



## ○ Featured Article

# Biosimilars: Where We Are, Where We Are Going, How We Get There

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When the FDA approved Momenta Pharmaceuticals and Sandoz's generic version of Lovenox (enoxaparin, Sanofi-Aventis) a few months ago, it represented one more step down the long and winding road to the establishment of a feasible, useable, regulatory pathway for biosimilars in the United States. After all, enoxaparin is a complex protein-based drug – the most complex the FDA has tackled to date. Although it took several years for the FDA to reach its decision, that's still an improvement over the first biosimilar approval back in 2006, when Sandoz had to sue the agency to gain clearance of Omnitrope. Even then the FDA emphasized that Omnitrope was not really a generic biologic because it was not substitutable for other approved human growth hormones.

For many, including myself, the current U.S. pathway does not quite reach the expectations that had been hoped for. However, it does help the regulatory professional begin to chart a pathway in the U.S. which is similar to that of the EU, in that it will cover a full quality dossier with a comparability program and detailed product characterization comparison with, optimistically, a reduced preclinical and clinical program.

But while a biosimilar pathway as robust as the EU's may be slow to emerge in the United States, there's little doubt it will eventually happen. Biosimilars just make too much sense – from a health economics standpoint and from the economic view of drugmakers – not to move forward.

That's not to say biosimilars are easy to make, straight forward from a regulatory perspective, or inexpensive.

### Cost of Development Considerations

In the U.S., a generic small molecule can be created for \$1 million to \$5 million, on average. Minimal pharmacokinetics and bioavailability work is required to establish bioequivalence.

A biosimilar, on the other hand, is not evaluated based on "sameness" to the innovator molecule. Creating one costs \$100 million to \$200 million on average. After that, assuming the biosimilar gains approval, it must compete head-to-head against the entrenched branded product, which is no cheap endeavor.

Biosimilar development is a landmine of complexities, covering areas such as regulatory, manufacturing and marketing, making it one of the most expensive development propositions in the pharmaceutical industry. The average \$100 million to \$200 million cost cited above is in addition to the cost and time commitments involved in a development period that can range from six to ten years, which is approximately equivalent to that required for a biopharmaceutical product.

Adding complexity and cost is the current fiscal state of the industry and the world economic issues. These will only add to the increase in development costs, which are already expected to increase in the long-term. As a result, biopharmaceutical companies are likely to find themselves at a cross roads having to choose between the development of a new product or a biosimilar. Taken all together it is easy to see that in its current state the type and amount of resources that will be required for biosimilar development can create high barriers of entry, not just for small to mid-sized companies, but even for the larger, well-established generics players and global biopharmaceutical companies.

So why bother to develop a biosimilar? Why not just develop your own biologic against the same target? The first reason is that regardless of the amount of money you have to spend developing the biosimilar, you're still probably spending far less than the innovator spent discovering the molecule in the first place. Second, the innovator has already proven the molecule works, so if you can follow in their footsteps, you'll be walking down a significantly derisked path. Third, even biologics that have been on the market for more than a decade can generate billions of dollars annually. Only a small percentage of that market is needed to make the investment worthwhile. This is not taking into account the fiscal changes within healthcare agencies worldwide, and rising insurance costs, with everybody searching for less expensive ways to provide as high quality a treatment as possible

So, it appears biosimilars are here to stay.

## Global Considerations

### United States

As noted above, the United States has made steps towards creating a workable pathway, but it is yet to establish detailed and significant formal regulatory guidelines for the development and approval of biosimilars, often referred to stateside as follow-on biologics.

The healthcare reform bill signed into law earlier this year specified that innovator biologics would have 12 years of data exclusivity protection against biosimilars, but it did not go into detail about the mechanics of establishing a path for the approval of biosimilars. Other key features of the U.S. biosimilars pathway include provisions relating to the assessment of biosimilarity, a first interchangeable biosimilar exclusivity period of at least one year, and regulations regarding patent listings and alleged patent infringement actions. However the lack of a clear pathway should not dissuade anyone from trying. As mentioned above, most regulatory executives would follow a strategy designed around a full quality dossier with a comparability program, and detailed product characterization comparison with, optimistically, a reduced preclinical and clinical program. The sponsor should also bring in the FDA early and often as the strategy develops.

### Europe

In Europe, a biosimilar pathway has existed since 2004, and common biosimilars like erythropoietin have their own guidance documents.

The European system for evaluating biosimilars is collaborative: despite the number of key regulations and guidance documents, the regulators know that "one-size does not fit all." As a result, they actively encourage the sponsors work with the EMEA to develop a strategy. As long as the biosimilar provides the same treatment effect as the innovator drug, there is a fair bit of flexibility in designing the most appropriate plan for the product.

The EMEA guidance documents related to approval could be described as being in two basic categories. The first category includes the general guidance documents that are needed for all biosimilars. The second category covers the product specific guidance documents. While having this level of guidance makes the regulatory pathway seem clear, the quantities and quality of the information and data that is required is enormous.

In addition to preclinical and bench work, clinical trials are required to compare quality, safety, efficacy, pharmacokinetic and pharmacodynamic data between the biosimilar and the reference product. For classic small-molecule drugs, an 80 percent to 125 percent acceptance range for comparative pharmacokinetic data is typically used by regulators. According to the EMEA CHMP guidelines, this range does not apply to biosimilars and a range specific to every product should be predefined and justified. However, for many if not all biotech-derived therapeutic proteins, this either is impossible or can be established only in extensive clinical trials which can add to the cost and time investment significantly. Yet the regulatory demand for clinical comparison between biosimilar and reference product is also questionable considering the practical consequences.

Supplementary trials may be required, depending on the complexity and formulation of the product, which will add to the cost, complexity, and time to market. These cannot always be predicted and are typically at the insistence of the regulatory authorities.

An example of the challenges faced can be illustrated thus: Omnitrope required an estimated phenomenal 18,000 syringes of the reference product Genotropin to be imported into Germany every week during the clinical trial process. The logistical complexity of such an activity poses a significant challenge even to the largest generics companies, not to mention cost.

## Asia

Asia is also entering the biosimilar market. The Ministry of Health, Labour and Welfare (MHLW) in Japan issued a guidance document in 2009 regarding follow-on proteins, and Sandoz gained approval of somatropin shortly thereafter. As a newer entrant to biosimilars, Japan has been able to evaluate the system in Europe and make its own variations. For example, MHLW does not typically require data on safety pharmacology or genotoxicity but will assess the data on absorption, distribution, metabolism, and excretion (ADME). Additionally, Japanese regulators prefer to see overseas marketing of a biosimilar prior to clearing it on their home turf.

### Biosimilar Best Practices

Biosimilar development is a risk-based activity that requires significant resources in R&D, manufacturing expertise, regulatory know-how, clinical trial capabilities, and a high level of financial investment.

As sponsors delve into the world of biosimilars, they face many challenges at each stage of the process, and a good CRO can provide valuable advice. For example:

**CMC/Manufacturing:** Don't cut corners. Yes, CMC is a significant up front cost, but it simply cannot be done retroactively. Some sponsors are tempted to rely on scientific literature rather than conducting a detailed characterization of the reference product, but this approach uniformly fails. If you don't have a robust characterization process, you don't have a product. Some sponsors are also tempted to rush into clinical trials, but the best approach is to do characterization, process development, manufacturing and validation before starting to collect data.

**Preclinical Development:** Remember that you are making a biosimilar, not a new biologic. Some sponsors get too creative in preclinical development, deciding to evaluate new biomarkers or run unnecessary extensive preclinical animal studies. The key here is to set up experiments that establish like for like. They should not be underdone, to avoid missing a side effect or other key information. Comparability to physical properties, amino acid sequence, high order structures and post-translationally modified forms are evaluated by physicochemical tests. In vitro receptor-binding or cell-based (binding) assays or even the in vivo potency studies in animals need to be performed to demonstrate comparable activity, despite them often being seen as imprecise. Levels of product related impurities (aggregates, oxidized forms, deamidated forms) and process related impurities and contaminants (host cell proteins, residual genomic DNA, reagents, downstream impurities) need to be assessed and quantified. The point here is to ensure that the preclinical plan has equal attention as the clinical plan, and that it is adequate to prove your point without going overboard.

**Clinical Development:** Planning and organization are key. At this point in the process, the science of your biosimilar should speak for itself, so the sponsor's role is to handle organization. Study the reference products and ensure your trials are designed with the right endpoints and the right patient populations. Additionally, if you want to market your biosimilar globally, it is important to conduct global trials in diverse ethnic populations. And proving that your biosimilar has an equivalent treatment effect to the innovator product may take a long time and a lot of patients – not to mention patience – so prepare for the long haul, especially if supplemental trials are requested by authorities.

**Regulatory:** Communicate with relevant regulatory bodies early and often. This is not generic development, where the sponsor gathers all of the data and submits it to the agency. In the world of biosimilars, the agency should be involved early in discussions of quality and nonclinical issues, as well as in the development of a clinical strategy. Even in countries where a guidance document exists, at the end of the day, it is just guidance. There's no substitute for face-to-face conversations throughout the entire process. Involving quality regulatory guidance early is particularly important in the clinical trial development arena. The regulatory agencies' demand for clinical comparisons between biosimilar and reference products has been questioned by most regulatory professionals, considering the practical consequences and the return on investment. Working with agencies on specifically tailored programs can reduce cost and time commitments.

Ultimately the biosimilar path is difficult and can be costly, but the rewards can be significant. In the end, the goal is not only to develop a product, but to enhance the lives of the millions of people each year that require treatment. To do this, the product needs to be on the market. Utilizing a full service CRO such as INC Research - with experts in regulatory, product development, medical writing, and science and medicine - can make this journey easier, particularly if you engage them as part of the team from the very beginning to help from creation to commercialization. INC Research has experience in helping companies create the optimal strategy for their biosimilar development program globally.

## About the Author

*Geoff Fatzinger brings a comprehensive scientific and legal background to the Global Regulatory Services group, plus extensive experience in global regulatory affairs including product and clinical development in both pharmaceutical and CRO environments, with extensive knowledge in Europe and Asia Pacific. He has expert knowledge in product development, including combination products and medical devices and regulatory study start-up; having successfully managed several global regulatory start-up groups with 98 percent first round approval rates and accelerated first patient in (FPI). His therapeutic experience in cardiovascular, CNS, oncology and women's health trials is well aligned with INC Research's therapeutic focus. Mr. Fatzinger is also a registered member and speaker for regulatory associations including The Organization for Professionals in Regulatory Affairs (TOPRA) and Regulatory Affairs Professionals Society (RAPS) and is a frequent lecturer on international regulatory requirements and legislation issues. In addition, Mr. Fatzinger has extensive strategic and operational experience in regards to CTD, PIP and market authorizations for Europe and Asia Pacific.*