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KEY CONSIDERATIONS FOR BIOSIMILAR CLINICAL PHARMACOLOGY STUDIES

"Altasciences has the perfect mix of innovator and generic drug development experience, with a thorough understanding of the regulatory complexities involved in biosimilar clinical pharmacology studies. Companies developing biosimilars are collaborating with us because of our firsthand experience, distinctive recruitment strategies and speed in conducting biosimilar clinical trials that require a customized approach based on the therapeutic indication and study-specific goals. Our expertise allows us to accelerate our clients' biosimilar development programs so they can offer greater treatment options and more cost-effective medications to patients in need."

Danielle Salha
Senior Director, Immunology & Immunochemistry, Ligand Binding Assays

THE RISE OF THE BIOSIMILAR MARKET

Biologics have become the fastest-growing class of therapeutic compounds, with the majority of the 10 top-selling drugs in 2017 being biologics, each exceeding sales of US$5 billion. They represent almost 40 percent of all prescription drugs spending and accounted for 70 percent of growth in drug spending from 2010 to 2015. The size of the market globally is expected to grow to US$287.14 billion by the end of 2020. Biologics have provided treatment options for people who suffer from some of the most serious medical conditions, such as cancer and genetic disorders. About 300 biologics are now available for human use, and the demand is growing exponentially due to the generally fewer side effects than the more broadly acting small molecule drugs. It is estimated that US$67 billion worth of biologic patents are set to expire before 2020. The expiration of patents and other intellectual property rights for originator biologics over the next decade opens up opportunities for biosimilars to enter the market and increase industry competition.

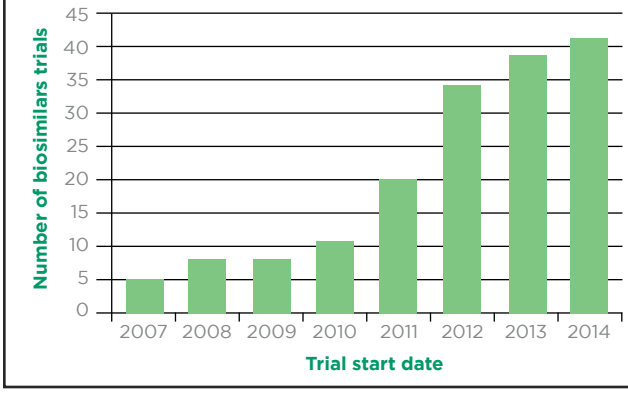
TOP SELLING BIOLOGICS	PATENT EXPIRY DATE	
	UNITED STATES	EUROPE
ADALIMUMAB (Humira)	EXPIRED	EXPIRED
ETANERCEPT (Enbrel)	2028	EXPIRED
INFLIXIMAB (Remicade)	EXPIRED	EXPIRED
TRASTUZUMAB (Herceptin)	EXPIRED	EXPIRED
BEVACIZUMAB (Avastin)	EXPIRED	2022
PALIVIZUMAB (Synagis)	EXPIRED	EXPIRED
CETUXIMAD (Erbitux)	EXPIRED	EXPIRED
DARBEPOETIN ALFA (Aranesp)	2024	EXPIRED
EPOETIN ALFA (Epogen/Eprex)	EXPIRED	EXPIRED
PEGFILGRASTIM (Neulasta)	EXPIRED	EXPIRED
FILGRASTIM (Neupogen)	EXPIRED	EXPIRED
RITUXIMAB (Mabthera)	EXPIRED	EXPIRED
ENOXAPARIN SODIUM (Lovenox)	EXPIRED	EXPIRED
INTERFERON BETA-IA (Avonex)	EXPIRED	EXPIRED
INSULIN GLARGINE (Lantus)	EXPIRED	EXPIRED
AFLIBERCEPT (Eylea)	EXPIRED	2021
RANIBIZUMAB (Lucentis)	EXPIRED	2022

Source: www.gabionline.net

A biosimilar is a copy of a biologic medicine that is similar, but not identical, to the original medicine. It enters the market subsequent to the patent expiration of a previously authorized version of a biologic. A biosimilar is approved only after showing that it is "highly similar" to an approved biological product, known as the reference product, in terms of structure, purity, potency, safety, pharmacokinetics, and in many cases, efficacy, with allowable minor differences. To be called a biosimilar, these compounds need to demonstrate *in vitro* and *in vivo* functional similarities with comparable pharmacokinetic (PK) and pharmacodynamics (PD) properties to the reference product. Biosimilars are usually given the same indications as the originator drugs but with reduced development cost, which translates to a lower market price, making them more accessible and affordable to patients.

Evidence of the growing interest in biosimilars is shown by the approximately eightfold increase in the number of clinical trials that have taken place between 2007 and 2014. As of December 2017, there were close to 60 biosimilars in the FDA's Biosimilar Biological Product Development (BPD) program.

Number of biosimilars clinical trials started between 2007 and 2014



Source: Citeline

In recent years, there has been an increasing comfort with biosimilars. So far, data has shown that biosimilars are safe and effective, and their acceptance has been growing among stakeholders. Extrapolation, interchangeability, immunogenicity, traceability, pricing and risk management continue to be topics of discussion, while stringent regulatory requirements, continued education of patients and physicians, the issue of switching between originator reference product and biosimilar, and rising competition remain ongoing challenges.

REGULATORY LANDSCAPE

Regulatory agencies, such as the European Medicines Association (EMA), the Food and Drug Administration (FDA), and Health Canada (HC), have developed guidelines for the evaluation and approval processes of biosimilars that pave the way for rapid development and approval, and increase market access and affordability. Specifically, they outline requirements for the physical, chemical, and clinical traits of biosimilars. In evaluating a sponsor's demonstration of biosimilarity, the FDA expects them to conduct human PK and PD studies, and will consider the totality of the data and information submitted in the application, including structural and functional characterization, preclinical evaluation, human PK and PD data, clinical immunogenicity data, and comparative clinical study data. The agency uses a risk-based approach to evaluate all available data and information submitted in support of the biosimilarity of the proposed product.

The pace of development and uptake of biosimilars in the U.S. and the EU has been accelerating, particularly since the approval of the first biosimilar monoclonal antibodies (Infliximab biosimilars Remsima/Inflectra in September 2013 in the EU), but the U.S. continues to be behind the EU. In Asian countries, there is a huge demand for biosimilars given that the majority of the population cannot afford originator biologics. Copies of biologic drugs, also called follow-on biologics in those regions, have been developed and marketed for quite some time in countries such as China and India, although these drugs have not been shown to meet the criteria for a biosimilar established by the EU or U.S. Regulations about development and approval of biosimilars vary greatly among Asian countries, with Japan and South Korea having adopted stringent guidelines similar to the EMA, whereas other countries have been more lenient.

To date, the FDA has approved 6 biosimilar applications in the U.S. with close to 150 potential biosimilars in various stages of development and review. The latter include medications in therapeutic areas such as oncology, immunology, and diabetes, with biosimilar producers showing particular interest in leading biologics with recent or pending patent expiry, including Avastin, Humira, and Levemir.

Approval Date	Biosimilar Product	Brand Product	Patient Population
March 6, 2015	Filgrastim-sndz/Zarxio* (Sandoz)	Filgrastim/Neupogen (Amgen)	Oncology
April 5, 2015	Infliximab-ddyb/Inflectra* (Celltrion/Pfizer)	Infliximab/Remicade (Johnson & Johnson)	Autoimmune
August 30, 2016	Etanercept-szzs/Erelzi (Sandoz)	Etanercept/Enbrel (Amgen)	Arthritis/Psoriasis
September 23, 2016	Adalimumab-atto/Amjevita (Amgen)	Adalimumab/Humira (AbbVie)	Arthritis/Psoriasis
April 21, 2017	Infliximab-abda/Renflexis* (Samsung Bioepis)	Infliximab/Remicade (Johnson & Johnson)	Autoimmune
August 25, 2017	Adalimumab-adbm/Cyltezo (Boehringer Ingelheim)	Adalimumab/Humira (Abbvie)	Autoimmune

**Due to ongoing litigation and intellectual property disputes, Zarxio, Inflectra and Renflexis are the only products currently marketed in the U.S.*

Source: Leading on Biosimilars. Bruce Leicher. 2017 AAM Biosimilars Council Conference.

With 6 biosimilars reaching the market, interchangeability with the reference product has become a hot topic. Interchangeability is seen and even defined quite differently in the EU and U.S. The EU uses a more broad definition, but in the U.S., it means that "the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product." In the U.S., an interchangeable product, in addition to being biosimilar, must meet additional requirements based on further evaluation and testing of the product. However, a number of EU countries have stated that an approved biosimilar is interchangeable.

In 2019, the FDA finalized the guidance on biosimilar interchangeability entitled *Considerations in Demonstrating Interchangeability with a Reference Product*, in which they recommend that sponsors conduct one or more studies to compare the safety and efficacy of the reference product and the biosimilar. Clinical pharmacology studies focused on PK and PD, when applicable, should be conducted with immunogenicity and safety as the secondary key endpoints.

Based on trends observed across the global biosimilar market, we expect to see more and more companies seeking interchangeability designations for their products. This would offer them a competitive advantage as pharmacists can then dispense an interchangeable biologic in the place of a prescribed originator without first obtaining approval from the prescriber, which would open the door for decreased healthcare costs and better patient access.

ALTASCIENCES PUTS BIOSIMILARS TO THE TEST

A biosimilar development program consists of the following stages: analytical, preclinical, clinical pharmacology studies focusing on PK and PD, and a Phase III efficacy study. It can cost anywhere from $100 to $300 million (USD), take up to 8 years to reach the market, and can sometimes require as many as 500 participants for the Phase III study. At Altasciences, we offer preclinical safety testing and bioanalysis, and full-service bioanalytical support and full-service support for clinical pharmacology studies to the global biopharmaceutical industry, with a particular expertise in developing programs and conducting full-service clinical pharmacology studies for novel biologics and biosimilars. We partner with our clients to develop an effective plan and execution strategy for their biosimilar trials, which require a customized, nimble approach based on the therapeutic indication and study-specific goals.

Our biosimilars development team members each have more than 15 years of experience in their respective areas and the insight needed to strategically advise and guide clients through the development process to deliver a successful biosimilar program, on time and within budget. Our Principal Investigators are intimately involved in all aspects of our clinical trials, ensuring that proper medical and technical procedures are completed to the highest degree of quality. This is especially important when conducting clinical trials involving monoclonal antibodies to ensure the safety of each participant.

What differentiates Altasciences from other contract research organizations (CROs) is our mix of experience with both innovator and generic medicines. Sponsors developing generic drugs are drawn to us because we understand that price, speed, quality, and a study design that meets recruitment milestones and regulatory requirements are vital to their drug development programs. Sponsors developing innovator drugs entrust us with their studies because of our experience in dosing innovator biologics and high-risk compounds, and designing complex studies with multiple endpoints.

Our effective approach to overcoming recruitment issues is also what draws sponsors to Altasciences for their clinical pharmacology studies with biosimilars. For many biosimilars, the clinical pharmacology studies looking at PK, PD, and immunogenicity can be conducted in healthy participants. While that makes recruitment of participants easier than if patients were required, clinical pharmacology studies with biosimilars can still present recruitment challenges.

Our access to a robust database of healthy normal participants as well as our comfortable facilities have enabled us to rapidly recruit, enroll and retain large numbers of participants. For example, we have successfully recruited close to 650 healthy participants in various biosimilar trials in one year alone. Our multi-site clinical facilities also facilitate recruitment to complete studies faster. Sponsors have accelerated their studies by months when our sites all recruited at the same time to conduct three studies concurrently, and benefited from the efficiencies of working with a single CRO.

Moreover, we have conducted numerous clinical pharmacology studies over the past 10 years for biosimilar submissions (14 PK Comparison of Test versus Reference studies, 6 immunogenicity studies and 8 PD studies), recruiting up to 250 participants per study. Our facilities are ideally designed to support biosimilar studies as we are equipped with an ISO Class 8 anteroom, attached to an ISO Class 7 cleanroom containing a Class 2 Biological Safety Cabinet. This is used for sterile compounding and is designed to support the evolving needs in the development of large molecule pharmaceutical products. Infliximab, Adalimumab, Evolocumab, Denosunab, and Trastuzumab are just some of the examples of biological products that our dedicated, full-time pharmacists have been working with over the years.

EXPERTS IN BIOANALYSIS

Altasciences supports method development, GCP/GLP-compliant biosimilar assay development validation, and sample analysis for PK and immunogenicity/anti-drug antibody (ADA) testing. We are proud of our bioanalytical expertise with LC-MS/MS and Ligand Binding platforms, and provide support for all stages of drug development (discovery to preclinical to Phase IV) for both small and large molecules programs.

LC-MS/MS

- PK assessment of recombinant proteins and monoclonal antibodies
- Product characterization including glycosylation patterns

Ligand Binding

- PK assessment of recombinant proteins, monoclonal antibodies and oligonucleotides
- Immunogenicity assessment by measuring ADAs
- Neutralizing antibody detection through competitive binding

Our state-of-the-art laboratory space, with capacity to analyze at least 60,000 samples per month, and a 24/7 staffing schedule allow us to design, conduct, analyze and report all our studies in-house, in addition to providing full PK/PD support.

Different strategies exist when it comes to the appropriate bioanalytical support for the comparative bioanalytical immunogenicity assessment of the biosimilar to its reference product. For instance, the EMA recommends a two-assay approach in which an assay is developed for the biosimilar and the reference product separately. This methodology captures the immunogenicity response of each product; it is challenging and can lead to variability between the different data sets. When the two-assay approach is used, the key factor is to demonstrate the equivalence of the two individual assays in regards to cut-points, sensitivity, drug tolerance and precision.

The FDA recommends a one-assay approach, where the biosimilar is used to capture and detect the anti-biosimilar/reference product antibodies, and to confirm the samples that are screened positive. In this case, a positive control raised against the biosimilar is suggested. The one-assay approach allows the comparison of the immunogenicity profiles of the biosimilar and the reference product within the same assay, thus identifying possible differences in the immunogenicity responses between the two products. In addition to the standard parameters evaluated during method development and validation of an immunogenicity screening and confirmatory assay, it is critical to evaluate the suitability of the one-assay approach during these phases. This consists of demonstrating that the positive control binding profiles to the biosimilar and reference drugs are comparable, establishing that the biosimilar and reference products have similar abilities to detect ADAs in the confirmatory assay, and ensuring that the drug tolerance using the biosimilar or the reference product are comparable. All samples that are confirmed positive are then titrated by performing a two- or threefold serial dilution series.

In terms of the bioanalytical evaluation for PK assessment, our approach (as recommended by the FDA) is to use a single assay to quantify the reference and biosimilar compounds. The method is developed and validated to demonstrate the similarity between the biosimilar and reference compounds in order to use a single assay for the study sample analysis. During the method development phase, the bioanalytical similarity is evaluated to demonstrate whether a single calibration curve (either the reference compound or the biosimilar compound) can be used to adequately quantify the two compounds. Following the completion of the method validation and the demonstration of bioanalytical similarity, the assay can be used with one reference material (either the reference compound or the biosimilar compound) to prepare the calibration curve and quality control samples, and analyze the study samples.

KEY CONSIDERATIONS FOR BIOSIMILAR CLINICAL PHARMACOLOGY STUDIES

Altasciences understands how to develop and conduct cost-effective, customized biosimilar clinical pharmacology studies, and the importance of minimizing bioanalytical and recruitment challenges to facilitate market entry after patent expiration. Early awareness of study challenges is crucial in running a successful early phase biosimilar development program; thus, the following considerations must be taken into account before beginning a study.

Recruitment Strategies

Recruitment is often one the most challenging aspects of the biosimilar clinical trial process and can lead to trial delays if not managed effectively. The inclusion and exclusion criteria for healthy participants in a biosimilar bioequivalence study are often much stricter than a standard bioequivalence study on a small molecule. The more rigid criteria often results in a higher screen failure rate, as was the case in a recent study where 80% of patients recruited didn't pass screening, and a larger number of participants had to be recruited to hit the enrolment target. The confinement period in biosimilar studies is often longer and the overall study duration can be up to one year. Using a clinical pharmacology unit that focuses on patient comfort and convenience is important for recruitment and retention in these longer studies.

When immunogenicity is assessed, follow up visits can extend from 6 to 12 months after the first visit. In such cases, the commitment from the participants is 2 to 4 times longer than typical clinical pharmacology studies, leaving trials open to high participant dropout rates. These factors affect recruitment as healthy participants do not receive any medical benefit from the treatment and prefer shorter studies.

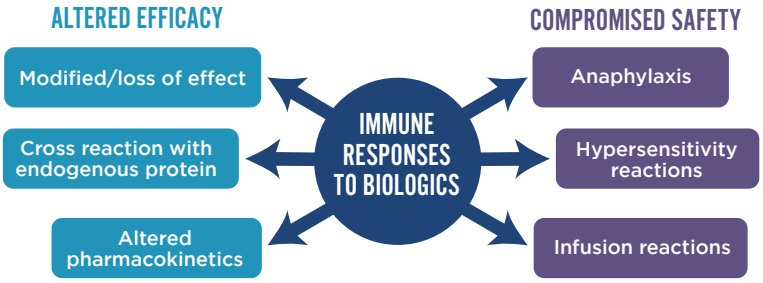
Working with a CRO that has a large database of healthy participants and a wide reach within the community to recruit new participants, with an established proven track record in recruiting long-term studies with biologics, offers the best opportunity for success.

Safety and Risk Management

As a biosimilar product is not exactly the same as the reference product, there are increased safety risks associated with the administration of the test product.

When conducting these types of complex trials, sponsors should select sites that have the pharmacy and medical expertise to understand and handle these risks, as well as the infrastructure in place to identify and mitigate any issues. Key safety considerations include immunogenicity, hypersensitivity reactions, and an increased risk for other adverse effects. Further safety precautions can range from additional nurses or paramedics on site, increased stagger between dosing participants, prophylactic treatment for suspected adverse effects such as immune reactions, and using telemetry to continually monitor the vital signs of participants.

Immune response can influence the efficacy and safety of a biologic



Source: Biosimilar safety factors in clinical practice. W. Reinisch, J. Smolen

Operational units should have a systematic way to assess each biologic, and ensure that the study protocol and site procedures are planned in a way that minimizes the increased risk to participant safety. This evaluation should consider all elements in the conduct of the trial. Participant screening to ensure compliance and mitigating for prior exposure to the particular biologic are critical steps. It is also important to take into account the adverse reactions that have been seen with the reference biologic. Key understanding about the innovator product and the mechanism of action should inform the site on how to handle safety concerns. Questions sites should consider include: how many participants can concurrently be dosed on a given day and what is the adequate staff-to-participant ratio for medical coverage?

Clinical trial sites should have advanced medical expertise and be able to provide the necessary oversight by staff trained to deal with severe drug reactions. Access to immunologists and emergency trained physicians is equally important. Understanding what stage sponsors have reached in their clinical development program, for instance whether patients or healthy participants have already been given the test product, is also a key consideration in the feasibility review when determining how to safely handle these trials.

Each biosimilar program is unique and the safety precautions taken need to be customized for each program.

Bioanalytical Considerations

Unlike small molecule drugs, biologics exhibit a significant level of complexity which is driven by the fact that their production is dependent on a living system, such as a microorganism, a plant, or animal cells. The manufacturing process and control are also unique to each manufacturer, for example, the choice of cell type, fermentation, purification, formulation, storage, and stability. Consequently, minor changes in the manufacturing process could result in major changes in the impurity levels for example, which may impact the safety and potency of the drug. These inherently complex manufacturing processes can lead to differences from lot to lot within the originator product; thus, when assessing the biosimilarity of an innovator drug, the challenges that may arise are significant.

Therefore, it is important to establish assay acceptance criteria to demonstrate equivalency between the two products early in method development to address any bias due to reagents, and method variability or robustness, versus product differences. For the PK assay, interference of ADAs on PK assessment may be different between the two products. Those differences could be due to minor 3D structural differences in the innovator product that would lead to a difference in the positive control hyper-immune serum generated, which would then bind differently to the two products. If this is the case, two separate positive controls may be considered for each product.

For immunogenicity comparability assessment, the reportable values are usually qualitative in nature and therefore variable, especially at the limit of quantification (LOQ) levels. Therefore, being able to distinguish between assay variability and equivalence of products is crucial. Finally, although critical reagents are usually qualified before use, it is prudent to minimize the number of lots used throughout the comparability studies in order to reduce lot-to-lot differences and any potential impact on the data generated.

ENSURING THE CONTINUED SUCCESS OF BIOSIMILAR PROGRAMS

Regulatory agencies will continue to play a critical role in facilitating increased access to biosimilars and are taking steps to more efficiently manage the review and licensure pathways to facilitate biosimilar competition. In the U.S., the FDA's Biosimilar Action Plan (BAP), released in July 2018, provides information about the key actions it is taking to encourage innovation and competition among biologics and the development of biosimilars by focusing on four key areas:

1. Improving the efficiency of the biosimilar and interchangeable product development and approval process
2. Maximizing scientific and regulatory clarity for the biosimilar product development community
3. Developing effective communications to improve understanding of biosimilars among patients, clinicians, and payers
4. Supporting market competition by reducing gaming of FDA requirements or other attempts to unfairly delay competition

In the coming years, we expect to see continuing growth in the number of approved biosimilar and interchangeable products, as the emergence of such action plans helps create greater incentives and removes roadblocks for sponsors to make the investments required to support future products that deliver more affordable versions of biologics after statutory exclusivities have expired.

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ABOUT ALTASCIENCES

Altasciences is an integrated drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services. For over 25 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis, program management, medical writing, biostatistics, clinical monitoring, and data management, all customizable to specific sponsor requirements. Altasciences helps sponsors get better drugs to the people who need them, faster.