers will need to work on innovative solutions for balancing the needs of the production of mAbs and COVID-19 vaccines to meet the needs of all patient populations.

Conclusion

Moving at this highly accelerated pace to develop a vaccine has required all industry stakeholders to work together. Paradigm shift changes in manufacturing and distribution are taking place as we speak to ensure that these molecular and clinical developments have globally meaningful effects—both to address COVID-19 vaccine scale-up and also to balance the production of mAbs and other therapies.

Step-change improvements in scale, documentation, and characterization of potential impurities in novel raw materials will continue to be required. Increased collaboration and prioritization across the industry is driving active reviews across all material suppliers of expansion strategies for key components and technologies. Rapid and transparent sharing of information between all stakeholders will be important to ensure these powerful biological drugs and therapies deliver on their potential. GEN

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