Seize the Market

Mid-size contract development and manufacturing organisations are well prepared for the current market requirements and offer services for innovative molecules and modern therapy concepts

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Modern biopharmaceuticals such as monoclonal antibodies (mAbs) and fusion proteins play an important role in the treatment of severe diseases, including cancer and autoimmune disorders. This market is expected to increase with a compound annual growth rate (CAGR) of 9.4% from 2015 to 2020, based on more than 280 biopharmaceuticals on the market and hundreds in clinical studies (1). In 2016, the FDA approved seven mAb drugs, three recombinant blood factors and three biosimilars (2-4). The number of approvals of new biopharmaceuticals by the EMA was in the same range (5).

The well-filled drug development pipeline of biopharmaceutical companies is the base for this notable progress, but the advancement of such complex products requires considerable effort and special expertise as well as state-of-the-art capabilities. Therefore, many firms outsource part of their activities to contract development and manufacturing organisations (CDMOs). The corresponding biopharma contract manufacturing market is predicted to grow with a CAGR of 13.4% from 2015 to 2020 (1).

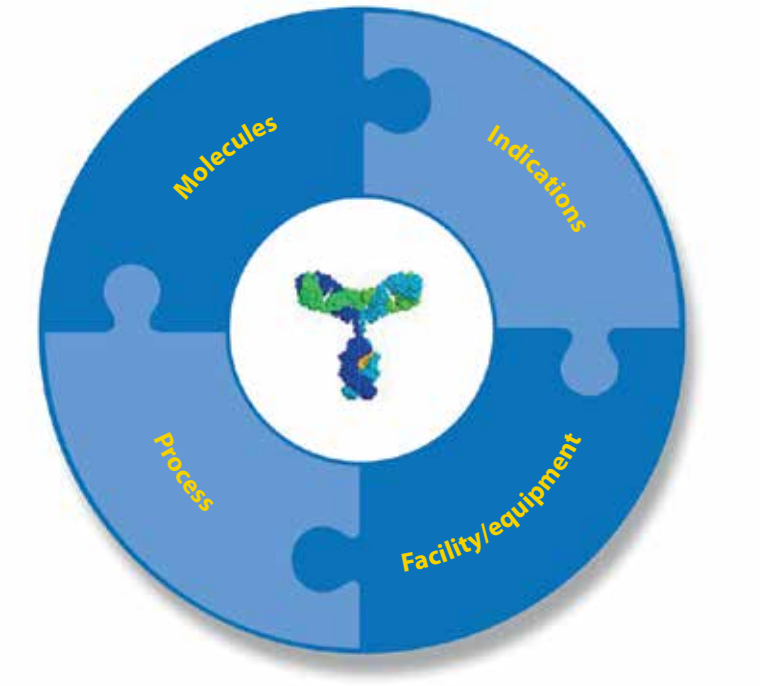
Under the current market conditions, mid-size CDMOs are particularly important. They often focus on special segments like mammalian- or microbial-based development of recombinant proteins and typically provide bioreactor scales smaller than 10,000L. Most have many years of experience and offer a broad range of services and capabilities along with proprietary innovative technologies and well-established manufacturing platforms. A lot of them have expanded their capabilities in the past few years and established new stainless steel or single-use bioreactor capacities, allowing them to act with a high degree of flexibility in manufacturing for various clinical phases and for market supply. Figure 1 provides an overview of important factors that contribute to the market success of mid-size CDMOs.

Biobetters and ADCs

The growing market is influenced by diversity in the development pipeline, as specific market opportunities for mid-size CDMOs arise from a changing molecule landscape.

Molecules
- Biobetters (fewer doses)
- Highly potent (eg ADC)

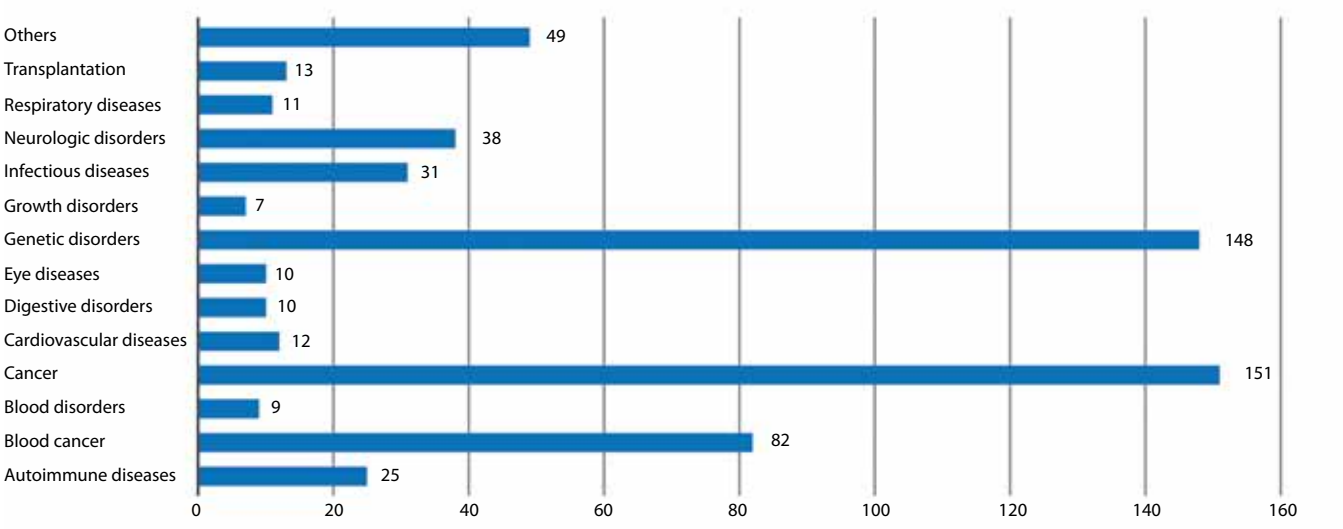
Indications
- Rare/orphan diseases
- Personalised medicine



Process
- Higher titres
- Continuous processing
- Scale out versus scale up

Facility/equipment
- Single-use bioreactors
- Prefabricated facility

Figure 1: Factors influencing the success of mid-size CDMOs



Source: PhRMA (9) (some medicines may be in more than one category)

Figure 2: Medicines in development for rare diseases

Many of the first generation therapeutic proteins suffer from a short plasma circulation half-life and therefore need to be administered frequently, putting a burden on the patient and the required amount of drug. Second generation molecules often have an improved half-life achieved through a multitude of fusion partners such as Fc-domains and albumin. These so-called 'biobetters' will still have the same mode of action (MoA) as the original, but display significantly enhanced pharmacokinetic and pharmacodynamics values. As a result, they need less frequent injections and, consequently, a lower manufacturing volume that could fit to mid-size CDMOs.

Another reason for these smaller scales is the heavy competition between the different variants. For instance, 26 different biobetter alternatives are in the pipeline alone for Epogen® (6). Their attractiveness is also related to lower development risk, as the target and the MoA are well known.

Besides the impact on half-life, they can also have an improved safety profile due to reduced toxicity, improved targeting and minimised immunogenicity or enhanced stability, as well as a novel drug delivery and formulation strategy. Biobetters represent new biological entities that have a high potential for intellectual property protection and the opportunity for a price premium as they deliver a clinical advantage. According to a recent analysis, close to 500 biobetter versions are at various stages of development for 146 reference products, and the pipeline is even larger than that of biosimilars in the US (7).

Highly potent compounds such as antibody drug conjugates (ADC) could also be a good fit for mid-size CDMO capabilities when looking at antibody manufacturing. ADCs are not chronically administered and typical antibody processes deliver high yield, both of which lead to smaller production quantities. Other highly potent products come from the growing field of immuno-oncology, like highly active T cell engagers that are administered at very low doses. Other new modalities are therapeutic cancer vaccines that can frequently be produced very efficiently in microbes and are administered in very low doses.

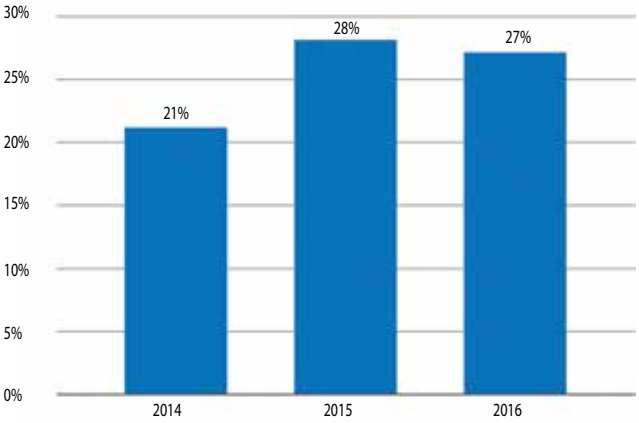
Getting Personal

A further market trend associated with the growing demand for small and medium bioreactor scales is the increasing development of drugs for rare and ultra-rare diseases – those with no more than 5 in 10,000 patients in the EU. Of the estimated 7,000 existing rare diseases, only about 5% are treatable, meaning that millions of individuals worldwide are waiting for alleviation – half of which are children (8,9). Numerous patient organisations are fighting for the development of appropriate medicines and the drivers for improvements are manifold:

- New insights into disease-inducing mechanisms
- The search for new, profitable drug targets
- The growing cost-effectiveness of complex manufacturing processes in smaller scales

Government support, national action plans and centres of expertise stimulate development. This special support is associated with the recognition of a new medicine as orphan drug by the regulatory authorities.

More than 560 drugs for the treatment of rare diseases were in clinical development in 2016, according to the Pharmaceutical Research and Manufacturers of America (PhRMA). Approximately 25% of these drugs are recombinant proteins including mAbs, and about 15% are emerging biologics (9). The pipeline of rare disease treatments focuses particularly on a wide variety of different cancer subtypes and genetic diseases (see Figure 2).



Source: Personalised Medicines Coalition (16)

Figure 3: Shares of personalised medicines of new molecular entities approved by the FDA 2014-2016

In 2015, about one third of the new products approved through the FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research were orphan drugs (10). Last year, both organisations granted 35 new approvals – 25% of which were orphan drugs (2,3). Two of these were recombinant proteins for the treatment of rare diseases. The EMA recommended 27 new drugs for marketing authorisation, including 16 orphan drugs – 60% of the total – and five of these were recombinant proteins (5).

A further market trend is the increasing emphasis on personalised medicines and a growing number of specific medicines for patient groups with dedicated molecular features are in development and on the market. The shift to tailored treatments is partly due to the possibilities of modern diagnostics, including that of genes. On this base, the best medicine for individuals can be found and the health system becomes more efficient. Personalised therapies are developed in combination with diagnostics to identify suitable patients, and these tests determine which medical treatment will work best for the patient – promising improved success and reduced side effects.

According to the PhRMA, 42% of the new medicines in development in 2015 had the potential to be personalised (11). Among cancer therapeutics, the share was significantly higher at 73%. The Tufts Center for the Study of Drug Development expected an increase of 69% in the number of tailored medicines in development over the next five years (12).

Of the drugs approved by the FDA's CDER in 2015, 13 were personalised medicines – five oncology therapies and three mAbs (13). In 2016, for the third year in a row, personalised treatments accounted for more than 20% of all approvals by the FDA (see Figure 3) (14). Of the 22 new drugs approved by the CDER in 2016, six were personalised therapies, with three being oncology drugs.

Evolution in Bioprocessing

The success of mid-size facilities is also related to progress in bioprocessing. Over the past few decades, the achievable product concentration has seen a steady increase, which results from a higher volumetric yield. This is caused by solving oxygenation issues to allow the cultivation of cells at higher densities; genetic engineering to improve expression and secretion levels; and better growth and feed media. In 2015, one third of commercial biologicals were manufactured at a titre of 2-3g/L – interestingly, the average titre of products in the clinic was above that, underlining the constant improvements (15).

Higher output can also be achieved by switching towards continuous processing and using bioreactors in perfusion mode. Here, cells are maintained at a constant but high concentration while continuously exchanging the cultivation media. Through this method, detrimental metabolites are removed, the product of interest is accumulated and cells are supplied with fresh nutrients so it is possible to deliver a larger amount of drug substance from relatively small bioreactors.

Many processes are scaled up during their lifecycle to match the growing demand during clinical trials and in manufacturing campaigns for market supply. This is usually done by increasing the bioreactor size and the scale of the subsequent downstream processing (DSP) unit operations. Another option is to multiply the number of bioreactors instead of increasing the size, which is called 'scale out'. This strategy is particularly attractive when:

- There is a huge uncertainty on the overall demand
- New facilities need to be erected in proximity to the end customer
- Speed to market is critical
- New geographic markets must be reached with local manufacturing capacities

It simplifies the transfer of projects as the receiving facility will be a copy of the site of development. This is particularly useful for mid-size CDMOs with a range of identical product lines that can either be occupied by a broad set of various different products to balance the risk, or by few products when increased market supply needs to be covered. In that case, usually more than just one reactor feeds into a shared DSP train.

Facilities and Equipment

The ability to generate more drug substance through scale out has been influenced by the introduction and general acceptance of single-use equipment. It is much faster and cheaper to erect a new facility in a disposable setting than to install stainless steel systems with fixed piping and complicated utilities, which require much more planning and construction time as well as a significantly higher capital

investment. Single-use equipment is also appealing for CDMOs since cleaning validation can be omitted, allowing much faster change over procedures between different products. Additionally, the risk of cross-contamination is reduced as all material with product contact is removed after the process.

Nowadays, the most frequently utilised single-use bioreactors cover the range of 1,000-2,000L, and more recently a 3,500L version was introduced – this is exactly the scale where mid-size CDMOs operate. Stainless steel facilities with a 6 x 15,000L set-up have a capital cost of approximately $600 million. A 6 x 2,000L single-use facility requires only a $70 million investment. At a titre of 3g/L, the net cost for producing less than 1,500kg of a drug substance per year favours the single-use six pack, indicating an interesting market niche for mid-size CDMOs (16).

With regard to capacity expansion, prefabricated facilities offer a fast and economically attractive solution. In principle, they follow the same idea of scaling out and establishing new geographical footprints. They can typically accommodate the maximum scale of single-use bioreactors and other equipment, which again benefits mid-size CDMOs.

Advantageous Market

Mid-size CDMOs can currently profit from a number of factors that generate an excellent market opportunity for them. Many new molecules such as biobetters and highly potent biologicals require less frequent administrations and lower doses, which corresponds to a smaller manufacturing scale. The increase of treatments for rare diseases and personalised medicines with much smaller patient bases also leads to a decreased need for large manufacturing volumes.

Mid-size bioreactor volumes are sufficient for many products due to the constantly increasing cell titres that can generate more drug substance from the same scale. Alternatively, continuous processing can be applied to deliver large volumes from relatively small bioreactors through repeated media exchange and high cell concentrations.

Finally, the introduction of single-use equipment supports the success of mid-size CDMOs by accommodating many of the aforementioned trends. This is also connected to scale out options or capacity expansions through premade facilities. In summary, it can be stated that there is an advantageous market situation for CDMOs with multiple bioreactors at scales below 10,000L.

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