REGULATORY FOCUS

Investment Decisions Based on Biosimilar Programs, Part 1

By Raymond A. Huml, MS, DVM, RAC, Kamali Chance, MPH, PhD, RAC, Allen R. Baum, JD, and Eileen Provost

As increasing numbers of highly-successful biologics come off patent, biosimilars are a promising area for investment, offering growth potential that is lacking in many other areas of the biopharma market. This two-part series examines the environment for third-party capital providers. Part 1 provides an introduction to this complex area, describing key players entering the biosimilars market, ongoing biosimilar trials and the rationale behind partnering. It then examines three hurdles that must be addressed: manufacturing, immunogenicity and data generation (from pharmacokinetic/pharmacodynamic studies and clinical trials). Part 2 describes three additional hurdles: access to capital, exclusivity and intellectual property, and commercialization.

Introduction

Biological medicines are large, complex molecules produced by living organisms and used for disease prevention, treatment or cure. The introduction of biological medicines to healthcare has had a significant, positive impact on patients, especially where they have provided the only available treatment for a disease. For example, biological medicines have extended the lives of patients with certain cancers, reduced disability for patients with rheumatoid arthritis and provided lifesaving replacement proteins for patients with rare diseases.[1, 2, 3] However, biological medicines are often very expensive, frequently making them unaffordable for patients who may benefit from them.

Biosimilars are highly similar versions of biological medicines with a primary amino acid sequence identical to that of their originators (the reference biological medicine) and are developed with the intention to be as close as possible to the originator biologic. The sponsors of biosimilar products have to demonstrate a high degree of similarity to the

reference product in quality and nonclinical (*in vitro* and *in vivo*, if applicable) and clinical (efficacy, safety and immunogenicity) considerations.

The biosimilars field is one of the fastest-growing industries globally, largely because many blockbuster biologics will be coming off patent in the next few years. By the end of 2012, more than 12 innovator biologics with global sales of more than $67 billion (US) had lost patent protection.[4] The global market for biosimilars is expected to total $2-3 billion by 2015 and $20 billion by 2020.[5] Biopharmaceutical companies are eager to take advantage of the promising opportunity presented by biosimilars.

The regulatory pathway for biosimilars in the EU has been in place since 2004. The European Medicines Agency (EMA) has approved more than 14 biosimilars and a number of others are currently under review, including infliximab biosimilar, the first monoclonal antibody lined up for biosimilar status. In contrast to the EU, the US is proceeding cautiously, although the *Public Health Service Act* (*PHS Act*) was amended in 2010 to allow for review and approval of biosimilars. The long-awaited draft US Food and Drug Administration (FDA) guidances issued on 9 February 2012 describe an abbreviated approval pathway known as a 351(k) application process for biosimilars. Until that date, European guidance documents provided the only International Conference on Harmonisation (ICH)-derived surrogate to guide the development of biosimilars in the US. Despite the fact that FDA has held many meetings with biosimilar sponsors and a number of Investigational New Drug (IND) applications have been received under the *Federal Food, Drug and Cosmetic Act* (*FD&C Act),* no biosimilar product has been reviewed or approved via the 351(k) pathway as of the end of July 2013.

Other countries, in general, are taking their leads from the larger markets, where guidance is available, and appear to be focusing on similar scientific concerns (e.g., immunogenicity). However, when guidance and experience are not available, they are forging ahead with region-specific regulations to bring cheaper copies of biologics to their citizens.[6] Because the authors have experience primarily with the US and EU, these regions are the focus of the remainder of this article.

The success of companies aspiring to manufacture biosimilars is related not only to the timing of expiry of the original product's patents, but also to their technical and financial ability to manufacture comparable products successfully. Considerable resources are required to finance the necessary studies.

This article discusses critical investment decisions related to biosimilar programs based on the authors' industry experience, including interactions with third-party capital providers. The content is based on key factors in our investment decision-making processes while reviewing hundreds of millions of dollars' worth of opportunities during due diligence exercises and the placement of tens of millions of dollars of capital committed to investments in biosimilars over the last 18 months.

Key Players Entering the Biosimilar Market

Most partnerships regarding biosimilars are established between generic companies and large pharmaceutical companies. Traditional generic companies such as Teva, Sandoz and Hospira are continuing to pursue biosimilars as part of their overall business plans to develop copies of small molecules and biologics whose patents have expired. Although generic companies have access to small-molecule chemists and the legal infrastructure to address patent issues, generally, they do not have the operational ability (e.g., manufacturing, conducting clinical trials, marketing, etc.) to register and market a biosimilar product by themselves. Unlike small molecules, biologics can be tricky to manufacture and trickier to copy.

Big pharmaceutical and big biotech companies, such as Pfizer and Amgen, respectively, are also moving ahead with biosimilars—as part of lifecycle development, to protect their current franchises, or just to take advantage of the opportunity. All of these companies seek to partner to access incremental funding, find complementary expertise (in manufacturing, legal, development or commercialization) or share in the risk of biosimilar drug development.

Examples of such partnerships include:

Amgen and Watson: a biotech-generic combination[7]

Amgen and Watson entered into an ambitious pact to develop biosimilars of some leading cancer therapies. Watson signed on with a capped investment of $400 million over the next seven years, while Amgen has an open-ended commitment to the deal. Analysts were intrigued by the notion of a leading biologics company's jumping into an arena that has already attracted a lineup of big pharma players such as Merck, as well as a group of multinationals.

Hospira and NovaQuest: a generic injectable powerhouse and private equity firm combination[8]

Hospira will be responsible for development, regulatory approval, commercialization and distribution of the products (Epoetin, Filgrastim and Pegylated Filgrastim). NovaQuest will contribute up to $150 million of development funding. Hospira will fund the remaining development costs associated with the products. In exchange for the development funding, Hospira will make milestone payments to NovaQuest upon achieving the first commercial sale for each product.

Many of these partnerships, however, have not garnered all the expertise needed to successfully develop compounds in the biosimilar space. For example, clinical development expertise, in the form of rapid and competent clinical trial recruitment and execution, is of paramount importance in successfully developing a biosimilar ahead of the competition and maximizing market potential. Amgen obtained that expertise from PRA International (a multinational contract research organization (CRO)).

A second example is Samsung, one of the world's leading electronics firms, which partnered with Quintiles, the world's largest CRO, to obtain clinical trial and manufacturing expertise. Samsung Electronics Co. and Samsung Everland Inc. will each own a 40% stake in the venture, with Samsung C&T Corp. and Quintiles each holding 10%. Samsung affiliates will focus on production, while Quintiles will help develop technologies.[9]

Since it is projected that biosimilars will retain more than two-thirds of the originator biologic's price after patent expiration, there remains an enormous opportunity for investment in biosimilar development for the biopharmaceutical industry.

Snapshot of Ongoing Biosimilar Trials

A search using ADIS's database yielded more than 80 ongoing biosimilar programs. The number of ongoing US clinical trials is significantly less than 80, according to a search of clinicaltrials.gov using the keyword "biosimilars." This discrepancy seems to be due to the fact that many biosimilar programs are conducted outside the US (and thus out of the purview of FDA, which mandates that all IND-generated trials be posted to clinicaltrials.gov).

Although many companies are pursuing biosimilars, the available targets are limited and, based on an ADIS search containing publicly available information, several companies are targeting the same biosimilar. Selected examples include:

- Adalimumab (BioXpress and Boehringer Ingelheim [BI])
- Bevacizumab (Biocad and BI)
- Epoetin (Hospira, Reliance, Sandoz)
- Etanercept (Hanwha Clinical, LG Life Sciences, Mycenax Biotech and Sandoz, among others)
- Filgrastim (Aequus BioPharma, Bio-Ker, Fuji Pharmaceutical, Mochida Pharmaceutical, Sandoz, Hospira and Lupin, among others)
- Trastuzumab (Celltrion Partnership with Hospira, Synthon, Shanghai CP Guojian and Biocad, among others).

Why Partner?

Based on the authors' experience working in this arena, the biggest challenges for providers of capital for biosimilar products are: 1., obtaining access to robust manufacturing and testing facilities, regulatory expertise, *in vitro* and *in vivo* (if applicable) nonclinical testing and clinical trials (Phase 1 and Phase 3); and 2., obtaining access to due diligence

resources to determine the positive, negative and unknown attributes of the biosimilar, including an assessment of manufacturing and supply chain capabilities. Suitable intellectual property (IP) experts are usually brought in via consultancy as part of the due diligence process.

Many third-party capital providers are partnering with pharmaceutical companies, creating new entities (usually for accounting purposes) and/or partnering with companies with proven manufacturing expertise and/or experience in running clinical trials, such as global CROs, to access clinical trial expertise.

Smaller third-party capital providers (e.g., with fewer than a dozen employees) often use their own experiences and resources for due diligence purposes; however, where functional area expertise (e.g., regulatory, chemistry, manufacturing and controls [CMC], clinical, commercial, sales analytics, forecasting, etc.) is lacking, they identify suitable expertise via consultancy. Other firms may partner with academic institutions, other pharmaceutical companies or the product partnering arms of CROs to access different areas of functional expertise (e.g., regulatory, clinical pharmacology, therapeutic area medical expertise, preclinical expertise, supply chain expertise, etc.) not available in-house.

To successfully place capital in the biosimilar arena and protect themselves via contractual language, third-party capital providers should address six key hurdles, each of which is discussed separately below or in part two of this article:

1) Manufacturing
2) Immunogenicity (safety)
3) Clinical trial design and execution
4) Sufficient capital
5) Sufficient exclusivity and IP protection throughout the duration of the deal
6) Commercialization

Hurdle One: Manufacturing

Biologics differ from conventional small-molecule drugs in that they are created from living organisms, either naturally or via genetic manipulation, or are manufactured from complex building blocks of living organisms. In either case, they demonstrate considerable molecular complexity and heterogeneity, and are more difficult to characterize physiochemically than synthetic chemical drugs. Indeed, some components of a finished biologic may be unknown. These large, complex molecules, or mixtures of molecules, are often manufactured using recombinant DNA technology. Examples include insulin, growth hormone, erythropoietins and monoclonal antibodies.

Small-molecular-weight drugs are much simpler and are chemically synthesized; consequently, generics are easy to make. The active ingredient for a generic drug is an exact duplicate of its originator products, which is not the case for biosimilars.[10] Drug makers can extensively alter the production process for generics and use laboratory tests to confirm that the product remains the same.

These differences are reflected when branded products are substituted with "generics" once patent life has expired, a step that has contributed enormously to making many medicines affordable. For biologics, demonstration of comparability between different forms of a biological product is very demanding, not least because the products cannot be identical, only similar; hence the term *biosimilar*. The active substance is similar to that of the reference product and the biosimilar is generally administered at the same dose to treat the same disease(s). While the primary amino acid backbone of a biosimilar protein should be identical to that of the reference product, post-translational modifications such as deamidation, phosphorylation or glycosylation often result in product changes that can affect the impurity profile as well as the safety and efficacy of these products. The complexity of production makes exact replication of the originator molecule virtually unattainable, and batch-to-batch variation in physicochemical properties, purity and quality of all biological products must be monitored carefully as these may affect biological activity, safety and immunogenicity. The use of novel expression systems may introduce additional risks, such as host cell protein, a different impurity profile and atypical glycosylation patterns, as compared to the reference medicinal product.

The suitability of the proposed formulation with regard to potency, stability and compatibility with excipients, diluents and packaging materials is stressed. If a formulation

and/or container/closure system (including any material that is in contact with the medicinal product) that differs from the reference medicinal product is selected, its potential impact on the safety and efficacy should be appropriately justified.

This means only a select number of companies have access to—or the capital required to obtain—manufacturing expertise and the current Good Manufacturing Practice (CGMP) facilities required to produce biosimilars. It also means that minor changes to existing manufacturing lines can lead to significant delays when manufacturing biosimilars.

Hurdle Two: Immunogenicity

ICH Q5E, "Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process," details the comparability assessment required when a sponsor of an approved biologic envisions making manufacturing changes. Demonstration of biosimilarity is not restricted to physicochemical properties, but also requires comparison of potency using pharmacodynamic (PD) endpoints and measures of efficacy and safety in patients with those of the reference product. A thorough investigation of immunogenicity is critical to address safety implications associated with changes in manufacturing.

Although this early guidance addressed some of the critical concerns associated with biologic products, the first EMA general guideline on biosimilar products was not published until the mid-2000s. It covered the subject of biotechnology-derived proteins as active substances.

An initial, unfortunate experience with a manufacturing site change by an innovator company, along with some changes to a container/closure in the late 1990s, served as an alert to the inherent risks of making apparently small changes to biological products. For example, the changes by the manufacturer to the formulation of erythropoietin marketed as Eprex (epoetin alfa) resulted indirectly in the induction of an immune response, which manifested as a dramatic increase in the frequency of cases of pure red cell aplasia and required some patients to have blood transfusions and dialysis. The problem was resolved, but this salutary lesson perhaps contributed to a rigorous approach by EMA and FDA to establishing the similarity of both structure and functional activity of biosimilars to those of the innovator/reference product.

Immunogenicity remains a key safety concern that needs to be addressed in all clinical trials conducted for biosimilar product approval. Concerns over safety have been discussed by sponsors of biosimilars and global regulatory agencies. This focus on immunogenicity may lead to greater expense if additional clinical trial work (or clinical trials conducted for longer periods or with more patients) is needed to allay fears that a proposed biosimilar may exhibit an untoward clinical safety signal.

Hurdle Three: PK/PD and Clinical Trials

EMA published several additional regulatory guidances after an initial overarching regulatory guidance on biosimilars in October 2005. Two general guidance documents addressed quality and nonclinical and clinical perspectives (June 2006) and four annexes covered product class-specific nonclinical and clinical issues (June-July 2006). The documents outline general expectations and specific biosimilar product testing strategies. They cover manufacturing, quality, nonclinical and clinical efficacy, safety and immunogenicity comparability assessments. Many early biosimilar guidance documents, including overarching guidelines and general guidelines on nonclinical and clinical development, are under revision in the EU based on EMA's experience working with these products over the last seven to eight years.

These guidances make it clear that quality, nonclinical and clinical comparability data are normally required, but the precise requirements for such data are established on a case-by-case basis. The criteria for selection of the reference medicinal product must be provided, and comparability parameters have to be pre-specified. Even if biosimilarity is accepted and the product is approved by EMA, the decision for interchangeability rests with each EU Member State because EMA does not have the authority to designate a biosimilar as interchangeable. These products are given proprietary names; therefore, a specific prescription is generally required from the healthcare provider.

The FDA guidance document, *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*, details nonclinical and clinical considerations for the development of biosimilars.

Both FDA and EMA highly recommend a strategic, stepwise development program for biosimilars that should result in a targeted approach to nonclinical and clinical studies, as warranted, on a case-by-case basis. Upon completion of analytical comparability studies, if comparative testing shows that the biosimilar product has additional impurities or degradation products, the sponsor should consider the role of nonclinical studies in assessing toxicity. EMA and FDA have both stated that animal toxicity studies generally are not useful unless relevant species are identified.[11, 12]

For clinical assessment, EMA and FDA both expect, at a minimum, comparative human pharmacokinetic (PK) and pharmacodynamic (PD) studies—if a relevant PD measure is available—with the US or EU-licensed reference product. PK and PD parameters must be predefined and scientifically justified. Both regulatory agencies now recommend a crossover design for PK/PD studies of products with a short half-life (i.e., less than five days) and for products with low immunogenic response. If a product has a long half-life (i.e., more than five days), a parallel study design is generally recommended. Scientific justification is needed for selection of study subjects (patients or healthy volunteers), dose, study sample size and route of administration.[13, 14, 15, 16]

Additional Phase 3 clinical studies that may be required include comparative clinical immunogenicity, clinical safety and clinical efficacy to ensure the proposed biosimilar product is clinically similar in potency, purity and safety to the reference product. All three aspects can be addressed in one well-designed clinical study. If global development is envisioned, analytical, nonclinical and Phase 1 clinical comparability data are generally required, followed by a two-arm Phase 3 study using the reference product. In addition, FDA requires a study of the transition from innovator to biosimilar that can also be incorporated in the Phase 3 study design. If interchangeability status in the US is desired, the sponsor will be required to conduct a Phase 3 study that includes multiple cycles of transition between the innovator product and the biosimilar.

Clinical development requirements for biosimilars are extensive, and even more so if a PD marker is not available. The more PK/PD work and clinical trials that are required, the greater the capital needed prior to registration. A credible partner needs to be identified to run the Phase 1-type PK/PD work as well as the Phase 3-type clinical trials. With more clinical trials being conducted globally, CROs with a global footprint will be more advantageous as partners for the development of biosimilars than smaller CROs.

Market exclusivity and interchangeability concerns need to be built into investment models or investment strategies because these pathways have the potential to change in the future.

References

1. FDA 101: Regulating biological products. US Food and Drug Administration website. Consumer Updates > FDA 101: Regulating Biological Products. Updated 25 July 2008. Accessed 26 July 2013.
2. McCamish M, Woollett G. The state of the art in the development of biosimilars. *Clin Pharmacol Ther*. 2012; 91(3): 405-417.
3. Krishnan E, Lingala B, Bruce B, Fries JF. Disability in rheumatoid arthritis in the era of biological treatments. *Ann Rheum Dis*. 2012; 71(2):213-218.
4. Sheppard A, Iervolino A. Biosimilars: about to leap? 10th EGA International Symposium on Biosimilar Medicines; 19 April 2012; London, UK. http://www.gabionline.net/Reports/Global-uptake-of-biosimilars.
5. Dang S, Baker L, Hasko J. Transactions in the Biosimilars Industry: Similar But Not the Same. Blooomberg BNA Life Sciences & Industry Report, 19 October 2012. ISSN 1935-7257.
6. Huml RA, Posner J. Chapter 38: Biosimilars. In: *Textbook of Pharmaceutical Medicine*. Chichester, West Sussex, England: John Wiley & Sons Ltd; 2013:744-750.
7. Carroll J. PRA grabs global biosimilar research pact with Amgen. FierceCRO website. http://www.fiercecro.com/story/pra-grabs-global-biosimilar-research-pact-amgen/2012-04-26. 26 April 2012. Accessed 9 July 2013.
8. Hospira and NovaQuest Co-Investment I, L.P. Enter Into Collaborative Arrangement. NovaQuest Capital Management website. http://www.nqcapital.com/2013/04/hospira-and-novaquest-co-investment-i-l-p-enter-into-collaborative-arrangement/. 29 April 2013. Accessed 22 May 2013.
9. Yang J. Samsung Group, Quintiles Plan $266 Million Venture to Make Biologic Drugs. Bloomberg website. http://www.bloomberg.com/news/2011-02-25/samsung-electronics-group-to-form-266-million-biopharmaceuticals-venture.html. 25 February 2011. Accessed 22 May 2013.
10. Chance K. US biosimilars guidelines: Summary and insights. *Regulatory Focus*. 3 April 2012. http://www.raps.org/focus-online/features/features-article-view/article/1190/us-biosimilar-guidelines-summary-and-insights.aspx. Accessed 30 July 2013.
11. *Draft Guidance for Industry on Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (issued jointly by CDER and CBER, February 2012). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

12. *Guidelines on Similar Biological Medical Products Containing monoclonal antibodies-nonclinical and clinical issues, December 2012*. EMA/CHMP/BMWP/403543/2010.
13. *Draft Guidelines on Similar Biological Medical Products, May 2013*. CHMP/437/04/Rev 1.
14. Merron A. Biosimilars: Market Access and Pricing Issues According to Surveyed and Interviewed Payers. BioTrends Research Group website. http://bio-trends.com/Articles/Biosimilars-Payer-Nov-2012. November 2012. Accessed 17 July 2013.
15. Howell, P. How much cheaper will biosimilars be? FiercePharma website. http://www.fiercepharma.com/story/how-much-cheaper-will-biosimilars-be/2012-03-02. 2 March 2012. Accessed 17 July 2013.
16. Sashidhar KS. Biosimilars in Europe: The Road Ahead. Analyst Briefing, 6 March 2012. http://www.slideshare.net/FrostandSullivan/biosimilars-in-europe-the-road-ahead#btnPrevious. Accessed 17 July 2013.

About the Authors

Raymond A. Huml, MS, DVM, RAC, is executive director and head of global due diligence for Quintiles Transnational Corp.'s Center for Integrated Drug Development. He can be reached at Raymond.Huml@quintiles.com. **Kamali Chance, MPH, PhD, RAC**, is a senior director and head of global biosimilars regulatory strategy for the Quintiles Global Biosimilars Strategic Unit. She can be reached at Kamali.Chance@quintiles.com. **Eileen Provost** is co-founder of Genesis Associates, a commercial strategy consulting company. She can be reached at eprovost@genesisassoc.com. **Allen R. Baum, JD,** is a shareholder and patent attorney with Brinks Hofer Gilson & Lione and is also the former president of the Licensing Executives Society in the US and Canada. He can be reached at abaum@usebrinks.com.

Acknowledgments

A special thanks to Jonathan Tunnicliffe, partner of NovaQuest Co-Investment I, L.P., and Jill Dawson, PhD, a consultant to Quintiles Corporate Communications, for their editorial contributions to this paper.