New Modalities Hog the Limelight

Cell and gene, mRNA, bispecifics, and ADC therapy industries turn the tide as CDMOs see service demand soar. This is the fourth of a nine-part series of articles addressing pharmaceutical outsourcing industry trends.

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Contract development and manufacturing organizations (CDMOs) specializing in large molecules are in hot pursuit of acquiring newer capabilities as the biologics industry increasingly embraces diverse therapies and modalities.

Highly sophisticated therapeutic proteins, cutting-edge nucleic acid drugs, cell and gene therapies (CGTs), and antibody-drug conjugates (ADCs) are rapidly becoming vogue in a pharma world that develops more biologic products than ever before.

"For novel modalities like mRNA, ADCs, and viral vectors we generally see higher growth than in established modalities like mAbs," says Dirk Lange, head of life science services, MilliporeSigma, the life science business of Merck KGaA, Darmstadt, Germany. The company offers contract testing, development, and manufacturing (CTDMO) services across various segments including ADCs, mAbs, mRNAs, and viral vectors.

Viral vectors are used to deliver genetic material into cells for gene therapies. For cell therapy, the genetic engineering of chimeric antigen receptor (CAR) T cells is a primary service.

CGTs are riding the wave with the promise that these "disruptive" technologies have the potential of even curing the disease.

Reports show that, presently, over 1,000 players are developing more than 3,500 CGTs collectively around the world. The burgeoning global cell therapy market is expected to expand at a compound annual growth rate (CAGR) of 14.15% from 2023 to 2030, according to Grand View Research. The gene therapy market is poised to flourish at a CAGR of 18.6% from 2022 to 2027, estimates Markets & Markets.

With outpacing growths, CGTs, mRNAs, and ADCs are fast emerging as important niches in the biopharmaceutical industry. And increasing outsourcing in these segments warrants CDMOs to acquire different sets of skills and equipment.

Emerging and virtual firms, which represent the majority of the advanced biotherapeutic developers, are driving the future biopharma pipeline. These small enterprises can't plausibly

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make it to the market without the help of an external development partner. Whereas, for bigger players it hardly makes sense to invest in building an all-new facility involving prohibitive costs for a mere one, two or a maximum of three assets, experts say. Moreover, it is difficult to develop expertise in so many different technologies these new modalities generally encompass.

Presently, as much as 86.9% of biopharmaceutical companies outsource at least some of their activities contributing to building a $14 billion biopharmaceutical contract manufacturing industry, according to a survey report published in March 2022 by Global Information, Inc., a market research firm. Viral vector manufacturing is currently the most outsourced task.

The survey also found that biopharma firms added at least eight more new activities to their outsourcing within 2 years' time span making it to a total of 26 from 18 functions in 2020.

CDMOS GAIN ACCESS TO EXPERTISE

As outsourcing companies increasingly raise the scope of contracting, many CDMOs choose the acquisition route to quickly gain access to expertise in emerging modalities.

Recipharm, which closed a series of three acquisitions on this front in one year, offers an example. In 2022, the Swedish CDMO bought the Massachusetts-U.S.-based mRNA therapy CDMO Arranta Bio and virotherapy CDMO Vibalogics as well as Portuguese CGT company GenIbet.

Piramal Pharma Solutions, a leader in ADCs, added capabilities in recombinant vaccines, RNA/DNA vaccines, mAbs and gene therapies as Piramal Pharma, its parent firm, boosted its stake in Yapon Bio, a Hyderabad, India-based CDMO in December 2021.

Chinese CDMO WuXi AppTec announced the purchase of UK-based CGT specialist Oxgene in early 2021.

Other noteworthy acquisitions in this field include Catalent's $1.2 billion buy of Paragon Bioservices, a leading viral vector development and manufacturing partner in 2019. In the following year, the Somerset, New Jersey-headquartered CDMO purchased Belgian cell therapy manufacturing specialists MaSTherCell and Bone Therapeutics and in early 2021 bought out Delphi Genetics, a pDNA specialist.

Similarly, Thermo Fisher acquired viral vector manufacturer Brammer Bio, paying $1.7 billion in 2019 and subsequently bought Novasep's viral vector business in Belgium.

VERSATILE MRNAS

Interest is increasing in mRNAs, next generation mAbs, and ADCs, provoking an upsurge in investments.

New modalities, such as CGT and mRNA vaccine technology, have increased from 11% to 21% of the drug development pipeline—the fastest growth ever seen in the sector, shows a report by McKinsey & Co. published last year.

The COVID-19 pandemic and the thundering commercial success of the mRNA vaccines have driven a wave of nucleic acid drug development. Researchers are currently exploring dozens of new possibilities for the mRNA platform.

"With the pandemic, we saw a very rapid adoption of RNA technologies, which we expect to drive continued strong growth in this modality," says Lange of MilliporeSigma.

MilliporeSigma, whose service offerings cover the entire lifecycle of mRNA products with capabilities in lipid manufacturing, drug substance manufacturing, liquid nanoparticle formulation services, and drug product manufacturing, is experiencing very high growth rates in this modality.

"This growth is further supported by the versatility of the modality with potential application across multiple therapeutic areas including infectious diseases, cancer, and rare diseases," Lange says. "For us as a CTDMO the emerging capabilities around this modality are a clear opportunity."

Presently, more than 195 mRNA therapeutics / mRNA vaccines are under development or commercialized, according to a recent report by Research & Markets, for the treatment of a variety of indications.

In terms of service offering, if we look at the mRNA molecule pipeline, there is a high concentration of early-phase programs and a very high growth rate of new molecules entering the pre-clinical and clinical stages. This, according to Lange, requires a strong template to advance client programs into the clinic in an accelerated and efficient way.

Through integrated offering across the mRNA manufacturing process, the CTDMO is decreasing supply chain complexity and enhancing speed-to-market, he avers.

mRNA products enjoy multiple benefits including shorter development timelines and higher biological efficiency. Proponents of RNA therapeutics argue that though in early stages, there is no more powerful class of therapeutics that has ever been developed in the history of pharmaceuticals and mRNA vaccines were a wonderful proof-of-concept for the industry.

Industry experts, however, seem more guarded when it comes to the yet-to-be-proven efficacy of mRNA therapeutics for indications beyond COVID-19.

"The biggest challenge [with mRNA products]," says Lange, "is to create prove points beyond the COVID indication."

THERAPEUTIC PROTEINS: THE TOP DOGS

Even as CDMOs expand or diversify their service scope to the new modalities, mAbs and recombinant proteins continue to make up the highest demand segment within the large molecules outsourcing industry, in terms of large volume production needs.

"In particular, there has been the rising client demand for the production of more complex mAbs and recombinant proteins such as bispecifics, multispecifics, and antibody-drug conjugates (ADCs)," says Ji Sun Choi, lead market intelligence specialist at Samsung Biologics, Incheon, South Korea.

The global bispecific antibody (BsAbs) therapeutics market is estimated to grow up to $16.7 billion in 2028 with a CAGR of 25.9% during the forecast period of 2022 to 2028, as per 360 Research Reports.

By dual specificity, BsAbs target different disease mediators. Besides the currently approved catumaxomab (anti-EpCAM and anti-CD3) and blinatumomab (anti-CD19 and anti-CD3), more than 60 different bsAb formats exist. Some of them are in clinical studies.

Samsung Biologics, which has the largest manufacturing capacity for mammalian-based biologics in the world, has a proprietary bispecific antibody development platform S-DUAL that can design and create a unique asymmetric, knob-in-hole paired bispecific antibody structure tailored to each client's needs, explains Choi.

For drug development, Samsung Biologics offers a suite of development services to quickly advance a drug pipeline from gene to Investigational New Drug Application (IND), from rapid target discovery and screening to expedited drug development for IND filings as fast as nine months.

Along with speed, it is essential, emphasizes Choi, that CDMOs operate with flexibility, quality, and efficiency to cater to each client's needs.

Choi also contends that nowadays, Big Pharma companies recognize the value of having competitive CDMOs as their long-term strategic partners.

Samsung Biologics has CDMO deals with as many as seven out of the top ten global pharma MNCs.

ADCS SOUND BIG DEALS

ADCs are another modality in biotherapeutics that is attracting huge outsourcing. As much as 70%-80% of ADC therapeutics developers prefer to outsource their operations to contract manufacturing organizations (CMOs), found a research survey published in September 2022 by Roots Analysis, a global business research and consulting company.

With about 37% of the installed manufacturing capacity available in the Asia-Pacific region, global demand for ADC contract manufacturing is anticipated to grow at a CAGR of 13%, during 2022-2035.

Due to their increased durability relative to traditional chemotherapy, ADCs have commanded the highest deal value compared to any other technology in oncology in the last five years. The blockbuster potential of commercially launched ADCs prompted venture capitalists to steadily increase funding since 2018, with an aggregate of about $1.8 bn invested by the end of 2022, show reports.

Currently, more than 500 industry-sponsored active clinical trials involving more than 140 ADCs are ongoing.

However, ADC developers face significant manufacturing hurdles, particularly the conjugation of the antibody to the highly active cytotoxic component.

Lange says MillporeSigma provides everything from raw materials to the antibody, payload and linker, and the CTDMO performs the conjugation. Its proprietary technologies help bring tangible benefits to ADC clients which result in increased flexibility and speed to the clinic.

TALENT CRUNCH: THE REAL CHALLENGE?

Evidently, biologics are getting increasingly complex. This coupled with an increasing focus on personalized medicine means more niche products and smaller batch sizes.

Even though the supply chain challenge is lightening up slowly, huge capital investments for capacity and capability development, compliance with stringent regulatory guidelines, and concerns about IP protection, etc., continue to remain as major hurdles for CDMOs.

However, the real challenge will continue to be having access to trained and skilled manpower with the required quality expertise. The challenges of hiring and retaining good staff will become more acute in the days to come, reports show. The CPHI 2022 annual report also identifies access to talented R&D and CMC personnel as the main potential headwinds to market growth, particularly for cell and gene therapy innovators.

"CDMOs must hire and retain highly skilled employees with distinguished expertise and capabilities to provide tailored services over various complex biotherapeutics," says Choi of Samsung Biologics. **CP**

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