Executive summary

This paper provides an overview of how biosimilars are regulated and outlines a stepwise approach, including how to plan and design smarter biosimilar clinical trials, to overcome complex regulatory hurdles.
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Introduction
The success of biologics for many debilitating medical conditions such as rheumatoid arthritis, cancers, etc. and their spiraling costs timed with patent expiries have led biopharmaceutical companies to develop biosimilar products. Biosimilars have the potential to increase access and provide lower cost options for treatment of many medical conditions.

Biosimilars pose very different challenges than those presented by small molecule generics: higher costs for development with required head to head similarity studies: analytically, nonclinically, and clinically. Before you consider putting your biosimilar drug through development, you need to be informed of the regulatory pathways and complexities that will be involved – as well as steps you should take to address these regulatory considerations for making important decisions about your biosimilar products.

As the largest provider of product development and integrated healthcare services, including commercial and observational solutions, Quintiles has been advising biopharmaceutical and other healthcare companies how to improve their probability of success by connecting insights from its deep scientific, therapeutic, and analytics expertise with superior delivery for better outcomes.

Read more about Quintiles’ recommendations on the following topics:

• The Patent Cliff: What happens to medicines coming off-patent and how are biosimilars capitalizing from these patent expirations?
• Why are biosimilars important to biopharma?
• Who are some of the top competitors in this space?
• What are the different components of biosimilar trials?
• How might your decisions today affect the future of your biosimilar trials and marketing success?

The Biosimilars Space: Overview and Competitive Landscape
Biological medicines are large, complex protein products produced in living cells and biosimilars are copies of biologic medicines that share the same amino acid sequence. Small-molecule medicines are chemically synthesized, so generics are relatively easy to make. Unlike chemically synthesized drugs with known structures that can be easily replicated, these products are made up of proteins with potential of many posttranslational changes during manufacture including glycosylation, phosphorylation, etc. The impact of these changes has to be studied to ensure that the efficacy and safety of the resulting product is not negatively impacted.

Biologics provide therapies for some of the most debilitating medical conditions and can prolong the life of patients suffering from diseases such as cancer. Examples of biologics include trastuzumab (Herceptin ™), an anti-HER2 monoclonal antibody for treatment of HER2+ breast cancer which has reduced mortality from this disease by one-third, rituximab (Rituxan/Mabthera ™), a monoclonal antibody that is the standard of care for patients with non-Hodgkin lymphoma and has increased survival in these patients, and belimumab (Benlysta ™) a human monoclonal antibody for the treatment of lupus, the first drug to be approved specifically for this autoimmune disorder in 50 years. Another example of biologics is a family of drugs known as anti-tumor necrosis factor (anti-TNF) antibodies such as Remicade and Humira, which have revolutionized the treatment of people suffering from inflammatory bowel disease and rheumatoid arthritis. Thanks to these drugs, patients have a better quality of life, longer remissions and a reduced need for surgery.

A major issue with these drugs, however, is their cost: Biologics are very expensive. The average cost of a biologic can be as much as twenty-five times the cost of a small-molecule drug and in rheumatology, the anti-TNF antibodies can cost as much as fifty times more than non-biologics. As a reference, Remicade costs approximately $550 per day compared to about $22 a day for an oral pill. With increasing development and approval of biologics, spending on these products in the U.S. is currently increasing about 15% to 20% every year. These costs are neither sustainable in the U.S. nor worldwide. The
increasing use of these expensive drugs is negatively impacting both families and governments and globally, healthcare agencies have been looking to seek lower cost alternatives to these innovator biologics.

The obvious alternative to these high-cost innovator biologics are the biosimilar products. Original biologics have a patent life and once the biologic is about to go off patent, a company can file an application with a regulatory agency wherever the biologic is marketed, to manufacture and sell the biosimilar version of the biologic once it is off patent.

The prices of biosimilars that have come to market so far are about 20% to 60% less compared to their biologics counterparts. In Europe, the price reduction is about 30% and in Asia—and particularly in India—the price reduction of a biosimilar can be as much as 60% to 70% of that of an originator biologic. Examples of companies developing and marketing biosimilar products include Sandoz, Pfizer, Celltrion, Amgen, Samsung, Mylan, and others.

How to Address the Regulatory Challenges of Biosimilars using a ‘Stepwise’ Development Approach

In highly regulated markets such as the U.S., Canada, Europe, and Japan, a stepwise biosimilar development from 1) chemistry manufacturing control assessment—a meticulous side-by-side comparison of the biosimilar and the referenced biologic product—followed by 2) non-clinical and then 3) clinical testing are required. These three aspects comprise of the “Totality of Evidence” that regulators require for approval of biosimilar products.

Totality of Evidence: Analytics

The first component is analytical: the comparison of the biosimilar composition to the referenced biologic. Regulatory agencies require biosimilar developers to start with the same amino acid sequence of the referenced biologics product and compare the higher order structures—secondary, tertiary, and quaternary structures—of the biosimilar to the referenced product upfront in what are known as analytical similarity assessment. The agencies want you to use state-of-the-art orthogonal methods, which means using more than one assay to assess a particular parameter. Comparisons of the post-translational modifications, charge variants, and N or C-terminal truncations of the biosimilar to the referenced product are also required. Additional comparative accelerated and stress stability testing which can detect degradants or impurities not found in the reference product are also needed. Another analytical component is sufficient real-time and real condition stability data to determine the expiry date for the biosimilar for marketing. Regulators now also expect repeat similarity assessments against the reference product when changes are made to the manufacturing process including scale up or change of manufacturing site, this is in addition to comparing the pre and post changes for the biosimilar product. It is recommended that all planned manufacturing changes for the biosimilar either be made prior to the start of any clinical trials or after marketing authorization of the biosimilar. It is known that after marketing authorization, a comparison against the the reference product will not be required. In addition, regulators emphasize the importance of developing an in-house reference standard for biosimilar product.

Unlike filing a New Drug Application (NDA), in which referencing Type II drug master file is allowed, the Food and Drug Administration (FDA) does not allow reference to drug master files for biologic (including biosimilar) products, instead FDA expects the biologic license application to contain all of the data. The agency’s reasoning is that it wants the filing company to have full control over everything that is happening with the product rather than another company having control over drug substance and making changes that may impact the quality of the product.

Agencies also expect manufacturers to conduct comparative accelerated and stress stability testing to provide evidence that there are no degradants or impurities in the biosimilar that

30%

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1. Thomas Reuters BioWorld; Putrik et al. 2014; Medscape Medical News 2014; European Commission 2013
don’t exist in the reference product. Both the FDA and European Medicines Agency (EMA) expect sufficient real-time and real condition stability data, primarily, to determine the expiry dating for the biosimilar when it is approved and becomes available to the market.

The initial acceptance criteria for the biosimilar needs to be established based on testing of the reference product over the shelf life of the reference product. Upon assessment of the biosimilar manufacturing process, the FDA recommends that sponsor first assign levels of criticality to the quality attributes and then differentiate them using a three tiers system approach as follows:

Tier 1: High Risk quantitative quality attributes associated with mechanism of action should be analyzed via equivalence testing.

Tier 2: High or Moderate Risk quality attributes should be analyzed by quality ranges.

Tier 3: Lowest Risk quality attributes should be analyzed by qualitative comparison of the distribution of values in a form of chromatograms, spectrograms, etc.

EMA doesn’t provide recommendation on the quantitative evaluation of biosimilarity, but, may, accepts biosimilarity results generated with FDA recommended approach.

Successfully completing all of these comprehensive and robust comparative structural and functional characterization studies means a better likelihood of streamlined animal and clinical testing.

**Totality of Evidence: Non-Clinical**

The second development component is non-clinical or *in vitro/in vivo* animal testing. In this phase, the biosimilar must also be directly compared to the reference product to assess bioactivity. *In vitro* testing includes binding assays to a target antigen or receptors, for monoclonal antibodies, Fab associated functions (e.g., neutralization, receptor activation or receptor blockade) and Fc-associated functions (ADCC and CDC assays, complement activation). The biosimilar must have highly similar outcomes in these assays compared to the reference.

*In vivo* studies need to be conducted in a relevant animal model, if available, and need to include repeated dose toxicity studies assessing full animal pathology, histopathology, pharmacokinetics, pharmacodynamics, and immunogenicity of the animal model. In the case of immunogenicity, the data are not directly relevant to humans but can provide information in the context of interpretation of animal data. For products such as monoclonal antibodies, which necessitate studies in non-human primates, the EMA does not require the testing unless absolutely necessary but the FDA does require some testing with refined study design using minimal number of animals.

**Totality of Evidence: Clinical**

The third development component is clinical testing, which must be conducted using biosimilar product from the commercial manufacturing process. Both the FDA and EMA require human pharmacokinetic and pharmacodynamics (PD) studies (if PD marker is available) with the proposed biosimilar and the reference product assessed in the same assay, with the same patient sera whenever possible. If a pharmacodynamic biomarker is available, and relevant to the clinical outcome, even if it is not validated, it should be used. Under updated guidelines by both the FDA and EMA, if there is meaningful correlations between pharmacokinetic and pharmacodynamics results and clinical effectiveness, a comparative efficacy study may not be necessary. But, collecting safety and immunogenicity data in a phase III or confirmatory trial would still be needed. For products that are likely to be approved for several indications, one confirmatory trial is likely to be sufficient. But if the mechanism of action is

different or unknown, there is the chance that regulators may require more than one study. For example, the FDA required the manufacturers of the Rituxan biosimilar to conduct at least two studies—a phase I in rheumatoid arthritis patients and a phase III trial in patients with follicular lymphoma.

Clinical studies are required to establish statistical evidence that the proposed biosimilar is neither inferior nor superior to the reference product by more than a specified margin. For a global program that includes the U.S. and Europe, a three way (US reference product/EU reference product/proposed biosimilar) similarity assessment needs to be conducted analytically, with in-vitro biological assays and PK/PD clinical trial. Once the scientific bridge between the European and the U.S. reference product is established, then both the FDA and EMA will allow the use of either the U.S. or EU reference product for Phase III confirmatory clinical trial.

A transition study is required by the FDA, unless waived. It utilizes one time transition from the reference product (half of the patients stay on the reference product and the other half transition to the biosimilar product) to the proposed biosimilar product after primary endpoint is reached. Its purpose is to assess if there is an increase, but often is by the FDA in safety/immunogenicity events in the transition arm. A transition study is not required by the EMA. The transition study does not need to be a stand-alone study but rather the transition can be built into a phase III study design. An interchangeability study may also be built into a phase III study design. After the primary endpoint is reached, a one-to-one switch with the proposed biosimilar product at specified intervals and there are no washout periods. Both of these study designs should, of course, be first vetted by the FDA. For chronic indications, studies should be carried out for 12 months and for other conditions, six months generally suffice.

If the mechanism of action is the same for several indications, the agencies do allow a single clinical trial with an extrapolation to other indications if scientific justification for each of the indications is provided. The data needed are the target, binding, dose concentration response, pattern of molecular signaling, and location and expression of the target for each relevant function. If there are extensive literature based data available to prove these points, these should be sufficient and additional testing need not be conducted. Biosimilar developers may gather any information, including expected differences in toxicity in each of the indications, and different patient populations, pharmacokinetics, among others, from the literature to build a case for extrapolation.

**Smarter Biosimilars Trials using Bioequivalence**

**Phase I**

The phase I is the bioequivalence assessment and needs to be considered within the context of the whole development plan, as described above. Depending on the marketing objective, the phase I trial can be either a two or three-arm design. If the biosimilar is to be marketed in a single region, a two-arm design is recommended. If marketing in multiple regions is planned, a multiple arm design is recommended, including using both a U.S. and European comparators.

The two design options are either parallel or crossover. A parallel design is typically used for longer half-life products while crossover designs are used for shorter half-life products. An advantage of a parallel design is no need for a long washout period, particularly advantageous for longer-half life products. The advantage of a crossover design is a relatively small sample size because of the intrasubject variability is typically smaller than the intersubject variability.

Phase I trial designs need to account for multiplicity, which affects sample size and power calculations. Because these trials are designed to assess an equivalence hypothesis, the multiplicity affects the power, not the Type I error rate, as is usually the case in clinical trials. When comparing three different treatment groups, multiplicity arises in the comparisons among the three treatment groups, and hence three correlated tests. To account for this, all of the known multiplicity comparisons can be applied including the Bonferroni inequality.
Additionally, there is multiplicity due to endpoints, where we typically would have AUC and Cmax as primary endpoints. However, the multiplicity due to multiple endpoints in the Phase I design typically has less of an impact than that for the comparisons among the three treatment groups, since the endpoints all share the same equivalence goalposts but have differing amounts of variability.

For some compounds, especially those that are particularly immunogenic, variability of AUC will increase as the concentration profile is measured further out into the tail. The cause of this is the antibody production, which eliminates the compound of interest from being observed, and hence increases the variability, especially when looked at on the logarithmic scale.

Variability in the primary endpoints drives the sample size. Many factors can increase variability, including immunogenicity, as discussed above, body weight variability, which can affect drug clearance, and other covariates. An imbalance in covariates that affect exposure, e.g. body weight in adalimumab, would affect a parallel design, but not a crossover.

**Phase III Designs**

The objective of the phase III trial is to show clinical equivalence. Unlike in the bioequivalence setting where an equivalence margin is presented in a guidance, the clinical equivalence guidance presents a process to establish an equivalence margin. The equivalence margin needs to be established based on historical data, and the agencies prefer a thorough literature review with all relevant studies incorporated into an analysis. From the historical data, a treatment effect (with 95% confidence interval) can be estimated using a meta-analysis. The equivalence margin would then be no wider than that which preserved 50% of the treatment effect. The FDA will accept a statistical analysis to support the equivalence margin, while the EMA will also request a clinical justification for the margin. The trial should be powered based on this defined equivalence margin.

Factors that affect sample size in this setting are the equivalence margin and the variability of the primary endpoint. In our experience, variability of the endpoint will affect sample size but not likely to the same extent as the equivalence margin. Other factors that affect sample size include power of the study, the confidence level used to test the equivalence margin, and the particular indication.

Since the equivalence margin is the driver of the sample size, we should discuss this a little. The equivalence margin is 50% of the treatment effect, defined as the lower confidence bound of the difference between the original product and the control group. For a rheumatoid arthritis product, the control group would be methotrexate arm; if the product is oncology, the control group would be standard of care. The larger the lower confidence bound, the larger the equivalence margin. This is a function of two parameters: the point estimate of the treatment effect, and the width of the confidence interval. To reduce the sample size, one needs to concentrate on reducing the width of the confidence interval, and this can most easily be accomplished by including more data in the meta-analysis. One should be aware, however, that including many heterogeneous studies may actually increase the width of the confidence interval, so our focus should be including as many homogeneous studies as possible. We need to look at various indications and find out which is going to be most sensitive to assess the equivalence of the particular product.

**How to handle missing data in your biosimilars trials**

Missing data is a topic of great interest at this time to the regulatory agencies for both innovator and biosimilars trials. Regulators are asking deep questions about methodologies. The current standard is modern imputation methods, while the last observation carried forward approach is probably not going to be acceptable as it biases treatment arms towards each other. The key is to be prepared to answer questions on methods from regulators: protocols and the statistical analysis plan (SAP) need to define the methods used and need to be provided in advance of analyses. One may be required to submit the SAP along with the protocol in advance of trial initiation.
**Improve Your Probability of Success: Design Your Biosimilars Trials with the End in Mind**

To fully realize the commercial potential of biosimilars, you need a partner who can effectively address the distinct challenges they pose in clinical development, market access, manufacturing, and sales and marketing. Quintiles has the broad range of expertise and flexible strategies to manage risks and optimize development of biosimilars and, overall, has helped gain market access for more than 135 products in the US since 2003.

Quintiles offers a full range of expertise – scientific, technical (Chemistry, Manufacturing and Controls), regulatory, clinical, registration and commercialization – critical to development. When you work with Quintiles, our dedicated team will help your products be successful. Quintiles expertise and experience has given our experts exposure to many of the issues manufacturers of biosimilars experience during the regulatory process.

Key takeaways:

- Consider commercialization goals upfront in order to meet regulatory requirements during the development process.
- Work with a vendor with experience in designing and running biosimilar trials and a breadth of knowledge of regulatory requirements of agencies around the world.
- Remember that cost and recruitment are two major and common challenges manufacturers encounter. Working with a vendor experienced in innovative strategies for optimization, like Quintiles, can be an advantage.
- Optimize your trial by selecting the best population and state of the art statistical strategies.
About the author

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Dr. Chance advises biotechnology companies for region specific and/or global regulatory strategy for the development of biosimilars. Her overall regulatory experience encompasses developing global regulatory strategy, preparation of briefing documents, meetings with FDA, IND/CTA submissions, Marketing Applications (BLAs, MAAs, etc. She has authored/co-authored number of articles on biosimilars.

She has provided global regulatory strategy on number of biosimilar products currently in development including biosimilars of Enbrel, Remicade, Herceptin, Rituixin/Mabthera, Humira, Avastin, Orencia, Erbitux, Epogen, Neupogen/Neulasta, Aranesp and Recombinant Insulins. Dr. Chance has over 25 years of work experience in the healthcare industry, including the last 18 years in regulatory affairs at CRO, pharmaceutical and biotechnology industries. Dr. Chance has a Ph.D in Nutrition/Nutritional Biochemistry and Masters of Public Health. She has a Regulatory Affairs Certification from the Regulatory Affairs Professionals Society.

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Dr. Reeve supports development of model-based drug development capabilities at Quintiles, manages the Innovation MBDD Advisory Board, and consults with clients on development and trial design strategies. He leads modeling and simulation projects for clients to support trial design. He is also a thought leader, engaging in research for peer-reviewed publications, and presents talks at leading scientific conferences. He is on NCSU’s College of Sciences Foundation Board, and George Mason University’s Statistics Department Advisory Board.

Since joining the CRO industry, Russell has supported more than 100 studies from Phase I through Phase IV. Dr. Reeve has published and has expertise in model-based drug development, including CATD and population modeling, has a patent in the field of metabolomics, and has been a leader in adaptive trial design and execution. Russell has taught graduate statistics courses at University of Rochester and Memphis State University. At Pharsight, he was responsible for the scientific development of modeling and simulation software (WinNonlin, WinNonMix, and Trial Simulator), and managing the scientific advisory boards in these areas. He has broad industry experience and has been involved in clinical modeling and simulation, designing a randomized concentration-controlled trial with Bayesian updating of the doses. He has worked on a number of biologics agents and vaccines, such as interferon-alpha, vaccines for HCV, HPV, and influenza, as well as in vitro diagnostics based on ligand-binding and bDNA technologies. He has developed designs for a number of biosimilar products, supported NDA submissions, represented clients at FDA meetings, and used MBDD methodologies to create development strategies. He leads the biosimilars statistical working group at Quintiles. Dr. Reeve has 25 years of experience in biostatistics with almost 22 years in the pharmaceutical industry. Dr. Reeve earned his Ph.D. in Statistics from Virginia Polytechnic Institute and State University, M.S. in Operations Research from Rensselaer Polytechnic Institute, and B.S. in Mathematics from Utah State University.