Biosimilars & Biobetters

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Biosimilars are a new class of biopharmaceutical products having received or on track to receive approvals through a number of countries' biosimilar approval mechanisms. With many major biopharmaceutical products starting to come off-patent, many countries have implemented biosimilar regulations allowing abbreviated comparisons-based approvals. Similar to generic drug approvals, candidate biosimilars must be shown to be substantially similar to a prior-approved product through comparative analytical and clinical testing. This allows biosimilars to avoid the large and very costly Phase III-type and placebo-controlled trials needed for innovative product approvals.

Over a dozen biosimilar approvals have been granted in the European Union and other countries, but the FDA is still implementing the Biologics Price Competition and Innovation Act (BPCIA), enabling it to grant biosimilar approvals with no applications yet filed. Despite this, the U.S. will, in coming years, be the major market for biosimilars. Market penetration in EU markets to date has been very poor, e.g., all of the approved biosimilars combined have EU sales of less than $250 million/year. But unlike in Europe, reimbursement and prescriptions in the U.S. are largely controlled by insurers, which will push cheaper biosimilar/biobetter alternatives as they become available.

Selecting a CMO

In our 9th Annual Report and Survey of Biopharmaceutical Manufacturing[1], we found consistent evidence that the critical issues concerning outsourcing of biopharmaceutical manufacturing to a contract manufacturing Organization (CMO) are relevant to both new products, and biosimilars. Of the 302 global facility respondents this year, we found that the key factors in outsourcing production included "establish a good working relationship," with 96.8 percent indicating it as important or very important.

"Protect intellectual property" was a significant concern of 87.3 percent (vs. 80.7 percent last year). This increase may be the result of the increased focus on outsourcing of operations. These data suggest a continuation of a trend from 2010, where sponsors are demanding greater levels of professionalism, performance, and effectiveness in both managerial and technical areas from their outsourcing vendors.

The summary of top outsourcing factors considerations, rated as very important, is as follows:

1. Comply with my company’s quality standards.
2. Effectively handle cross-contamination issues.
3. Establish a good working relationship.
4. Protect intellectual property.
5. Stick to a schedule.

CMOs Well-Suited for Biosimilars & Biobetters

Biopharm CMOs and, particularly, those providing good manufacturing practices (GMP) scaleup/manufacture are and will likely see increased biosimilars and biobetters business. With most biosimilar developers being small companies and most lacking needed facilities, these companies have few manufacturing choices, and CMOs will figure prominently.

Further, CMOs are collectively involved with a large portion of large-pharma biosimilars/biobetters’ development programs. CMOs are also working on biosimilars, and many biobetters are being developed in-house by current reference product manufacturers as next-generation replacements.

With biosimilars and biobetter, CMOs can stay within their comfort zones. Biosimilars and biobetters involve previously-approved off-patent active agents, making them ideal for outsourcing to CMOs. Unlike innovative products, much has been published and is known about reference products, their active agents and bioprocessing; and most related bioprocessing technology is also off-patent.

Some biosimilar developers are seeking to emulate and copy legacy reference product bioprocessing, and many are using more state-of-the-art, cost-effective, higher-yield, bioprocessing technologies. Most sponsors likely end up using CMOs in-house expression systems and platform technologies, reducing costs and accelerating development.

Benefits to CMOs

Biosimilars and biobetters will enable many more CMOs to become cGMP-marketed product manufacturers. With many competing products expected, most biosimilars (and to a lesser extent, biobetters) will only attain a relatively small market share. But this will often still require large-scale manufacturing, e.g., a company targeting less than 10 percent of the current Humalog can expect a market of up to $250M and need about 100 kg of active pharmaceutical ingredients (API) a year, based on ~2.5 billion/year on current Humalog sales.

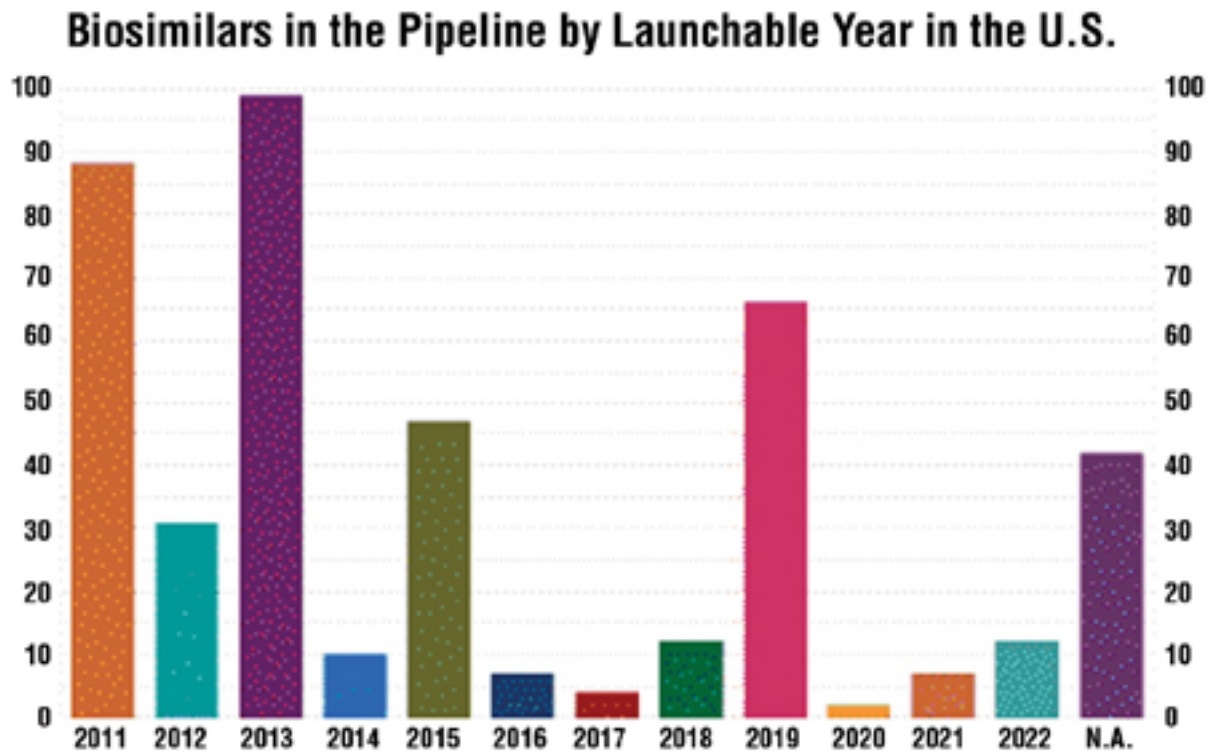
Biosimilars/biobetters are also ideally suited for use of single-use/disposable bioprocessing systems, with these increasing preferred, including by CMOs, compared to more expensive stainless steel-based systems. With

biosimilars/biobetters inherently having smaller markets, compared to reference products, their commercial manufacture is at smaller scale, e.g., using less than 2,000-L bioreactors, making use of single-use systems feasible and ideal.

Follow-on products will, by design and necessity, generally be priced at a 25 to 30 percent or more discount relative to the established reference product, with at least one future major player planning discounts of 50 percent. Also, each biosimilar and biobetter will have to compete against its other similar competing products. So, cost-effective, if not inexpensive, manufacture is essential for biosimilars and biobetters to be competitive and profitable.

Biosimilar/biobetter developers will generally want to get to full scaleup at cGMP as soon as possible, generally a straight line from start to cGMP scale-up for commercial manufacturing, much unlike innovative products in which CMO work is done in spurts. Innovative products' development involves more delays, e.g., waiting for testing and trial completion. Biosimilars/biobetters require much less preclinical studies, and clinical trials are fewer and can be completed much quicker than with innovative products. CMOs are ideally suited for these more continuous vs. episodic projects, with rapid development and scaleup among their core skills.

Biosimilar & Biobetters in the Pipeline



A recent study shows the biosimilars pipeline to be very robust (1, 2). This includes over 450 biosimilars and nearly 400 biobetters, nearly all recombinant proteins or monoclonal antibodies, in development worldwide, with the U.S. and other major markets their primary targets. The nearly 400 companies involved tend to be either small biotech companies, or the largest big pharma and generic drug companies, with few mid-sized companies, mostly involved with innovative products, involved.

Many developers are newcomers to biopharmaceuticals. Figure 1 shows the projected U.S. launch dates for over 100 marketed recombinant proteins and monoclonal antibody reference products with a current ~$100 billion/year market.

As much as 10 generic versions of the asthma drug Singulair recently received FDA approval on the first day possible, for each blockbuster reference product, 10 or more biosimilar and biobetter versions can be expected to very rapidly enter the U.S. and other major markets. Biosimilars and biobetters, particularly those targeting U.S. and other major markets, will be dramatically expanding the number of biopharmaceutical products and manufacturers. And with more competing products, their markets will tend to be smaller. Biosimilar/biobetter developers are concentrating on developing versions of reference products with the highest current sales — sales of greater than $1 billion/year.

Dealing with Conflicts of Interest

Conflicts of interest are a major concern for CMOs and their sponsors. With so many biosimilar and biobetters in development, inevitably, sponsors will seek CMOs to develop much the same or similar products, i.e., biosimilars and biobetters targeting the same reference products. Also, some CMOs are developing their own biosimilars, seeing this as well within their capabilities, whether on their own or with partners.

CMO clients need to consider any potential conflicts of interest. In some situations, using a CMO already developing similar products for others may be welcome, potentially providing a faster proven route to product development. But for many, if not most, sponsors, such similar CMO work for others will be unacceptable. And of course, innovator product clients and clients with biosimilars/biobetters already in development will generally not want their CMOs to be doing similar work for others. Despite CMOs handling each project independently, clients rightly have concerns that knowledge and technologies from their projects will be applied to others' similar projects.

CMOs are dealing with these conflicts of interest in different ways. Most are handling each client's project totally independent from others. This even includes duplicating testing and development. This allows these CMOs to honorably accept projects. Even if conflicts of interest are not currently a concern with a CMO, it would be prudent to include in any contracts how the CMO will handle similar projects.

References

1) 9th Annual Report and Survey of Biopharmaceutical Manufacturing, BioPlan Associates Inc., April 2012, www.bioplanassociates.com [1]

2) Biosimilars.com: The Biosimilars Information Resource for the Biopharmaceutical Industry, Biotechnology Information Institute, online at www.biosimilars.com [2]

3) Charting the Biosimilar and Biobetter Development Pipeline, FirstWord Pharma,

Sept. 2012, 428 pages.

Links:
[1] http://www.bioplanassociates.com/
[2] http://www.biosimilars.com/