

The Future of the U.S. Biosimilars Market: Development, Education, and Utilization

October 18, 2016

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ABOUT FRIENDS OF CANCER RESEARCH

Friends of Cancer Research (Friends) drives collaboration among partners from every healthcare sector to power advances in science, policy and regulation that speed life-saving treatments to patients.

During the past 20 years, Friends has been instrumental in the creation and implementation of policies ensuring patients receive the best treatments in the fastest and safest way possible. We've been successful to date due to our ability to convene the right people at the right time and put forth revolutionary, yet realistic ideas that will lead to life-saving treatments for patients.

Previous and current initiatives include the passage of the Breakthrough Therapy Designation, the launch of the groundbreaking clinical trial Lung-MAP, and establishing a blueprint for drug/diagnostic co-development through our annual forums. Now, in our 20th year, we are energized more than ever to continue this critical work with our trusted partners, creating innovative solutions to overcome barriers standing in the way of conquering cancer.

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INTRODUCTORY NOTE

BIOSIMILARS IN 2016 AND BEYOND

Since the enactment of the Biologics Price Competition and Innovation Act (BPCIA) in 2010, a market for biosimilar products in the United States has steadily taken shape. The U.S. Food and Drug Administration (FDA) has established a regulatory pathway for biosimilars, and continues to engage external stakeholders in promulgating key definitions and developing guidance around issues such as naming, labeling, and interchangeability. Industry has invested in clinical development programs, with four biosimilar products approved by FDA to-date, and several more are in the pipeline. Clinicians and payer groups have started to develop or refine clinical practice guidelines and formularies when biosimilars are an available treatment option. In all, it has been six years of productive cross-sector dialogue around a set of highly challenging, interlocking scientific and policy issues.

Friends of Cancer Research and the Duke-Margolis Center for Health Policy have partnered with a number of experts to continue collaborative discussion around these topics in order to identify important barriers to the ongoing development and utilization of biosimilars. As such, this series of white papers outlines current challenges in development, regulatory review, coverage, and patient access as well as potential options for addressing them. The issues highlighted are not meant to be consensus recommendations or policy objectives, but rather a snapshot of the current state of implementation of the BPCIA and areas where additional work by stakeholders is needed to fully realize the aims of the Act.

In order to advance key concepts and resolve challenges that are specific to the emerging biosimilars market, robust, concerted education efforts for stakeholders from across the healthcare continuum will be needed. Inconsistent use and awareness of terminology, ongoing work on regulatory guidance documents, and questions around how biosimilars may be prescribed and dispensed to patients in practice have contributed to an uncertain and sometimes murky picture. Stakeholders, especially patients, need help to understand this complex and growing component of drug development and how it will affect their health care. We urge all involved to work together to ensure that improved education becomes a reality.

We would like to thank the researchers, drug developers, regulators, clinicians, payers, and patients who have contributed to this work. They have highlighted many important areas where unresolved scientific, technical, or delivery challenges still need to be addressed, as well as promising signs of progress. We hope that these papers spur discussion and collaboration, and look forward to continued engagement on this topic.

- Jeff Allen, Greg Daniel, Mark McClellan, and Ellen Sigal

PAPER ONE

THE CURRENT LANDSCAPE OF BIOSIMILARS DEVELOPMENT, REGULATORY REVIEW, AND STAKEHOLDER EDUCATION

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INTRODUCTION

Therapeutic biologic products are large, complex molecules made in living systems and are used in a variety of diseases, such as cancer, rheumatology, and inflammatory bowel disease. In 2010, the Biologics Price Competition and Innovation Act (BPCIA) provided FDA the authority to establish an abbreviated approval pathway for biosimilar products, which are defined in this Act as those products which are highly similar to and have no clinically meaningful differences from a reference therapeutic biologic. Under the BPCIA, reference, or originator, biologics are provided 12 years of exclusivity from first licensure before a biosimilar can be approved and enter the market. Several reference biologics on the market are nearing or have already reached the end of this exclusivity period prompting companies to develop biosimilars. Although an abbreviated pathway (ANDA) for the approval of generic small-molecule drugs has existed since the passage of the 1984 Hatch-Waxman Act, the regulatory requirements for these do not reflect the greater complexity and testing needed for biologics.

In contrast to small molecule drugs, which are chemically-derived and can be readily characterized and purified, biologics are larger and more complex. Because of this, chemical synthesis is not sufficient, and biologics need to be produced and manufactured in living organisms. This manufacturing process results in differences between batches, and thus it is not possible to produce a 100% identical biologic. This is not specific to biosimilars, as it occurs with all biologics, and this variability is natural. In addition, manufacturing process changes during the life cycle of a biologic that occur also create differences between the pre- and post-change biologics. Manufacturing changes are a normal process of biologic drug development and occur for several reasons, such as site changes, scaling up capacity, improving Good Manufacturing Practice, and increasing purity and yield.¹ As such, the regulatory process for biosimilars is primarily focused on comparative analytical testing for structural and functional biosimilarity and the “totality of evidence” concept (as described below) that builds off of the comparability exercise outlined in FDA’s guidance document “Comparability of biotechnological/biological products subject to changes in their manufacturing process”.²

The European Union first developed a regulatory pathway for biosimilars in 2004 and has since licensed over 20 biosimilars.³ The uptake of biosimilars in Europe has varied among the different countries for various reasons that extend beyond potential concerns related to safety and efficacy, and these experiences may offer insights to improve the U.S. practice. The biosimilar paradigm and approval pathway is new, and as the field continues to evolve, education will remain important for all stakeholders. As such, building an educational campaign and identifying policy approaches to disseminate educational information and engage stakeholders is necessary. Stakeholder understanding of the regulatory pathway may not be well understood, as documented in recent FDA advisory committee meetings. An assessment of the educational needs of stakeholders (see Appendix) is necessary to identify where to direct educational efforts and optimize utilization of biosimilars to ensure patient access to these medicines. The FDA has released several guidance documents for biosimilar development to address these issues, and although there are no deadlines for issuing guidance, FDA has said it will also release guidance on the requirements to demonstrate interchangeability and the proper statistical analyses needed for analytical data by the end of 2017. To date, four biosimilars have been approved in the United States, and several other biosimilars are currently under review. Stakeholder involvement in identifying key issues is necessary to ensure current regulatory practices and guidance address stakeholder questions. Downstream issues related to utilization, coverage, and reimbursement are covered in the companion document to this white paper.* The

* For an overview of these outstanding issues, see “Biosimilar Uptake: Considerations for Clinical Decision-Making, Coverage and Reimbursement Decisions, and Postmarket Evidence Development” which was developed as the companion document to this white paper.

Center for Health Policy at Duke University and Friends of Cancer Research have therefore convened a multi-stakeholder working group for this purpose.

FDA REGULATORY PATHWAY FOR BIOSIMILARS

The BPCIA stipulates that a product may be designated as biosimilar to a reference product based on analytical studies, animal studies, and clinical studies, as needed. This abbreviated licensure pathway allows reliance on certain existing scientific knowledge about the biologic characteristics, safety, and effectiveness of the reference product and enables a biosimilar to be approved based on results from analytical tests and appropriate non-clinical studies, and supplemented by clinical studies as necessary. Analytical tests are routinely performed to measure quality attributes to ensure safety and efficacy throughout the life cycle of biologics, but are often unknown to physicians and patients. Building on this routine practice, FDA Guidances, “Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product” and “Scientific Considerations in Demonstrating Biosimilarity to a Reference Product,” were developed to outline the agency’s expectations for these studies.^{4,5} Analytical studies should determine structural and functional characteristics, critical quality attributes, identify clinically active and inactive components, and biochemical characterization to demonstrate that the biosimilar is “highly similar” to the reference product. Biosimilarity requires that there be “no clinically meaningful differences” in terms of safety, purity, and potency. The FDA guidance suggests biosimilar sponsors follow a stepwise approach:

- Analytical studies of the proposed biosimilar and reference product to assess physical, chemical and functional similarity;
- Nonclinical (animal) studies to assess toxicities;
- Comparative clinical studies to evaluate pharmacokinetic (PK) and pharmacodynamic (PD) profile of the proposed biosimilar and reference product, and to compare clinical immunogenicity; and
- Potentially, additional clinical studies if residual uncertainty remains.

The FDA utilizes the totality of evidence to determine biosimilarity (Figure 1). Evidence generally includes structural and functional data characterization, animal study data, human PK and PD data, clinical immunogenicity data, and other clinical safety and effectiveness data. The FDA has the discretion to decide whether one or more of these elements is not necessary. This approach allows for a biosimilar to build off of the foundation of knowledge of the reference product. The comparative analytical, nonclinical and clinical demonstrations decrease residual uncertainty regarding demonstration of biosimilarity and reduce the need for extensive clinical studies. Due to the nature of biologics, differences between the biosimilar and reference biologic will almost always be found (just as differences can be expected between batches of the reference product, particularly after manufacturing changes), but the key is determining the clinical relevance of those variations. The amount of clinical data requested is dependent upon the level of uncertainty that remains following analytical and nonclinical studies. Notwithstanding, if high similarity between the reference product and the biosimilar is not demonstrated at the structural and functional level, the proposed biosimilar cannot be approved, irrespective of any results obtained in clinical studies.

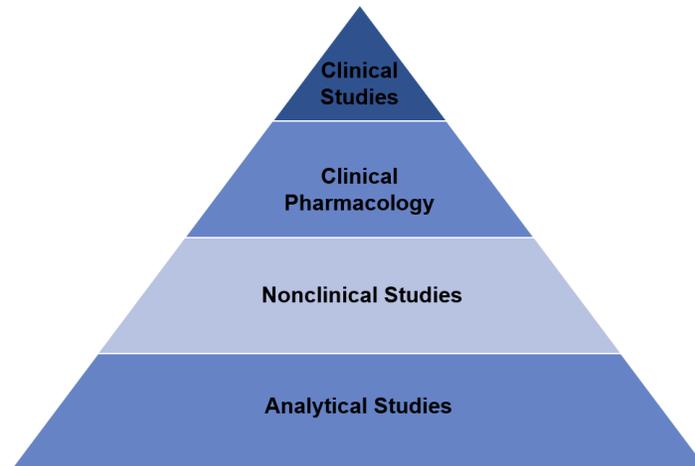


Figure 1. The Totality of Evidence Used to Demonstrate Biosimilarity to a Reference Product.

The FDA guidance discussed above also allows for and describes requirements for extrapolation. That is, if the totality of evidence, including data derived from a clinical study performed in one or more conditions of use of the reference product demonstrates biosimilarity, then the sponsor of the proposed biosimilar may seek approval for one or more additional conditions of use for which the reference product is approved. In these situations, clinical data would not be required for the additional indications if there is sufficient scientific justification for extrapolation, which should address the following issues for the tested and extrapolated conditions of use:

- Degree of structural and functional similarity;
- Mechanism of action;
- PK (and PD if there is a relevant PD measure) of the product;
- Immunogenicity of the product;
- Differences in expected toxicities in each condition of use; and
- Any other factor that may affect the safety and efficacy of the product.

Differences between indications in these factors do not necessarily preclude extrapolation. A scientific justification should address these differences in the context of the totality of the evidence supporting a demonstration of biosimilarity. The FDA recommends that clinical studies, if needed, be conducted in a patient population that is expected to be adequately sensitive to detect any clinically meaningful differences between the two products, if any were to exist.

BIOSIMILAR CASE STUDIES

In the United States, four biosimilars are currently approved for marketing in the US: Zarxio (filgrastim-sndz), Inflectra (infliximab-dyyb), Erelzi (etanercept-szsz) and Amjevita (adalimumab-atto). Though all are biosimilars, they vary in size and complexity.

BIOSIMILAR FILGRASTIM-SNDZ (ZARXIO)

Filgrastim is a hematopoietic agent that works by stimulating the production of neutrophils to reduce time and degree of neutropenia in patients receiving chemotherapy. Zarxio, a biosimilar to Neupogen (filgrastim), has a well characterized structure and established mechanism of action, and is a relatively simple biologic both because of its smaller relative size and lack of glycosylation (sugar side chains). Because Sandoz performed an adequate scientific bridge between EU-approved Neupogen, US-licensed Neupogen, and Zarxio, Sandoz was able to use data generated with the EU-approved product as part of the FDA biosimilar application. Sandoz submitted a variety of data to support biosimilarity between Zarxio and Neupogen:

- Analytical studies;
- PK and PD studies;
- Immunogenicity results from five clinical studies;
- Two efficacy and safety studies (one of which was pivotal and the other supportive); and
- Rationale for extrapolation to other indications.

Quality attributes were measured using multiple methods to evaluate analytical similarity of the biosimilar to the reference product. Quality attributes measured included primary structure, bioactivity, receptor binding, protein content, higher order structure, clarity, sequence variants, and posttranslational modifications. Zarxio demonstrated a high level of similarity in these attributes.

PK and PD were evaluated in four studies. The studies supported the demonstration of PK and PD similarity between Zarxio and the reference product Neupogen. Comparative safety and efficacy were evaluated in 214 patients with breast cancer. The study in breast cancer patients incorporated three switches between the two products and compared the results to that obtained with patients who were not switched. The switching had no impact on clinical response or safety. The primary endpoint was duration of severe neutropenia, and key secondary endpoints included febrile neutropenia, days of fever, absolute neutrophil count (ANC) nadir, and time to ANC recovery in Cycle 1. The safety and efficacy profile of Zarxio was similar to that of Neupogen in all measured parameters. Although, the pivotal study was performed in a patient population that addressed only one of the five indications approved for US-licensed Neupogen, Sandoz provided scientific justification for extrapolation in the following indications as US-licensed Neupogen:

- Patients with cancer receiving myelosuppressive chemotherapy;
- Patients with acute myeloid leukemia receiving induction or consolidation chemotherapy;
- Patients with cancer undergoing bone marrow transplantation;
- Patients undergoing autologous peripheral blood progenitor cell collection and therapy; and
- Patients with severe chronic neutropenia.

Ultimately, the totality of evidence led to a favorable Oncologic Drugs Advisory Committee vote and FDA approval in all US-licensed Neupogen indications. Finally, although not part of the decision making process of the FDA, the extensive post-licensure safety database generated since the product's approval in Europe in 2009 was reassuring to the Advisory Committee panel.⁶

BIOSIMILAR INFLIXIMAB-DYYB (INFLECTRA)

Inflectra, a biosimilar to Remicade[®], was the first biosimilar monoclonal antibody approved in the US. The primary mechanism by which TNF-antagonists, including infliximab, act is by directly neutralizing the activity of soluble TNF α by preventing its binding to the two TNF α receptors. Celltrion submitted a variety of data to the FDA to support biosimilarity on the basis of the following:

- analytical data;
- PK studies;
- a comparative clinical study to demonstrate similarity in efficacy and safety;
- an assessment of safety and immunogenicity in patients undergoing a single transition from EU-approved Remicade to Inflectra; and
- rationale for extrapolation to other indications.

Similar to Sandoz's Zarxio, Celltrion performed a scientific bridge between EU-approved Remicade, US-licensed Remicade, and Inflectra to utilize data from the EU-approved product in the FDA application. Two comparative safety and efficacy studies were performed in patients with ankylosing spondylitis (AS) and rheumatoid arthritis (RA). The studies demonstrated similar safety and efficacy profiles between Inflectra and Remicade. Taking into account the totality of evidence, Celltrion sought approval in the six indications US-licensed Remicade is currently licensed for in the US:

- RA;
- AS;
- Psoriatic arthritis (PsA);
- Plaque psoriasis (PsO);
- Crohn's disease (CD; adult and pediatric); and
- Ulcerative colitis (UC; adult and pediatric).

During the advisory committee meeting, concerns were raised regarding whether comparative clinical studies in RA and AS were sufficient to warrant extrapolation to all Remicade approved indications, specifically IBD. However, because the primary mechanism of action is deemed the same as that for RA and AS, there is an expectation for similar responses across all indications. FDA included an independent FDA review of the pertinent scientific literature and deemed that reverse signaling together with TNF sequestration were likely the predominate mechanism of action for all indications, although other mechanisms may also be relevant for IBD. Ultimately, the totality of evidence led to a favorable Arthritis Advisory Committee vote and FDA approval in all US-licensed Remicade indications except for pediatric ulcerative colitis and Crohn's disease due to exclusivity limitations and not data-related issues.

BIOSIMILAR ETANERCEPT-SZZS (ERELZI)

In July 2016, the FDA approved Erelzi, a biosimilar to Enbrel[®]. The therapy works by reducing the effects of TNF by acting a decoy receptor for soluble TNF α . The application submitted by Sandoz for Erelzi consisted of the following components:

- Analytical data;

- Three single-dose PK studies in healthy volunteers;
- A comparative clinical trial between EU-approved Enbrel and Erelzi in patients with plaque psoriasis, including assessment of safety and immunogenicity in patients undergoing predefined switching between EU-approved Enbrel and Erelzi; and
- Scientific justification for extrapolation of data to unstudied indications.

Because Sandoz used a non-US-licensed comparator (EU-approved Enbrel) in some studies, a scientific bridge was established between EU-approved Enbrel, US-licensed Enbrel, and Erelzi. This allowed Sandoz to utilize data previously submitted for EU approval. Sandoz’s application sought licensure in the following indications US-licensed Enbrel is licensed:

- RA;
- Polyarticular Juvenile Idiopathic Arthritis (JIA);
- PsA;
- AS; and
- PsO.

The review of submitted data resulted in the determination that there are no clinically meaningful differences between Erelzi and US-licensed Enbrel. In considering the totality of evidence, Erelzi was determined to be highly similar to US-licensed Enbrel with no clinically meaningful differences observed with safety and efficacy, and purity in clinical study of patients with PsO. The data package adequately addressed the scientific considerations for extrapolation, and the Arthritis Advisory Committee voted in favor and FDA approved Erelzi for US licensure.

BIOSIMILAR ADALIMUMAB-ATTO (AMJEVITA)

Adalimumab is a TNF inhibiting anti-inflammatory biologic medication. Amjevita, a biosimilar to Humira®, is the latest biosimilar approved by the FDA. The FDA’s approval of Amjevita is based on review of evidence that included structural and functional characterization, animal study data, human pharmacokinetic and pharmacodynamics data, clinical immunogenicity data, and other clinical safety and effectiveness data that demonstrates biosimilarity. The following data elements were included in the application:

- Analytical data to demonstrate similarity and justify relevance of comparative data using the EU-approved Humira;
- Single-dose PK study;
- Comparative clinical study in patients with RA to demonstrate no clinical meaningful differences;
- A second comparative clinical study in PsO to assess efficacy, safety, and immunogenicity in patients undergoing a single transition; and
- Scientific justification for extrapolation of data to support biosimilarity in additional indications.

The totality of evidence in combination with the data submitted by Amgen supported the demonstration that Amjevita was biosimilar to US-licensed Humira. The scientific considerations for extrapolation of data to support biosimilarity to other conditions of use for US-licensed Humira led to Amjevita approval for the following conditions:

- RA;

- PsA;
- AS;
- CD;
- UC;
- PsO; and
- JIA.

Amgen provided justification for the proposed extrapolation of clinical data from studies in RA and PsO to each of the other indications approved for US-licensed Humira. After analysis of known and potential mechanisms of action of US-licensed Humira in the conditions of use sought for licensure, it was determined reasonable to extrapolate to indications not directly tested in clinical studies. After reviewing and discussing the data, the FDA Arthritis Advisory Committee voted in favor of the biosimilar, and FDA approved Amjevita in September 2016.

ANTI-CANCER THERAPEUTIC BIOSIMILAR PRODUCTS

Currently, there are no approved anti-cancer therapeutic biosimilars in the US. However, data were recently presented at the annual meeting of American Society of Clinical Oncology in Chicago, IL, June 3-7 for a biosimilar to trastuzumab (Herceptin), a monoclonal antibody which recognizes the HER2 receptor. According to the Phase 3 clinical trial data, the biosimilar showed similar safety, efficacy, and immunogenicity results as the reference biologic and could represent the first FDA approved biosimilar for cancer.⁷ In the Heritage trial, 500 patients with metastatic HER2-positive breast cancer were randomized into two arms to receive taxane chemotherapy plus the biosimilar or reference biologic every 3 weeks for 24 weeks, followed by trastuzumab alone until disease progression. Women treated with the trastuzumab biosimilar had a 69.9% objective response rate compared with 64% among women receiving the reference biologic. Serious adverse events were comparable, with neutropenia being the most common in both arms. Other anti-cancer biosimilar products currently being developed include rituximab, bevacizumab, and cetuximab.

The ongoing development of anti-cancer therapeutic biosimilars, many of which are monoclonal antibodies, has raised a number of questions among stakeholders:

- Is it important to have a distinction between a therapeutic biosimilar agent versus a supportive care biosimilar agent?
- What is the appropriate endpoint? Is response rate sufficient as a measure of biologic activity given the extent of analytical and functional data available?
- A single monoclonal antibody may act through different mechanisms to treat different diseases. Should clinical trials be required for every indication?
- Many therapeutic monoclonal antibodies are given as infusions in hospital settings. How does this impact concerns about pharmacy-based substitutions?
- How likely is it that a patient would be switched multiple times between the originator product and the biosimilar version during the course of cancer care?

DETERMINING THE LEVEL OF EVIDENCE REQUIRED TO DEMONSTRATE INTERCHANGEABILITY

Although four biosimilars have been approved by the FDA, there are currently no biosimilars approved as interchangeable biologics. The BPCIA allows a product to be designated as interchangeable with the reference if it is biosimilar and it is expected to produce the same clinical result in any given patient. In addition, for those products that are given for more than one dose, the risk, in terms of safety or diminished efficacy, of alternating or switching between the proposed interchangeable and the reference product is no greater than solely using the reference product. A product deemed interchangeable may be substituted by a pharmacist without prior consent of the prescribing physician. Post-dispensing communication and record keeping requirements are regulated by states, and about half of the U.S. states have passed legislation and more are considering such legislation. FDA is currently developing guidance on demonstrating interchangeability. Several topics may be addressed by this guidance:

- The nature and extent of similarity required;
- The clinical evidence that is required, including what clinical trial designs (e.g., crossover, parallel) may be needed to support interchangeability (see Figure 2 for an example of a potential trial design to support the designation of interchangeable biologic);
- Naming and labeling of interchangeable biologics; and
- The role, if any, postmarket data could play in supporting a determination of interchangeability.

FDA guidance states that applicants may need to submit data from a single transition (i.e., data from a small group of patients who change from the originator to the biosimilar) in order to rule out a major risk in terms of hypersensitivity, immunogenicity, or other reactions. FDA recently clarified that these type of data are used to support the safety of a biosimilar product because the biosimilars will not be limited to use in treatment-naïve populations. It is noted that these data may also show that patients that undergo a single transition from the reference product to the biosimilar do not suffer major immune-mediated adverse events. These data for a single transition may not sufficiently support a demonstration of interchangeability.

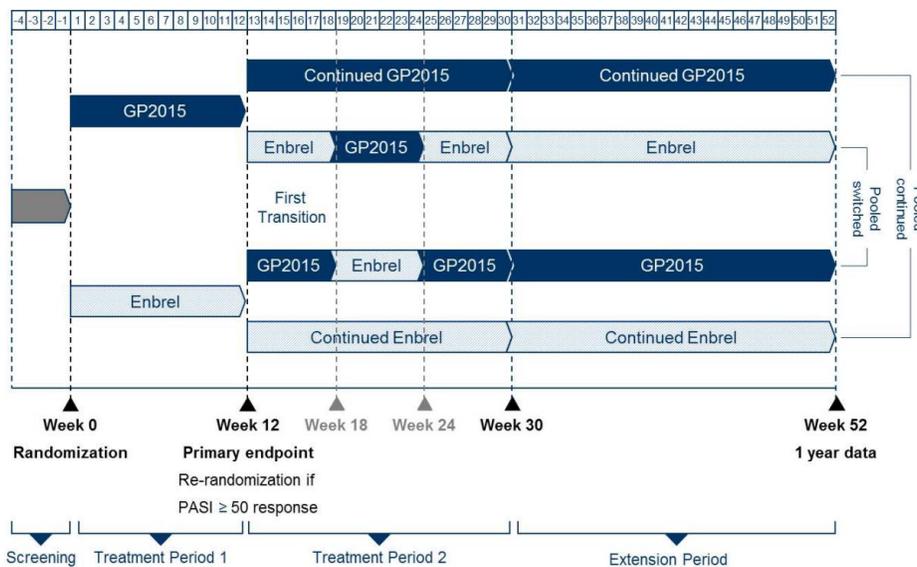


Figure 2. Schemata of a Clinical Trial Evaluating Multiple Switches Between Enbrel and Erelzi (GP2015).

Source: Figure is an excerpt from Sandoz 351(k) BLA submission FDA review documents.

Figure 2 provides an example of a completed biosimilar trial that incorporated multiple switches. The multi-switch clinical data may provide support for an interchangeability application in the future; however, an interchangeability designation was not sought at the time of the original approval. Until FDA releases guidance on demonstrating interchangeability, the clinical trial requirements to support regulatory approval will remain unclear.

There are theoretical concerns on whether substitution from a reference product to the corresponding biosimilar will lead to immunogenicity or diminished efficacy. To date, there is little evidence to suggest this will be the case, based on post-approval pharmacovigilance and other data derived from Europe, where biosimilars have been in the market since 2006, and where some patients on reference biologics have been switched to biosimilars due to various reasons, including tender decisions and payer coverage. There is also a growing body of evidence, including published data that suggest that switching between a reference product and a biosimilar does not result in safety issues or concerns.⁸ More recently, additional studies submitted to the FDA, including two single switch studies from infliximab and adalimumab reference product to the corresponding biosimilar, and two studies evaluating multiple switches between filgrastim and etanercept reference product and the corresponding biosimilar, did not reveal significant safety or efficacy concerns.⁹ Although it has been noted that some patients discontinue treatment after switching to a biosimilar, but presently, most existing data suggest that the process of switching or interchangeability is not inherently a reason for concern. However, it is important to continue to study the issue and to be open to the results that will be reported.^{10,11} The role of postmarket data collection for additional evidence development and demonstrating value is discussed in the companion document.*

Other considerations for a determination of interchangeability include how FDA will communicate data differences between a biosimilar and an interchangeable biosimilar, how will payers interpret biosimilarity versus interchangeability, and what impact will that interpretation have on patients that switch therapy to a biosimilar due to higher cost of the existing product (via mechanisms other than automatic substitution).

ADVANCING BIOSIMILARS THROUGH EDUCATION AND GUIDANCE

The novelty of the biosimilar pathway and its reduced emphasis on clinical testing has resulted in the need for education amongst stakeholders. An overarching concern for all stakeholders is whether a biosimilar product is as safe and effective as its reference biologic. Healthcare professionals have been trained to rely on clinical data in each indication as the primary determinant of the suitability of a given therapeutic agent for a given patient. Biosimilar development and review employs a different paradigm based on the totality of data, with an emphasis on structural and functional analytical data, and a tailored, more limited role of clinical studies as compared to the development and approval of originator drugs. Extensive education will be required to explain and gain acceptance of this concept by all stakeholders, including patients, physicians, nurses, pharmacists, and payers. This education will assist stakeholders in understanding how FDA ensures the safety of biosimilars, how biosimilar products work, and when they can be substituted for a reference product. Historically, physicians were initially concerned about the use of generic drugs and even the first monoclonal antibody therapies. A positive shift in views is credited to education efforts led by various stakeholders, which included industry, patients, advocacy groups, trade associations, and FDA.

* See “Biosimilar Uptake: Considerations for Clinical Decision-Making, Coverage and Reimbursement Decisions, and Postmarket Evidence Development” which was developed as the companion document to this white paper

In order to educate stakeholders, the FDA may need to play a more active role in providing education support than is typically expected of the agency. Currently, the FDA has developed a free Continuing Medical Education (CME) directed towards healthcare providers. Additional education efforts targeted to other stakeholder groups is also needed. To ensure appropriate utilization and adoption of biosimilars, a plan will need to be developed by the stakeholder community to effectively educate the community and address information gaps. Some questions to address to promote effective education include:

- What methods of dissemination and education are needed to reach all stakeholders? Is there a role for FDA in education dissemination?
- Who should be educating stakeholders? How to promote consistent messaging?
- What policy approaches are needed to help biosimilar adoption?
- What evidence will patient and providers require to alleviate concerns? Are there explicit topics which are not well understood and for which directed education is needed?
- Are there specific groups of stakeholders that need education on certain topics, perhaps, more than other groups?

¹ Ramanan, S. and Grampp G. Drift, Evolution, and Divergence in Biologics and Biosimilars Manufacturing. *BioDrugs* 2014;28:363-372.

² http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf

³ <http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe-as-of-May-2016>

⁴ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>

⁵ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf>

⁶ Gascón P, Tesch H, Verpoort K, et al. Clinical experience with Zarzio® in Europe: what have we learned? *Support Care Cancer* 2013;21:2925–32.

⁷ Rugo HS, Barve A, Waller CF, et al. Heritage: A phase III safety and efficacy trial of the proposed trastuzumab biosimilar Myl-14010 versus Herceptin. *J Clin Onco.* 2016;34 (suppl; abstr LBA503).

⁸ Ebber HC, Muenzberg M, and Schellekens H. The safety of switching between therapeutic proteins. *Expert Opin. Biol. Ther.* 2012;12(11):1473-1485.

⁹ Braun J and Kudrin A. Switching to biosimilar infliximab (CT-P13): Evidence of clinical safety, effectiveness and impact on public health. *Biologics* 2016;44:257-266.

¹⁰ Jahnsen J., Detlie T., Vatn S., Ricanek P. Biosimilar infliximab (CT-P13) in the treatment of inflammatory bowel disease: a Norwegian observational study. *Expert Rev Gastroenterol Hepatol* 2015;9: 45–52.

¹¹ Siczekowska J., Jarzębicka D., Banaszkiwicz A., Plocek A., Gawronska A., Toporowska-Kowalska E., et al. Switching between infliximab originator and biosimilar in pediatric patients with inflammatory bowel disease. preliminary observation. *J Crohn's Colitis* 2015;10(2): 127–132.

Naming

Survey data

United States

- 68% of pharmacists believe the FDA should require non-proprietary names¹
- 81% of pharmacists believe the label should identify the product as a biosimilar; 88% believe the label should indicate if the product is interchangeable¹
- 90 percent believed that the name of the biosimilar should be uniquely different than the name of the original biologic medicine to allow for adequate tracking of any adverse reactions²
- Over 75 percent of rheumatologists surveyed say the FDA should mandate that biosimilars have a different non-proprietary name than the innovator biologic medicine³
- 74.6% of pharmacists indicated that they would be confident or very confident in substituting an interchangeable biosimilar with the reference product if both shared the same active ingredient or non-proprietary name of the reference biologic; 25.3% of pharmacists were confident in substituting when the non-proprietary name is not shared with the biologic; and 37.3% of pharmacists expressed confidence in substituting when the biologic and biosimilar product did not share the same non-proprietary name because of a prefix or suffix⁴
- The vast majority (99%) of physicians refer to biological medicines by name for both recording in charts and for reporting adverse events⁵
- Less than 1% of prescribers use national drug code numbers for records or reporting⁵
- 48.1% of participants reported a preference for the naming convention that used the nonproprietary (active ingredient) name plus suffix⁶
- Those participants reporting preferences for the nonproprietary name plus suffix preferred the use of a suffix tied to the manufacturer name (83.4%), compared with the random assignment of a 4-letter suffix (16.6%)⁶

Europe

- 53% of physicians surveyed felt that an identical non-proprietary name implies identical structure⁷
- 61% of surveyed physicians said that identical non-proprietary names imply that the medicines are approved for the same indications⁷
- 24% of reporting physicians record only the non-proprietary name of the biological product in the patient record⁷

Educational Needs

- Information on adverse event tracking
- Should FDA require non-proprietary information?

FDA Guidance

- FDA’s non-proprietary naming proposal would permit a biosimilar to use the same core name as the reference biological product, but then add a unique four-letter suffix to identify each product

<http://www.fda.gov/downloads/drugs/guidancecomplianceandregulatoryinformation/guidances/ucm459987.pdf>

Labeling**Survey data****United States**

- 96% of rheumatologists surveyed said the FDA should require labeling to identify a medication as a biosimilar and distinguish any important differences between it and the innovator biologic³
- 90% of respondents believe the label should indicate the biologic is a biosimilar⁸
- 79% of respondents believe the product label for a biosimilar should define what biosimilarity means⁸
- 82% of respondents find it important to include analytical data developed by the biosimilar sponsor to demonstrate its analytical similarity to the reference product on the label⁸
- 83% of respondents find it important to include clinical data from the biosimilar sponsor to demonstrate that it is highly similar to the reference product on the label⁸
- 79% of respondents find it important that a label clearly distinguishes those data generated by the biosimilar sponsor from those generated by the originator sponsor⁸

Educational Needs

- Should labels include clinical trial data collected for the biosimilar?
- Should the label indicate which tests were done to determine biosimilarity?

FDA Guidance

- Biosimilar labeling should be consistent with the label of the reference product
- Biosimilar labels should heavily rely upon their reference products
- Biosimilar product labeling should not need to describe the specific studies and data collected by the biosimilar developer to demonstrate that it is “highly similar” to the reference product
- Biosimilar labels should only include biosimilar-specific information when that information is “necessary to inform safe and effective use of the product”
- The Agency is requiring “biosimilarity statement” at the top of the professional package insert

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM493439.pdf>

Biosimilarity

Survey data

United States

- Over 90% of seniors did not know that ACA allowed for approval of biosimilar²
- 86% wanted a requirement that drug companies that are developing biosimilars conduct human clinical trials to ensure a given biosimilar is safe²
- 93% do not believe all biologics are equally effective⁹
- 72% of AGA members report that they would be likely to prescribe biosimilars if they became available in the U.S.¹⁰
- 80% of respondents say they are very concerned with the level of clinical similarity in terms of effectiveness and safety to the reference biologic and the biosimilar efficacy¹⁰
- 78% of respondents are very concerned about biosimilar safety/immunogenicity¹⁰
- Among respondents who are unlikely to prescribe biosimilars, 69% report that they would be unlikely to prescribe biosimilars because they do not have experience with biosimilars¹⁰
- 66% of respondents who are unlikely to prescribe biosimilars believe there will not be enough clinical data on biosimilars¹⁰
- 80% of prescribing specialists say they would want to learn about biosimilars through expert-led digital content¹¹
- Only 17% of prescribing specialists report they would be “very likely” to prescribe biosimilars to eligible patients¹¹
- Specialty societies were prescribing specialists’ most trusted source of information about biosimilars (25%), followed by peers (19%), and key opinion leaders (18%)¹¹

Canada

- 59% of survey participants (rheumatologists) think it is appropriate to offer a biologic-naïve patient a biosimilar¹²
- 31% of survey participants would feel comfortable prescribing biosimilars to patients if approved today¹²

Educational Needs

- Should biosimilars be tested in every indication?
- Concerns include safety/efficacy, drug substitution regulations, and accurate evaluation of when to prescribe a biosimilar vs. branded therapy

FDA Guidance

- In order to establish biosimilarity, the Biologics Price Competition and Innovation Act (“BPCIA”) requires that the proposed biosimilar product:
 1. be “highly similar” to the reference product (i.e., the FDA-approved biological product that the biosimilar sponsor is seeking to copy) based on data derived from analytical studies, animal studies, and one or more clinical studies;

2. utilize the same mechanism of action as the reference product, to the extent known;
 3. be for one or more conditions of use previously approved for the reference product;
 4. have the same route of administration, dosage form, and strength as the reference product; and
 5. be manufactured in a facility that meets standards designed to assure the biosimilar is and will continue to be safe, pure, and potent
- FDA evaluates biosimilarity on a product-by-product basis considering the “totality of the evidence.” In addition to the five statutory biosimilarity requirements above, FDA has provided informative guidance regarding data necessary to support a biosimilarity showing. For example, biosimilars may have a different formulation from the reference product, so long as the biosimilar remains “highly similar” and any formulation differences are not clinically meaningful
 - FDA’s “stepwise approach” to assessing biosimilarity means that more robust initial analytical and comparative evidence of biosimilarity – e.g., structural comparisons, functional in vitro and in vivo assays – may reduce any remaining “residual uncertainty” regarding biosimilarity. Minimized “residual uncertainty,” in turn, may reduce the nature and scope of clinical studies that FDA will require in order for the sponsor to demonstrate biosimilarity

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf>

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf>

Indication Extrapolation

Survey data

United States

- 92% of seniors wanted a requirement that drug companies test the safety of biosimilars for all conditions the drug will be used to treat²
- 67% of AGA members favored a policy whereby FDA would not allow indication extrapolation in the approval of biosimilars for IBD¹⁰

Europe

- 63.7% of respondents said that they would not switch a patient onto a biosimilar monoclonal antibody as there is no disease-specific evidence about their interchangeability¹³

Educational Needs

- Is it reasonable to assume that efficacy and safety in one indication will be similar in other indications?

- How do you identify the most sensitive patient population to test?

FDA Guidance

- Scientific justification for extrapolation should address:
 1. the mechanism of action (MOA) in each condition
 2. the PK and bio-distribution of the product in different patient populations
 3. PD may provide important info on MOA
 4. Differences in expected toxicities in each condition and patient population
 5. Any other factor that may affect safety and effectiveness in each condition and patient population

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>

Interchangeability

Survey data

United States

- 91% want physicians to be notified when a biosimilar is substituted for the original biologic drug they prescribed for their patient²
- 94% believe patients should be notified when a biosimilar is substituted for the original drug prescribed by their doctor²
- 95% of respondents were concerned their disease would worsen if their biologic medicine were switched⁹
- 98% support legislation that would prohibit non-medical switching without patient/provider notification⁹
- 86% agreed that only patients should have a say in which biologic medicine they are prescribed⁹
- More than 82% of respondents believe that the U.S. Food and Drug Administration (FDA) approval standards for designating a biosimilar as "interchangeable" must be very rigorous to ensure patient safety³
- 35% of respondents believe that pharmacy-level substitution should never be allowed¹⁰
- 85% of responding physicians want the authority to designate a biological medicine as 'Dispensed as Written', just as they have it for chemical products⁵
- 86% of physicians want to be notified before a patient is switched to a biological other than the one prescribed even if there are no known concerns associated with the product⁵

Canada

- Only 7.5% of survey participants (rheumatologists) think it is appropriate to switch a biologic treatment-stable patient to a biosimilar.¹²

Educational Needs

- Concern about switching when currently stable on a biologic
- Should the label indicate whether a biologic is biosimilar or interchangeable?
- If clinical trials are required, how many switches should be required to demonstrate interchangeability?

FDA Guidance

- Draft guidance not provided yet
- FDA may deem a biological product “interchangeable” with a reference product if the sponsor can show that the product is biosimilar to the reference product, that the biosimilar product is expected to produce the same clinical result as the reference product, and that the risk of switching between the biosimilar and reference product is not greater than the risk of using the reference product alone

1. The American Autoimmune Related Diseases Association (<https://www.aarda.org/wp-content/uploads/2015/02/BiosimilarsWhitePaperPressRelease.pdf>)
2. RetireSafe (<http://www.prnewswire.com/news-releases/statement-from-retiresafe-to-congress-274605751.html>)
3. The Coalition of State Rheumatology Organizations (<http://csro.info/app/document/8382846;jsessionid=P5zJOo6TwPYoXVXzswSYawvyM.undefined>)
4. The Academy of Managed Care Pharmacy, the American Pharmacists Association, and the American Society of Health-System Pharmacists (J Manag Care Spec Pharm. 2015. 3:188-195)
5. Alliance for Safe Biologic Medicines (<http://gabionline.net/Biosimilars/General/Naming-and-interchangeability-of-biosimilars-raised-in-new-survey>)
6. The Journal of Managed Care and Specialty Pharmacy, ([http://www.jmcp.org/doi/pdf/10.18553/jmcp.2016.22.8.919/Biosimilar Naming Conventions: Pharmacist Perceptions and Impact on Confidence in Dispensing Biologics](http://www.jmcp.org/doi/pdf/10.18553/jmcp.2016.22.8.919/Biosimilar%20Naming%20Conventions%20Pharmacist%20Perceptions%20and%20Impact%20on%20Confidence%20in%20Dispensing%20Biologics))
7. Alliance for Safe Biologic Medicines (<https://safebiologics.org/2013/11/asbm-presents-new-european-survey-findings-on-biosimilars-and-the-importance-of-nonproprietary-naming/>)
8. Alliance for Safe Biologic Medicines (<http://docs.house.gov/meetings/IF/IF14/20160204/104408/HHRG-114-IF14-20160204-SD010.pdf>)
9. Global Healthy Living Foundation (<http://www.50statenetwork.org/wp-content/uploads/2015/04/GHLF-survey-4-222.png>)
10. American Gastroenterological Association (http://www.gastro.org/press_releases/2015/7/29/national-survey-reveals-gastroenterologists-views-on-biosimilar-drugs)
11. Quantia Report (<http://www.businesswire.com/news/home/20150818005839/en/Quantia-Report-Reveals-Physician-Attitudes-Biosimilars>)
12. A Survey of Canadian Rheumatologists (Clin Rheumatol. 2015. 34:1427–1433)
13. European Crohn’s and Colitis Organisation (<http://gabi-journal.net/ecco-2013-survey-highlights-lack-of-confidence-in-biosimilars.html>)

PAPER TWO

BIOSIMILAR UPTAKE: CONSIDERATIONS FOR CLINICAL DECISION-MAKING, COVERAGE AND REIMBURSEMENT DECISIONS, AND POSTMARKET EVIDENCE DEVELOPMENT

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INTRODUCTION

The enactment of the Biologics Price Competition and Innovation Act of 2009 (BPCIA) marked the culmination of a years-long effort to create an abbreviated licensure pathway for biological products that are demonstrated to be either “biosimilar” to or “interchangeable” with an existing FDA-licensed biological product [For full definitions of key terms, please see the glossary on page 37].¹ The legislation was also an important step in the broader effort to foster competition in the US biologic drug market after a period of patent exclusivity, with the goal of generating substantial long-term cost savings in the health care system while still providing financial returns to innovation in biologics. In 2013, the top 10 highest-expenditure drugs covered under Medicare Part B were all biologics, and spending on those drugs alone represented 48 percent of all Part B drug expenditures. (By contrast, total spending on the ten most frequently used Part B drugs accounted for less spending than any one of the top ten highest-expenditure Part B drugs.)²

The review and approval process established under the BPCIA (also known as the 351(k) pathway) was designed to provide an expedited pathway for the approval of biosimilars, similar to the Abbreviated New Drug Application pathway established under the Hatch-Waxman Act of 1984 (a key factor in the development of the modern generic drug market). One study estimates that overall savings in Europe and the US will be between \$56-\$110 billion through 2020 as a result of biosimilar market entry and use.³ However, market competition between biosimilars and their reference products will not be a perfect analogue of the generic small-molecule market, owing to fundamental differences between biologic and small-molecule drugs. Biologic drugs are more complex, more expensive to develop and produce, more sensitive to manufacturing changes, and pose immunogenicity risks that may make substitution or therapeutic switching challenging.

Biosimilar	Approval date	Sponsor	Reference product	Approved for same indications?
Zarxio	March 2015	Sandoz	Neupogen (Amgen)	Yes
Inflectra	April 2016	Pfizer/ Celltrion	Remicade (Janssen)	No—Remicade holds pediatric exclusivity for one indication
Erelzi	August 2016	Sandoz	Enbrel (Amgen)	Yes
Amjevita	September 2016	Amgen	Humira (AbbVie)	No—Humira holds orphan exclusivity for four indications

Table 1: Biosimilars approved by FDA as of October 2016

As a result, overall progress in the development of a robust biosimilars market has been limited. Since the passage of the BPCIA, FDA has approved four biosimilar products (see Table 1).⁴ Though the approval of these drugs has

helped to clarify some of the uncertainties surrounding FDA’s requirements for approval, there are a number of outstanding regulatory, legal, and scientific questions that must be addressed in order to facilitate development and approval of more biosimilars.* These include clarification on the standards for interchangeability, extrapolation of biosimilar approval for one disease or condition to additional indications, and the finalization of guidance on naming and labeling.

Further, there are a number of downstream issues related to utilization, coverage, and reimbursement that also raise distinct concerns. The majority of biologic drugs are reimbursed under the medical benefit rather than under the pharmacy benefit (though at least two of the four approved biosimilars are largely reimbursed under the pharmacy benefit). Consequently it may be necessary to adapt traditional payer strategies aimed at encouraging generic substitution in order to more effectively drive biosimilar use. Additionally, continued postmarket evidence development will be important to build trust in biosimilar safety and efficacy, demonstrate value to stakeholders, and inform approaches to clinical practice and payer decision-making.

Ultimately, the uptake of biosimilars—and the resulting cost savings, access to biologics, and health outcomes—depends on a range of factors that are not yet resolved. This paper reviews several of the major issues that will influence biosimilar availability and use beyond regulatory marketing approval, including: 1) existing and emerging coverage and reimbursement strategies that payers and pharmacy benefit managers (PBMs) could employ to guide utilization; and 2) the potential role that postmarket evidence generation could play, both in terms of informing the design and implementation of these payment strategies, as well as in addressing outstanding questions related to the relative cost, quality, and effectiveness of biosimilars.

GUIDING BIOSIMILAR UTILIZATION - POTENTIAL PAYER STRATEGIES

As with generic drugs, payers and PBMs will play a critical role in influencing biosimilar utilization and price discounts from manufacturers. Many of the tools that have been used by these stakeholders to encourage generic drug use could be adapted and leveraged to promote the adoption of biosimilars and facilitate lower negotiated prices for the original biologics. However, the design and application of these tools and strategies will depend on whether a given biosimilar is administered by clinicians in an office setting (generally covered under a medical benefit plan) or obtained from outpatient pharmacies and self-administered by patients or their caregivers (usually covered under a pharmacy benefit plan).

BIOSIMILAR COVERAGE UNDER THE PHARMACY BENEFIT: FORMULARY DEVELOPMENT AND IMPLEMENTATION

For drugs covered under the pharmacy benefit (typically dispensed by a retail or specialty pharmacy and self-administered by the patient), a key approach to utilization management is through the formulary. Pharmacy and Therapeutics (P&T) Committees—which develop and maintain formularies for organizations—traditionally base formulary inclusion and tiering decisions on a range of considerations, including the potential cost savings, current

* For an overview of these outstanding issues, see “The Current Landscape of Biosimilars Development, Regulatory Review, and Stakeholder Education” which was developed as the companion document to this white paper.

clinical guidelines and practices, logistical implications, and physician and patient preferences.⁵ Importantly, the actual price paid for a given drug—as well as its placement on a payer or PBM formulary—depends in part on that payer’s ability to negotiate volume-based discounts or rebates, which pharmaceutical companies may offer in exchange for more favorable placement on a formulary.

Formulary tiering

Most US payers—including Medicare Part D—rely on a tiered formulary structure designed to encourage the use of preferred therapies. Based on the P&T evaluations, drugs are generally assigned to a particular tier according to their cost and their incremental value (uniqueness). Generic drugs are typically assigned to the tier with the lowest patient copay, while more costly drugs are grouped into tiers with progressively higher copays or coinsurance rates. The most expensive therapies—many of which are biologics—are often grouped into a specialty tier that includes both higher levels of cost-sharing as well as additional layers of utilization control, such as prior authorization from the payer or limits on the number of units administered or dispensed at a single time.⁶

It is unclear how tiering and cost-sharing approaches will impact the uptake and utilization of biosimilars. While an online survey of 102 health plans found that 49 percent intend to place biosimilars at a lower tier than branded specialty biologics, a number of characteristics unique to the biosimilars market may limit how effective these approaches are when compared to their success in accelerating uptake for small-molecule generics.^{7,8} For example, most biologics are intended for patients with chronic, complex conditions that require ongoing treatment, which means that if these drugs are on a higher tier, affected patients will incur substantial costs before reaching the out-of-pocket maximums. For example, the exchange plans established by the ACA set the out-of-pocket maximum at \$7,150 for individual coverage and \$14,300 for family coverage in 2017. The continued proliferation of patient assistance programs (many of which are funded by pharmaceutical manufacturers) will further limit how cost-sharing arrangements affect patient behavior, patient costs, and total spending on biologics.

Formulary exclusion and step therapy requirements

Related key strategies for enabling formulary design to influence utilization and costs are formulary exclusion and step therapy requirements. These approaches are typically applied in cases where there are multiple therapies that are highly similar in terms of both safety and efficacy.⁹ In such cases, payers and PBMs may choose to exclude certain products from their formulary or engage in exclusive contracts with a single manufacturer in exchange for price discounts or rebates, thus incentivizing (or requiring) the selection of preferred options. Plans may also require a step therapy process that requires patients to try a preferred option first, with the option to switch to an alternative therapy at a later date. These strategies have been successful in driving down costs in certain therapeutic classes, and can be applied to biosimilars. Payers may also apply prior authorization (also called pre-certification), requiring patients and their providers to document that diagnostic criteria and, in some cases, prior treatment criteria are met before receiving payment for the more expensive options.

The extent to which these strategies are applied will depend on several considerations. One is the therapeutic context. For certain cancers, for example, a step therapy process that requires a preferred option prior to switching to an alternative in the same drug class would likely not be appropriate owing to concerns over emergence of drug resistance following exposure to the initial drug. In addition, state and federal regulations restrict the design and application of these approaches. For most categories of drugs covered under Medicare Part D, for example, plans are required to include at least two drugs from each drug category or class unless only

one is available, or only two are available but one drug is clinically superior to the other. In the six protected classes – including oncology drugs, drugs for autoimmune conditions, and other conditions where biologics are common treatment – CMS initially mandated and then Congress legislated that all drugs must be covered (though potentially on higher tiers or with prior authorization).¹⁰ CMS indicated in 2015 that it would review off-cycle plan decisions to remove biologic products from their formulary and replace them with a biosimilar on a case-by-case basis.¹¹

State laws regarding pharmacy substitution may also have an impact. While small-molecule generic drugs can typically be automatically substituted without authorization by the prescriber, (provided that the prescriber does not explicitly request the branded drug), non-interchangeable biosimilars are not considered therapeutically equivalent, and no biosimilar appears on track for approval as interchangeable at this time.¹² In addition, over the last four years, 36 states have either considered or enacted laws that would introduce additional administrative controls on the automatic substitution of interchangeable biosimilars. These provisions vary but share common features, including requirements that pharmacists notify physicians or patients when a substitution has been made, or that pharmacists obtain patient consent before substituting the interchangeable biosimilar. Many states would also require that pharmacies retain a record of this substitution for a certain number of years.¹³

In addition to such policy decisions, the extent to which price competition and shifting occurs will depend importantly on the level of evidence available to demonstrate that the differences between the biosimilar and its reference product are inconsequential, particularly for scenarios where a payer may seek to induce a patient already on an originator to switch to the biosimilar, or vice versa. Extensive price competition and shifting from brand to generics has occurred because patients and physicians generally view the drugs as therapeutically equivalent. The evidence, and thus the willingness to switch, will differ for biosimilars. While postmarket surveillance in Europe has not detected immunogenicity concerns related to switching between biosimilar and reference products, payers and PBMs will need to evaluate the potential impact of any therapeutic interchange or step therapy requirements on a case-by-case basis, as switching patients from one biologic therapy to another may have clinical implications and the evidence is still evolving on how individual patients may respond differently to such substitutions.

Payers and PBMs may instead consider limiting step therapy requirements to treatment-naïve patients until further postmarket safety and substitution evidence becomes available. A given patient's treatment status or history may be challenging to determine if they are newly enrolled, and will likely require a prior authorization process to ensure that patients have not previously been treated with another biologic.

These various factors are likely to promote more intense competition between reference and biosimilar manufacturers to capture initial administration of a therapy.¹⁴ Payers will need to implement strategies to ensure patients receive a prescription in line with their insurer's formulary. Such strategies could include making patient-specific formulary information more widely available at the point of prescribing and implementing prior authorization requirements. It will also be necessary to develop coverage policies to address cases where the biosimilar might be approved for fewer indications than the reference product, as well as cases where the branded biologic is routinely prescribed off-label as part of standard of care practices.

BIOSIMILAR COVERAGE UNDER THE MEDICAL BENEFIT: PROVIDER FEE SCHEDULES

The majority of biologics are covered under a patient's medical benefit and are purchased by providers and administered in an inpatient setting, physician's office, or other outpatient setting. Drugs administered in these

contexts are processed as a medical claim rather than as a pharmacy claim. Hospitals and health systems purchase these drugs from distributors, often through group purchasing organizations, and like PBMs or other payers, may be able to negotiate lower drug prices in return for emphasizing use of certain drugs where alternatives exist (historically, this process has been developed much more extensively for devices). The reimbursement mechanisms for medical benefit therapies—which include high priced cancer and rheumatoid arthritis drugs as well as comparatively inexpensive products such as corticosteroids and vitamin B12—are structured very differently from pharmacy benefit drugs and the prices paid are influenced in different ways.

Inpatient hospitalizations and procedures are typically reimbursed on either a prospective, bundled basis (e.g., Medicare’s Diagnosis Related Group payment structure under Part A) or a per diem basis (e.g., many commercial insurance plans). These payments are intended to cover all costs related to care, generally including drugs, though specific providers may bill separately for the administration of the drug. Hospital or health system formularies may diverge from those of third-party payers and PBMs, which can complicate care transition. For example, patients in an inpatient setting may receive a therapy based on the hospital’s formulary, but upon discharge to the outpatient setting may find that their insurer’s formulary specifies a different therapy for their condition. As noted above, formulary decision support at the point of prescribing can help address this issue.

Reimbursement for biologics administered in the outpatient setting is typically structured as a flat rate per dose. Medicare Part B drug payments are based on the average sales price (ASP) of the drug plus a fixed percentage mark-up, so the total payment to the provider who “buys and bills” for the drug is ASP plus six percent.¹⁵ The ASP of a given drug is updated on a regular basis to reflect price changes over time, with a lag. Many commercial payers follow the Medicare structure, generally with a higher markup rate above ASP. This reimbursement structure means that higher-priced drugs generate larger margins for the administering provider.

Reimbursement levels for biosimilars covered under medical benefits—and the corresponding margins they generate for providers—will also be influenced by how they are treated in the ASP system. Drugs that are reimbursed under the medical benefit are billed using a Healthcare Common Procedure Coding System (HCPCS) code. Under recently finalized CMS rules, an originator biologic will continue to receive its own HCPCS billing code, while all biosimilar products that reference that biologic will be grouped together under a single separate HCPCS code.¹⁶ Reimbursement for all biosimilars will be set at the ASP of all of the biosimilars grouped under that code, plus six percent of the *reference* product’s ASP.

Though this policy is intended to spur price competition between biosimilar manufacturers, there are ongoing questions about how it may affect prescriber behavior and the potential downstream consequences for biosimilar market entry. While the payment rule provides a higher percentage mark-up for selecting biosimilars, in some cases the absolute dollar margins may still be higher for the reference product, giving providers a financial incentive to select the more expensive products.¹⁷ The separate (and potentially higher) payment for the reference product provides a stronger incentive for providers to prescribe it than if all products were grouped into the same payment code. On the other hand, grouping all biosimilars together under a single billing code may discourage manufacturers from competing based on the relative value of their products (such as the quality, safety, or effectiveness of the products for certain types of patients). Grouped coding may also discourage manufacturers from remaining in this nascent market long-term, thus limiting competition and potential savings of biosimilars. Grouping all biosimilars together does not create a structure that supports payers in selectively negotiating preferred pricing and access from one company. Private payers may have more flexibility to shift margins away from reference products to cheaper biosimilars, but additional incentives and tools (e.g., separate

coding modifiers and other steps to encourage formulary approaches within the medical benefit) may be necessary to encourage such approaches.

Alternatives to provider fee schedules

Given the challenges associated with buy-and-bill reimbursement under the medical benefit, commercial payers have begun piloting alternative approaches to managing utilization and costs for drugs covered under the medical benefit. Under one approach, providers are required to purchase specialty pharmaceuticals from a contracted specialty pharmacy which has negotiated a particular price for that drug.¹⁸ Because the cost of infusible or injectable drugs can vary depending on the setting where the drug is administered, some plans have also used patient cost-sharing incentives in benefit design to encourage the selection of less-expensive drugs and drug administration settings.

In addition, several payment methods have been proposed or are currently being implemented as alternatives to traditional buy-and-bill reimbursement methods, including:

- reference pricing, which sets a drug's payment rate no higher than that for currently available treatments, unless evidence shows that the drug improves patient outcomes;
- indication-based pricing, which allows the negotiated price for a drug to vary based on its demonstrated clinical effectiveness for different indications; and
- outcomes-based payment, which links a drug's payment level to beneficiaries' observed outcomes (or markers of outcomes) through a risk-sharing agreement with the manufacturer.¹⁹

Experience with these arrangements to date has identified a number of practical challenges and has proven controversial, including in a recent CMS pilot proposal to test many of these approaches for drugs reimbursed under Part B (in the second, currently conceptual phase of the pilot).

These value-based pricing models have also been proposed for drugs covered under the pharmacy benefit. Broader obstacles to implementation need to be addressed, including off-label communication restrictions, anti-kickback statutes, and best price regulation. It may also be necessary to address the uncertainties regarding FDA's promotional and scientific exchange rules on companies' abilities to discuss postmarket data. This additional clarity could help to further encourage data generation in the biosimilars context, ultimately leading to better health outcomes and lower overall costs.

EMERGING VALUE-BASED PAYMENT APPROACHES THAT MAY IMPACT BIOSIMILAR USE

Broader changes to the healthcare system, spurred in part by the ACA, have led payers and providers to begin experimenting with payment models that seek to align payment with better patient outcomes, higher-value care, and more flexible and innovative care delivery. Because these value-based payment models are expanding, they may have a greater short-term impact on biosimilar use than reforms in drug pricing. Some of these reforms may involve modifications of the fee-for-service payment rates for providers. Some private payers currently reward higher generic prescribing with a payment bonus incentive, which could be extended to biosimilars.²⁰ For example, biosimilar prescribing could potentially contribute to provider value metrics under the Medicare Access and CHIP Reauthorization Act of 2015 (MACCRA).

Beyond fee-for-service payment adjustments, many emerging alternative payment models (APMs)—such as accountable care organizations, patient-centered medical homes with accountability for costs and outcomes, and bundled payments for episodes of care tied to quality incentives—could have a significant impact on biosimilar use, depending on how utilization and spending for physician-administered drugs is incorporated into these models. The models shift some financial risk from payers to providers, in conjunction with more flexibility in how providers can deliver services (e.g., extended office hours, team-based care, telemedicine, and other services could get more financial support) and more accountability for improvements in performance metrics and other quality outcomes. These broader changes to the way care is reimbursed may help to drive clinical decision-making toward the use of lower-cost biosimilars, particularly if the benefit to given categories of patients is similar.

Some commercial health plans have implemented reimbursement linked to greater use of clinical pathways based on evidence and expert consensus, particularly in oncology. Standardized clinical pathways are designed to support provider decision-making and will often specify the selection, dosing, and ordering of drugs for a given condition, as well as the use of supportive therapies. Under these programs, providers are offered financial incentives to follow pathway recommendations, such as higher reimbursement rates or care management fees.²¹ The Anthem Cancer Care Quality Program, is one of the largest clinical pathway programs.²² Launched in 2014, the program is designed to reduce the variation in treatment and cost of 19 types of cancer by providing a \$350 monthly care management fee to providers whose treatment regimen adheres to a standardized clinical pathway that specifies the use of treatments selected on the basis of efficacy, toxicity, and cost.^{23,24}

Bundled or episode-based payments reimburse providers at a prospectively set rate for a group of services they furnish during an episode of care. These bundles often include associated pharmaceutical costs as part of the medical benefit. Even without changes in medical benefit payment for physician-administered drugs, this new financial accountability could help to shift providers towards using less-costly biosimilars.

Payers and PBMs have also begun implementing alternative cost-sharing strategies aimed at linking patient decision-making to higher-value care, referred to as “value-based insurance design”, or VBID. These strategies vary, but typically include cost-sharing reductions for patients that meet certain criteria (e.g., particularly high-risk patients, or patients that enroll in disease management or wellness programs).²⁵ Though VBID strategies have shown some success in increasing adherence, most strategies employed to-date have been applied to small-molecule drugs rather than biologics. Such approaches could be generally applicable to biosimilars covered under the pharmacy benefit by waving copays or setting lower fixed copays for the biosimilar.²⁶ Similarly, VBID could be matched to episode payments and other alternative payment models, enabling patients to save money or receive other nonfinancial benefits if they choose providers who are higher-performers in the models.

CMS recently announced that it would be expanding its own VBID pilot to include rheumatoid arthritis (RA) patients, which could potentially incorporate biosimilars.²⁷ Two of the recently approved biosimilars – Erelzi, which is biosimilar to Enbrel, and Amjevita, which is a biosimilar to Humira – are alternatives to leading treatments for RA and could be eligible for the pilot. However, the pilot ends in 2022 and it is currently unclear when these two products might formally launch in the US market, owing to pending patent disputes.

SUPPORTIVE STRATEGIES: PROVIDER EDUCATION

Payers and PBMs have employed a range of education and information-supplying strategies to help guide prescriber decision-making. In addition to the formulary decision support approaches described above, another

approach is to provide individually tailored information on optimal drug use. Trained educators visit providers to share neutral, up-to-date information on the safety, efficacy, and cost-effectiveness of medications and other therapeutic options, including any available information on comparative effectiveness.²⁸ This approach, known as academic detailing, is modeled after the interactive communication practices used by medical sales staff. Though academic detailing may involve many different kinds of approaches, evaluations have found that it can be effective in influencing prescribing behavior.^{29, 30} However, the quality and effectiveness of treatment guidelines or academic detailing efforts will largely depend on what is known about the relative safety, value, and effectiveness of a given treatment.

ADDITIONAL CONSIDERATIONS AFFECTING PRICING AND UPTAKE OF BIOSIMILARS

FDA has issued a number of guidance documents related to biosimilar development and approval to date, but there are still several outstanding questions that could impact payer decision-making and, ultimately, biosimilar uptake and access. For example, FDA has not yet finalized guidance on naming, label format, and interchangeability. It is also unclear whether FDA will view two biosimilars of the same reference product as biosimilar to each other, or whether two interchangeable biosimilars will also be considered interchangeable with each other. The final FDA positions on these issues might affect payers' decisions to shift patients from one biologic to another (singly or in multiple incidences). It is unclear what standard payers will use to assess whether it is safe to transition patients from an originator biologic to a biosimilar. The standards that payers set will also have broad implications for provider and patient trust and could affect confidence in switching to a biosimilar.

Until these issues are more clearly resolved, supply chain maintenance will be an important consideration. Retail and specialty pharmacies may need to take steps to ensure that patients maintain access to a single biosimilar product, and payers and providers may also need to assess a manufacturer's capacity to reliably supply the product as one of the criteria included in the formulary review process.

DEMONSTRATING BIOSIMILAR VALUE THROUGH POSTMARKET EVIDENCE DEVELOPMENT

A key factor in payer and PBM decision-making will be the level of evidence supporting the use of a biosimilar within a particular disease context or in specific patient populations, relative to the reference product. Continued postmarket evidence development and dissemination of that evidence will be an important component in building trust in the safety and efficacy of the therapies, demonstrating value to stakeholders, and informing the approaches to clinical practice and payer decision-making described above. This is particularly important given that, compared to originator drugs, the biosimilar development paradigm relies heavily on analytical characterization and to a lesser extent on clinical data.

Prospective, randomized controlled trials (RCTs) are and will remain an important source of information on long-term outcomes and comparative effectiveness, but due to their cost, complexity, and duration, they are challenging to implement in practice. RCTs also have well-known limitations in terms of understanding a treatment's effect outside of the population studied in the trial. For many outcomes or populations of interest, alternative approaches such as pragmatic clinical trials, adaptive clinical trials, observational studies, and meta-analyses will play an important role.

Postmarket research can provide additional evidence on the risks and benefits of switching biologic therapies, on the use of the originator and biosimilar, and on the impact of formulary designs and other policies affecting this use. Studies could also assess the impact of patient support programs on outcomes with various biologic therapies. Just as with traditional small-molecule drugs and medical devices, stakeholder groups will need evidence and information that can be met through more systematic data capture and dedicated postmarket studies.

European Union health systems have already adapted their postmarket surveillance approaches to monitor biosimilar products specifically, as these products have been available since 2006. Some post-approval studies have been designed to confirm biosimilarity for extrapolated indications. Many are designed to assess the safety and efficacy of switching from an originator biologic to a biosimilar. There are several well-known examples, including NOR-SWITCH, an ongoing study sponsored by the Norwegian government where patients will undergo a single switch from Remicade to an infliximab biosimilar across several disease states. Data are expected to be available by early October 2016. One of the largest data points on switching is the recently published data from the DANBIO registry in Denmark. This study assessed 647 patients with rheumatoid arthritis, psoriatic arthritis, or axial spondylitis who had been treated with Remicade for a median of nearly 7 years before undergoing a switch to the biosimilar infliximab. The authors conclude that “[d]isease activity remained largely unchanged 3 months prior to vs. after the switch.” However, more long-term follow-up is needed, as roughly 6 percent stopped treatment due to loss of efficacy or adverse event.³¹

In the United States, there are a number of challenges associated with collecting robust, reliable postmarket data. The fragmented nature of the U.S. healthcare system makes it difficult to follow patients across multiple providers, systems, and payers.³² Healthcare settings differ in the level of detail that is captured for health records and claims, and electronic health records (EHRs) are often extensively customized within institutions, which can result in significant variation in how data are characterized and catalogued.³³ Reimbursement models for outpatient and inpatient settings can further complicate efforts to make comparisons between patients or synthesize outcomes data, as coding requirements for healthcare claims may be different in each of these settings.³⁴ Creating stronger incentives for the development of a postmarket evidence infrastructure could be an associated benefit of a shift to more value-based payment models, where such evidence has more direct bearing on payment. It has been challenging to ensure that postmarket studies, including those tracking safety issues, are completed in a timely manner.^{35, 36} These issues cut across all postmarket research activities and would pose similar issues for biosimilars.

FACILITATING AND INCENTIVIZING POSTMARKET EVIDENCE GENERATION

One of the key issues in developing postmarket evidence is the broader research infrastructure necessary to support studies. In the last decade, there has been substantial investment from the public sector in building more robust and comprehensive data networks that can develop real-world evidence more effectively and comprehensively, including FDA’s Sentinel System, PCORnet, and the Medical Device Epidemiology Network. Efforts are currently underway to expand and harness the Sentinel System to conduct studies that go beyond safety surveillance. The Innovation in Medical Evidence Development and Surveillance (IMEDS) program is in the process of developing the governance and processes for non-FDA entities such as manufacturers to sponsor safety queries utilizing the Sentinel infrastructure.³⁷ Importantly, Sentinel is also part of a collaboration formed by the Academy of Managed Care Pharmacy to monitor and assess the impact of biosimilars on patients. The Biologics and Biosimilars Intelligence Consortium, or BBIC, is currently using Sentinel’s data and infrastructure to conduct

descriptive analyses of four biologic drug classes. These analyses are intended to lay the groundwork for future studies of biosimilars and their reference products.³⁸

These efforts will help to reduce operational and technical barriers to research and bring down the costs of evidence generation. Engaging patients at the outset of a research project before the launch of clinical trials and studies by asking for signed consent to authorize data linkages for aggregate use (such as the approach set forth in the Precision Medicine Initiative) could facilitate these efforts.³⁹ Existing health IT platforms, such as the American Society of Clinical Oncology's CancerLinQ, can also be leveraged to track and evaluate patient outcomes after the introduction of biosimilars into the market, providing evidence on long-term safety and efficacy.

Additional incentives will likely be necessary to support systematic postmarket evidence generation. As noted above, new APMs being adopted and tested by payers and providers to drive higher value care could encourage more utilization of biosimilars. In turn, the expected pressure from value-based payment reform could increase incentives for developing a stronger postmarket evidence infrastructure, which will be critical to understanding the real impact of these payment models on the uptake and use of biosimilars on cost and quality outcomes. Value-based purchasing contracts between payers and manufacturers, such as those utilizing outcome- or indication-based pricing, may also create stronger incentives for the development of better evidence on biosimilars.

Successful implementation of these approaches will require better and standardized measures that can adequately capture the value of alternative treatments, and the underlying data to construct the measures.

DATA SOURCES FOR POSTMARKET EVIDENCE GENERATION

Post-approval safety and comparative effectiveness studies commonly rely on data collected through registries or databases derived from administrative or EHR data, which is used to measure exposure to the drug and the associated outcomes.⁴⁰ Prospective registries have several advantages for research purposes, as they contain very complete information on exposures and outcomes for as long as they are maintained (this adherence is often enforced by restricting distribution of the drug to providers who have joined the registry). However, registries are complex and expensive to establish and maintain, particularly for a large cohort of patients. They also do not typically contain data on control groups of similar patients who do not receive the medication, and thus are not able to address questions of comparative safety or effectiveness. As a result, registries are typically used for safety surveillance of specific products that are particularly expensive or carry significant risks.⁴¹

By contrast, large databases draw from routinely collected claims and clinical data, which reduces the burden on the health system and in some cases can be used to identify control groups of patients for comparative purposes. Using these databases to evaluate biosimilars and their outcomes depends on the ability to distinguish biosimilars from each other and from their reference product in the data. The most widely used identifiers for research purposes are billing codes; namely, National Drug Codes (NDCs), which are applied to claims for drugs reimbursed under the pharmacy benefit, and HCPCS codes, which are used for drugs reimbursed under the medical benefit.⁴² In some cases, EHR data may contain NDCs or a proprietary coding system that can be used to identify the product prescribed.⁴³

As the majority of biologics are administered by physicians and billed as medical claims, HCPCS codes will be an important component of postmarket research on biosimilars. However, this presents several challenges. First, while NDCs are drug-, manufacturer-, and dosage-specific, HCPCS codes are not, which can make it difficult to

identify which product was administered. CMS recently finalized its rules for biosimilar reimbursement under Part B, mandating that all biosimilars that reference a particular product will share the same HCPCS code. To facilitate pharmacovigilance, the agency will assign a manufacturer-specific, two-digit modifiers to each biosimilar product.⁴⁴ The assignment of permanent HCPCS codes is a months-long process, which can hinder surveillance in the first 6 to 18 months of utilization. Once CMS publishes the modifier its use will be mandatory.

There are several strategies that could be implemented or expanded to improve the completeness, timeliness, and accuracy of the data that supports postmarket evidence generation. For example, billing could be shifted for physician-administered drugs from HCPCS to NDCs, though in the hospital system setting this may present an informatics challenge. Barcode administration could allow these sorts of data to travel from the pharmacy with the product to the patient bedside and the EHR. Researchers could also make increased use of new analytic approaches to safety surveillance, such as data mining (i.e. the use of computational processes to discover patterns or relationships in large data sets). Such approaches can be used to identify early safety signals that can then be investigated further to determine if the link between the biosimilar and the identified adverse event was valid and clinically meaningful.⁴⁵

TARGETING KEY QUESTIONS AND OUTCOMES

The outcomes targeted through postmarket research will naturally depend on the purpose of the study and the stakeholders interested in the results. While many outcomes (such as immunogenicity and other serious adverse events) are important to all stakeholder groups, the value proposition for a given biosimilar may vary somewhat among patients, clinicians, and payers. For example, providers and patients may place relatively more emphasis on comparative clinical effectiveness or ease of use or administration, while payers and PBMs may place relatively more emphasis on cost or the dependability of supply (See Table 2 for a list of key questions that could be addressed through postmarket evidence development). It will be important for those involved in evidence development to consider the information needs of each group when planning a study.

Well-designed outcomes research on biosimilars could not only align across multiple stakeholder needs, but also contribute to broader efforts to establish a national evidence development system. This has been identified by FDA, policymakers, and others as a key national priority and efforts are already underway to address the outstanding questions and uncertainties related to the collection and use of the evidence that could be generated. Enhancing the use of real-world evidence in regulatory decision-making has also been identified as a key commitment for FDA under the next iteration of the Prescription Drug User Fee Act (expected in 2017), and several groups are working in parallel to support the agency's efforts in this area.

Tracking the utilization and effectiveness of biosimilar products could further motivate sponsors, payers, and others to contribute toward building this system. Making meaningful connections among the constellation of ongoing evidence development systems mentioned above and tackling challenges with data standardization and integrity will require the investment of substantial time and resources. Biosimilars could prove an important test case for addressing these issues and realizing a national infrastructure.

Question/Outcome of interest	Primary audience
Does the biosimilar product lead to lower total costs of care without any impact on quality, safety, effectiveness outcomes compared to the reference product?	Physicians, patients, payers, manufacturers
Do lower out-of-pocket costs associated with biosimilars lead to increased utilization and adherence? (i.e., is there a net benefit with using a biosimilar because of improved access?)	Payers, manufacturers, patients
Is switching or alternating between the biologic therapies safe and effective for all patients?	Physicians, patients, payers
What value – in terms of improved compliance, better outcomes, and/or reduced costs – do ancillary services such as patient and physician support services provide to the healthcare system?	Physicians, patients, payers

Table 2: Key Questions/Outcomes of Interest in Biologic Evidence Generation

CONCLUSION AND NEXT STEPS

The emerging biosimilars market offers enormous potential to reduce healthcare spending and expand access to life-saving drugs. However, a number of issues relating to utilization, coverage, reimbursement, and postmarket evidence generation remain that may inhibit biosimilar uptake. Building consensus on the optimal approaches for addressing the challenges outlined in this white paper will be essential for ensuring the success of this nascent market. In particular, determining which payment reforms are most promising for the effective use of biosimilars and what evidence capabilities would be most helpful for implementing those reforms will be important. Building physician and patient confidence in the use of biosimilars will require additional investment in both postmarket research as well as stakeholder education.

While building consensus in these areas is no small task, a concerted effort by stakeholders to tackle these issues is an important next step to fulfill the promise of biosimilars. The key next steps for addressing the gaps and challenges identified in this white paper are:

- Further FDA guidance or general principles regarding issues like interchangeability or patient switching that will impact price negotiation and use;
- Ongoing stakeholder education efforts to increase confidence in the use of biosimilars;
- Continuing to build the infrastructure for the capture of high-priority postmarket data and methods for using these data to develop more extensive evidence on biosimilar comparative effectiveness and impacts on costs of care;
- Development of evidence on PBM and payment reform strategies that will impact drug choice and switching.

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GLOSSARY OF TERMS

Biologic	Medical products derived from a variety of natural sources (human, animal or microorganism) and used for the prevention or treatment of disease. Examples of biological products include: vaccines; blood and blood products for transfusion; human cells and tissues used for transplantation; gene therapies; and cellular therapies.
Biosimilar	A biological product that is approved based on a demonstration that it is highly similar to an FDA-approved biological product, such that there is no clinically meaningful difference in terms of safety, purity, and potency between the two products.
Comparability	Refers to the practice of assessing biotechnological/biological products before and after changes are made in the manufacturing process for the drug substance or drug product to ensure the quality, safety and efficacy of drug product produced by a changed manufacturing process.
Immunogenicity	The propensity of a biologic drug product to generate a host immune response to itself and to related proteins, or to induce immunologically related adverse clinical events.
Indication extrapolation	If the proposed product meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the applicant may seek licensure of the proposed product for one or more additional conditions of use for which the reference product is licensed.
Interchangeable	Refers to the medical/pharmaceutical practice of switching one medicine for another that is equivalent, in a given clinical setting. A product is considered to be interchangeable if it can be administered or dispensed instead of another clinically equivalence product without significant risk of an adverse health outcome.
Reference product	A biological product licensed under section 351(a) of the Public Health Service (PHS) Act against which a biological product is evaluated in a 351(k) application for biosimilarity or interchangeability.

Substitution The practice of dispensing one medicine instead of another equivalent and interchangeable medicine in any given patient at the pharmacy level without consulting the prescriber.

The FDA believes that products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product. There is no ‘substitutability determination’ at the EU level

Small molecule drug Medical products typically derived from a process of chemical synthesis; comparatively much smaller in chemical size and less structurally complex than biologic (also known as large molecule) drugs.

Switching Decision by the treating physician to exchange one medicine for another medicine with the same therapeutic intent (e.g., from originator to generic/biosimilar or vice versa, or among different drugs within the same therapeutic class) in a patient during the course of treatment. In hospitals, the decision to switch a medicine is made by a multidisciplinary team including the clinical community (therapeutic/formulary committee). *Non-medical Switching* is also a term that has been increasingly used in the biosimilar field to describe a situation where a patient’s medicine is switched to a chemically distinct alternative for reasons other than the patient’s health and safety. Examples of non-medical switching include switching between structurally distinct blood pressure medications, statins, NSAIDs, or anti TNFs.

Therapeutic equivalence The determination that a particular drug can be substituted for another (or vice versa) with the expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product. Drug products are considered to be therapeutically equivalent if they are pharmaceutical equivalents (contain the same active ingredients; dosage form and route of administration; and strength).

Therapeutic interchange The dispensing of a drug that is therapeutically equivalent to but chemically different from the drug originally prescribed by a physician.



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