CGT CDMO Partnering: More than just Manufacturing

The biotech footprint has been exponentially expanding around the globe and no division has increased more feverishly in recent years than the Cell and Gene Therapy (CGT) space. With hundreds to thousands of products in the pre-clinical and clinical phases, the industry has improved in both a quantitative and qualitative way, but it has also exposed numerous pain points that have created critical bottlenecks affecting the ability for a smooth transition into clinic and subsequently to market. With the CGT space being at a critical inflection point, the current ways of working to develop, manufacture, and deliver products and treatments to customers (and subsequent patients) results in a greater need to access GMP manufacturing capacity for meeting clinical and commercial demand, particularly for small biotech firms developing cell andgene therapies. With continuing pressure coming from accelerated timelines and milestone deliveries without sacrificing quality, many of these firms lack the expertise, facilities, and supply networks needed to quickly scale up for clinical or commercial development. This is where partnering with an experienced CDMO can de-risk your path to said critical milestones and provide that seamless transition from development to clinic and into both a regional and global commercial supply.

While the cell therapy and gene therapy field has been around in some way, shape, or form since the 1950s and 1970s respectively, only in recent years has the industry really started to take off. Over those previous decades of predominately research and development, the landscape has morphed from viral vector to allogeneic to autologous and everywhere in between. Today's landscape is a healthy mix of all three modalities and is expected to continue as such as depicted in Table 1.

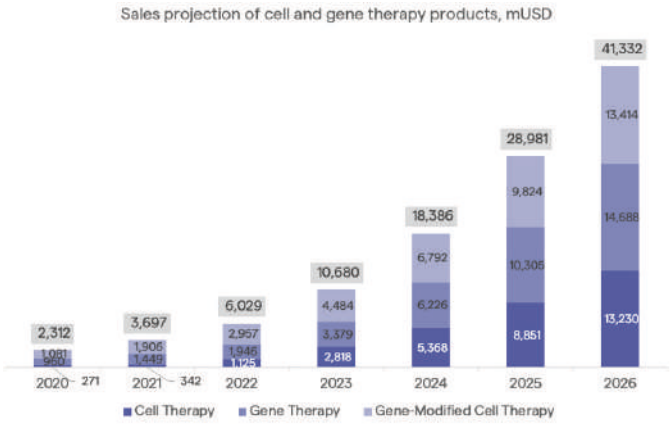


Table 1: Sales Projections of CGT Modaltities[1]

Today's CGT field has seen twenty products go to market[2] and even despite the COVID-19 global pandemic, the market continues to rapidly expand. The expectation is that by 2025 there will be 10 to 20 Biological Licence Application (BLA) approvals per year for the Food and Drug Administration (FDA) alone. Of the 10 to 20 BLA approvals, there is expected to be nearly 10 times the amount of Investigational New Drug (IND) applications per year.[3] This isn't to suggest that the market is minimal and expected to ramp up, this is much the case of "the rich get richer" as the market continues to blossom more from prior blooms, and no modality has been greater affected than the autologous cell therapy modality. With the successful commercial approvals of Kite's Yescarta and Novartis' Kymriah in 2017, the autologous market grew at a rate that few projected even a few years prior. Since then, other major autologous products have been approved consisting of Bristol Meyer Squibb's Abecma and Breyanzi, and Kite's Tecartus drug products.[4] However, getting to the BLA or Marketing Authorisation Application (MAA) submission and approval stage is a steep hill to climb and the challenges of providing the market with a regional or global product begin much sooner.

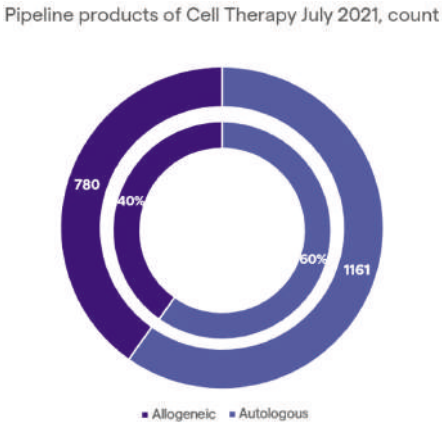


Table 2: Cell Therapy Modality by Molecule Number[5]

Cell Therapy, specifically autologous cell therapy, has become the recent focus in cell therapy over previous years as depicted in Table 2, but faces, arguably, the most critical bottleneck in the industry, due to requiring the product-receiving patient to also be the donor of the product starting material that initiates the entire process: market reimbursement. When manufacturing an end-to-end cell therapy that results in a single dose or treatment, the costs tend to skyrocket, and the product is only as successful as the value the market will bear. But, despite this being one of the toughest challenges within the Product lifecycle, there are still numerous bottlenecks created upstream that add to the difficulties.

The current ways of working to deliver CGT products to customers and subsequent patients utilises a variety of product flow paths that utilise variable entities, systems, and materials at numerous critical process touch points. This creates a variety of pain points throughout the Chain of Identity (CoI) and Chain of Custody (CoC) pathway that

makes the path to clinical, commercialisation, and subsequent scalability extremely difficult and quite frankly overwhelming.

With all of the challenges the industry imposes on young cell therapy products, there is much discussion around how a company can both deliver a safe product with a high efficacy that is commercially viable and deliver it efficiently as speed is often the main driving factor for many therapies (first in clinic and first to market). This is where a partnership with a reputable CDMO can give large and small biopharma firms access to development, external GMP manufacturing capacity, and valuable expertise needed to meet critical milestones and control both the CoC and CoI pathways.

When choosing to partner with an external manufacturing company, the benefits stretch well beyond simply the manufacturing. To best understand the right fit for your company, you need to understand what the core drivers for your product are. Product drivers could fall into a number of categories, but a majority of the driving forces behind what CMO or CDMO a company should partner with fall within the timeline, cost, or manufacturing capacity buckets. Each of these buckets has a multitude of subsets that contain variable flexibility and options that may or may not fit your product.

Regardless of what the core driver is, a company needs to adhere to the plan that was put in place whether it's for budgeting purposes, milestone achievements, board reports, etc. Within the CDMO space, the mantra in response to this need should always be "right first time" and what this results in is that de-risking the product process becomes the core driver a majority of companies aren't aware they need. De-risking ensures that the Product moves through the Product lifecycles with minimal rework and ensures that targets remain on track – critical for accurately measuring actuals vs proposed post-milestone achievement.

Due to CGT products being dominated by early clinical stage programs, most products still require some sort of development on the process, analytical, material, or equipment end and are not ready for clinical/commercial approval right out of the gate. This results in the external manufacturing CGT space being dominated by CDMOs as compared to CMOs. A CDMO will have a wider array of established development, operations, quality, and support departments dedicated to providing services with a variety of options providing flexibility to their partner.

Often, flexibility is a critical behind the scenes core driver that often exceeds the more dominated drivers such as cost and timeframes. This is driven by the understanding that time and cost saved now, isn't necessarily saved later on in the product lifecycle. Pushing through a process for early clinical may expedite your time into clinic, but often will slow your time to market due to process optimisations driven by compliance and scale requirements; also, typically at cost magnitudes higher than previously would have been required. This is where partnering with a CDMO is recommended as the CDMO partner can leverage the existing expertise, experience, and resources to de-risk your product right out of the gate and allow the customer to possess any stage of a product whether it be a process as simple as a late-phase "drop-in" process that needs minimal optimisation or an idea based off of a gene of interest (GOI) and be confident that the CDMO can accurately and efficiently move that Product from the developmental stage into the GMP readiness phase with a process that is not only phase-appropriate, but focused on the long-term goal as well.

In the CGT industry however, talk is cheap: costs and timelines can be promised and never delivered. In an industry where speed and cost are critical to patient centricity, more than time and money are sacrificed when CDMOs over-promise and under-deliver. This is where experience plays a major factor in how a CDMO can successfully support a customer's product. When selecting a CDMO, past experiences and market domination are often more valuable than upfront speed or cost. When developing a process or analytical method for a CGT product, issues are bound to arise through the initial product stages. However, what this results in is an experience that can be learned upon and passed onto future partners to better streamline their own product process and expedite time to clinic or market thus, creating a base that can be continued to build upon as time goes on.

This can be achieved a number of ways. When bringing in a product process, a CDMO can evaluate the process and process inputs/outputs and compare to past experiences to better prepare for any pain points that may have been apparent in past experiences. As shown in Table 3, the market modalities are often dominated by a common cell type leading to increased efficiencies. However, at some leading CDMOs this is taken a step further by establishing platforms where inputs/outputs are pre-evaluated and reviewed to allow a customer to drop seamlessly into a platform that has already been evaluated for clinical and potentially commercial implementation. This can be as straight forward as defining a full chimeric antigen receptor t cell (CAR T) process inclusive of analytical methods, materials, and equipment or take a bracketed approach where individual unit operations can be added/removed to streamline a portion of the process if other areas require customisation. Of course, there is always the full customisable approach as well if a customer wishes to develop the full process from end-to-end, as leading CDMOs offer. Each of these options allows the customer to pick a product pathway within the CoC pathway that best fits their core product driver(s).

By focusing on late-stage or commercial viability earlier on in the clinical phase, it allows a customer to move more fluidly through the commercial readiness portions of the product lifecycle where typically processes slow down as they are extensively analysed through both a quality and regulatory microscope. This would include, but are not limited to, PLE studies, L/E studies, method validation, shipping/stability studies, hold time studies, RM qualification, etc. A CDMO will be able to focus on the areas that have previously provided bottlenecks to better plan for a streamline path to commercial rather than merely running through a list and coming across bottlenecks real-time without warning. As with the earlier stages of the product lifecycle, an experienced CDMO will treat this as a partnership and not focus on one party driving, but focus on a "how we can help you" approach as getting to market and successfully pushing through an approved therapy is a win-win-win situation for the customer-CDMO-patient.

Leading CDMOs should be agnostic to the approach a customer wishes to take and instead focus on the successful product implementation for patient centricity and the priorities of the customer; all while providing consultation throughout each stage listed above without sacrificing overall quality.

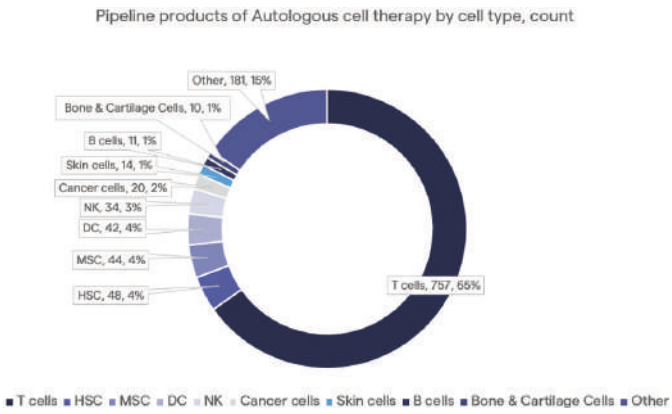


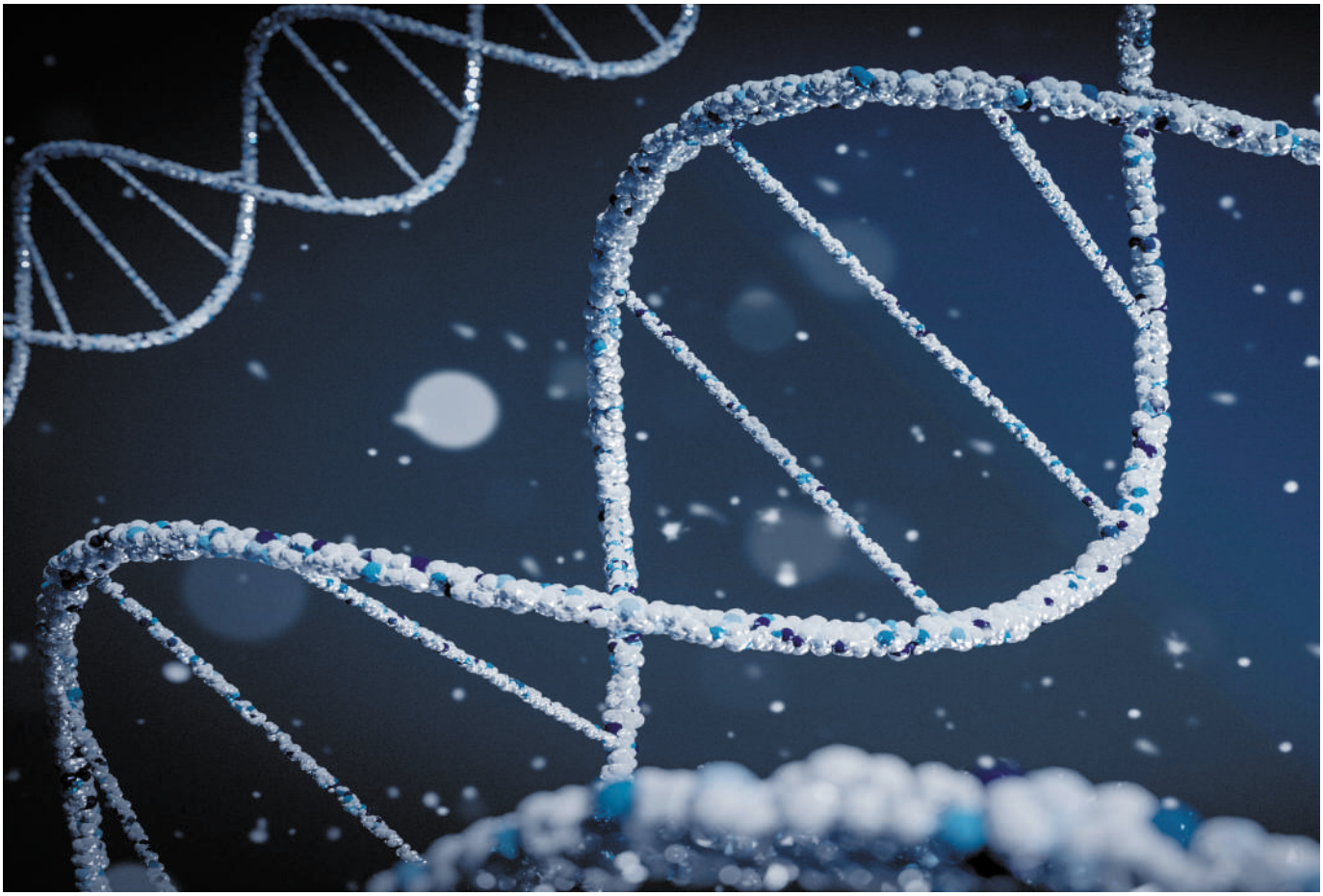
Table 3: Autologous Cell Type per Module Number[6]

While so much of the focus is on successful manufacturing of the drug product, the supply chain aspect of the product process is often heavily overlooked. This is understandably so as the system has set up products to be developed in a staged approach focusing on specific deliverables as the product moves through the product lifecycle and/or clinical phases. Drug products that target common indications such as solid tumours or blood cancers do not procedurally require any automation for scalability until the later phases of the clinical trials when the demand forces the conversation and processes to be initiated. While the initial focus is (rightly so) on safety and quickly followed by product efficacy, there needs to be a focus on the supply chain side of the product earlier on during the process.

There are few integrated service offerings available in the market today that can assist in industrialising and streamlining the supply chain logistics with full traceability throughout the CoI/CoC processes; let alone at the scale demanded by common target indications. To attack these pain points and establish a robust and reproducible end-to-end process, CDMOs have looked externally to de-risk the overall "vein-to-vein" processes and the available services that currently support the industry.

This allows for large CDMOs to supplement their capabilities by utilising clinical management companies (Be The Match Biotherapies) and logistics' companies (Cryoport) that all have the capability to be linked by an orchestration platform (Vineti, TrakCell, Salesforce). The outcome of this approach is a resolution for the more common pain points of logistic delays, process variability, scheduling adherence, compliance issues, and scalability. Additionally, this allows companies that may lack the necessary bandwidth allow the CDMO to manage areas outside of the standard CoC pathway and integrate traceability throughout the entire CoI pathway at a stage much earlier than initially planned.

CGT is often not alone within a larger CDMO and companies typically involve additional business divisions



that are aimed at improving the likelihood of moving a CGT product through the lifecycle stages. For example, Lonza leverages a Bioscience division to focus on improved transfection methods for non-viral genetic modification via electroporation and improved mediums for more improved and cost-effective culture conditions. Additionally, the Personalized Medicine division focuses on scalability through a proprietary GMP-in-box system combined with both a centralised and de-centralised manufacturing approach in the event a more pointed, point-of-care manufacturing approach is required.

Additionally, when selecting a CDMO partner, security of supply is a critical regulatory requirement needed to show commercial viability of your product. CDMOs often offer global footprints to extend patient supply across multiple areas of the globe; autologous especially as the logistics pathway is a bit more limited than more traditional viral vector or allogeneic manufacturing and trial support. When selecting a CDMO, the regional and global footprint is to be considered based on the long-term supply of your product. The growth also needs to be considered to ensure that the selected CDMO has available capacity for not only the existing demand, but the demand that extends into the commercial launch and peak commercial years.

Combining the expedited time into clinic, the commercial viability assessment in the earlier clinical phases, and the scalability through assistance of other business divisions, a CDMO gives a great chance of pushing forward not only a product that works, but a product that will bear the weight of the market.

With the CGT industry expanding at a rate never seen before combined with a variety of pressure coming from expedited timelines, security of supply, and robust processes, partnering with an experienced CDMO allows the customer to allow experience, resources, and facility networks to do the driving on a road previously paved. Speed bumps are inevitable throughout a product lifecycle, but getting from point A to point B on the road to clinic or market is always much more efficient with a partner who has a map and knows all of the bottleneck areas to avoid or refocus on. In the end, this allows the therapy to have the best chance of succeeding and treating the patients, the top priority and focus.

REFERENCES

1. EvaluatePharma. Export: June 28, 2021
2. Approved Cellular and Gene Therapy Products. Food and Drug Administration, 27 Mar. 2021, https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products. Accessed 30 Apr. 2021
3. Hanover, Larry. The Untapped Potential of Cell and Gene Therapy. AJMC, February 2021, Volume 27, Issue 2, Pages: SP51, 16 Feb. 2021, https://www.ajmc.com/view/the-untapped-potential-of-cell-and-gene-therapy. Accessed 30 Apr. 2021.
4. Approved Cellular and Gene Therapy Products. Food and Drug Administration, 15 Jun. 2021, https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products. Accessed 14 Sep. 2021
5. Citeline Pharmaprojects Pipeline Search, July 1, 2021; Lonza internal analysis
6. Citeline Pharmaprojects Pipeline Search, July 1, 2021; Lonza internal analysis

Joe Garrity

Joe Garrity is the Head of Autologous Cell Therapy, Commercial Development at Lonza Cell and Gene Technologies where he works within their global Cell and Gene business unit. He works within the business leadership team to enable strategic development and growth of the autologous modality in Lonza CGT, as well as works with operations, development, and quality teams to streamline the clinical and commercial manufacturing services and offers provided by Lonza. Joe has an educational background in biochemistry and a professional background of nearly a decade within the cell and gene CDMO space that has covered positions within development, operations, and business functions.