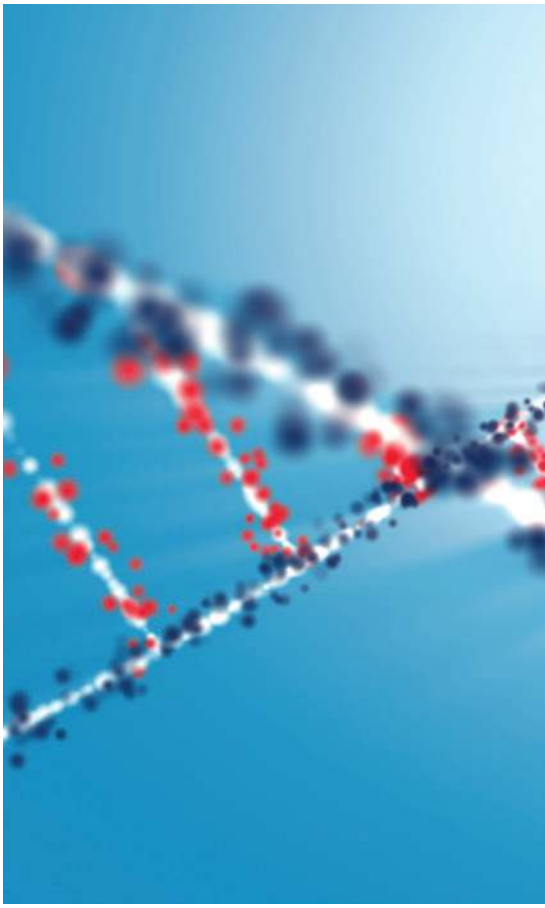
VISUALIZING THE FUTURE OF CONTRACT DEVELOPMENT AND MANUFACTURING FOR CELL AND GENE THERAPIES



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Next-generation medicines, such as cell and gene therapy, are providing significant opportunities for growth in the innovator, CRO, and CDMO marketplaces. However, there are numerous challenges associated with these therapies that create measurable risk.

WE LIVE IN AN AGE OF BOUNDLESS DISCOVERY

The opportunities in advanced biological modalities seem endless. There are currently more than 1,000 clinical trials for a variety of cell therapies, including Chimeric Antigen Receptor (CAR) T cell treatments, which focus on oncology. Immunotherapies based on immune checkpoint inhibitors are being investigated in more than 3,000 preclinical and clinical trials.

Immunotherapy drugs called immune checkpoint inhibitors work by blocking checkpoint proteins from binding with their partner proteins. This prevents the "off" signal from being sent, allowing the T cells to recognize and kill cancer cells. The first of these to be researched is PD1/PDL1. Other checkpoint inhibitor proteins being studied are CTLA-4 and BCMA.

Gene therapies under development are designed to address defects in the genetic code, which cause a wide range of diseases. Many of these are rare diseases, affecting fewer than 100,000 affected patients.

In the U.S., it is estimated that 3 out of 10 Americans have one of the 6,000 identified rare diseases. The top three areas of focus for gene therapies at present are retinal diseases, liposomal storage disorders, and hematological disorders. The majority of gene therapies are delivered via viral vectors, including adenovirus, adeno-associated virus (AAV), lentivirus and herpes simplex virus – AAV accounts for 70% of all delivery vectors.

There is significant interest in non-viral delivery of gene therapies to address challenges in manufacturing (e.g., scalability, reproducibility) and safety (e.g., mutagenicity, toxicity) posed by the use of viral vectors. Physical approaches (e.g., genetic guns, electroporation, hydrodynamic techniques), naked nucleic acids, and chemical nanoparticles all show potential owing to their lower cost and simpler production requirements. AskBio, in particular, is developing Doggybone™ DNA constructs – a linear, double-stranded DNA vector which can produce longer, challenging sequences.

Current solutions, however, come at a trade-off: they are not as efficient as viral vectors at delivering genetic material to its intended target. Significant opportunities lie in both improving existing viral vector technologies and advancing nonviral delivery methods.

MAY YOU LIVE IN INTERESTING TIMES

Developers of cell therapies, including all types of stem cell therapies and modified cell therapies, such as CAR-T, have fundamental choices to make regarding their delivery approach. Autologous or personalized therapies are derived from a specific patient sample. Cytotoxic T cells (also referred to as "Killer T cells" or CD8+ cells) are isolated, in many cases engineered, expanded, and delivered back to the patient for infusion. These therapies require maintenance of the chain of identity, and each production batch is an individual product, thus requiring scale-out rather than scale-up for larger volume manufacturing.

DEVELOPERS OF CELL THERAPIES, INCLUDING ALL TYPES OF STEM CELL THERAPIES AND MODIFIED CELL THERAPIES, **SUCH AS CAR-T, HAVE FUNDAMENTAL CHOICES TO MAKE REGARDING THEIR DELIVERY APPROACH.**

Allogeneic therapies depend on samples taken from healthy people. The cells are isolated and genetically engineered (gene editing is one approach) to remove components that illicit immune responses in people other than the initial donor. As a result, they can be produced in large batches using scalable processes and packaged for future use.

Both of these technologies involve ***ex vivo*** delivery – the cell therapy is engineered outside of the patient's body in a manufacturing facility and delivered back to the patient for infusion into the body.

The latest area of development is focused on ***in vivo*** delivery. Gene delivery vectors are used to deliver CAR-T–like products, but with cell/gene modification taking place within the body. Alternatively, gene-editing tools are delivered to a specific target within the body where they repair genetic mutations.

Solid tumors are more challenging and represent the greatest opportunity. The tumor microenvironment is difficult to access, both from a physical standpoint and from an immunological perspective. The stroma, which includes connective tissue, blood vessels, and, very often, inflammatory cells, all of which are interposed between the malignant cells and normal host tissues prevents physical access for T cells.

Additionally, the tumor releases cytokines and other agents making cancer cells invisible to the immune system. Importantly, T cells become exhausted due to repeated activation, disappear from that environment and thereafter do not reside in memory B cells for future expansion.

BEYOND THE SCIENTIFIC CHALLENGES, A SHORTAGE OF MANUFACTURING CAPACITY POSES **A MASSIVE HURDLE FOR GROWTH IN THE CELL AND GENE THERAPY MARKETPLACE.**

ONLY 5%–10% OF THE REQUIRED CAPACITY EXISTS TODAY

Beyond the scientific challenges, a shortage of manufacturing capacity poses a massive hurdle for growth in the cell and gene therapy marketplace. Biotechs looking to outsource cell or gene therapy process development and/or production face an 18-to 24-month wait to access capacity at existing CDMOs.

This outcome has been due, in part, to a rapid confluence of investment and approvals of both CAR-T and gene therapies. The regulatory environment is quite favorable, and Kineticos estimates that an additional 10 new therapies a year will be approved in the U.S. alone by 2025.

With traditional biologics, approximately 35% of the process is outsourced. Our research indicates that for cell and gene therapies, 65% or more is outsourced. This can be largely attributed to the fact that about two-thirds of the innovation in this field is achieved by small biotechs that lack the expertise, capacity, or resources to commercialize products on their own. For many of these companies, investors want to know how they will manufacture their products at an early stage, making process development and production capabilities critical to their success from the outset.

The rapid growth of the clinical pipeline is another factor. The number of clinical trials is expanding at approximately 30% per year. While investment in CDMO capacity has been high at 30% – 35% annually, market growth is occurring at this same level. Furthermore, while there are approximately 130 CDMOs offering services to cell and gene therapy innovators, A full 80% of that capacity is to support clinical-stage projects, and 40% operates within the academic sphere. Just three companies — Thermo Fisher Scientific through its acquisition of BrammerBio, Catalent through its purchase of Paragon Biosciences, and Lonza have commercial-scale production capabilities.

Before those large transactions, several smaller deals were made in the space: Fujifilm Diosynth Biotechnologies bought Cellular Dynamics, Lonza purchased Pharmacell, and Hitachi acquired Apceth Biopharma. Most recently, Catalent announced that it is purchasing MaSTherCell, a European cell therapy CDMO.

YOU'LL LOSE YOUR TOE

The many advances in technology — RNAi, tumor-cell receptor (TCR), and tumor-infiltrating therapies, as well as gene editing and cell and gene therapies — are having a significant impact on the process development and manufacturing side as well as a tremendous effect on the infrastructure of the biopharmaceutical marketplace. To meet the growing demand for development and manufacturing support, CDMOs must add capacity — and they must determine whether to do so organically or inorganically.

Capital requirements must also be considered. Thermo Fisher Scientific and Catalent were able to acquire BrammerBio and Paragon Bioservices respectively, in part, because of their access to capital. This allowed them to meet the capacity and infrastructure investment requirements. In the gene and cell therapy space, CDMOs have to be fully committed, owing to the scale that is required. As the saying goes, this is not the place to dip a toe in the water.

Acquisitions in developing fields, regardless of size, create challenges. Integration of smaller, entrepreneurial CDMOs into larger organizations must be managed delicately. With just 5% – 10% of capacity needed in the next 10 years available, even the biggest CDMOs may struggle to keep up.

Coming back to the change of innovation, there is also a risk from a science perspective. The rapid rate of innovation within the sector could potentially lead to the obsolescence of initial technology investments. The complexity of gene and cell therapies and next-generation RNAi medicines adds further risk. Production of these products is an equal combination of art and science. Manufacturing solutions must be developed that enable robust, reproducible, and scalable processes to increase the science behind commercial production.

All companies involved in the cell and gene therapy field face a talent shortage. There are not enough people with expertise in process development and manufacturing of these complex next-generation medicines. This shortage is one key reason why 40% of capacity for early clinical materials production is academic-based. Training and development will, therefore, be crucial to the success of CDMOs and the field in general.

BIOPHARMA IS GOING H-U-U-U-U-G-E

Large biopharmaceutical companies are also active in the cell and gene therapy space. Novartis, Bristol-Myers Squibb (BMS), and Merck are investing billions into cell and gene therapy programs and manufacturing facilities. These companies have the capabilities, skill sets, and resources to build internal capacity, enabling quicker entry into clinical trials and presumably a shorter time to market. Unlike smaller biotechs, they do not have to wait for CDMO capacity. They have also established strong IP positions. In some cases, smaller biotechs are electing to form strategic partnerships with these big biopharma companies through technology licensing deals rather than wait for the chance to deal with CDMOs on a tactical basis.

Medium-sized companies are having the hardest time. They lack the power of big biopharma firms, but they aren't start-ups either. Some have sufficient investor backing, though, to invest in their own manufacturing capacity. Two examples in the United States are Precision Biosciences, which has a market cap of less than $1 billion but is investing $100 million in a plant in North Carolina. Locus Biosciences, a Series A funded biotech, is investing significantly in its own facility, also unwilling to wait for capacity to be available, even at second-tier providers. Elevate Pharma is pursuing yet another model that bridges the CDMO and biopharma worlds,

investing $200 million in cell and gene therapy manufacturing capacity, which it intends to use both for its own products and external customer projects.

The private equity/venture capital world is also getting directly involved in addressing the capacity shortage. One example is Deerfield Management Company, which has partnered with The Discovery Labs to form The Center for Breakthrough Medicines, a CDMO and specialty investment company focused on cell and gene therapies. The $1.1 billion facility will provide preclinical through commercial manufacturing of cell and gene therapies and component raw materials, offering process development, plasmid DNA, viral vectors, cell banking, cell processing, and support testing capabilities under one roof.

WHAT I WOULD DO (REALLY!)

With both great opportunities and significant risks associated with cell and gene therapies – and other advanced biological modalities – CDMOs should have strategies in place to maximize those opportunities while minimizing the risks. They also need plans for responding if the risks become real problems. Here are some steps CDMOs should consider.

Through the Looking Glass

CDMOs generally focus on the development and manufacture of drug substances and drug products. However, smaller biotechs – and to some degree large biopharma companies – want to partner with outsourcing providers that mirror all of the things they are responsible for doing, from research and development to manufacturing, testing, and regulatory approvals.

No one organization can offer all of these services. However, one innovative construct is for leading CDMOs to partner with CROs to provide end-to-end CMC and clinical development services. These CDMO/CRO partnerships could support biotech customers from discovery through development, manufacturing, and distribution through to patient recruitment and clinical trial management, and on to approval and commercialization.

Channel Your Inner Tortoise

While advanced complex biologics are high margin opportunities and require higher levels of outsourcing, they will be critical drivers of growth in the CDMO market of the future although they carry significant risk. Consequently, having a margin of safety with a balanced portfolio of stable, albeit, at lower margins, oral solid dosage (OSD) drugs help to de-risk the enterprise.

Oral Solids will continue to account for a significant percentage of the pharmaceutical market. CDMOs that are diversified in OSD and conventional biologics, as well as next-generation medicines, will be best positioned to survive a downturn in cell and gene therapies.

Imitation Is the Sincerest Form of… Learning

Small biotechs, which dominate innovation in the next-generation medicines marketplace, have unique requirements. A number of leading CROs have had great success in creating business units within the core of the larger organization focused exclusively on small biotechs. For example, IQVIA Biotech and PPD Biotech are separate organizations within the larger enterprise.

CDMOs that establish smaller business units focused specifically on biotech needs, with processes, pricing schemes, and support services that are designed for these agile and entrepreneurial firms, will be best positioned to succeed. It's not hard to see how a ThermoFisher Biotech or Catalent Biotech could gain even more share.

Get Ava on Your Side (Does Anyone Besides Alex Garland's Mother Get this Reference?)

Those CDMOs that also invest in artificial intelligence, machine learning, and real-time tracking will further enhance their performance and achieve even greater competitive advantage. We live in the age of Amazon. Not only do we want things free, now and, perfect, we also demand real-time updates and status.

CDMOs that can understand the promise of data, analytics, AI and ML and deploy these technologies to problem solve real issues and enhance communications with sponsors will gain a competitive advantage. Don't know how to do that? There are lots of smart people working on this for CDMOs already.

Listen to Greta or How Dare You?!

Yes, I know – I'm throwing in a zinger from left field, but hear me out. According to a recent Gallup poll, big pharma is the least admired out of 25 industries, right below the federal government! I don't believe that's a fair assessment. Let's just imagine a life without innovation in drug development and its effect on human health. That's a pretty scary thought for me. But it is reality, and the reasons for this predicament are fairly straightforward.

For CDMOs, addressing climate change could be a near term advantage not only externally with sponsors and shareholders but internally with employees. Human activity is causing temperatures to rise globally – this is a fact. Manufacturers that do not take steps to become carbon negative will be disadvantaged in the future. The pharmaceutical industry, including the outsourcing sector, is no exception. It's good business – plus it's the right thing to do. P

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Shailesh Maingi is Founder/CEO of Kineticos Life Sciences, an award-winning life sciences advisory firm. In 2019, Shailesh launched the Kineticos Disruptor Fund, investing in life science start-ups. In 2020, he started Inceptor Bio, a biotech accelerator hub focused on advanced biological modalities such as gene therapy, cell therapy and gene editing. He cofounded the InVincible Cancer Research Fund in 2019. Shailesh serves on the Board of Directors for numerous biotechs and is Adjunct Faculty at UNC's Kenan-Flagler School of Business.

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