DESIGNING A CUSTOMER-CENTRIC CDMO

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As biologic drug substances and their manufacturing processes become more complex, and smaller biotechs play a greater role in drug development, outsourcing to contract service providers is also growing. Successful biopharmaceutical CDMOs must offer advanced technologies and flexibility that enable highly efficient, lower-cost production of high-quality products across the entire development cycle to support clients located around the world.

RAPIDLY EXPANDING BIOPHARMA MARKET

Growth of the global biologics market has been fairly steady over the last 15 years, expanding on average at a very healthy rate of approximately 12% per year. Revenues have increased by 6250%, and today biologic drugs account for approximately one-quarter of the total biopharmaceutical market.[1] In both 2002 and 2017, biopharmaceuticals accounted for 35% of the new drug approvals issued by the U.S. Food and Drug Administration (FDA), and throughout the period the percentage varied only slightly up or down.[2] Today, of the top selling drugs worldwide, seven of the first 10 and 12 of the first 20 are biologic therapies. Seven of those top 12 biopharmaceuticals were based on mAbs.[3]

The value of the global biopharmaceutical market, including monoclonal antibodies (mAbs), recombinant growth factors, purified proteins, recombinant proteins, recombinant hormones, vaccines and synthetic immunomodulators, was estimated to be slightly more than $237 billion in 2018 and may reach nearly $389 billion in 2024.[4] A different analysis assessed the market at $186 billion in 2017 and projected growth to $526 billion by 2025.[5]

Biosimilars, while initially growing more slowly than expected, may be experiencing a resurgence of interest that could drive even greater growth in the overall biopharmaceutical market.[6] A greater number of biosimilars is expected to be approved going forward while much of the ongoing litigation slowing the introduction to the market of many biosimilars will be resolved. In addition, the FDA is implementing initiatives designed to increase biosimilar uptake. The global market for biosimilars is estimated to be expanding at a compound annual growth rate (CAGR) of 31.7% from $4.49 billion in 2017 to $23.63 billion by 2023.[7]

In the next few years, breakthroughs in immunotherapies, and gene and cell therapies will bring more novel, diversified biologics into the market and contribute to significant growth. Gene and gene-modified cell therapies were approved for the first time by the FDA in 2017. According to the Pharmaceutical Research and Manufacturers of America, in the United States alone, nearly 300 cell and gene therapies were in development for a broad range of diseases in 2018.[8]

SHIFT IN FOCUS FROM BLOCKBUSTERS TO NICHE THERAPIES

Expansion of the biologic drug market has been occurring simultaneously with a shift in focus of the overall pharmaceutical industry away from blockbusters to niche therapies that treat rare diseases. This shift has in large part been driven by legislation passed in several countries encouraging and incentivizing drug manufacturers to develop treatments for the thousands of rare diseases that currently have no cures.

Estimates for the value of the global market for orphan drugs vary, with the market expanding at CAGRs of 6.8% to 12.1% to $169[9] to $209[10] billion by 2022 and $318.5 billion by the end of 2025.[11] It is predicted that orphan drugs will account for 21.4% of global prescription sales in 2022, excluding generics (up from 6% in 2000).[10] Biologic drugs have the greatest market share, owing to their ability to precisely target disease pathways.[12]

GROWING ROLE FOR BIOLOGICS CDMOs

While initially many biopharmaceutical manufacturers preferred to maintain control of all of their development and manufacturing efforts, as the market — and the complexity of branded biologics and biosimilars — has grown, the interest in outsourcing manufacturing for established products has also increased. The growing importance of emerging and small biotech firms is also driving the growth in the outsourcing sector, as these companies do not have the in-house resources or capabilities and prefer to rely on third-party experts.

The decision to outsource is often made by the needs to expedite research and development, shorten the time to market, gain access to novel technologies and regulatory expertise, increase flexibility and minimize risks, all at a competitive cost. The use of CDMOs can also help drugmakers address potential capacity constraints.

More recently, biopharmaceutical innovators have begun to engage with their contract manufacturers much earlier in the development cycle, given the growing preference for using quality-by-design (QbD) and the desire to better understand products and processes. Full-service contract development and manufacturing organizations (CDMOs) offer a comprehensive set of services from early development to commercial manufacturing in an integrated process.

THE DECISION TO OUTSOURCE IS OFTEN MADE BY THE NEEDS TO EXPEDITE RESEARCH AND DEVELOPMENT, SHORTEN THE TIME TO MARKET, GAIN ACCESS TO NOVEL TECHNOLOGIES AND REGULATORY EXPERTISE, INCREASE FLEXIBILITY AND MINIMIZE RISKS, ALL AT A COMPETITIVE COST.

CHARACTERISTICS OF A SUCCESSFUL CDMO

Compared with the synthetic chemical processes used for the production of small molecule APIs, the biopharmaceutical manufacturing process is more complex and costlier to develop, operate and maintain. Successfully developing biologics requires a combination of state-of-the-art facilities and a broad array of technological and operational expertise.

Biopharmaceutical CDMOs must be agile in adopting technological advances in order to lead process innovation and operational efficiency, including single-use technologies and continuous bioprocessing solutions. They must also implement proprietary technology platforms consistently across development phases and global networks of manufacturing facilities to reduce project costs and

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timelines. In addition, as the industry shifts away from large-scale to smaller-scale production of niche and targeted therapies (e.g., personalized medicines and orphan drugs), flexibility in operational capabilities, production scales and multiple-product operations are essential for CDMOs.

DESIGNING A CUSTOMER-CENTRIC CDMO

Owing to the nature of process development, results are not always exactly as expected. To ensure the success of a given molecule, we encourage an open communication framework with our customers. To build the trust necessary to overcome these challenges, a customer-centric CDMO concept is essential, in which every employee treats the product and processes as their own, where communication flows between the customers and the core team and all customers and employees have easy access to top management in order to make timely decisions.

AGC Biologics was formed with all of these requirements in mind. Integration of the capabilities of AGC Bioscience, Biomeva GmbH and CMC Biologics generated a CDMO with deep industry expertise in both mammalian cell culture and microbial fermentation methods for the scale-up and cGMP manufacture of protein-based therapeutics, from preclinical to commercial production.

AGC Biologics is a customer-centric CDMO that employs technical acumen and innovation to develop and manufacture complex biologic clinical material and provide secure global clinical and commercial supply for mammalian- and microbial-based therapeutics. We have manufacturing facilities at a variety of scales for mammalian cell culture and microbial fermentation in Berkeley, California and Bothell, Washington, as well as in Heidelberg, Germany, Copenhagen, Denmark and Chiba, Japan.

We have implemented the same systems, technologies and management practices across all of our sites, integrating nine different business areas, including operations, quality, IT and our supply chain. Our people are also encouraged to share best practices with different sites and to work at multiple locations so they can learn from one another. As a result, transfer and scale-up of projects as they move from early to late-phase or expand to meet demand in new geographies can occur seamlessly within our global network.

AGC Biologics also has an ambitious strategic growth plan that includes significant investment in our various production facilities. We expanded our site in Copenhagen, Denmark to support demands from current and potential new customers developing orphan drugs and niche products. The expansion includes addition of a proprietary Single-Use Bioreactor (SUB) 6Pack™ suite, consisting of six 2,000-L production bioreactors and a 2,000-L seed train to enable more flexible, innovative and customized cGMP production capabilities at scales from 2,000-L to 12,000-L within a single run. Capabilities for harvesting, purification, buffer and media production to support the processing of different therapeutic proteins, including high antibody titer processes, were also added.

AGC Biologics is now in the process of adding to our microbial manufacturing capabilities in Chiba, Japan a new state-of-the-art mammalian cell-culture process development and manufacturing facility – the first facility of its kind in Japan. Expected to be operational in Q3 2019, the new facility will include 500-L and 2,000-L single-use bioreactors suited for the production of monoclonal antibodies (mAbs), fusion proteins and other therapeutic proteins.

In March 2018, we announced the addition of a 2,000-L single-use bioreactor (SUB) as part of a production expansion project at our Berkeley, California facility. In July 2018, we opened our new global headquarters in Bothell, Washington, which houses Process Development labs and Corporate Administrative offices, as well as provides expansion space for additional manufacturing capacity. The new headquarters enables us to further integrate the development, manufacturing and commercial functions at our global headquarters and reinforce the effectiveness of our extensive global network.

We also plan to install 2x 6Pack™ (12 additional 2,000-L single-use animal cell bioreactors) at our Bothell site and establish a new CDMO facility for microbial cells, an offering that was previously only available in Europe and Japan. This expansion will triple AGC's biopharmaceutical production capacity in the United States while also ensuring seamless operation of microbial and animal cell-based biopharmaceutical CDMO activities across the Japan, Europe, and U.S. regions. The total investment for this expansion is estimated at about $75 million, with full-scale operations slated from July 2020.

Collectively, our global network of facilities provides us with well-aligned development, manufacturing, and quality/compliance systems and procedures and is capable of providing seamless tech transfers and scale-up, geographical expansion and out-licensing, and security of clinical and commercial supply of mammalian- and microbial-based therapeutics.

Additional expansion in the United States is planned for the near future. AGC Biologics has also been actively investigating M&A opportunities in the cell and gene therapy space, which we expect to be a key growth area for the company going forward.

DEEP EXPERTISE AND FLEXIBILITY

AGC Biologics has deployed unique technologies that enable acceleration of de-

velopment timelines, getting customer projects from the DNA stage to IND filing in less than 14 months.

Our proprietary CHEF1® mammalian expression system is a robust and scalable expression platform that enables the development of cell lines in a 12- to 14-week period. The system is well recognized by regulatory authorities, with four approved products on the market and many more in clinical trials that have been developed using CHEF1® technology.

We have also developed expertise in continuous cell culture – or perfusion – processing. High cell densities can be achieved and operated for extended periods, resulting in higher volumetric productivity than traditional fed-batch manufacturing. The product is harvested continuously, enabling continuous downstream purification at a small scale, making continuous bioprocessing more capital-equipment efficient. We are also exploring continuous chromatography for enhanced downstream processing capabilities.

OVERALL, AGC BIOLOGICS HAS MANUFACTURED MORE THAN 200 BIOLOGICAL PROJECTS, FROM PRECLINICAL STUDIES THROUGH COMMERCIAL APPROVALS, **INCLUDING RARE-DISEASE TREATMENTS AND PERSONALIZED MEDICINES, MORE TRADITIONAL ANTIBODIES AND PRODUCTS WITH ACCELERATED APPROVAL PATHWAYS.**

Overall, AGC Biologics has manufactured more than 200 biological projects, from preclinical studies through commercial approvals, including rare-disease treatments and personalized medicines, more traditional antibodies and products with accelerated approval pathways. Within our portfolio, we are currently working on getting 12 late-phase products to market within the next three years.

One major trend in the industry that we are closely following is the growth in niche products that target rare or orphan diseases. These drugs tend to be the kinds of complex molecules that we specialize in working with, so we are well positioned to support clients working in this space.

We are interested in working with companies that are looking for a CDMO that will collaborate closely and serve as an extension of their own operations. We can support projects from cell line development to commercial launch and market growth. With our flexible capacity that grows as needed, advanced technologies including continuous manufacturing and our ability to work on accelerated pathways, as well as a customer-centric culture that fosters a warm and positive collaborative experience, AGC Biologics makes it possible for our customers to get their high-quality treatments to patients as quickly as possible. P

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Patricio joined AGC Biologics (previously CMC Biologics) in August 2012 as General Manager and Managing Director of the CMC Biologics A/S based in Copenhagen. He then served as Chief Operating Officer for over two years before the board appointed him to the role of CEO in May of 2019. During his 20-year career, Patricio has held several key executive positions at MSD AH, Intervet/Schering-Plough, Biogenesis-Bagó and other Biotech companies in Spain, Brazil and Argentina developing, manufacturing and controlling biotechnological products and vaccines for human and animal health. Patricio holds a biochemist degree from the University of Buenos Aires and a Master's of Business Administration from UCEMA.

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