Biosimilars Impacting Biopharmaceutical Manufacturing and CMOs

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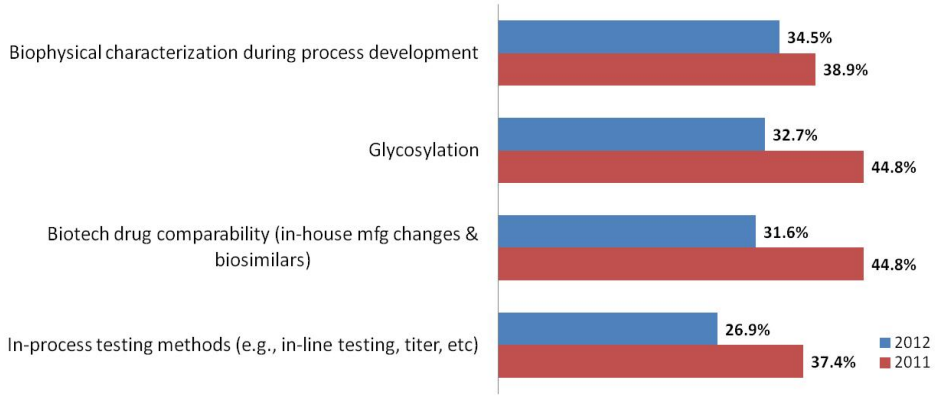
Biosimilars (and biobetters) are definitely coming to the U.S. and markets worldwide. One measure of the impact of these important new products is how the industry is addressing a critical hurdle affecting regulatory approvals, and marketability: Measuring a new biologics' comparability to a reference product (see sidebar regarding comparability studies). In our 9th Annual Report and Survey of Biopharmaceutical Manufacturing[1] we asked 302 global biomanufacturers which assays were 'urgently requiring new, improved testing methods." We found that 31.6% of biomanufacturers indicated that assays related to the comparability of drugs (i.e., biosimilars) were urgently required. While down from 44.8% last year, this still represents a substantial percentage of the market recognizing that biosimilars are coming, and the tools necessary to facilitate their market entry must be improved.

Fig 1: Bio-Assays 'Urgently' Requiring New, Improved Testing Methods"



Status of Biosimilars

The biosimilars/biobetters pipeline includes over 410 biosimilars and 360 biobetters in development, with a large number expected to enter the market (patents and other granted exclusivities expiring) in the next few years, followed by another set of products, including many monoclonal antibodies, later in the decade[2]. With over 350 companies involved in product development for follow-on biologics, including a large number of new entrants to the biopharmaceutical industry, we estimate that the growth in bio-facilities is likely to expand by 20-25% over the next five years. Many of these companies view biosimilars/biobetters as an affordable way to enter the lucrative U.S., European and world biopharmaceutical markets and gain credibility as a biopharmaceutical developer.

Much as with generic drugs, it is likely that soon after products become marketable (patents and market, e.g., orphan designation, and data exclusivities expired) there will be 5-10 or even 10-20 biosimilars and biobetters for each current major reference product, particularly those with current significant sales! Thus, in the next few years, biosimilars/biobetters will greatly increase the number of:

a) Biopharmaceuticals being manufactured and marketed
b) Facilities manufacturing biopharmaceuticals
c) Companies involved in biopharmaceuticals, including R&D and marketing

However, while increasing the number of products, manufacturing activity and companies involved, the coming waves of biosimilars (and biobetters) will result in an overall collective *contraction* of the market value for similar products (the original reference product plus the biosimilars/biobetters that largely emulate and seek to replace this in the market), along with fragmentation of these markets. Biosimilars are expected to be priced below their similar reference products; these cheaper products will take market share from the reference product, while the overall market value for these products (reference and biosimilar/biobetter) will shrink due to competition from the lesser-expensive new products. While studies in Europe, post introduction of biosimilars, have indicated that while prescribing may increase ~10-20%, we project that the overall market effect will be a reduction in market value.

In parallel with this market trend, the overall number of products and manufacturing activity (e.g., number of facilities) will expand. Our global analysis of bio-facilities (see www.top1000bio.com) show there are currently about 1,000 biopharmaceutical manufacturing facilities worldwide[3] manufacturing at least at clinical scale. These are reported and ranked by facility manufacturing capacities, employment, and number of products/facility. With biosimilars and biobetters, there will be many new facilities coming online and expanded use of current in-house and CMO facilities.

Companies of all sizes and types are currently developing and will be active in biosimilars/biobetters. These include the largest pharmaceutical, biopharmaceutical and generic drug companies. It may be good business for biologics innovator companies to round-out their broad product portfolios as biosimilars/biobetters become marketable, e.g., their patents expire. Many of these large companies with marketing muscle will be likely leaders in terms of capturing market share for their products. Marketing of biosimilars will be challenging, with physicians and consumers needing to have confidence in what many will perceive as

Biosimilars are off-patent follow-on biopharmaceuticals that receive approvals through formal abbreviated, comparison-based "biosimilar" pathways. These approvals are based primarily on showing biosimilarity or lack of significant differences in structure, activity and clinical efficacy and safety compared to an already-approved "reference" product. This abbreviated approval process generally involves direct comparisons of the biosimilar and a reference product, including analytical profiles and pharmacokinetics clinical trials, while traditional full, innovative product approvals generally involve larger and more costly placebo-controlled trials. Over a dozen biosimilars are already marketed in the European Union and some other major market countries having implemented biosimilar or equivalent approval pathways. In the U.S., the FDA is still struggling to implement regulations after passage of enabling legislation several years ago, with no biosimilar approvals or even formal filings yet in the U.S.

'Biobetters' (with many synonyms used) are rather similar follow-on biopharmaceuticals, i.e., same or very similar active agent, that are sufficiently dissimilar from any prior approved products such that they must receive traditional full approval as an innovative product. Biobetters are really nothing new, just the term, with most of these products involving molecular or other modifications that alter product performance, such as pegylation of the active agent or a different delivery system, e.g., oral administration of a currently injectable product.

being lower quality "generics;" and biosimilars (and of course, biobetters) will have to largely be marketed much the same as innovative reference products, since at least for the foreseeable future no biosimilars can be expected to be approved with generic drug-like interchangeability (in prescription writing) and substitutability (in filling the prescription, e.g., with the pharmacist providing the biosimilar when the reference product was prescribed). There are also a large number of smaller, companies, and large experienced organizations in developing countries, that already manufacture biosimilars/biobetters for domestic populations. As regulatory approval pathways are formalized, the number of products will expand, along with the number of companies involved as they target major market biopharmaceuticals.

Contract Manufacturing and Biosimilars

Contract manufacturer organizations (CMOs) will likely be a major beneficiary from these biosimilars/biobetters trends. Many are already experiencing increased demand for bioprocess development, scale-up and manufacture of preclinical and clinical supplies. With the trend among established companies, particularly the largest ones, being to outsource and downside, many biomanufacturers now seek external expertise. Especially as larger companies devote their in-house manufacturing capacity to innovative, higher-profit products. Thus, many of the likely major players in biosimilars/biobetters, particularly in terms of their marketing, may be using the services of CMOs to manufacture their products. In many cases, companies can also be expected to license-in biosimilars/biobetters from many of the current small and foreign developers, and then contract manufacturing to a CMO. Most smaller companies lack bioprocessing facilities and expertise, and must use the services of CMOs. We project that 40%-50% of biosimilars and biobetters could be manufactured by CMOs.

Cost Control

Biosimilars (and biobetters) will have to compete against their reference product and multiple other biosimilar and biobetter versions. Cost to the consumer will likely be the number one factor affecting market share for most products. Thus, the cost of goods or cost of manufacture is a critical factor for market success and profitability of any biosimilar or biobetter. Realizing this, many biosimilar/biobetter developers are adopting the newest and improved bioprocessing methods, expecting to achieve process improvements lowering the cost of manufacture. These companies have to minimize the costs of manufacture to be competitive.

To minimize manufacturing costs, biosimilar manufacturers are pursuing high yields and efficiencies in product manufacture. For some, this involves having a CMO plug their product into that CMO's well-established in-house manufacturing platform, such as the CMO adapting its current preferred CHO expression system to the manufacture of the biosimilars/biobetter. In many other cases, the in-house or CMO manufacturer will adopt or adapt the latest state-of-the-art bioprocessing methods, including novel expressions systems, and equipment, in order to attain

needed process efficiencies. In some cases, developers may decide to use older, long-established, legacy methods and equipment, with this allowing them to avoid paying patent royalties associated with newer technologies. Thus, the number of facilities and those with new equipment and bioprocessing technologies will rapidly increase in coming years.

Many biosimilar (and biobetter) manufacturers will be using single-use disposable bioprocessing equipment as much as possible. Some products may even be fully manufactured in single-use equipment. Current single use equipment involves use of plastics in place of stainless steel, e.g., plastic vs. steel containers and plastic liners inserted into bioreactors. Use of disposable equipment allows increased flexibility, requires much less infrastructure and results in considerable cost savings vs. the alternative of building a dedicated facility with fixed but reusable stainless steel equipment. Currently, single-use (plastic-based) equipment thoroughly dominates precommercial biopharmaceutical manufacture. Products for preclinical and clinical studies are generally made in single-use bioreactors and increasingly also downstream purification equipment. However, essentially all current marketed biopharmaceutical (commercial-scale cGMP) manufacture involves use of fixed bioreactors and other stainless steel equipment.

Conclusions

The advent of biosimilars (and biobetters), particularly their introduction into the U.S. market, the market with by far the largest market potential for these products, will rapidly increase the number of biopharmaceutical developers and manufacturers. And while it will take time for this market to fully develop, CMOs can expect significant growth in the number of products they commercially manufacture.

About the Author:

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Survey Methodology: The 2012 Ninth Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production in the series of annual evaluations by BioPlan Associates, Inc. yields a composite view and trend analysis from 325 responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations (CMOs) in 30 countries. The methodology also included over 150 direct suppliers of materials, services and equipment to this industry. This year's survey covers such issues as: new product needs, facility budget changes, current capacity, future capacity constraints, expansions, use of disposables, trends and budgets in disposables, trends in downstream purification, quality management and control, hiring issues, and employment. The quantitative trend analysis provides details and comparisons of production by biotherapeutic developers and CMOs. It also evaluates trends over time, and assesses differences in the world's major markets in the U.S. and Europe.

NOTE: IMPORTANT TO INCLUDE THIS SO READERS UNDERSTAND HOW THE STUDY WAS CONDUCTED

References:

1) 9th Annual Report and Survey of Biopharmaceutical Manufacturing, BioPlan Associates, Inc, April 2012, www.bioplanassociates.com
2) Rader, R.A., "Biosimilars, Biobetters and Biogenerics" Web site, www.biosimilars.com.
3) *Top 1000 Global Biopharmaceutical Facilities Index*, BioPlan Associates, Web site at www.top1000bio.com .