Karl Pinto
CEO, Goodwin Biotechnology

Dave Cunningham
Dir. of Corp. Devt., Goodwin Biotechnology

The Biopharma FUTURE

A look at current trends driving volume reductions in biopharmaceutical manufacturing and keys for successful outsourcing partnerships

The biopharmaceuticals market is expanding far more rapidly than the overall pharmaceutical industry, with U.S. biotech sales more than doubling the growth rate of pharmaceuticals sales, according to IMS Health. In large part this is based on the impact that biopharmaceuticals have made in advancing early disease detection, and enabling greater efficacious, targeted treatments with far less "collateral damage" and side effects, all of which have translated into a significant reduction in the number of deaths due to a variety of cancers, HIV/AIDS, and autoimmune diseases in the U.S. since the early 1990s.

NEW BIOLOGICS – THE TREND TOWARDS "SMALL"

The biopharmaceutical field itself is undergoing significant changes, and scientific progress and new approaches are necessitating that many of these drugs are required in far smaller doses than in the past and thus are required to be made in smaller volumes than before. In industry parlance, these are being called "new biologics."This impacts the supply chain of such drugs and calls for a new perspective in how they are manufactured. There are important trends that are driving volume reductions and consequently, its effect on the manufacturing infrastructure of biopharmaceuticals.

ENHANCED CLINICAL EFFICACY—BETTER AND MORE PERSONALIZED DESIGN OF DRUGS

Advances in targeting therapies are key driving forces that have enhanced clinical efficacy. One key aspect seeing dramatic improvement is the medical progress around the specificity of monoclonal antibodies (mAbs) and/or their fragments. Historically, a large percentage of the mAbs didn't efficiently reach and sustain an attachment to their targets. As a result, high amounts of mAbs were required per dose to generate the desired clinical outcomes.

However, higher amounts of mAbs journeying through one's body tends to contribute to unwanted side effects and lack of efficacy. As a result of progressive sophistication in the development of mAbs with greater specificity including effecting minute structural changes which are shown to affect potency, the efficiency of antibodies are enhanced; therefore, fewer antibodies are needed per dose.

Another exciting advance is in the field of bioconjugation, leading to the therapeutic category called ADCs, or antibody drug conjugates. By attaching small molecule payloads, radioisotopes, photo-sensitive dyes, and/or other "warheads" including chemotoxins to a mAb or fragment, the impact of the resultant compound is far greater than with the mAb alone and thus, requires smaller doses to reach and impact the target cells in order to be successful, while minimizing the untoward side effects. These technological advances are making significant strides in diagnostic, treatment, and monitoring of diseases.

In a variety of cancers, for example, mAbs conjugated with a payload such as a drug or radioisotope are showing a great level of promise based on their ability to target and treat diseased cells; and resulting in far less collateral damage or "good cell" death when compared with traditional chemotherapy protocols, due to their ability to hone into the tumors.

To date, there have been a number of ADCs approved by the FDA. Some examples include:

- Adcetris (brentuximab vedotin) from Seattle Genetics was approved in 2011 for treatment of Hodgkin lymphoma and anaplastic large cell lymphoma;
- Kadcyla (ado-trastuzumab emtasine) from Genentech/Roche/Immunogen was approved in 2013 for treatment of HER2 positive, late-stage breast cancer; and
- Besponsa (inotuzumab ozogamicin) from Pfizer is an antibody-drug conjugate used to treat relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). The compound was approved in 2017 and consists of a humanized monoclonal antibody against CD22 where inotuzumab is linked to ozogamicin, a highly cytotoxic agent from the class of calicheamicins.

In addition to the marketed compounds, there are literally hundreds of ADCs in clinical development. The vast majority of ADCs in clinical trials are in Phase I studies and approximately 25% are in Phase II & III trials.

Due to great advances in better understanding the human genome, patient populations are being better understood and defined at the genomic level, and it is becoming more and more clear that one general treatment may not work for all patients, leading to specialized approaches for specific subsets of patients becoming increasingly mainstream.

Personalized medicine is the tailoring of medical treatment to the individual characteristics of each patient. Equipped with tools that are far more precise than before, scientists are designing research approaches and physicians can select a therapy or treatment protocol based on a patient's specific biologic profile that may not only minimize harmful side effects and ensure a more successful outcome, but can also minimize the required amount of drug to do so.

Personalized medicine is impacting patient care in many diseases. One of the most common examples of personalized medicine came with the introduction of trastuzumab in 1998. Trastuzumab is a monoclonal antibody used to treat breast cancer in the approximately 30% of patients that overexpress the HER2 receptor protein. Improved protocols of treatment with trastuzumab have ensured that a majority of treated patients show a reduced recurrence of their tumors. Trastuzumab is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system.

Moving into the future, new biopharmaceuticals targeted to smaller patient cohorts are likely to continue producing a greater level of efficacy with fewer side effects, resulting in better clinical outcomes against which the blockbuster models have struggled to deliver. In other words, many more products across a range of conditions could be developed that treat a smaller population of patients than the traditional blockbuster medicines, but which are more clinically tailored and efficacious for a particular patient cohort. Regulators are also helping by providing designations of "orphan drugs" for those that treat very small, specific patient populations and offering up "fast track" approvals for an increasing number of highly specific drugs.

So, while huge volume, blockbuster medicines will always exist because science and companies will continue important research for therapies that appear to be a panacea for a given condition at a given time, there is a definitive trend towards smaller (volume), better targeted medicines, often developed by smaller, nimble biotech firms, as the industry marches into the future.

BIOPROCESSING TECHNOLOGY TRENDS TOWARDS HIGHER PRODUCTIVITY, HIGHER YIELDS, AND BETTER DELIVERY APPROACHES

From the perspective of the manufacturing of biopharmaceuticals, there are also many exciting changes happening. Molecular biology and cell line development techniques have advanced rapidly. It is becoming more and more commonplace for biopharmaceuticals, particularly mAbs and recombinant proteins, to be expressed by cell lines which achieve multiple grams per liter (g/L) in yield. For example, in a mammalian cell culture environment where it once was a challenge, even up to a few years ago, to achieve an expression level of 1g/L in a CHO-based mAb cell culture process, it is now realistic and even normal to generate levels of productivity multiple times higher. In fact, the average titers reported at both clinical and commercial scales were about 3.20g/L based on the findings of BioPlan Associates from their "15th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production" in April 2018. According to another recent study, since 2010 average cell line titers have increased more than 10 times! And, this number is advancing even further.

As a result, the amount of product that can be produced today on a given scale of manufacturing platform footprint (typically, a bioreactor) is 3-5 times that which could be produced by the same manufacturing bioreactor footprint less than 5 years ago. In other words, from a cell line yield perspective alone, today's 500L bioreactor may be able produce a similar amount of product as a 2,500L bioreactor could, about five years ago. Thus, it is fast being observed that adequate amounts of Biopharmaceutical product can be manufactured for a larger percentage of products' late-stage clinical trials and even cGMP commercial manufacturing campaigns in scales from 500L to 2,000L bioreactors. As a matter of comparison, in the past product sponsors would hardly ever even consider a scale of less than 5,000L as their product approached the later stages of development and were entering the marketplace.

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Single-use bioreactors, concentrated fed batch processing, and other ready-for-use and disposable technology components and approaches have also greatly enhanced manufacturing turnaround times, increased capacities, and reduced costs in today's bioprocessing facilities. Significant advances have taken place in bioreactors, especially in single-use/disposable bioreactors and other equipment, and they now dominate small- and mid-scale bioprocessing with their markets increasing significantly over the last few years. This growth is further fueled by products being developed using single-use systems receiving approvals and graduating to commercial manufacture.

The utilization of continuous processing approaches in both upstream and downstream aspects of bioprocessing has also contributed to more efficient manufacturing, less human intervention, and greater control of the processes that greatly reduce regulatory and quality-related risks.

Formulation and packaging techniques have also advanced greatly and the industry is now being able to formulate biologics in ways that ensure concentration and stability levels which are high enough to ensure that far less product is required per dose for patients. This means that less product needs to be processed.

The technology trends noted above are pushing the bioprocessing industry to reconsider its traditional blueprint for growth, which was to build additional scale by adding upstream and downstream capacity. Over the years this has been achieved by making huge capital investments in new, large-scale facilities and through industry consolidation which has been happening at a very fast pace, particularly over the past few years. In most maturing industries, the push for economies of scale call for this approach, but in the biopharmaceuticals industry, with products becoming smaller and technologies increasing rapidly, one must perhaps consider a different approach to growth in order to be able to efficiently support these new industry requirements.

As one of the world's largest and most pioneering biotech companies, Genentech, part of Roche, recently admitted, “Our manufacturing infrastructure is built around large, economies-of-scale, facilities. They can be adjusted, but getting into small volumes is all a bit new to us. We are seeing an increase in the number of small-volume products and adjusting our capability.”

Small-to mid-volume products are certainly forming an increasingly larger portion of the company's pipeline and Genentech has stated its intent to “develop and deploy disruptive technology for fast and agile response to capacity demands with minimal changeover, transfer, staff, and regulatory observations, coupled with the intent to decrease operational and capital expenditure.”

SMALL- TO MID-VOLUME PRODUCTS AND SUCCESSFUL OUTSOURCING PARTNERSHIPS

Certainly within the contract development and manufacturing organization (CDMO) services space, the traditional biopharma manufacturing model of consolidating manufacturing capabilities and increasing scale will continue to have its place, particularly in this evolving age of biosimilars and the ever-greening of blockbuster drugs. But as a result of the trends discussed in this article, a new space is becoming attractive, certainly within the CDMO services industry. There will be an increase in smaller and more flexible manufacturing CDMOs and facilities with an appropriate, efficient scale and compliance for their clients' cGMP biopharmaceutical manufacturing campaigns.

Sponsor companies seeking outsourcing partners have been increasingly examining smaller companies that have the manufacturing platforms required to meet the needs for late-stage clinical trials and even commercial quantities of the next generation of biopharmaceuticals, “new biotech” products. Smaller facilities have lower capital and running costs, thus ensuring efficiency in outsourcing prices. As well, smaller facilities can have an increased breadth of capabilities under the same roof, thus improving turnaround times, lowering product risk—as in-process products do not need to be shipped to different corners of the world for further processing—and they operate within the same, consistent quality system, making the task of ensuring controls far simpler.

Further, a smaller manufacturing partner may be more flexible in their approach and offer engagement models that are more amenable to the needs of their partners. This is particularly important since a major slice of new biotech products are being developed by smaller companies, often having single or a few products in their pipeline. For such entities, being able to work with one partner who provides the flexibility that they need becomes far more efficient and productive from a development and a relationship standpoint.

The CDMO of the future will offer a customized approach, be cost-efficient, and specialize in catering to small-to mid-volume product requirements, and also to smaller product companies, and academia, as well as large, multinational companies, who are adapting their business model to make up for the lack of blockbuster products. **CP**

AT GOODWIN Biotechnology, Inc., Karl Pinto is the Chief Executive Officer and Dave Cunningham is the Director, Corporate Development. More information can be found at www.GoodwinBio.com or via e-mail at info@GoodwinBio.com.