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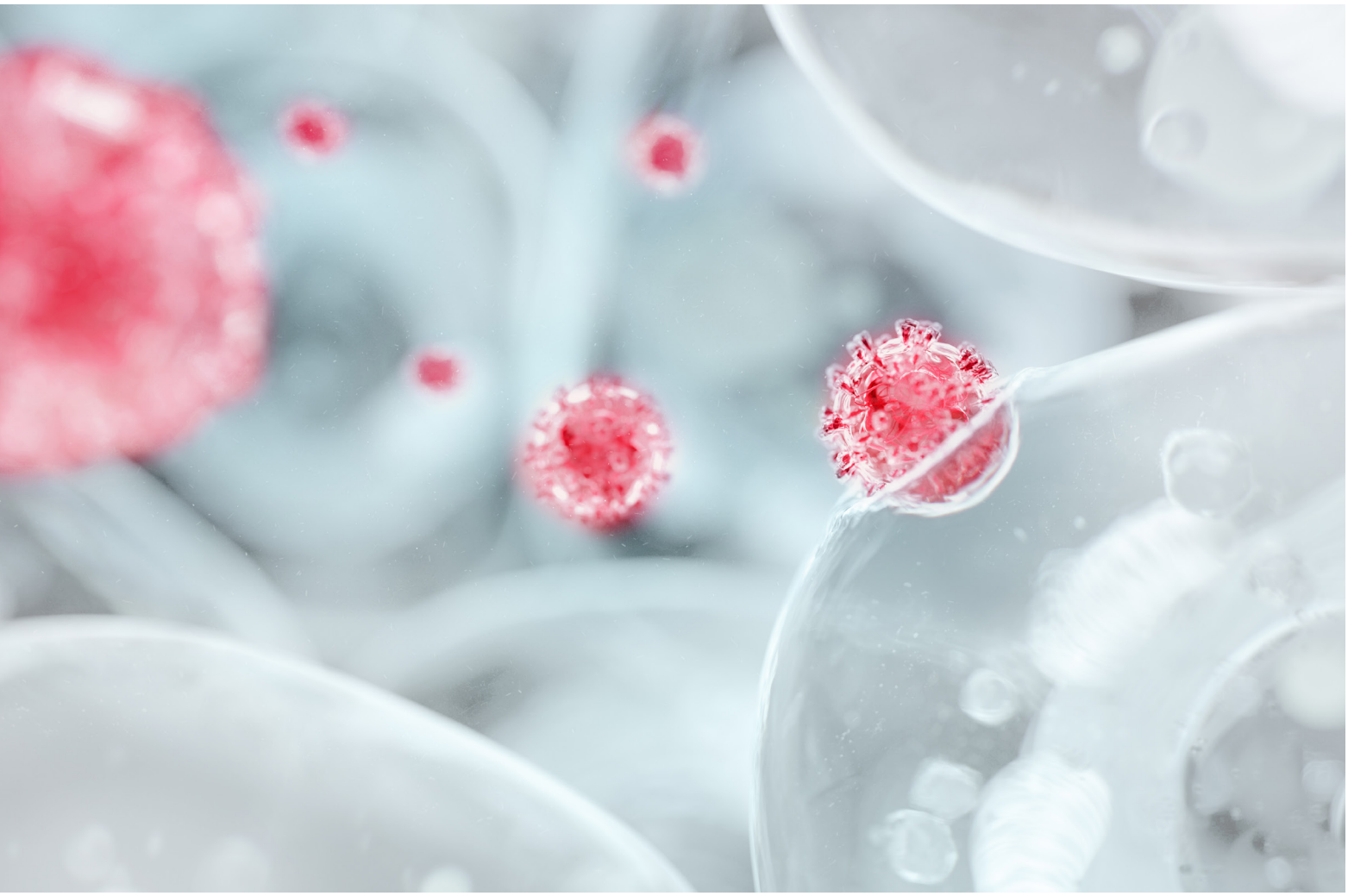

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WHITEPAPER

Addressing the complexity of process validation for cell and gene therapy products

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Abstract

The complexity of cell and gene therapy (CGT) products requires evolution of robust process understanding throughout the development and commercial life cycle. The expectation from health authorities on these products is that scientific and risk-based approaches will be used to define and validate the safe operating ranges for your process by identifying potential sources of variability and understanding what impact these have on product quality. However, validation is not complete once a process performance qualification (PPQ) campaign is done or once a process has been approved for commercial sale. Instead, knowledge continues to evolve throughout the life cycle of a product using the large bodies of data collected during commercial manufacturing.

In the cell and gene therapy space, the FDA and the EMA have published several documents that offer guidance about early stage filings; however, these have provided limited reference to process validation and product commercialization. The expectation — just as it is with biologics — is that the process is the product. However, cell and gene therapy products have unique features that must be considered during process validation.

Unique challenges in CGT products

First and foremost, the complexity and the novelty of CGT products is significant. CGT products can be composed of proteins, nucleic acids, and membranes. Each of these are highly complex, biologically active components, and they are each impactful to the safety and efficacy of those products.

Additionally, there is significant diversity in products and process types with little information about their clinical outcomes and very limited manufacturing histories to leverage for process or product understanding

And finally, the tools, systems, processes, and materials in CGT products are still in a nascent state. To bridge the divide between the emergent products of today and the future, experience in a wide array of products and processes will be beneficial in understanding these complex therapies.

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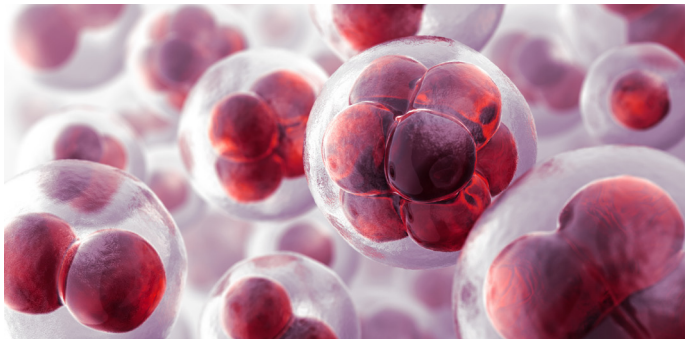
Bringing CGT products to market today requires a very aggressive approach. Most of them are under accelerated timelines, whether through Regenerative Medicine Advanced Therapy (RMAT) or similar designations, and they typically have a very limited development history.

Often, these processes have been developed in academic labs, transferred into an industrial setting, and then moved very rapidly into a commercialization space. CGT products typically have a relatively small clinical trial background and a limited number of manufacturing campaigns behind them.

Most importantly, because of the development speed, the commercial process is rarely locked by Phase III, leading to development work being done in parallel with characterization and validation work.

There is also a limited suite of analytical tools that are reliably used today. And lastly, the understanding of the structure-function relationships or how the biophysical characterization of these products is connected to the clinical efficacy and safety is not well understood.



Considering these factors, the question that comes back to the innovator companies attempting to understand these processes and products is—which of these quality attributes are critical, and which ones can contribute from a characterization perspective to these molecules?

Translate expectations into action

With these factors about CGT products in mind, how then should a company plan a commercial product launch approach to process validation? The first step is to understand the quality attributes that need to be measured. From a health authority standpoint, product quality comes down to the safety and efficacy for the patient.

These are clinical outcomes, and they are measured as part of the clinical trials. Yet, those are typically not assessed directly as part of characterization studies; instead, the biophysical properties of the product are measured to identify the product's quality attributes.

The analytical toolbox used within this scope—for example, with viral vectors—typically come in the form of potency, nucleic acid containing ratio, post-translational modifications, charge isoforms, aggregation, and impurities.

Many of the analytical methods for these attributes are not particularly well developed today, though, and do not have clear connections to the clinical outcomes outlined for product quality. Therefore, when looking at this analytical toolbox, one must identify which attributes impact the quality of our product and which are more for an understanding of the consistency of that product.

There are additional limitations that affect the decision of which assays to run, such as access to analytical materials, the amount of sample you can generate from studies, and the capacity and time available due to the accelerated timeline for the development of these products.

Selecting the right analytical toolset for any one study requires a robust and risk-based assessment of the product itself, the unit operation being evaluated, and the conditions that must be explored to understand the correct parameters and attributes to test and characterize.

Leading into the exploration of any process or product, there is consideration of what factors are relevant for the parameters and materials and which ones are going to be impactful to the process and the product being explored. Once the right tools have been identified to understand the product being generated, these tools can then be applied to develop the process parameter ranges and control strategy.

In the end, Thermo Fisher recommends using a broad integrated approach, which offers the ability to leverage existing knowledge, such as about the platform and its unit operations or from early development data derived from execution of the process in the past. This provides historical data that can accelerate the commercialization process.

Understanding at-scale manufacturing processes is also critical to modeling of the clinical manufacturing process for a cell and gene therapy product. Execution of the process at manufacturing scale not only demonstrates the process can be run consistently but also reveals any excursions or deviations, which can be very valuable in developing preliminary operating limits and defining characterization study scope.

Process characterization of cell and gene therapy products

The current state of process development for most cell and gene therapy products is limited. Typically, their processes are inherited from diverse sources and built on limited data and process knowledge. Laboratory unit operations, such as ultracentrifugation, are difficult to scale and characterize, and they have a known amount of variability in manual operation. There are also likely to be significant process changes as the program moves through clinical development.

The current state of process development for most cell and gene therapy products is limited

To overcome these challenges, Thermo Fisher is driving platform-based process development, beginning with building out that platform and process knowledge and using a body of information to design a better process from the start. As part of early phase development, Thermo Fisher is targeting commercial needs from a program before Phase I begins.

A flat stock process is not ideal if a program needs to generate large volumes of viral vector, so a suspension process may be a more desirable option. Therefore, selecting the production process in line with commercial needs for Phase I trials will simplify the bridging studies necessary to go from your Phase I process into Phase III and commercial production.

An additional goal is to eliminate any non-manufacturable units where operations are hard to validate and execute and/or are not particularly scalable or robust when you move them into a manufacturing space. There is also a need to use robust intermediate stability data to understand how the product can be stored at the various intermediate stages without impacting quality before the manufacturing process begins. Finally, Thermo Fisher aims to design the initial process development studies in a way that allows exploration of the ranges and criticality of process parameters before manufacturing.

Within this framework, we will be able to leave the development phase and move into Phase I manufacturing with a solid understanding of what the critical parameters are going to be for the commercial product.

As a program moves through clinical phase development, the manufacturing history is another essential part of developing process understanding.

As a program moves through clinical phase development, the manufacturing history is another essential part of developing process understanding. It can be used to better design the process and process control parameters, allowing you to prioritize the parameters and leverage a risk-based analysis with an appropriate source of information.

From at-scale data, established acceptable parameter ranges can be used to identify where additional knowledge is needed. If clinical manufacturing is done in parallel with Phase III development or pre-commercialization characterization work, support protocols can be applied in the GMP manufacturing process to collect additional data that could potentially feed into that body of knowledge and simplify the characterization scope down the road. Overall, understanding process characterization allows you to successfully commercialize a robust manufacturing process.

The approach that Thermo Fisher takes to the process characterization framework is to start with an exhaustive process parameter failure mode and effects analysis risk assessment for your program. This includes extraction of all process parameters as part of the current process within the scope of the batch records as well as parameters that may not be currently tracked, such as the temperature of the manufacturing suite or unclear in-process hold durations.

The goal is to assess and understand what may or may not be impactful and then identify a set of potential critical process parameters that impact either the process consistency or the quality of your product. Based on that and a subsequent series of characterization studies, it is then possible to define the proven acceptable ranges for those to lock the commercial scale manufacturing process. These are the critical stages necessary to move that process into the PPQ and, eventually, commercial manufacturing.

Parameter and material classifications are made utilizing a risk-based approach and data from development, characterization, and at-scale manufacturing. If those critical parameters are not controlled, it will lead to a rejected batch, which emphasizes the importance of identifying process ranges and the proven acceptable range around those parameters to support the robustness of the product.

Any parameter identified as critical requires the establishment of a proven acceptable range, which should not just be the operating set point as there is the risk of those to vary during a commercial lifespan.

And once again, if a proven acceptable range on a critical process parameter is exceeded, the batch will be rejected. Thermo Fisher offers diverse product and process knowledge, which can assist in extracting relevant knowledge from existing process data, identifying high-risk parameters, and validating the process using robust risk-based analysis.

Engaging the experience with dozens of CGT products ranging from pre-clinical to commercial stage development and manufacturing, Thermo Fisher Viral Vector Services team can help guide through the complexity of the commercialization of CGT therapies.

Conclusion

The manufacturing processes used in the production of gene therapy products are complex, as are the raw materials used during production. Controlling both is critical to ensuring the safety and the efficacy of these products, and process validation is one of the key elements required to successfully deliver them to patients. To do so, development data, manufacturing history, and specific designed studies are needed. It is also necessary to leverage both the body and history of knowledge available to develop a sufficient and robust CMC package that creates a path toward commercialization.

Cell and Gene Therapy products engage accelerated clinical timelines that require an active planning mechanism to ensure characterization is well planned and scheduled sufficiently early to support the timelines necessary for commercialization of the product, in order to deliver on what are often highly aggressive filing goals. In the end, although the regulatory guidelines around validation are evolving, the expectation about the scientific robustness and thought process leading into validation are unlikely to change. Therefore, it is important to develop a robust validation package that supports these novel therapies.

About us

Thermo Fisher Scientific provides industry-leading pharma services solutions for drug development, clinical trial logistics and commercial manufacturing to customers through our Patheon brand. With more than 65 locations around the world, we provide integrated, end-to-end capabilities across all phases of development, including API, biologics, viral vectors, cGMP plasmids, formulation, clinical trials solutions, logistics services and commercial manufacturing and packaging. We give pharma and biotech companies of all sizes instant access to a global network of facilities and technical experts across the Americas, Europe, Asia and Australia. Our global leadership is built on a reputation for scientific and technical excellence. We offer integrated drug development and clinical services tailored to fit your drug development journey through our Quick to Care™ program. As a leading pharma services provider, we deliver unrivaled quality, reliability and compliance. Together with our customers, we're rapidly turning pharmaceutical possibilities into realities.

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