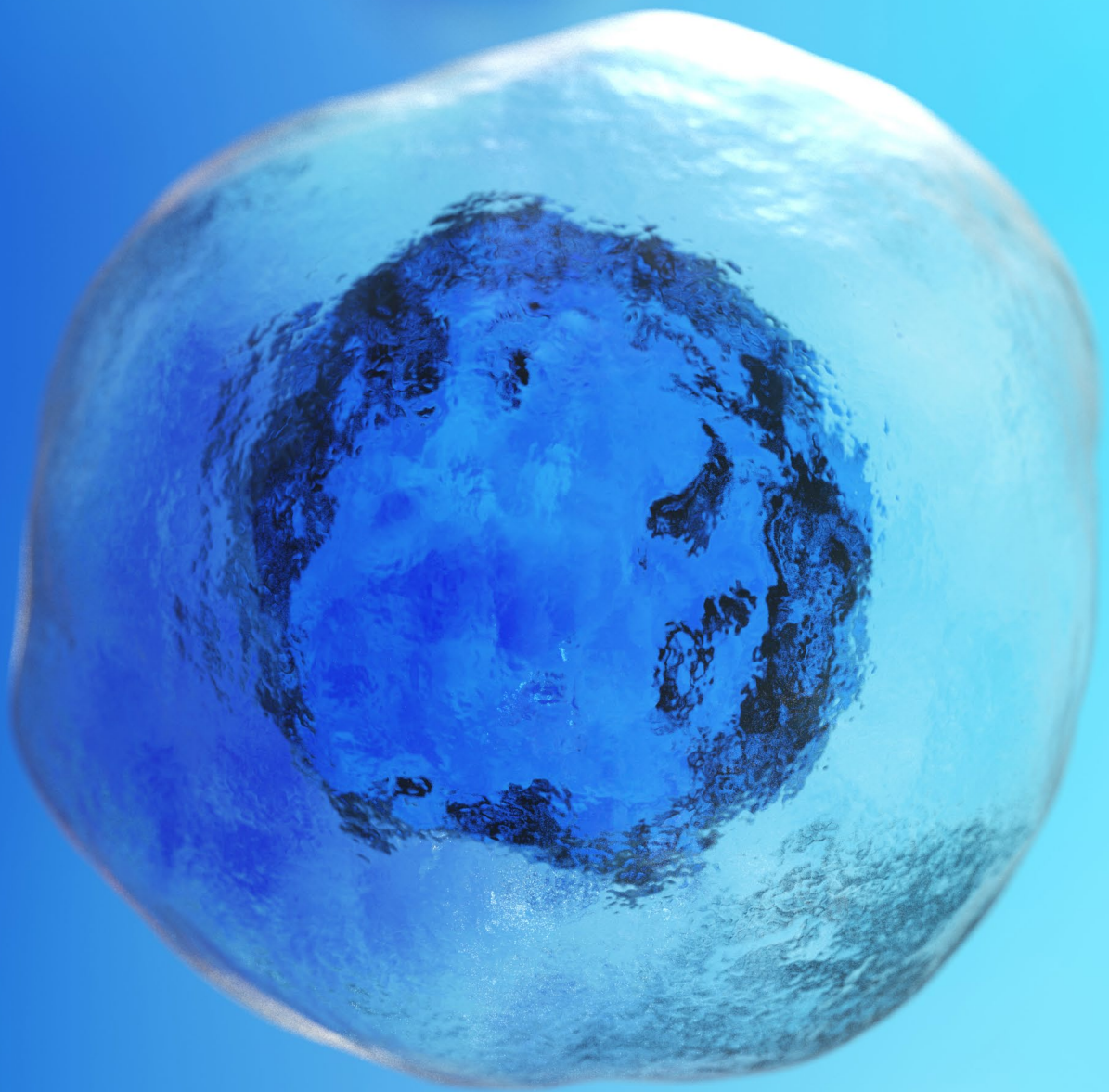
EXECUTIVE SUMMARY

Scale-Up Strategies for Late-Stage Cell Therapies



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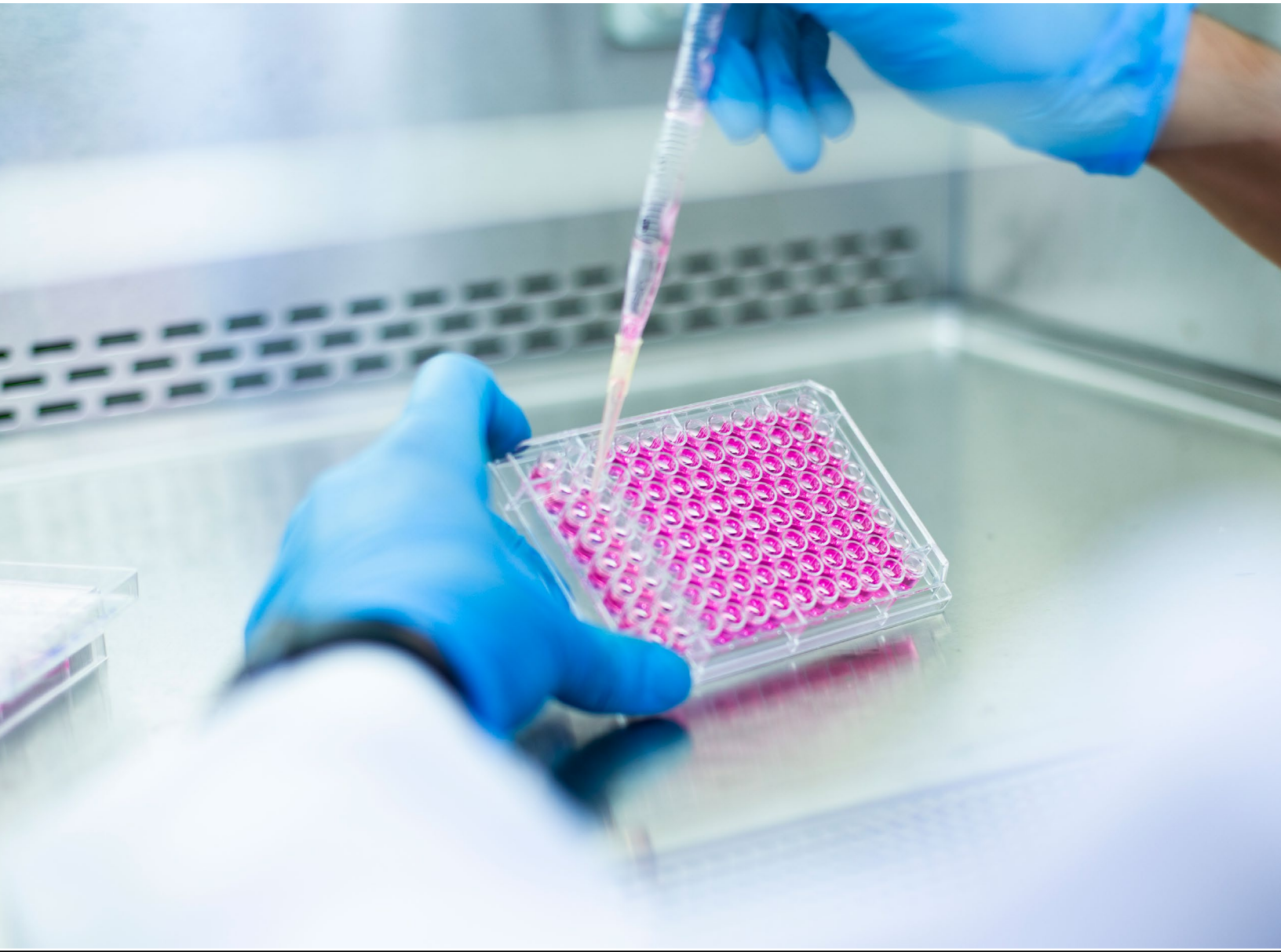
CONTENTS



INTRODUCTION

The outlook for cell and gene therapies continues to be strong. Cell therapies are broadening their reach as they enter trials as an earlier line of treatment, especially in immuno-oncology. Advanced therapies continue to receive expedited review designations that can accelerate the development timeline. As more of these therapies reach late-stage clinical studies and regulatory decisions, strategies to help scale-up for commercial manufacturing, including meeting reduced timelines and the growing capacity demands, are critical to getting cell and gene therapies to patients.

Cell therapy manufacturing has unique challenges as the industry continues to mature, with no true "one size fits all" method for manufacture yet. Autologous and allogeneic therapies are at different stages of their product lifecycles, each with specific requirements for manufacturing that need to be accommodated. For autologous therapies, one area of focus is reducing the variability in starting materials, as it can impact process robustness and manufacturing output. It is also critical to implement processes to fast track the product release in order to minimize the vein-to-vein process lead time. As allogeneic therapies shift to late-stage clinical development and offer an opportunity to reach more patients, scaling up is key, including cell expansion and higher capacity fill and finish operations.

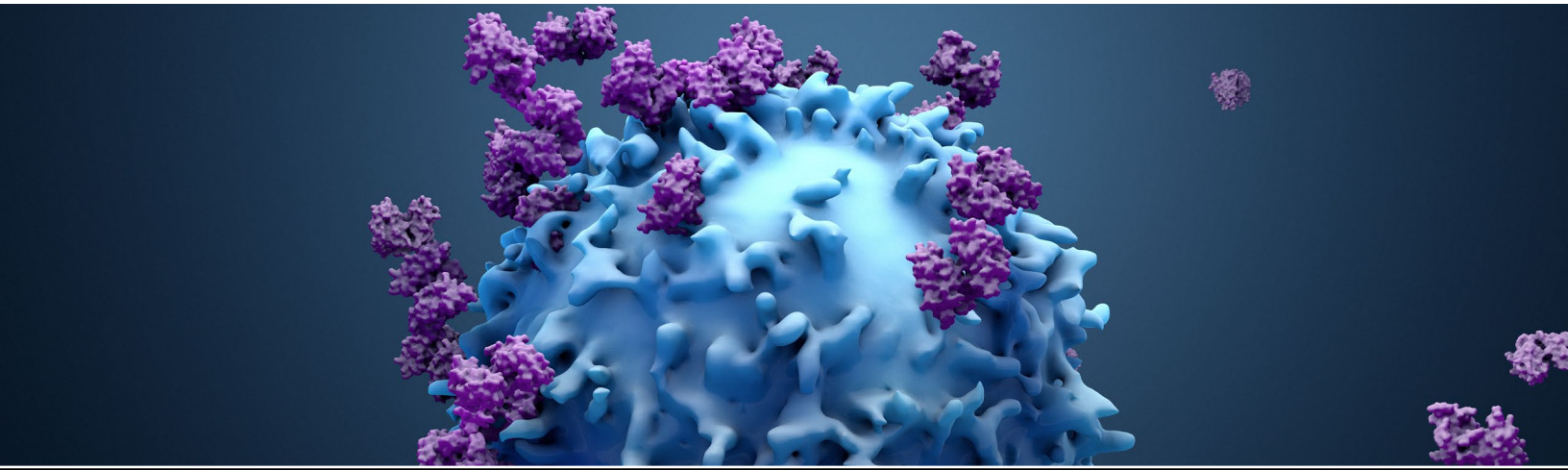
To address the challenges facing late-stage cell therapies, facility design and manufacturing strategies are needed to help overcome the complexities. Catalent provides expertise in scaling-up therapies in late-stage development through a strategy designed to optimize infrastructure to deliver larger-scale and/or high-throughput capabilities and to ensure the supply chain can meet the demands for high-quality and high-throughput production. Catalent's Manufacturing by Design (MbD) strategy helps partners find ways to achieve efficiencies, drive cost savings, and develop and implement a robust, reproducible manufacturing plan for late-stage and commercial launch.

MANUFACTURING BY DESIGN BUILDS ON QUALITY BY DESIGN

The biopharmaceutical industry uses the Quality by Design (QbD) approach to improve processes by integrating scientific knowledge and risk analysis into the development process for manufacturing. The QbD method uses a systematic approach starting from a product profile that will meet business and patient needs and the quality profile for the product, including potency. From there, the design phase of the development and manufacturing plan begins with risk assessments considered and experiments conducted to develop the process. Once the design is set, a control strategy is implemented that will help support regulatory filings. The product is managed throughout its lifecycle to look for opportunities for continuous improvement.

The QbD method addresses process characterization and focuses on the quality of the end product, but considerations such as labor-saving strategies, process automation and closure, and integration of manufacturing steps must also be considered. Many of these are critical for the scale up of cell therapies. MbD is a methodology focused on alleviating autologous and allogeneic manufacturing challenges by elevating attributes that are absent within the QbD methodology.

Catalent developed its MbD methodology to assess and improve the manufacturing process to support product quality and provide a robust and rapid tech transfer strategy. Starting with the target product profiles and critical quality attributes, MbD looks to establish the target manufacturing profiles and critical manufacturing attributes necessary to meet the quality goals. Target manufacturing profiles are determined by reviewing economics (cost of goods, business continuity), process efficiency (scalability, operability, robustness), end-to-end vision (drug substance, drug product, analytical strategy, raw material, and supplies), and other considerations such as regulatory and intellectual property.



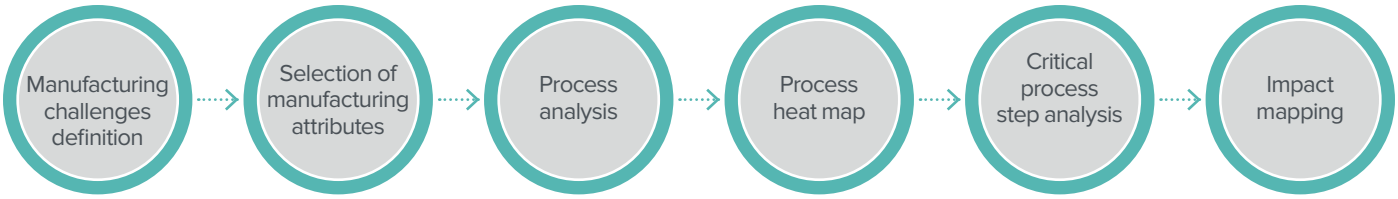


Figure 1. MbD methodology overview with the six steps used to review the manufacturing process.

The MbD methodology includes the six steps outlined in Figure 1. In summary, through MbD:

- the manufacturing challenges, such as raw material supply and consistency, supply chain, starting material variability, processability, and fill and finish needs, are classified and mapped
- manufacturing attributes are selected for analysis
- attributes are assessed and ranked for their impact on the production process
- a heat map is generated to illustrate the level of criticality of each process step and manufacturing attribute (example in Figure 2)
- critical intersections are further analyzed in order to understand the drivers of significance, potential solutions for mitigation, and the feasibility of implementation
- impact mapping is conducted to visualize the relationship between the criticality of a topic and the difficulty in implementing a solution

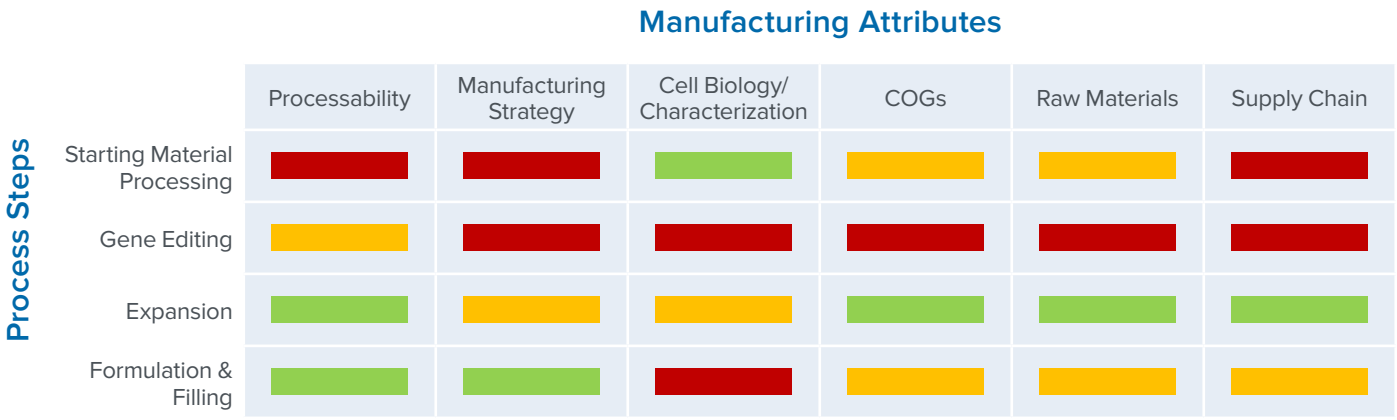


Figure 2. An example heat map created by scoring each process step and manufacturing attribute, and color coding to show criticality (green for low, yellow for medium, red for high).

The Catalent team works to understand each customer's process, develop a target manufacturing process, and conduct a gap analysis between the original and adjusted processes. A recommendation list and an implementation plan are shared and then used to develop, optimize or transfer a process.

DE-RISKING THE TECH TRANSFER PROCESS

The tech transfer process from the customer to the manufacturing partner is often an area of concern as a smooth transition is imperative for speed and maintaining or improving the product profile. Through the MbD assessment, some steps may be highlighted as difficult to transfer, for instance, a complex, manual operation that needs significant hands-on training. For this example, the recommendation may be to implement an automated operation that could provide multiple benefits including reduced training time and deviations.

In addition to individual steps, Catalent looks to de-risk the tech transfer process from facility fit through lifecycle management. The team confirms the process and product fits with the facility and is ready for scale- and ramp-up. Supply chain security is confirmed for clinical and commercial needs and second sources for supply and testing are qualified. Equipment is identified and qualified and analytical methods are reviewed for comparability and validation. First batches are conducted in the facility in order to finalize documentation, train staff to help ensure continuous coverage, and to generate material for the comparability and validation testing. Depending on the product development stage, additional validations, such as aseptic processing, may be conducted. Future regulatory filings and continuous improvement are also considered as the tech transfer process is risk assessed.

CATALENT'S STRATEGY TO MEET MANUFACTURING DEMAND

After the process risks have been assessed and mitigation plans have been implemented, having the manufacturing capacity and capabilities to meet the clinical and commercial needs for the advanced therapy is critical. Catalent has built a network of facilities and capabilities to support the development and manufacturing of cell and gene therapies. Catalent has global clinical- and commercial-scale facilities, offering end-to-end capabilities, from plasmid DNA and viral vectors to autologous and allogeneic cell therapy manufacturing. The Catalent approach includes assessing supply chains, addressing critical raw materials, standardization of processes, and building flexible, state-of-the-art cell and gene therapy manufacturing facilities operating under a single quality system.

Catalent has invested in plasmid DNA manufacturing capabilities which, through close integration, reduce timelines and provide a seamless transfer to its viral vector and gene-enabled cell therapy production campuses. Catalent's plasmid DNA facilities are located in Maryland, United States (US), and Gosselies, Belgium, and offer process and analytical development capabilities, research- and high quality-grade production, and CGMP manufacturing at up to 500-liter scale.

For viral vectors, Catalent's Maryland network of sites includes extensive process and analytical development facilities in Baltimore and Gaithersburg. The latter also offers formulation development and central testing laboratories for viral vectors.

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The late-stage and commercial flagship campus in Harmans includes two facilities with up to 18 CGMP suites and is FDA and EMA approved for viral vector manufacturing.

Supporting the cell therapy industry, Catalent has four locations across the US and Europe. The induced pluripotent stem cell (iPSC) center of excellence in Düsseldorf, Germany provides iPSC development, cell bank manufacturing, differentiation and cloning services, and off-the-shelf GMP cell lines. Process and analytical development and clinical manufacturing of cell therapies are offered in Houston, Texas, Princeton, New Jersey, and Gosselies.

To support late-stage and commercial cell therapy partners, Catalent has invested significantly to offer global capabilities and capacity. Its facility in Princeton houses 16 ISO 7 clean rooms supported by QC labs and warehouse storage, with significant room for expansion. Additionally, at the Gosselies campus, a new large-scale, high-throughput manufacturing facility for both autologous and allogeneic platforms will be operational by the end of 2022. The 60,000 square foot facility is designed to support either dedicated, segregated suites or ballroom-style manufacturing with bioreactor scale capabilities and also includes dedicated QC and storage capabilities.

Catalent's expertise in accelerating and de-risking cell therapy programs is evident through its growing number of partnerships, successful tech transfers, and batches produced. With the MbD process and manufacturing infrastructure, Catalent is ready to support advanced therapy partners as they bring life transforming therapies to patients.

For more information on the MbD method and Catalent's facilities, view the on-demand webinar or visit Manufacturing by Design Methodology.

70+
CELL & GENE THERAPY PROGRAMS

100+
ALLOGENEIC BATCHES MANUFACTURED

300+
AUTOLOGOUS BATCHES MANUFACTURED

10+
CELL MODALITIES

75+
CELL & GENE THERAPY COMPANIES

15+
TECHNICAL TRANSFERS

Cell Types				
	CAR-T	TIL	iPSCs	MSCs
	TCR	Treg	ESCs	HSCs

Why Catalent

Catalent Cell & Gene Therapy is an industry-leading technology, development and manufacturing partner for advanced therapeutics. Its comprehensive cell therapy portfolio includes a wide range of expertise across a variety of cell types including CAR-T, TCR, TILs, NKs, iPSCs and MSCs. With deep expertise in viral vector development, scale-up and manufacturing for gene therapies and viral vaccines, Catalent is a full-service partner for plasmid DNA, adeno-associated viral (AAV), lentiviral and other viral vectors, and oncolytic viruses. An experienced and innovative partner, it has a global network of dedicated, small- and large-scale clinical and commercial manufacturing facilities, including an EMA- and FDA-licensed viral vector facility, and fill/finish capabilities located in the US and Europe. With integrated solutions for plasmid DNA, viral vectors and autologous and allogeneic cell therapies through clinical trial packaging and logistics, Catalent can provide full supply chain control, helping innovators get their advanced therapies to patients, faster.

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Catalent®