BUILDING A ONE-STOP SHOP CDMO FOR BIOPHARMACEUTICALS

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The rapid growth of the biopharmaceutical market has created increasing demand for contract development and manufacturing services. Contract development manufacturing organizations (CDMOs) that can provide support across the full development life cycle, from cell line development to commercial manufacturing, can reduce the time to market for their clients. However, there are few true one-stop shop organizations providing support to pharma companies developing biosimilars and branded biologics.

STRONG BIOPHARMA DEMAND

The global market for biopharmaceuticals was valued at $192.2 million in 2016 and projected to grow at a compound annual growth rate (CAGR) of 8.6% to reach $291 billion by 2021, according to Mordor Intelligence.[1] Biopharmaceuticals currently represent approximately 20% of the entire pharmaceutical market revenue, and this is expected to increase in the future, as growth is predicted to exceed that of non-biologics.

Although outsourcing of biopharmaceutical manufacturing provides access to advanced technologies and necessary capacity, while also offering the potential for project acceleration and cost reductions, reliance on CDMOs does introduce risk into a project and has its own challenges. There are, in fact, a limited number of contract manufacturers with the capacity to provide large-scale biopharmaceutical manufacturing. According to McKinsey & Co, there are only 10-20 biopharmaceutical CDMOs, and in 2015 only three suppliers had six or more 12,000 L bioreactor lines,

RAPID PROCESS DEVELOPMENT AND OPTIMIZATION ARE ACHIEVED THROUGH THE **EXTENSIVE USE OF MULTIVARIATE EXPERIMENTAL DESIGNS FOLLOWING QBD PRINCIPLES.**

with a few others possessing one or two 12,000 L lines.[2] Furthermore, in 2015 the overall cell culture capacity utilization for biopharmaceutical CDMOs is >85%, and was expected to increase with the growing acceptance of biosimilars combined with increasing interest in novel biologic drugs.[2]

What the market needs is CDMOs that offer a comprehensive portfolio of services supporting the entire biopharmaceutical development cycle, from cell line development through clinical and commercial manufacturing with full analytical capabilities and regulatory expertise. Ideally, these highly integrated CDMOs will be located where they can readily support the European and North American markets, which account for over 80% of the consumption of biologic drugs.[2]

NEED FOR FULLY INTEGRATED CDMOs

Recognizing the significant need in the marketplace for integrated biopharmaceutical CDMO services, Polpharma Group began to take steps in 2013 to establish comprehensive capabilities to support the full drug development cycle. With more than 80 years of experience producing generics and over-the-counter medicines, and as one of the largest pharmaceutical companies in Central and Eastern Europe, Polpharma has extensive expertise in GMP/regulatory compliance and the quality assurance to support such an endeavor.

Polpharma Biologics was established in 2013 as a division of Polpharma Group. Today, the company has five biosimilars in development. Cell line development capabilities were added in 2016 with the acquisition of Bioceros in the Netherlands. In addition, Polpharma Biologics is currently adding the capability to produce final drug product (five million vials/syringes per year) at the Gdańsk facility. Construction of a commercial manufacturing facility at Duchnice near Warsaw is underway, which will eventually have 12 x 2,000-liter production trains and an annual fill-finish capacity of 30 million vials and syringes. The additional capacity in Gdańsk and the new site in Warsaw will be operational for drug substance and drug product manufacturing in 2019.

All of these activities are directed toward the vision of a CDMO that can serve as a true modular one-stop shop for pharma-biotech companies looking for support for their biologics or biosimilars. Polpharma Biologics has, in fact, been specifically structured as a European biopharmaceutical CDMO that offers fully integrated solutions along the biopharmaceutical development and production value chain to serve global market needs, not only for today but also into the future. It provides fast, flexible, responsive service with a focus on mammalian cell culture and capabilities, spanning the full range from cell line, process and analytical development to GMP manufacture of drug substance and drug product meeting international quality standards.

MAGIC IN THE CELL

With an increasing emphasis on the cost of goods (COGs), identification of highly productive cell lines is essential for the successful development of biosimilar and innovator drug processes. High-yielding cell lines allow the use of smaller-scale upstream and downstream processing equipment, resulting in reduced capital expenditure and the potential for fewer batches per year for lower operating costs.

For more than 10 years, Bioceros, part of Polpharma Biologics, has generated high-yield production cell lines for both biosimilar and innovative proteins based

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on its proprietary CHO$^{BC®}$ platform technology. This platform is complemented by a comprehensive science-based toolbox for targeted modulation of post-translational modifications to accomplish fingerprint biosimilarity, which can be readily analyzed using robust in-house bioassays.

The CHO$^{BC®}$ master cell bank contains cells intensively tested for the absence of viral elements according to the ICH guidelines, with CHO$^{BC®}$ cell lines successfully upscaled to 1,000 L. Currently, a monoclonal antibody (mAb) biosimilar generated using a CHO$^{BC®}$ production cell line is in clinical trials. Bioceros has developed a range of innovative therapeutic mAbs that are available for clients to quickly embark on new clinical programs.

Bioceros is equipped with a full range of cutting-edge, high-throughput technologies capable of achieving rapid generation of optimum, high-producing cell lines that meet specific quality-attribute requirements. These technologies are supported by a wide range of advanced analytical capabilities, including mass spectrometry, in addition to state-of-the-art chromatography systems for clarification and purification, as well as the custom design and execution of bioassays. With this approach, Bioceros is able to achieve a locked 50 L process (using single-use disposable bioreactors) ready for upscaling within 18 months for a new molecular entity, and within 22 months for a biosimilar.

OPTIMIZATION AND UPSCALING OF MANUFACTURING PROCESSES

With its one-stop-shop approach, Polpharma Biologics is positioned to provide a comprehensive range of services tailored to each individual project, including *de novo* process development, process optimization and manufacturing of fully developed processes.

At the beginning of a typical biosimilar program, for instance, more than 40 different analytical methods are developed in-house to deeply characterize the protein of interest and further identify its core quality attributes, which play a crucial role in the biosimilarity of the final product. For projects that begin with cell line development, further optimization of the upstream and downstream processes greatly increases productivity while maintaining all relevant quality attributes.

Rapid process development and optimization are achieved through the extensive use of multivariate experimental designs following QbD principles. Customized formulations for both drug substance and drug product can also be developed in-house and subsequently tested for stability according to ICH standards. Upstream process development capabilities include research cell bank production and media feed optimization.

Clinical manufacturing takes place at the Biotechnology Center in Gdańsk, which houses bioreactors that contain volumes up to 1,000 liters for cell culture and 500 liters for bacterial processes. Commercial GMP manufacturing using scale-down models, as well as high-throughput mini- and regular bioreactor systems for parallel screening, will be operational at the new Duchnice facility by 2019. Downstream development services include identification of optimum protein purification processes based on design of experiment (DOE) models combined with full scale-down and scale-up capabilities. A wide range of chromatography systems and single-use tangential flow filtration (TFF) are employed.

With successful technology transfer being crucial for effective biologic drug development and commercialization, Polpharma Biologics has fully aligned technologies at all of its facilities. The use of comparable – and in many cases identical – equipment for research, development and production combined with intense collaboration between manufacturing and development teams facilitates smooth and fast in-house transfer.

PARTNERSHIP FOR THE FUTURE

CDMO services from Polpharma Biologics are tailor-made for customers from all over the world for both biosimilars and innovative molecules, including next-generation biologics such as newer antibody frameworks and antibody-drug conjugates (ADCs). As a fully integrated CDMO, Polpharma Biologics offers support for all steps in biopharmaceutical development programs and works with clients through a variety of relationships, from a purely fee-for-service basis to risk-sharing co-developments and strategic partnering. Investments in laboratory and production facilities, state-of-the-art single-use production, analytical equipment and highly qualified and talented bioprocess experts are backed by a long and successful history of Polpharma, which has demonstrated commercialization capabilities and industrial CDMO expertise.

At Polpharma Biologics, we are eager to develop partnerships with clients looking for a biopharmaceutical one-stop shop that can provide both development and large-scale industrial production services. P

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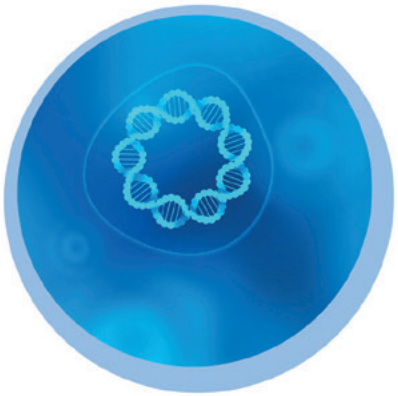

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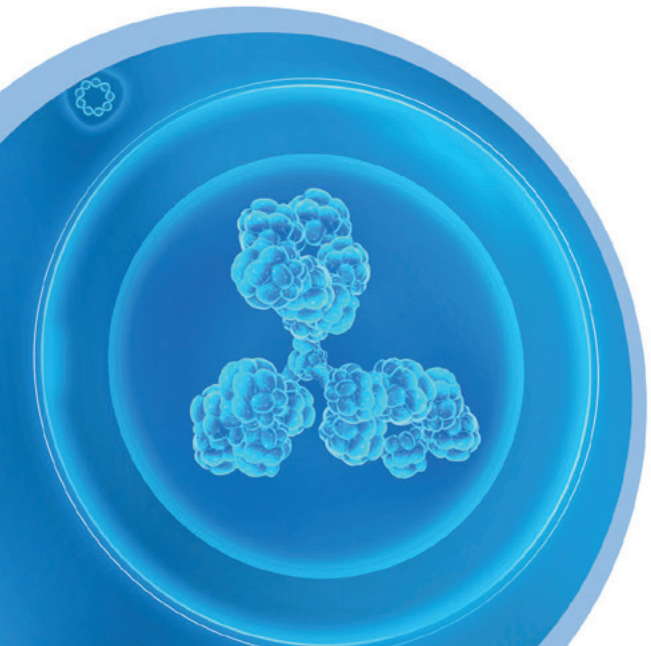

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