BIOPHARMA CMO MARKET TRENDS

All signs point to continued strong growth in the biologics segment driven by robust development pipelines, increased drug approvals, the rise of biosimilars and incentives to go after neglected or unmet medical needs.

The biopharma market is robust and the biopharmaceutical contract manufacturing industry continues to grow as the demand for outsourced services increases. Strong growth in the biopharma market is being driven by both new biologic products and biosimilars.

“We are seeing exciting new therapies in development across multiple therapeutic areas that could transform patient treatment,” said Mike Riley, vice president and general manager, Catalent Biologics. “Continued growth in demand from an aging population in developed markets, as well as increased investment in biologics in developing markets is fueling overall market growth. We also continue to see significant technology innovation opening up opportunities around new targets, molecules, and delivery approaches. We are seeing strong growth in the contract manufacturing market, and believe that growth will continue based on strong underlying market demand and increasing propensity for the industry to outsource.”

Most industry reports have the biopharmaceutical market growing at between 10-15% annually in sales of biologics with similar growth projected in the coming years. Currently sales of biotherapeutics are in excess of $200 billion and are doubling every 5 years. Given that many predict that this rate of growth trend will continue, companies are investing more in biomanufacturing-related R&D, including hiring staff and expanding manufacturing capacity. Also, new facility construction budgets are at an all-time high. While the biopharma market is global, the U.S. continues to be the source for most invention, development, and manufacture of biopharma products.

“The current biopharma market is very dynamic with a lot of activity,” said Martin Meeson, president, FUJIFILM Diosynth Bio-
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“...technologies U.S.A. “We are seeing new kinds of therapeutic approaches aiming for the clinic. We are also seeing more and more therapies getting closer to the commercialization stage. This is a great time for our industry and the patients that we serve. There are several factors that we can see are having a big impact. For one, venture capital funding is certainly having a huge impact on the number of new companies with new approaches. Immunotherapy is a good example of this, entering the industry and aiming for an IND. We are also seeing regulatory agencies having an impact with orphan and breakthrough status designations that are propelling the industry forward.”

**BIOSIMILARS FUELING GROWTH**

The interest in biosimilars is fueling growth in the biopharma market. The global biosimilars market value reached approximately $20 billion by the end of 2015 and could exceed $55 billion by 2020.

“...There are approximately 20 biosimilars approved in Europe, one of which is a monoclonal antibody,” said David Cunningham, director, corporate development, Goodwin Biotechnology. “This reflects a 50% acceptance rate, and the number of biosimilars is expected to increase significantly in the upcoming years.”

However, the United States has fallen behind Europe in approving biosimilars. But, the logjam has started to break, according to Mr. Cunningham. “In late 2015, Novartis/Sandoz launched the first U.S. biosimilar, Zarzio (filgrastim), an alternative to Neupogen,” he said. “Most recently, the FDA has approved an infliximab biosimilar. Further, the FDA is currently reviewing Sandoz’s biosimilar to Enbrel (etanercept) and the FDA is reviewing a biosimilar to Neulasta (pegfilgrastim). With these biosimilar approvals, coupled with the others that are in the queue, the number of biosimilars is expected to outnumber their reference products, changing the underlying nature of the biopharmaceutical industry with everything becoming more like traditional drugs with generics dominating.”

The development pipeline is strong according to the PhRMA 2016 Biopharmaceutical Research Industry Profile with over 7,000 biopharmaceutical medicines in development around the world.

“Investment by large pharmaceutical companies and venture capital firms remains strong,” said Don Paul Kovarick, technical marketing specialist, Althea. “With a few exceptions, there aren’t many opportunities to develop drugs for blockbuster indications anymore. As drug developers increasingly focus on personalized medicine and orphan designations, more lower-volume products are being introduced to the market. Smaller indications require smaller production batches and this creates a need for flexible, multiproduct facilities. Manufacturing operations need to become more efficient and the time needed to changeover from one production run to the next needs to be shortened.”

In majority of the developed world, populations are aging and the associated diseases are on the rise. Examples include cardiovascular disease, dementia/Alzheimer’s disease, diabetes and cancer. According to the National Council on Aging, about 92% of older adults have at least one chronic disease, and 77% have at least two. In addition, chronic diseases account for 75% of the total money spent on healthcare.

“There is a tremendous opportunity for biopharmaceutical companies to help millions of people manage or potentially cure these diseases,” said Mr. Kovarick. “With healthcare costs increasing year over year and brand name drugs being a primary driver, the pharmaceutical industry is increasingly under pressure from politicians, patient advocacy groups, and the general public. Affordability and sustainability are very real concerns for all stakeholders. As a result, developers are looking to reduce production costs, simplify supply chains, and optimize manufacturing networks and infrastructure. Some of the burden will be passed on to its development partners to implement new technologies to increase yields, reduce waste, speed up development and keep cost of goods low. In addition, the FDA has implemented a number of accelerated approval tracks that have shortened development timelines. These time pressures are shared by development partners.”

In the U.S., the Biologics Price Competition and Innovation Act of 2009 created a streamlined pathway to regulatory approval for biosimilars. The EU had already enacted their own version back in 2004.

“These laws allowed developers to reference preclinical and clinical study data of the already marketed product as part of the application process; thus, saving time and resources by not having to repeat some of the human and animal testing,” said Mr. Kovarick. “As a result, biosimilar programs generally have more condensed development timelines. There is even more time pressure as developers race against each other to be the first to market with their own versions of the biosimilar.

**TECHNOLOGY INNOVATION TRENDS**

Technology innovation is the root to continued strong growth in the biologics segment, which will lead to growth in the CMO market as well.
Catalent’s Mr. Riley said there is a trend to more niche and orphan products with smaller target patient populations. “Given that many of these products can move quickly through the clinic, chemistry, manufacturing and controls (CMO) can become a critical path item to product approval and launch,” he said. “We also see increasingly complex analytical requirements earlier in development, both for NBEs and biosimilars. Catalent is investing in capabilities in all of these areas.

He also said mammalian production of traditional monoclonal antibodies and other proteins is a significant market, “but we are also seeing significant growth in other molecules types like antibody drug conjugates and other bioconjugates. Traditional monoclonal antibodies and proteins are the largest segment, but we are seeing significant growth from next generation molecules like bioconjugates, multi-specifics and other enhanced proteins. Areas like cell and gene therapy are also emerging growth opportunities.”

For Althea’s Mr. Kovarick, the use of stainless steel systems that require lengthy changeover times, labor-intensive set up, and costly clean/steam in place (CIP, SIP) procedures doesn’t fit with the demands of today’s marketplace that is seeing more and more smaller indications. “Contrast that with single use systems that offer many benefits such as reducing contamination risk, increasing operation flexibility, and shortening changeover times, all of which generate tangible cost savings and increase speed to market,” he said.

Monoclonal antibody (mAb) products, which include full-length monoclonal antibodies, Fc-fusion proteins, antibody fragments, and antibody-drug conjugates are the fastest growing segment of biologics, Mr. Kovarick said. According to BioProcess Technology Consultants, in 2014 more than 75% of the biologics products in development in U.S. and Europe are mAb products.

In terms of market restraints, “new and evolving regulatory requirements remain a challenge for the industry as a whole,” said Mr. Kovarick. “In addition, contract manufacturers historically have invested conservatively in facility expansions. Capacity is cyclical, with booms and busts. One of the most likely scenarios is that a CMO is having to absorb the costs of an expensive and under-utilized facility.”

With the contract manufacturing market performing very well, FUJIFILM’s Mr. Meeson said that CMOs will continue to evolve by way of expansion, implementation of new technologies, creation of partnerships with other companies, or a combination of any of these, in order to provide their customers with the speed, capacity, and level of quality that is needed to bring therapies to market. “Some of the trends we see are the need for cell culture and gene therapy capacities.”

He also said there is the resurgence of technologies such as perfusion making a comeback. In terms of cell culture technology there are several that are taking over. At the same time the immuno therapy space is booming, with CAR-Ts as a big example. The ADC space is also growing.

“A manufacturing approach to process development, new manufacturing agency regulations, and our industry reaching a new level of maturity is really what is pushing the industry to the next level,” said Mr. Meeson. “We will be seeing more and more biologics getting approved in the next decade than we have seen before. With regards to restraints, I can see that we need to get faster analytical tools to keep up with HT development which will then have an impact on getting companies fast to IND.”

DEPENDING ON CMOs

Contract manufacturing is extremely important to help provide the capacity needed in order to fulfill a fast growing demand. “We believe that the high growth and fast pace of technology innovation in biologics creates significant opportunities for technology and service providers,” said Mr. Riley. “A large percentage of new product development is being driven by smaller companies with limited infrastructure. These companies can accelerate a path to the clinic by leveraging the established capabilities and expertise of a strong partner. Larger companies are also finding the ability to gain speed and flexibility by conducting development and manufacturing externally, and are also able to access new technology and expertise that they may not have in house.”

Pharmaceutical companies, like all successful companies, are always looking to focus on their assets that perform best. When it comes to manufacturing, optimizing supply chains and infrastructure are important.

“Outsourcing partners play an important role by filling expertise and capacity gaps in the development process,” said Mr. Kovarick. “In addition, they also take the role of secondary suppliers to help mitigate supply risk. The increasing number of orphan designations and personalized medicines require smaller production batches. Manufacturers are expected to run their facilities and equipment extremely lean and efficient while maintaining the highest possible quality standards in order to keep COGS as low as possible.”

Outsourcing also plays a role in product life cycle management, according to Mr. Kovarick. “As patents expire or substitutes enter the market, these competitive pressures push sales volumes down,” he said. “The cost of maintaining a facility with reduced utilization becomes cost prohibitive. To make room for a product with better margins, the mature product often gets transferred to manufacturing partners.”

International growth in outsourcing of biomanufacturing is growing too. “China and India are maturing biomanufacturing locations and they and other countries are rapidly developing domestic, mostly biogenics-oriented, biopharmaceutical industries,” said Goodwin’s Mr. Cunningham. “While outsourcing of various operations to these areas may be an opportunity, outsourcing costs are rising and quality problems in many developing countries are becoming more apparent. Problems have plagued the Indian manufacturers, and they are trying to get out from under them including their data integrity issues. Despite that, the outsourcing use of these CMOs has increased, with 14.3% of respondents in a recent survey reporting offshoring bioprocessing in the last year.”

In the end, all signs point to continued growth in outsourcing in the years ahead. “Outsourcing is becoming more mainstream,” said Mr. Cunningham. “The percentage of facilities performing all production in-house shifted from 57.6% in 2006 to 35.3% in 2015, the lowest point in a decade.”