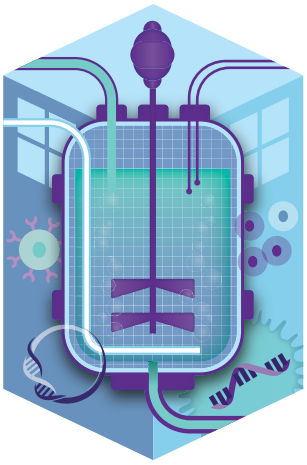
Catalent®
CELL & GENE THERAPY



Integrated Solutions for Advanced Therapies

FROM CRITICAL RAW MATERIALS TO CLINICAL TRIAL SUPPLY:

Securing the Path to the Clinic

Advanced therapies such as cell and gene therapies are recent entries into the therapeutic toolbox that physicians have to treat diseases. Cell therapies involve using patient- (autologous) or donor-derived (allogeneic) cells to replace diseased tissue or as therapies targeting tumor cells. Gene-enabled cell therapies, such as chimeric antigen receptor (CAR) T cell therapies, use viral vectors to alter the cells outside the body (*ex vivo*) and are returned to the patient post modification. Gene therapies typically treat monogenic diseases and use viral vectors to deliver the replacement DNA within the body (*in vivo*), so the patient's cells can produce the corrected or missing protein.

Cell and gene therapies have reached clinical and commercial success as evidenced by the steady number of first approvals over the past 4 years (1). The promise of cell and gene therapy continues to expand, with therapies gaining approvals in additional countries, for new diseases and some as earlier lines of treatment (2). According to the Alliance for Regenerative Medicine, at the end of June 2022, globally there were over 2000 cell and gene therapy clinical trials ongoing (2). Fast-track designations are helping candidates progress towards commercial approvals at an accelerated pace. Drug developers face mounting challenges linked to rapid increases in demand for the complex modalities while also accounting for the need to drive process efficiencies at scale. Working with the right partner, that offers integrated services, can help ease the increasingly common problems with scale, access to high-demand raw material, viral vector production, and quality requirements.

Planning Early for Late-Stage & Commercial Needs

As cell and gene therapies expand into larger populations and different diseases, there is an associated increase in demand for development and manufacturing capacity and the supporting supply chain. In addition to consumables, such as bioreactor bags and chromatography filters, access to raw materials, including plasmid DNA, or pDNA, is critical to meeting clinical milestones. Planning for large, commercial scale manufacturing should be done as early in the life cycle of a therapy as possible in order to evaluate and address the potential gaps and risks in the process.

Things to consider when developing a manufacturing plan for a cell or gene therapy include:

1. What are the critical raw materials?
2. Is your cell culture process adherent- or suspension-based?
3. How easy is the process to scale-up or scale-out to meet potential demand?
4. What are the critical quality attributes and what analytical tools are needed for assessment?
5. How will you deliver the therapy to the clinic?

For raw materials, especially GMP-grade, it is necessary to look at the full process to identify the critical items. Figure 1 illustrates how **plasmid DNA is a critical building block** for several advanced therapies, including viral vector-based gene therapies, mRNA, and gene-enabled cell therapies. If your target therapy is a CAR T cell, you will need a source for the plasmid DNA used to produce the viral vectors, as well as a partner for the viral vector manufacturing. Do you have the logistical and regulatory capabilities to manage the patient or donor sources of the cells that will be transformed?

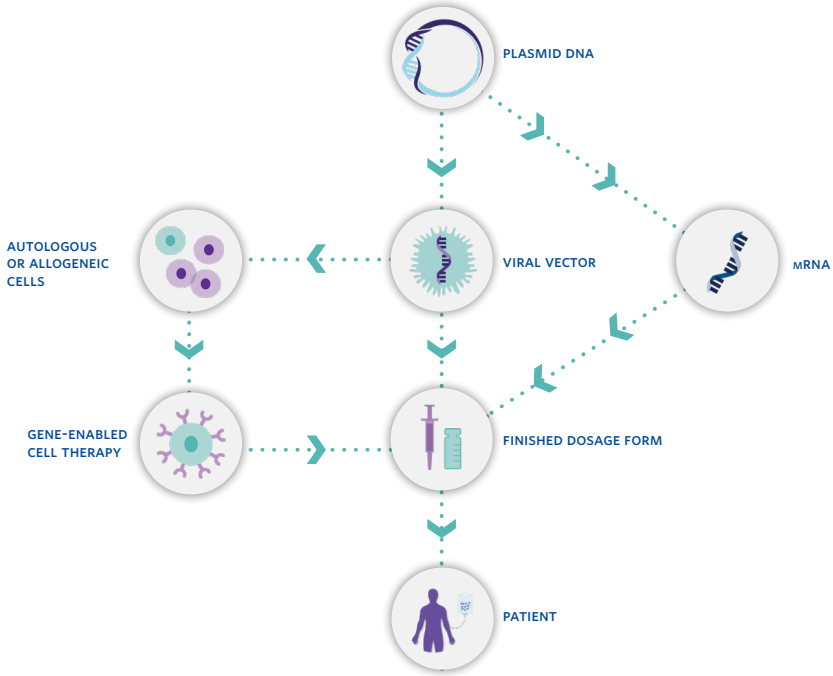


FIGURE 1. From plasmid DNA to viral vector, mRNA and cell therapies, Catalent has the capabilities and expertise to help partners get their advanced therapies to patients.

Many advanced therapies originate at academic labs. The manufacturing methods established at those labs typically work well for small volumes but scale poorly, creating a bottleneck as candidates advance into late-phase development and onto the market. For therapies developed in adherent cell culture, a **scale-up plan must be considered early**. Some suppliers offer larger scale adherent-based bioreactors to address the challenge of scaling. Another option is to consider adapting the process to a suspension culture-based cell line suitable for use in standard, scalable, single-use bioreactors. Recently, progress has been made in standardizing processes for manufacturing plasmid DNA and viral vectors using suspension-based fermenters and bioreactors. These scalable platform processes are helping to secure consumable supply chains, stabilize timelines, and possibly reduce development costs.

An **individualized approach for cell therapy** manufacturing needs to be considered to incorporate the numerous variables involved with the cell source. For example, allogeneic cells require donor consent for use while autologous cells need to be tracked from vein-to-vein to maintain the chain of custody. Strategies to meet the larger demand for allogeneic-based therapies should include finding the right balance between standardized scale up processes and maintaining the complexity and quality of these materials. Efficient coordination and management of all the steps involved in the cell therapy supply chain are essential to provide these potentially lifesaving therapies to patients.

As reliable and robust manufacturing processes are developed to produce therapies meeting established critical quality attributes (CQAs), the development and qualification of **innovative assays to analyze and characterize** these new modalities is critical. The complexity of cell and

gene therapies creates a challenge to establishing platform assays to assess some CQAs, for instance potency. As many of these therapies have expedited review designations, methods to help with real-time decisions can help address accelerated timelines. Innovative analytical tools will continue to be developed and partners who actively investigate their use can be at the forefront of meeting analytical needs.

The demand for capacity is still greater than the available supply, so locking in manufacturing space early is important for estimating project progression and, potentially, securing funding. When evaluating a contract development and manufacturing organization (CDMO), in addition to experience and open capacity, one should consider the types of services and the level of expertise they offer. If you need plasmids and viral vectors, how might having more than one vendor impact the development and manufacturing timeline compared to a CDMO offering both? Do you have long term plans for global clinical trials? Do you have a **plan for packaging, storage and getting the therapies to the clinic**? The right balance between standardized scale up processes and integrated services requires the right blend of scientific, manufacturing, regulatory, and logistical expertise. Finding the right outsourcing partner can help overcome these challenges and prepare your advanced therapy program for clinical and commercial success.

Catalent, a Committed Manufacturing Partner for Advanced Therapies

Catalent is a technology and service provider offering development through manufacturing services that span from clinical to commercial supply. As a global provider across the large molecule pipeline, including monoclonal antibody, recombinant protein, and vaccine production, analytical testing, and clinical trial logistical services, Catalent expanded its biologics offerings to help address the growing need for capacity and expertise for cell and gene therapies. Beginning in early 2019, Catalent has made significant investments to build a global network of experts and state-of-the-art facilities offering end-to-end solutions for plasmid DNA, viral vectors and cell therapies at the clinical and commercial scale. Figure 2 shows the locations of the Catalent cell and gene therapy facilities.

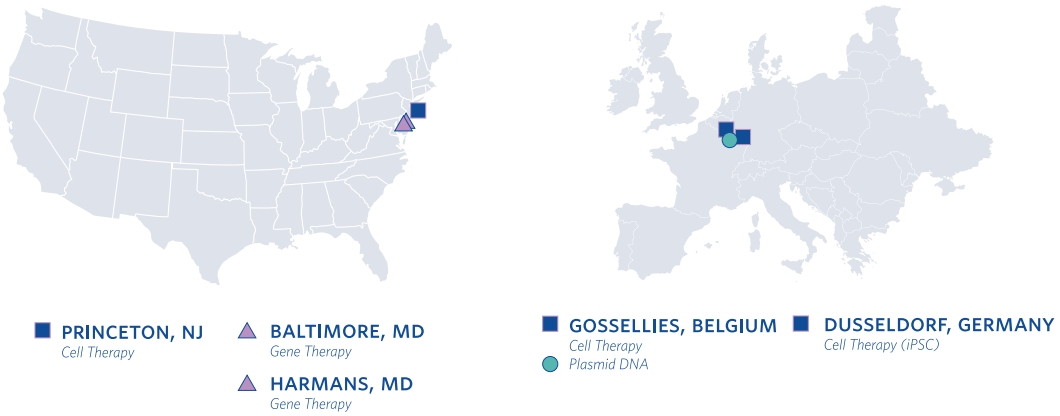


FIGURE 2. Catalent has a global network of plasmid DNA, cell and gene therapy development and manufacturing locations, totaling over 650,000 sq. ft.

In the United States (U.S.), Catalent's Maryland network includes the viral vector process development and analytical center in Baltimore. Located in Harmans is the late-stage and commercial manufacturing campus featuring flexible, multi-room suites that can accommodate adherent- and suspension-based systems up to the 2,000 L scale. The Harmans campus includes the EMA and FDA approved facility for viral vector manufacturing and offers fill and finish capabilities. The proximity of the facilities allows for easy communication and

collaboration between the experts at each site and is instrumental in the implementation of the scalable, GMP-ready AAV UpTempo platform production process that is capable of yielding drug product in nine months.

Catalent's U.S.-based cell therapy facility, which offers large-scale clinical and commercial manufacturing, is located in Princeton, New Jersey. The facility complements the cell therapy center of excellence in Gosselies, Belgium, that features multiple buildings supporting the development and manufacturing of autologous and allogeneic cell therapies. In addition to the Gosselies clinical-scale site, a new FDA and EU compliant commercial-scale facility opened in 2022. The Gosselies campus also includes Catalent's plasmid DNA development and manufacturing facility for research-, high quality- and GMP-grade plasmids.

To support innovation for cell therapy starting material, Catalent offers GMP induced pluripotent stem cells (iPSCs) from its Düsseldorf, Germany, facility. The iPSCs are derived from human leukocyte antigen (HLA)-homozygous cord blood donors and carry informed consent for commercial use for therapeutic applications. iPSCs offer many advantages including the ability to be expanded indefinitely, cryopreserved, and recovered easily, which facilitates their handling compared to other cell types and allows for the establishment of off-the-shelf stocks. As iPSCs are easily manipulated, they can be differentiated into various human cell types (Figure 3), making them an ideal universal cell source for therapies addressing a range of indications to treat a broad patient population in the future. Additionally, fully documented and characterized clonal cell lines will help meet future regulatory requirements for clinical studies. Many of these features imply that iPSCs can be distributed globally with proportionally less effort compared to the logistics necessary for autologous-based therapies, potentially increasing accessibility and reducing costs.

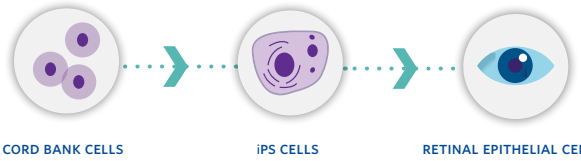


FIGURE 3. Catalent utilizes specialized reprogramming technology to transform donor consented, clinically approved, cord blood collections into HLA-homozygous iPS cell lines that are immune compatible with multiple patients. GMP-compatible differentiation protocols provide options to transform the iPSCs into the cell types needed to develop therapies for targeted diseases, for instance, retinal epithelial cells for ocular diseases.

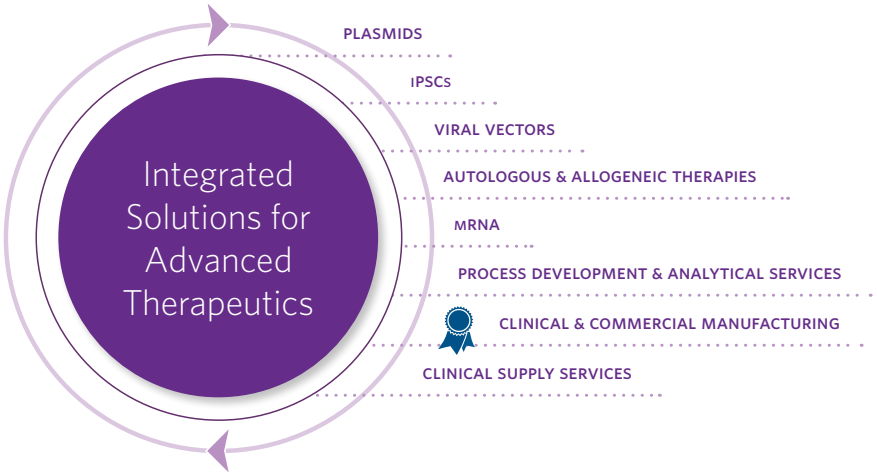
Broad Capabilities in Analytical & Clinical Supply Services

The analytical and regulatory requirements for biologics, cell and gene therapies can be complex. Catalent offers one of the widest ranges of analytical services for biologics and other large molecules in the industry, all under full GMP compliance. Expanding in-house analytical offerings, such as analytical ultracentrifugation for empty and full capsid analysis, has helped reduce analytical timelines. Ongoing evaluations of new technologies provide the opportunity to offer enhanced analytical methods to further support product quality measurements. Its biologics analytical services can be provided as a standalone service from the U.S. based sites in Kansas City, Missouri, and Durham, North Carolina, or integrated into development and manufacturing at one of its production campuses, and can support the drug development pipeline, from pre-clinical testing through to post-approval release and stability. With an experienced scientific team and a range of capabilities, Catalent strives to develop analytical methods and implement innovative tools to help support the testing needs of its partners.

REFERENCES

1. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products
2. https://alliancerm.org/sector-report/h1-2022-report/

Catalent's global network includes the broadest spectrum of development and clinical supply services for studies of all sizes and complexity from Phase 1 to commercial launch. Catalent recently increased cold chain packaging capabilities at its Philadelphia, Pennsylvania, facility to support increased demand for the distribution of biologic drugs, and advanced cell and gene therapies. Case management services designed specifically for cell and gene therapies can help give customers greater control and visibility across their supply chains. Leveraging integrated supply chain services is an important strategy for mitigating risks and smoothing the path from bench to clinic for these emerging therapies.



Catalent's Integrated Solutions Help Expedite Treatments to Patients

With global facilities and clinical- through commercial-scale production capabilities, the Catalent team is ready to help define and deliver an integrated program from the development of the optimal plasmid and its manufacturing process to seamless transfer into viral vector and cell therapy production, including fill/finish and clinical supply services. A CDMO like Catalent with commercial manufacturing experience, offering end-to-end services is well suited to help manage the manufacturing challenges, including securing manufacturing slots and timelines, and balancing the complexities of logistics, analytical and regulatory requirements. Catalent can provide full supply chain control and support its partners at every stage of the candidate's journey and is committed to helping its partners get their advanced therapies to patients, faster.

more products.
better treatments.
reliably supplied.™

Discover more solutions at biologics.catalent.com

GLOBAL + 1 888 SOLUTION (765-8846)
eu 00800 8855 6178
solutions@catalent.com