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Biosimilars in the Rest of the World: Developments in Lesser-Regulated Countries

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Introduction

Biosimilars, and related biopharmaceutical biobetters and biogenerics, are still relatively new, but are already starting to impact worldwide biopharmaceutical markets. Most discussions of biosimilars center on developed regions where markets are mature and manufacturing capabilities allow for the cost-efficient manufacture of these complex molecules. This article covers the development of these products outside the United States (US), European Union (EU), and other developed, generally rather affluent and high-technology economy-based countries. To start, we first offer some definitions.

Understanding the Terminology

Any discussions of *biosimilars* and related terms, particularly those concerning developing countries, require careful definition, as interpretations can vary significantly.^[1-4] For example, as defined in this article, the term *biogenerics*, rather than *biosimilars*, best describes the products most associated with biopharmaceutical development and use in less developed, less intensely regulated countries. Commonly used terms are shown below.^[5]

Biopharmaceutical. A pharmaceuticals manufactured using biotechnology (living organisms such as cells, microbes, and so on).

Reference (Innovator) Product. An already-approved biopharmaceutical that is: (A) used for comparisons (in analytical and clinical testing) to support approval of a generic product; or (B) compared to a new *similar*, but not a *generic* biopharmaceutical for approval purposes.

Follow-On Biologic. A biopharmaceutical similar enough to be marketable as being much the same, but only after expiration of the reference product's related patents, data, and market exclusivities. *Biosimilars*, *biobetters*, and *biogenerics* are all follow-on biologics.

Biosimilar. A biopharmaceutical similar to the reference product's active agent and indications, which has been approved or is on track for regulatory approval following

well-defined biosimilar approval mechanisms.

Biogeneric. A rather similar biopharmaceutical portrayed as identical, or simply being used for the same indications, to a reference product—an interchangeable, generic equivalent. Biogenerics are produced and marketed primarily in lesser-regulated international markets.

Biobetter. A biopharmaceutical that is similar but not similar enough to the reference product or its indications, such that it is not eligible for biosimilar approval. Biobetters must go through a more stringent full approval process rather than the more abbreviated biosimilar approval track.

What are Biosimilars and Biogenerics?

Biosimilars are products approved through a formal biosimilar regulatory mechanism that compete in the marketplace with the off-patent reference biopharmaceuticals. Thus, biosimilars are defined by regulatory status, not the agents or products themselves. For the foreseeable future, biosimilar development, approvals, and subsequent product marketing will be largely confined to highly regulated and affluent parts of the world (*e.g.*, US and EU). These are the same regions supporting the markets for innovative and costly biopharmaceutical products, and where biosimilar approval mechanisms have or are being established.

Simply stated, *biogenerics* can be viewed as biosimilar-like products not on track for rigorous new-product full approvals or as biosimilars, with these approvals mostly restricted to highly-developed countries. Because this is a quicker and lower-cost pursuit, including many biogenerics simply marketed in international commerce without formal approvals, biogenerics are generally developed and manufactured in lesser-regulated, developing countries.

The *biosimilar* approval process requires proof that the candidate shows no analytically- or clinically-significant differences from the already fully-approved reference product. The biosimilar does have to show generic bioequivalence or similar pharmacokinetics/dynamics. Because biosimilars are produced by biotechnology methods (living organisms), heterogeneity, with some allowable structural variations, are fully expected when compared to the innovator product. It is not likely, in the near term, that regulatory bodies will agree that a biosimilar is fully interchangeable with

the reference products given that the two are not produced identically. This is different than with generic, chemically synthesized drugs where small molecule products are presumed to be equivalent (not just similar) to their brand name counterparts if they contain the same (from a primary structure perspective) active agent and show bioequivalence.^[6]

With clinical testing not including large Phase III-type efficacy and safety studies, *biosimilars* require less investment and time for their development, and thus, provide cheaper alternatives and more competition for reference products previously lacking generic-like competition.

Biobetters are similar products that are simply too dissimilar in some aspects (*e.g.*, structure, formulation, efficacy, etc.) to be approved as biosimilar versions of corresponding reference products. Biobetters generally involve some additional innovation and are mostly produced by companies in, and targeted to, markets in more developed countries.

The EU is the leader in biosimilars with over a dozen approved and marketed, although this statistic includes multiple biosimilar versions of multiple reference products, with multiple biosimilar versions of erythropoietin (EPO), somatropin (human growth hormone), and filgrastim (G-CSF) approved as biosimilars in the EU. Other developed countries having adopted biosimilar approval pathways include Australia, Canada, Japan, Korea, and the US. The US is lagging, however, and guidance documentation is limited. Despite the Biological Price Competition and Innovation Act (BPCIA) law enabling FDA biosimilar approvals (enacted in 2010), no licensing applications have been filed yet. So far, no developing countries have adopted formal biosimilar approval pathways (although a few, such as India, are approving *biosimilars* under loose guidelines using existing mechanisms), and this will be discussed later in the article.

Biosimilar approvals require that the candidate product's active agent has very few differences in significant features and molecular structure as compared to the innovator product (*i.e.*, in terms of diverse analytical and bioassay testing, including immunogenicity). The US, EU, and most other countries with biosimilar approvals generally require active agents to have the exact same primary structure, although other structural aspects, such as glycosylation, can vary. These products must also demonstrate bioequivalency in

comparative clinical trials. Oftentimes additional or larger trials can be required before approval to prove safety and efficacy for the reference product's indications. Post-approval pharmacovigilance studies may also sometimes be required in developed countries.

To achieve analytical and clinical efficacy, and safety similarity matching that of a marketed biopharmaceutical is a significant technological accomplishment. Little, if any, detailed (and proprietary) bioproduction information is published for public access, so little is known about reference products manufacturing. Biopharmaceuticals are incredibly hard for third parties to accurately replicate, which is why, for the most part, countries that invest the most money in biopharmaceutical R&D and medical care are the ones successfully developing and adopting biosimilars.

Table 1 shows the most popular reference products being targeted for biosimilar and biogeneric product development and marketing worldwide. The largest portion are blockbuster (>\$1 billion/year sales) recombinant monoclonal antibodies.^[7,8]

TABLE 1. Leading active agents, the targeted or leading reference products (with multiple versions of some products, *e.g.*, somatropin, on the market) and the number of biosimilars/biogenics on the market or in development worldwide.

Active Agent	Exemplary Reference Product	Biosimilars in Development
Tumor necrosis factor mAb	Humira® (AbbVie)	16
Tumor necrosis factor mAb	Remicade® (Janssen/J&J)	9
Erythropoietin; epoetin alpha	Epogen® (Amgen)	59
Granulocyte colony stimulating factor; filgrastim	Neupogen® (Amgen)	54
Granulocyte colony stimulating factor, pegylated; pegfilgrastim	Neulasta® (Amgen)	15
Tumor necrosis factor, mAb-like fusion protein	Enbrel® (Amgen)	21
CD20 mAb	Rituxan® (Genentech/Roche)	34
Her2 receptor mAb; trastuzumab	Herceptin® (Genentech/Roche)	30
Insulin glargine	Lantus® (Sanofi)	6
Vascular endothelial growth factor mAb; bevacizumab	Avastin® (Genentech/Roche)	16
Insulin	Humulin® (Genentech)	40
Natural/non-recombinant interferon alpha	Multiferon® (Viragen)	57
Interferon beta-1a	Avonex® (Biogen Idec)	28
Human growth hormone; somatropin	Nutropin® (Genentech)	28

*Note: US trademark and primary US marketing companies are reported. Also, all but one product (labeled) are recombinant proteins or antibodies.

Biosimilars, or More Accurately, Biogenerics in Developing Countries

Developing countries generally lack biosimilar approval pathways. These markets have long been based primarily on biogenerics and generic drug substitutions. Any biologic product considered close enough to share the same generic International Nonproprietary Name (INN)^[9] nomenclature as its reference product is considered the same or close enough, and is either approved or simply just used for the same indications as the reference drug product. Products that can be simply presumed to be biosimilar are just treated as fully biogeneric equivalents in most developing countries, and this is driven mostly by economics. Making fine distinctions among similar biopharmaceuticals is not of interest in these countries. The freedom to use what they want or need to is driven by costs, with the same government departments often both regulating and providing (procuring) pharmaceuticals for the country's government-run healthcare system. Thus, most biosimilars being developed within, or for lesser-regulated, poorer international markets should be called *biogenerics*, unless a product is actually on track for biosimilar approval. As discussed later, some of these biogenerics may, in the long term, graduate to become biosimilars in highly regulated markets.

An analysis of the biosimilar pipeline shows a considerable number of biogenerics (here, included as marketed *biosimilars*) already in lesser- or non-regulated international markets, with these ≥ 85 –90% of all currently marketed *biosimilars* or over 175 products.^[7,8] Figure 1 shows the number of biosimilars and biobetters in development by phase of development (the latest phase anywhere worldwide). Figure 2 shows the number of biosimilars and biobetters in the pipeline by some of the leading countries (and regions) of their developers.

As is the case with most developmental pipelines, the majority of biosimilars are in the preclinical stages of development. Also, numerically, the largest number of biosimilars (mostly biogenerics) are being developed by companies in Asia, primarily India and China, as fully expected. Combined, the US and EU have much the same

numbers as Asia in development, but these are almost exclusively biosimilars and biobetters. The US and EU totally dominate the biobetters category, with these generally involving something new, which highly-developed country markets tend to favor. Developing biobetters involves more innovation vs. trying to copy or emulate reference products.

The marketed products shown in Figure 1 include >175 biogenerics in international markets (essentially all but approximately 20 products to date having received biosimilar approvals), most originating from India, China, and various other developing countries. Some of these biogenerics have been manufactured

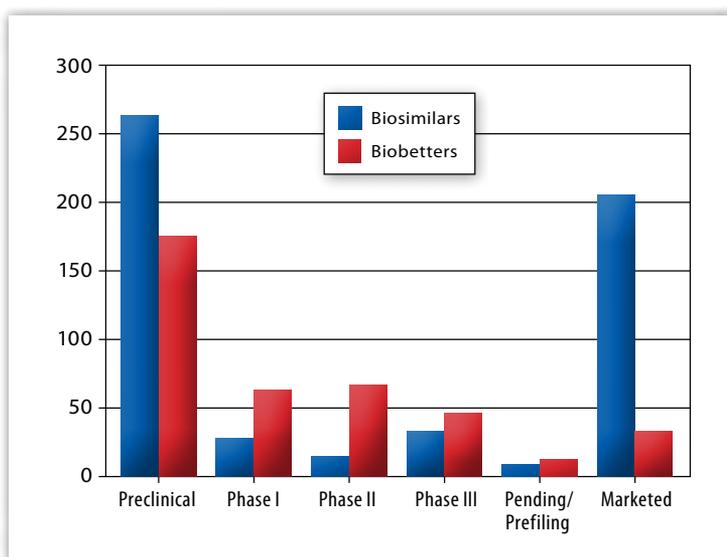


FIGURE 1. The number of biosimilars and biobetters in development by phase of development (the latest phase anywhere worldwide).

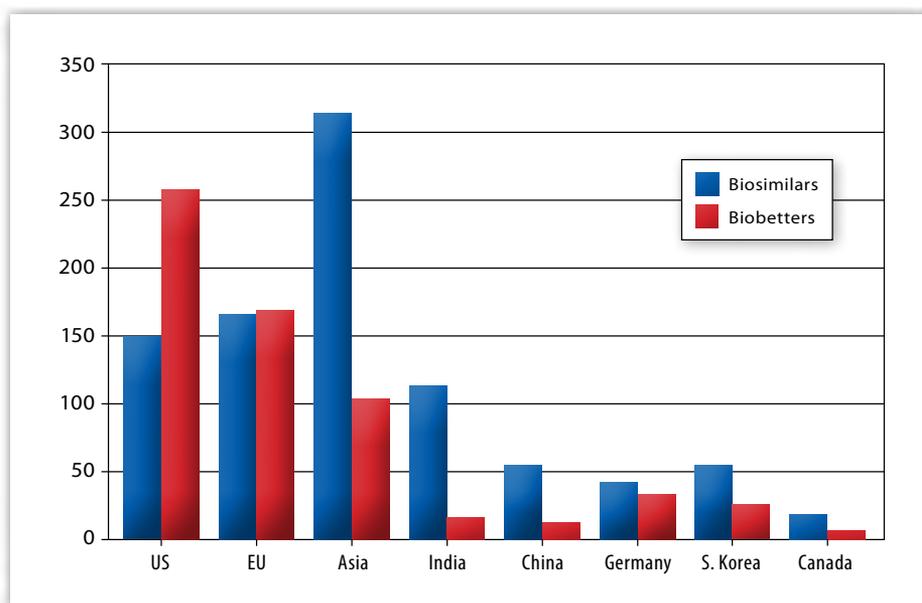


FIGURE 2. The number of biosimilars and biobetters in the pipeline by some of the leading countries/regions of their developers.

and marketed for quite a long time, even decades, including legacy products such as recombinant interferons, somatropin, erythropoietin, etc. For example, there are over 20 interferon alpha products marketed in China. Only a few of the more modern products (e.g., recombinant monoclonal antibodies) have been brought to market as biosimilars/biogenics, even by companies in developing countries.

Of note, many countries commonly cited as having *biosimilars* may actually have zero biosimilars (by this article's definition) but rather, *biogenics*. One example is in India where *biosimilar* is the preferred domestic term although it doesn't equate to the *biosimilar* classification of highly regulated countries. Many, if not all of these biogenic approvals to date, much like related generic drug approvals, have been based on limited analytical, and particularly, clinical studies. For example, Dr. Reddy's Reditux™ and Cipla's Etacept, both commonly noted as being biosimilars and major milestones for their Indian and Chinese developers, have received approvals in lesser-regulated countries based on pivotal open-label trials involving <100 patients, with this providing a level of (un)certainly and data robustness generally not acceptable to highly regulated countries.

Developing countries generally have little interest in implementing domestic biosimilar approval mechanisms, preferring (or needing) to use the least costly substitutable products available, even if of lower quality. They are doing what is most affordable even though it is commonly thought that even the cheapest biogenics may still be too expensive for many developing countries. For the immediate future, there will not likely be many actual biosimilars developed and marketed domestically in developing countries. For example, a developing country might prudently consider it preferable to pay a fraction of the cost for a domestically manufactured biogenic version of EPO even with a serious adverse event rate of ≥1% (unacceptable in developed countries) rather than pay full price for the reference product or developed country biosimilar versions. Here, buying the cheaper product enables life-saving treatments vs. the alternative of not providing the biogenic and more patients dying.

True Biosimilars Produced by Developing Countries

Developing countries generally have no interest in implementing biosimilars nor, do their nationalized health-care systems wish to pay for costly imported biosimilars. However, both private sector and government-captive companies generally have great interest in developing biogenics for their domestic and lesser-regulated international export markets. This is particularly the case if the potential for technologically feasible biosimilars can be developed for worldwide markets, including developed countries. In developing countries where healthcare is often provided through the government and with foreign aid or philanthropic assistance, governmental agencies are generally the sole source for pharmaceuticals. As such, they have great incentive to seek the cheapest sources, including domestic production.

In the future, many companies and governments in developing countries will increasingly seek to develop genuine high quality, current good manufacturing practices (cGMP)-manufactured, US- and EU-approvable, biosimilars suitable for export. For many companies and countries, getting a biopharmaceutical product into the US and other major markets is an invaluable milestone showing technological, quality, and regulatory expertise. By obtaining biosimilar approval in the US, such organizations could likely see stock valuations increase many times over the actual cost involved in producing these products.

And who will succeed first? This seems likely to first involve products from the leading larger Indian and Chinese companies. For example, Reditux, a biogenic version of Rituxan (rituximab), a recombinant monoclonal antibody developed by Dr. Reddy's Laboratories, and Etacept, a biogenic version of Enbrel (etanercept) developed and manufactured by Shanghai CP Guojian Pharmaceutical Co., Ltd. and marketed in India by Cipla, could be among the first developing country-developed biosimilars. This presumes that their bioprocessing, analytical profiles, and clinical trial results can meet highly developed country *biosimilar* standards. Also, many of the long-marketed biogenics (e.g., legacy products) in international markets could potentially



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become biosimilars as the experienced producers of these products upgrade their biomanufacturing process and conduct needed trials.

Biosimilars from Developing Countries Are Predicted for the Distant Future

The ability of Indian, Chinese, and Latin American (e.g., Cuba and Brazil) organizations/governments to bring domestically-developed biosimilars or any biopharmaceutical products into the US, EU, and other highly-regulated markets remains doubtful for the near future, likely 5–10 years off. There simply are no precedents for a biologic manufactured in a lesser-developed country receiving US/FDA approval, with one exception: an orphan equine antivenin/immunoglobulin product used for scorpion bites, manufactured in Mexico. No developing countries, including India and China, currently have the technological experience and infrastructures needed for cGMP manufacturing. This includes *not* having:

- Shipping cold chains
- Dependable utilities (e.g., electricity, water)
- A critical mass of experts with hands-on experience in cGMP manufacturing and regulatory filings for highly-regulated countries
- The necessary educational and vocational training
- Quality business practices and ethics training to inhibit shortcuts and cover-ups
- Corporate cultures fully conducive to cGMP manufacturing, including the willingness to report problems or protests to upper management, combined with support for whistle blowers
- A sufficient reduction in bribery and corruption (more common among government officials), which casts doubts on domestic inspections and approvals, etc.

It has been discussed that one way for developing country-based organizations (or any company, for that matter) to develop high-quality biosimilars is to outsource the work. They can hire US or EU-based contract manufacturing organizations (CMOs) to develop and manufacture products for developed country markets, and then attempt to clone the manufacturing in their home countries. Single-use bioprocessing systems and, particularly modular bioprocessing facilities, will increasingly make cloning of bioprocessing more attainable and common.

Once developing country-based developers bring a biosimilar to developed country markets, what will they do about marketing? As discussed earlier, biosimilars are handled very differently. Biogenerics are typically distributed without any marketing, relying on lower prices to compete against the reference product (and other generics). Biopharmaceuticals are the most complex of commercial products, and there will not

likely be such generic drug-like interchangeability for years in the highly-regulated, developed countries. Even the EU, the leader in biosimilars, is still discussing how to best accomplish this. In this context, developing countries developing biosimilars will either seek to establish a marketing presence with their product(s) in selected developed countries or establish licensing agreements with Western companies for marketing. For some foreign companies, biosimilars will be their path for entry into the lucrative biopharmaceutical markets in developed countries.

Bioprocessing Advances Are Making Biosimilars More Attainable

The latest bioprocessing methods and systems are increasing efficiency and productivity, particularly with the integration of single-use and modular systems. Such advances are greatly assisting biopharmaceutical producers in the lesser regulated, developing regions of the world. As the developing countries incorporate such systems and manufacturing practices into their own processes, better biogenerics and biosimilars will become a reality in time. Advanced expression systems and cell line improvements, exemplified by ever-increasing yields, are allowing bioprocessing with smaller, scaled-down, equipment in adaptable, multi-product facilities. We can expect developing countries to contract with well-established Western companies, including reference product and biosimilar manufacturers, to develop domestic facilities for manufacture of their products. Also, more Western companies will be partnering with local companies for domestic manufacture of their products.

Numerous countries now require the domestic manufacture of their domestically approved biopharmaceuticals, and in many countries (e.g., China) this has long been required for access to domestic markets. For example, the Brazilian government recently licensed UPLYSO™ (taliglycerase alfa), the first plant expression-based biopharmaceutical manufactured using carrot cell culture technology, from its developer, Protalix BioTherapeutics. The government contracted with GE Healthcare and iBio, Inc. (a company with plant expression technology), to build a large manufacturing facility in Brazil to supply product for the country's needs.

To achieve parity with US and EU manufacturers, including attaining cGMP manufacturing, rest-of-world (ROW) manufacturers recognize improvements are needed. According to our *10th Annual Report and Survey of Biomanufacturing*,^[10] in addition to the quality and regulatory shortfalls, critical technical areas are now being addressed. We surveyed how developed and ROW performance improvements were being achieved over the prior 12 months. Areas where respondents indicated ROW improvements were significantly more impactful included: *better operations staff*

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training, implementing new quality programs, and improved validation services. ROW biomanufacturers continue to be concerned with basic operations, making efforts to improve

all aspects of process control and development. In contrast, US and EU companies tend to report improvements in more specific areas such as process optimization.

Conclusions

In developing countries, we can expect to see several changes in the coming years:

(A) The development and manufacture of biogenics for domestic and international (lesser-regulated countries) marketing.

(B) More companies and governments (with their proxy companies) initiating the development of products intended for domestic use, and then eventually for approval

as biosimilars to export and market in highly regulated, affluent countries, particularly the US and EU.

(C) The adoption of single-use and modular systems for biogenic and biosimilar manufacture to establish or improve biopharmaceutical manufacturing processes.

(D) Significant advances and improvements in bioprocessing expertise and hands-on experience, process control, and quality.

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