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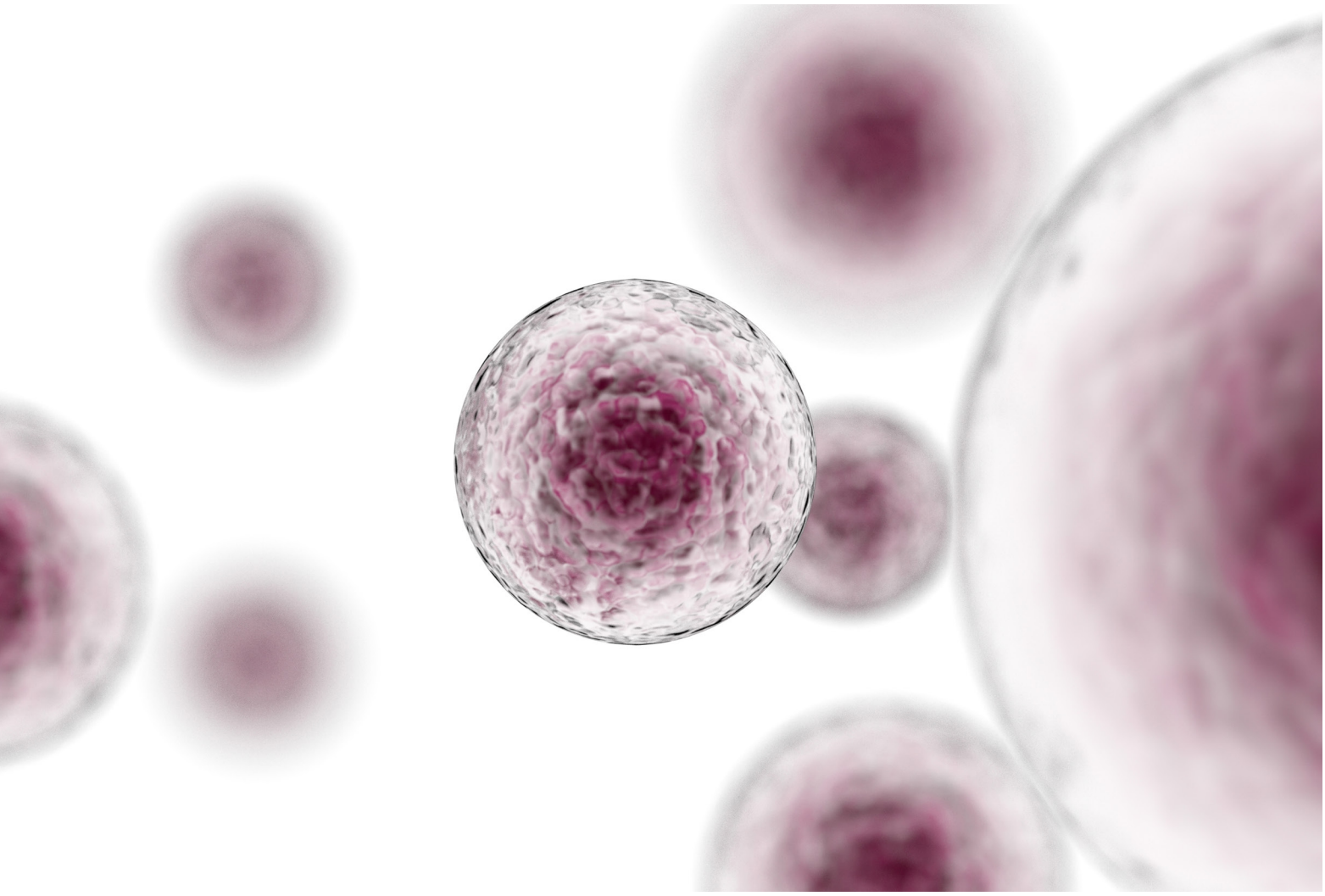

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WHITEPAPER

Understanding the CMC regulatory landscape for cell and gene therapy products

Monica M. Commerford, PhD

Manager, Regulatory Affairs, Viral Vector Services
Thermo Fisher Scientific

Abstract

Cell and gene therapies can dramatically impact patients' lives by providing a cure for a disease rather than a long-term treatment. In addition, many of these products are targeting rare diseases, leading to an increase in molecules following expedited approval pathways. These factors are driving the industry's passion and motivation to gain a better understanding of the evolving regulatory guidelines for cell and gene therapies, in order to bring them to market faster. However, collaboration and communication between the industry and regulators is needed to commercialize these products without sacrificing quality.

Unique attributes of viral vector products

Viral vectors are modified viruses used as tools to deliver genetic material into cells in gene and gene-modified cell therapies to treat a specific disease. Without an intact viral vector, the cargo cannot be transported to the correct tissue and then cross into each of the targeted cells. In the 1980s, the adeno-associated virus (AAV) genome was isolated and cloned. Advancements using viral vectors in the 1990s included the production of recombinant AAV and further improvements in their scalability and purification, which has heralded significant developments in engineering novel AAV capsids that would allow for efficient gene transfer. One example of this is the use of AAV to intravenously deliver a Hemophilia B treatment directly to the liver.

While the manufacture of cell and gene therapies is similar to the manufacture of proteins/monoclonal antibodies (mAbs), the major difference between both is based on the complexity of the manufacture of viral vector. For example, development labs must be designed for viral vector containment and designated as biosafety level 2 (BSL-2), which creates safety and space challenges for decontamination and management of BSL-2 waste.

In addition, viral vector manufacturing relies heavily on single-use technology because it allows for multiple production platforms to be used within a closed system and assists in the overall contamination control strategy for a multiproduct facility. Because of this, the importance of ensuring that the single-use systems are sterile is paramount to the success of the operation and the goal of delivery safe cures to patients. Therefore, there must be processes in place to ensure that the single-use equipment used is verified sterile, such as assessing sterility validation packages in addition to qualifying the manufacturer through routine vendor audits.

Facilities manufacturing products using viral vectors must also have an HVAC system designed using single-pass air that is focused on segregation and prevention of cross-contamination.

Using these single-use technologies is not without its challenges. Many single-use systems are sourced from single suppliers, which makes interchangeability of components difficult. The challenge is to determine the compatibility of the system with the biologic being manufactured using appropriate extractable/leachable studies. Finally, maintaining a closed system during manufacturing for these single-use systems is key to preventing microbial ingress. In fact, the United States Food and Drug Administration (FDA) has issued Inspection Observations (483s), citing manufacturers for failing to recognize that incompatible parts had led to leaking of their single-use systems.Therefore, careful consideration needs to be paid to prevent leaks that are introduced either through incorrect parts use in the manufacturing process or shipping/handling.

More recently, the FDA indicated that it is considering allowing applicants to leverage previously approved manufacturing platforms in biologics license applications through a modified 510(k)-like process. Any modifications are reviewed to ensure they meet FDA efficacy standards and that they do not increase safety risks. The agency is potentially open to this approach for gene therapy products as it will allow sponsors to streamline the development of products, which can also lead to a global and harmonized approach that can accelerate product development. In fact, the PaVe-GT program is an NCATS-led platform vector gene therapy pilot project that seeks to answer whether the efficiency of gene therapy trial startups can be significantly increased using a standard process. Currently, this program is using AAV as a standardized platform—with the same capsid and manufacturing method—to treat four rare diseases. The goal is to develop a manufacturing platform that will save time and resources using a single vector, manufacturing process, and team.

The advantages of single manufacturing platforms include—but are not limited to—streamlining preclinical work, the same manufacturing process can be used, and multiple different diseases can be treated.

The advantages of single manufacturing platforms include—but are not limited to—streamlining preclinical work, the same manufacturing process can be used, and multiple different diseases can be treated. While a single manufacturing platform is being pursued, current challenges for getting cell and gene therapy products to market are compounded by the impetus to develop cures for rare and ultra-rare diseases that have been given a fast track designation to the market.

Another unique feature of the dynamic and fast-paced cell and gene therapy sector is its quality management system (QMS), which has been tailored to the market's specific needs for scalability and speed while also maintaining robustness. As compared to the traditional pathway to commercialization, the cell and gene therapy sector is seeing compression in development from Phase II to Phase III and process validation.

One attribute of the scalable QMS includes a fluid technology transfer process that outlines critical stages and plan for achieving validation, rather than existing as simply a box-checking exercise, which trains staff to work within the scalable environment. The system's ability to navigate the varying approval pathways while ensuring all risk and associated mitigation activities are well documented and approved is critical to a product's success.

Growing clinical and regulatory landscape for advanced therapies

By the end of 2019, over 1,000 clinical trials underway for regenerative medicine/advanced therapies were underway with nearly $10 million raised by companies, globally, that are active in gene and cell therapies and other regenerative medicines[1]. The FDA is also seeing an increase in investigative new drug applications (IND), with Former FDA Commissioner Scott Gottlieb anticipating the approval of 10 to 20 cell and gene therapies a year by 2025[2].

These numbers are an indication of not just the success of these products but also of the FDA's support of their development, as the scale and scope of this rapidly evolving industry requires guidance—both formal and informal. This expected growth from the FDA also correlates with the prediction from MIT that there will be 40 to 60 product launches and more than 500,000 patients treated with these therapies by 2030[3].

Recently, the FDA has published several finalized cell and gene therapy guidance documents to help provide additional information to those companies that need it. They include:

Final FDA guidance issued in 2020[4]

- Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug (IND) Applications
- Testing of retroviral vector-based human gene therapy products for replication competent retrovirus during product manufacture and patient follow-up
- Human gene therapy for retinal disorders
- Human gene therapy for rare diseases
- Long term follow-up administration of human gene therapy products
- Human gene therapy for hemophilia

In addition to these guidances, the FDA has also relied on review pathways and specialized product designations to expedite applications to ensure therapies for these conditions are approved and available to patients as soon as it can be concluded that the benefits of the therapies justify the risks. These programs are outlined in Figure 1:

Priority review (1992)	Accelerated approval (1992 and amended 2012)	Fast track (1997 and amended in 2012)	Breakthrough therapy (2012)	Orphan product designation and/or exclusivity (1983)	Regenerative medicine advanced therapy (2019)
Demonstrates potential to have significant improvement in safety or effectiveness • Short review clock • FDA takes action within 6 months after filing (10-month standard) • FDA notifies applicant within 60 days of BLA submission	Significant improvement in safety or effectiveness • Approval based on surrogate or intermediate clinical endpoints • Shorter review clock • Phase IV confirmatory trials needed	Nonclinical or clinical data demonstrate potential to meet unmet medical need • Frequent communication with FDA • Eligible for accelerated approval, priority review, or rolling review	Clinical evidence indicating substantial improvement over available therapy • All features of Fast track • Guidance on drug development • Organizational commitment • Received by FDA NLT EOP2 meeting	For safe and effective treatment, diagnosis, or prevention of rare diseases (< 200,000 patients) • Tax credit for qualified clinical testing • Exempt from PDUFA • 7 years marketing exclusivity, if approved	Preliminary clinical evidence suggests potential to address a serious unmet medical need • Same features as a BT • Early discussion of potential surrogate or intermediate clinical endpoint

Figure 1: FDA expedited programs

The FDA has also demonstrated a willingness to work with companies that want to better understand these programs and to meet the required milestones. For example, the Center for Biologics Evaluation and Research has started a new meeting pathway program called Initial Targeted Engagement for Regulatory Advice on CBER Products (INTERACT) to engage biologics developers during early stage product development prior to a pre-IND meeting. This does not negate the need for a pre-IND meeting, but it does allow companies to get early guidance on their projects, particularly when science and technology is rapidly advancing and there is a need to get these therapies to patients quickly.

Regulatory and CMC challenges with cell and gene therapy

In the past, CBER and the Center for Drug Evaluation and Research (CDER) have been open about the difficulty they have in keeping up with pharmaceutical innovation, accelerating their assessment timelines while still maintaining quality and patient safety, and also determining how to perform risk-benefit assessments. In recent conferences, CDER has discussed how incomplete chemistry, manufacturing, and controls (CMC) packages can also affect the review of the biologic drug application upon submission as well as lead to more questions from regulators and/or even potential timeline extensions.

From the industry perspective, aligning CMC development timelines—that are often accelerated—with clinical development, managing time, supply, and availability constraints, and providing a full product characterization package with critical CQA understanding has been challenging due to the accelerated pace of development.

However, despite this challenges, increased communication between regulators and industry will only help in bringing these amazing therapies to market faster, and it is imperative that we work together to make that happen.

In the face of these regulatory and CMC challenges, Patheon Viral Vector Services offers the expertise to help their customers face these issues while delivering with innovation and integrity. This includes regulatory services that range from early phase development all the way to late stage development to commercialization and post commercialization. By working with one CDMO throughout the lifecycle of their product, cell and gene therapy manufacturers can have confidence in knowing they have the expertise and capabilities necessary to help bring these products to market faster.

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Monica M. Commerford, PhD

Manager, Regulatory Affairs, Viral Vector Services
Thermo Fisher Scientific

Monica M. Commerford, Ph.D., is currently the Head of Regulatory Affairs, Viral Vector Services at Thermo Fisher Scientific in Cambridge, Mass. She previously worked as a Microbiologist and Consumer Safety Officer in Branch IV in the Division of Microbiology Assessment, Office of Process and Facilities, Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research at the Food and Drug Administration. She is an expert in the microbial control, product quality microbiology, and sterility assurance of Investigational New Drug Applications and Biological License Applications submitted to CDER and performed pre-license inspections of biological product manufacturing facilities. In addition, she has participated in writing policies and a draft guidance document. Dr. Commerford earned her B.S. in Biochemistry and Molecular Biology from Michigan State University and her Ph.D. in Microbiology and Molecular Genetics from Harvard University. In addition to her regulatory experience, she was also a Sallie Rosen Kaplan post-doctoral research fellow in the Laboratory of Molecular Biology at the National Institutes of Health.

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