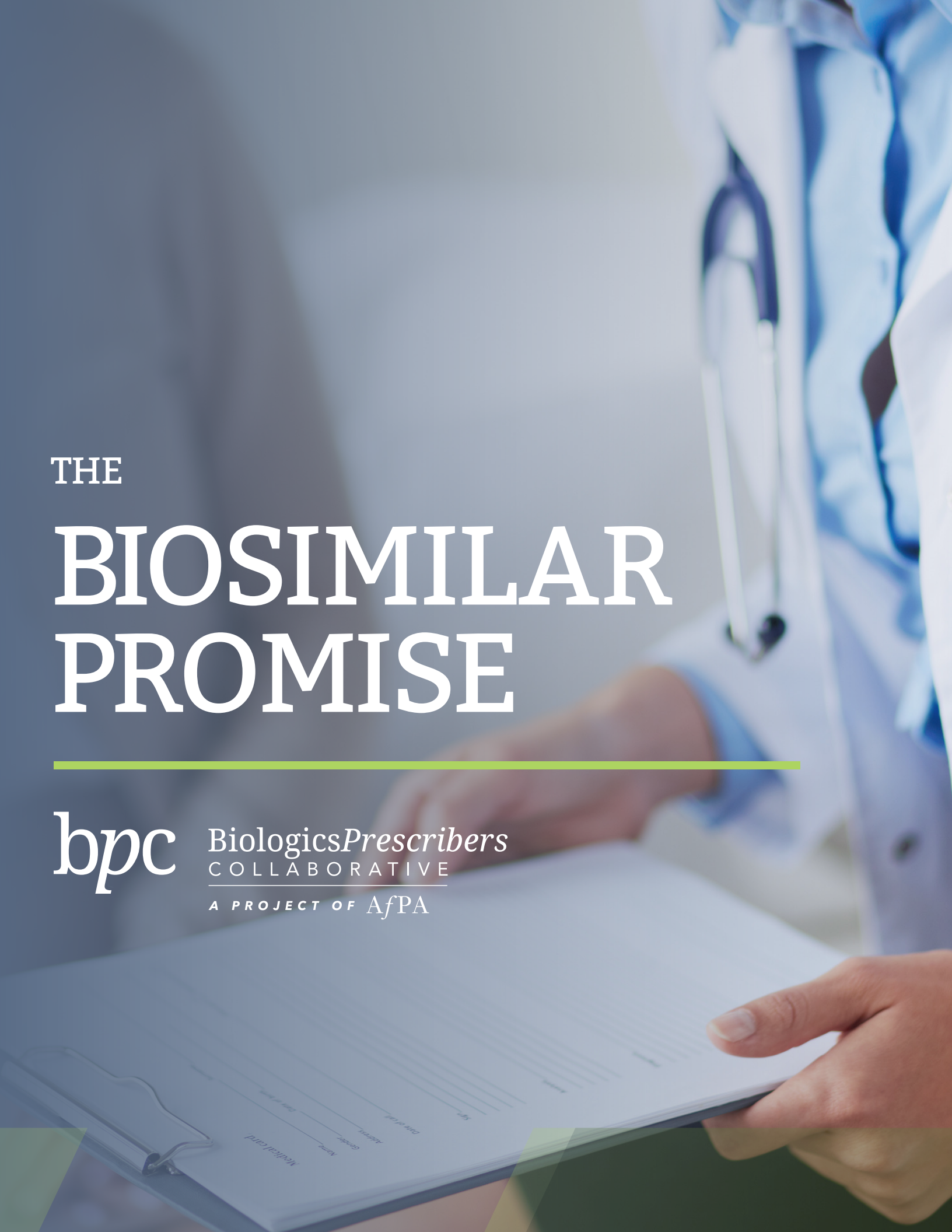


THE

BIOSIMILAR PROMISE

bpc BiologicsPrescribers COLLABORATIVE

A PROJECT OF AfPA

Thank you:

The Biologics Prescribers Collaborative (BPC) thanks our member groups and those who provided insights and assistance in developing this educational handbook.

In particular, the BPC appreciates the continued support of the following groups and individuals in developing and reviewing this handbook.

Stay tuned for additional resources expanding upon topics discussed in this handbook.

PHYSICIAN CO-CONVENERS

Dennis R. Cryer, MD
David Charles, MD
Gregory Schimizzi, MD

MEMBER GROUPS

Alliance for Patient Access
American Association of Clinical Endocrinologists
American College of Allergy, Asthma & Immunology
American College of Rheumatology
American Gastroenterological Association
Coalition of State Rheumatology Organizations
Endocrine Society

For more in-depth clinical information by specialty, please consult your professional society and look to the Biologics Prescribers Collaborative for updated education about biosimilars. Together, we will realize the promise biosimilars have to treat our patients for years to come. Visit www.biologicsprescribers.org for additional resources.

Please note, this publication is intended to be an educational and informative resource only. It is not intended or offered as legal, medical, regulatory or investment advice. For questions or concerns about a specific biosimilar product, please contact the manufacturer or the FDA at 1-800-FDA-1088.

April 2017 – Biologics Prescribers Collaborative

Updated November 2018

Preface

The biosimilars age has arrived with the promise of an expanding array of therapeutic options for patients and physicians battling serious diseases and conditions.

Biosimilars are a new category of biologics that are similar – as their name indicates – to original biologic drugs. They are not generic copies. Recognizing the difference, Congress established a rigorous but abbreviated regulatory pathway tailored to this new category of biologics.

As prescribers of biologics, we believe that realizing the biosimilar promise requires awareness of the differences between biosimilars and generics, and among biologics themselves, as well as an understanding of the distinctive therapeutic choices they represent.

To that end, this introductory handbook:

- Places biosimilars within the context of the biologics revolution
- Outlines the regulatory process
- Describes the development and manufacturing challenges
- Reviews prescribing considerations
- Discusses the importance of safe use and monitoring

We, the BPC, a project of the Alliance for Patient Access (AfPA), see it as a gateway to the more in-depth clinical information available from professional societies whose members regularly prescribe biologic drugs and now biosimilars.

Members of the BPC:

Table of Contents

INTRODUCTION:

THE BIOSIMILAR OPPORTUNITY

First available 25 years ago and now approaching 200 in number, biologics are revolutionizing the treatment of many serious illnesses for more than 325 million patients throughout the world.[1,2]

They come from living cell cultures and many are induced by DNA insertion to create therapeutically valuable proteins, peptides, monoclonal antibodies and viral vectors.[3]

BIOLOGICS

Early biologics replicated proteins that stimulate hormones for human growth, red blood cells for anemia and white blood cells to help prevent infection, especially in patients undergoing chemotherapy.[4,5,6]

Soon after, more advanced monoclonal antibodies and chimeric proteins were developed to fight cancer and other diseases like rheumatoid arthritis (RA), multiple sclerosis (MS), psoriasis and inflammatory bowel disease (IBD). In a critical breakthrough, some biologics target the immune system by binding to and inactivating pro-inflammatory-mediating proteins called cytokines.[7]

Further, a recently launched biologic, the first to use a viral vector, targets cancerous melanoma cells in two ways. The biologic only affects cancer cells, causing cancer cell death, and also stimulates the immune system to attack the cancer cells.[8]

Exciting disease discoveries and new ways of designing and manufacturing biologics are driving work on 600 more advanced biologics for 200 serious illnesses.[1]

BIOSIMILARS

Meanwhile, a large number of biologics representing $81 billion in global sales, will go off patent by 2020, opening the door to additional therapeutic options called biosimilars.[9] The goal is that access will be improved through the lower cost of biosimilars, although the decline in costs may not be as dramatic as what has occurred in the generics market. For example, average sales prices for infliximab biosimilars are currently approximately 15% below the reference product.[10] This is because biosimilars are not generic drugs; they are a new category of biologics.[11]

Chemically-based generics and their originator brand drugs have relatively simple structures, making replication simple through a chemical process. However, as living cells make biologics, it is currently impossible for a biosimilar to be an identical copy of the innovator compound.

Biologically-constructed molecules are far larger than small molecules of chemically-based drugs – by 200 to 1,000 times.[12] Their larger size is one reason why patients receive most biologics by injection or intravenous infusion, instead of oral forms like chemically-based drugs and their generics.[13] Oral administration would result in the gastrointestinal tract destroying or altering a biologic's structure and configuration.[14]

APPROVAL

Because of these and other important differences, the U.S. Food and Drug Administration (FDA) uses a dedicated regulatory pathway, which Congress created specifically for biosimilars under the Biologics Price Competition and Innovation Act (BPCIA), as incorporated in the Patient Protection and Affordable Care Act of 2010.[15]

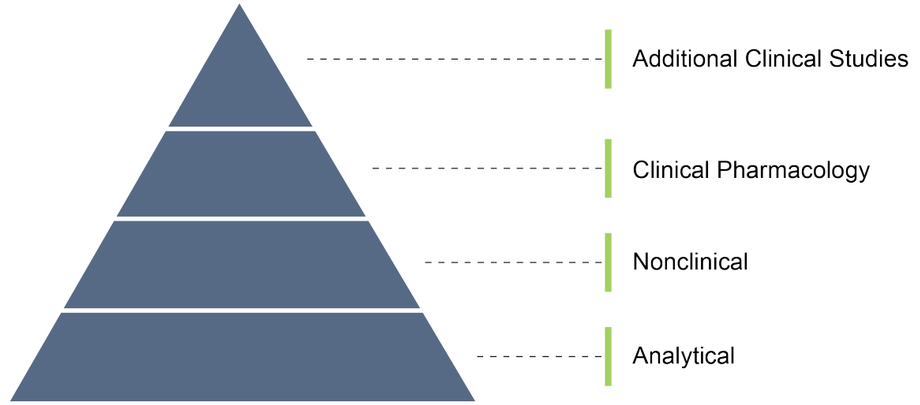
Biosimilars, while different from their innovator biologic counterpart, must nevertheless be "highly similar" in terms of structural characteristics, safety and efficacy.

THERE CAN BE MINOR DIFFERENCES WITH THE INNOVATOR, BUT THESE DIFFERENCES CANNOT HAVE A CLINICALLY MEANINGFUL EFFECT IN PATIENTS.[16]

Addressing each biosimilar application on a case-by-case basis, FDA and the manufacturer agree at the outset on the studies required for approval. Depending on the results of these studies – analytical, non-clinical and clinical – the agency may require additional studies.[17]

FDA then considers the totality of the evidence in deciding whether to approve the biosimilar. Using this approach, encompassing the overall quality and quantity of evidence, a manufacturer can secure approval with data and information sufficiently demonstrating that any formulation or minor structural differences are not clinically meaningful.[18]

FDA approved the first U.S. biosimilar in March 2015 – Zarxio™ (filgrastim-sndz).[19] It is a biosimilar to Neupogen® (filgrastim), approved in 1991 to help reduce the chance of infection due to a low white blood cell count. FDA is reviewing a growing number of biosimilar applications, so additional approvals are possible.[20]



In the biosimilar approval process, FDA considers the totality of evidence based on results from analytical nonclinical and clinical studies

As of publication in April 2017, FDA has approved five biosimilars. FDA has indicated the agency anticipates at least one biosimilar application per reference product will go before an Advisory Committee panel.[21]

Unlike the U.S., the European Commission approves synthetic insulin and hormones as follow-on products as biosimilars, as shown in 2014 for Lantus® (insulin glargine).[22] In the U.S., FDA regulates hormones such as insulin, glucagon, and human growth hormone as drugs under the Food, Drug and Cosmetics Act, not as biological products under the Public Health Service Act, where the biosimilar approval pathway resides.[23,24]

REIMBURSEMENT

As of January 1, 2018, the Centers for Medicare and Medicaid Services (CMS) placed newly approved biosimilar biological products with a common reference product into different Healthcare Common Procedure Coding System (HCPCS) codes, known as J-codes.[25,26]

The reimbursement policy has been controversial, but stakeholders, including patient groups, medical societies and manufacturers, have asserted current law states that calculation for reimbursing biosimilars should be made separately, strongly implying that each biosimilar should have its own unique payment rate and HCPCS code.[27] In the U.S. alone, the cost savings from using biosimilars in comparison to their original biologics are projected to be between $40 and $250 billion over the next 10 years.

The best way to deliver the promise of biosimilars to patients is a competitive market based on differentiated benefits, including price. For that market to thrive, each biosimilar needs a unique billing code.[28]

THE MAKING OF BIOSIMILARS:

A HIGHLY COMPLEX PROCESS

Developing and manufacturing a high quality biosimilar mandates intense and comprehensive understanding of biologics in general, significant manufacturing expertise and an intimate understanding of the innovator biologic and its functionality.

Significant development time is also required, ranging from seven to eight years, together with substantial investment, amounting to as much as $100 to $250 million.[29]

In contrast, generic chemical drugs take approximately two to three years and $1 to $4 million to bring to market.[29]

PROCESS

Why does it take so much time and money to bring a biosimilar to market? A biosimilar manufacturer begins only with a market-available version of the originator product plus any publicly available information, and then must reverse engineer the biosimilar and its manufacturing process.[30,31]

The originator biologic is the product of a highly complex process where the number of steps exceed those of a chemical drug by thousands of steps.[32] In addition, 250 tests – five times those used for a chemical drug – are required to validate potency, quality and purity.[33]

The process begins with identification of a human gene and the therapeutic potential of its translated protein, followed by the insertion of the requisite DNA into a cell line for protein production.[33] Known as recombinant DNA technology, this quite literally involves the transfer of a gene from one organism into another.[35]

The cell line, reproducing at high volume, utilizes the new, inserted DNA to manufacture and then secrete the desired protein for collection.[36]

While in-solution, before purification, the protein's structure folds over itself, changing its three-dimensional shape.[37]

Further, while in-solution, molecular modifications occur, including the attachment of sugars, as well as other changes.[38,39]

CHANGE

Adding to the complexity, because these modifications can vary, the protein molecules in a single biologic may differ slightly from each other. When they do, the difference is usually in the potentially varying composition of the sugars attached while in-solution.[40] The production process must therefore achieve a therapeutically optimal ration of these sugars, called glycans.[41]

For example, different numbers of attached mannose – a ringed sugar molecule – cause variability in a product's clinical efficacy.[42]

Uncontrolled, these levels can lead to wide variation in the clearing of protein-based biologics from the body.[42] The production process must also account for the high sensitivity of biologics to temperature and pH. These factors can cause differences, which may affect a biologic drug's safety, efficacy and shelf life.[43]

They also constitute yet another reason for injecting, instead of orally administering, biologics.[44]

ALTERATION OF BIOLOGIC PRODUCTS CAN ALSO OCCUR DUE TO INTENTIONAL PROCESS CHANGES OVER TIME.[45]

This is called "evolution." Not all products evolve with every process change. Yet, for major process changes involving any drug or biologic, FDA requires before-and-after product comparability studies.[46]

In 2010, a manufacturer withdrew an intravenous immune globulin (IVIG) product upon detecting a higher-than-normal rate of thrombotic and thromboembolic events.[47] A manufacturing process alteration had unintentionally increased the coagulation factor XIa, which caused the events.[48] The manufacturer and FDA developed a scientific method to measure factor XIa levels, permitting the product's market return.[48]

In addition, biologic products, including innovator compounds, can change through a process called genetic "drift," resulting in an unintended, unexplained or unexpected trend away from intended structure or product targets.[49]

Experienced biologics manufacturers minimize drift with strict process controls and a sophisticated ability to modulate processes to meet specific product specifications consistently.[50]

CONTROL

Variation occurs in all drug production processes and manufacturers work to understand, monitor and control processes within ranges that maintain product quality, efficacy and safety.[51] Biologics manufacturers need to monitor hundreds of process parameters against proven acceptable ranges.[52]

Biologics manufacturers must maintain product consistency largely by minimizing batch-to-batch variation.[53] They know from clinical and other studies the impact specific process variations, such as changing molecular glycan content, may have on a product.[54]

PRESCRIBING BIOSIMILARS:

CLINICAL CONSIDERATIONS

Biologic drugs and their biosimilars are a lot like Swiss army knives, capable of several therapeutic mechanisms of action against different diseases. Hence, multiple indications are often associated with a biologic drug.[55]

INDICATIONS

When FDA approves a biosimilar, it can extrapolate clinical data submitted for one disease indication to approve other indications associated with the originator reference product.

For example, FDA used extrapolation through in-vitro data and totality of evidence of approvals for infliximab biosimilars in IBD.[56]

It is very likely that the agency will approve extrapolated indications for diseases that share the same pathophysiology as the disease state in the actual clinical study.[57] FDA has acknowledged the distinct possibility of approving biosimilars for fewer indications than their originator biologics.[58]

ZARXIO

When FDA approved the first U.S. biosimilar, Zarxio™ (filgrastim-sndz), the agency did so for all indications:

- *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*
- *Patients with severe chronic neutropenia*[59]

The mechanism of action – binding to the granulocyte colony-stimulating factor receptor

(G-CSF-R) – is the same for each, as well as between the originator reference product and the biosimilar. Extrapolation utilized clinical data from 174 healthy volunteers, 388 breast cancer patients receiving myelosuppressive chemotherapy and 121 healthy stem cell donors.[60]

The European Medicines Agency (EMA) also approved Zarxio for the same indications as those of the originator biologic.[61]

INFLECTRA

However, in the case of Inflectra™ (infliximab), Health Canada approved a biosimilar (or, in Canada, subsequent entry biologic) for Remicade® (infliximab) for all indications except those related to IBD: Crohn's and ulcerative colitis.[62]

Health Canada decided that the excluded IBD indications depended on an additional, secondary mechanism of action, FcγRIIIa receptor binding as reflected in antibody-dependent cell-mediated cytotoxicity (ADCC). This mechanism of action is not active for the approved indications, such as rheumatoid arthritis (RA).[62]

Health Canada determined that differences in ADCC between the two products precluded extrapolation from RA to IBD indications relying on another mechanism of action, soluble and membrane-bound tumor necrosis factor –alpha (TNFa).[62]

On the other hand, EMA recommended approval of the IBD indications based on its own weighing of the evidence, notably that TNFa is involved in the pathophysiology across all indications, notwithstanding the secondary role of ADCC for IBD.[63]

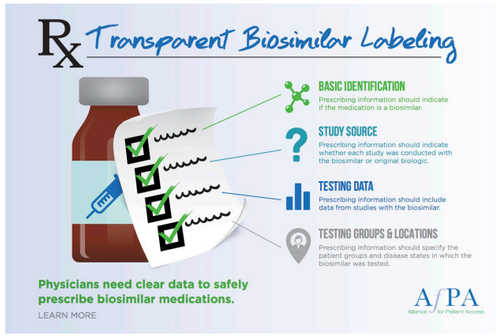
In addition, EMA did not consider the ADCC difference between the two products "clinically meaningful, as it did not affect the activities of [the biosimilar] in experimental models regarded as more relevant to the pathophysiological conditions in patients."[64] In 2016, FDA held an Advisory Committee recommending approval for six indications for which Remicade was approved, including IBD (Crohn's and ulcerative colitis) and RA. However, Inflectra was not approved for one indication, pediatric ulcerative colitis, because Remicade has exclusivity for that use until September 2018.[65]

LABELING

Ideally, the results of studies comparing a biosimilar with its originator biologic would be included in the full prescribing information that is part of a biosimilar's label.[66,67,68]

However, when FDA approved the biosimilar Zarxio (filgrastim-sndz), which was before FDA issued its draft labeling guidance, it approved a label essentially identical to the originator biologic, Neupogen (filgrastim), excluding critical information specific to Zarxio (filgrastim-sndz). In particular, the label fails to state clearly that Zarxio is a biosimilar and, importantly, that it has not been evaluated for interchangeability.[69] Indeed, it is not clear from the label that the data presented is Neupogen data, not data on Zarxio. Data from Zarxio clinical studies is available, though not easily accessible, as part of briefing materials prepared for FDA Oncologic Drugs Advisory Committee.[60]

FDA's draft guidance, issued in March 2016, slightly changed course on biosimilar labeling.[70]



The agency said, when clinical studies or data derived from studies with the originator biologic are described in biosimilar product labeling, the (originator) biologic's proper name should be used.

However, FDA said the biosimilar label should not include information and data from clinical studies of the biosimilar unless "necessary to inform safe and effective use by a health care practitioner." Instead, the agency said biosimilar labeling should reflect FDA-approved product labeling for the originator biologic.

In doing so, the agency was unmoved by arguments that biosimilar labeling should include a concise description of pertinent data supporting licensure of the biosimilar.[71] Still, it agreed that biosimilar labeling should include a statement that the product is a biosimilar, although a biosimilar label could refrain from mentioning that the biosimilar product is not interchangeable with the originator biologic.[72]

As of July 2018, FDA has issued its final guidance for labeling. As of August 2018, FDA has not yet issued a final interchangeability guidance.

INTERCHANGEABILITY

The law establishing the biosimilar pathway also provided for approval of interchangeable biosimilars. FDA issued draft guidance on biosimilar interchangeability in January 2017.[73]

Similar to the labeling guidance, FDA has not yet issued final interchangeability guidance as of May 2018.

BPCIA requirements and the draft guidance affirms that applications for an interchangeable product must include information sufficient to show that the proposed interchangeable product "can be expected to produce the same clinical result as the reference product in any given patient."[73]

FDA's draft guidance outlines additional specifics to demonstrate interchangeability, including applicant's data, studies on changing and scientific justification for indication extrapolation.[73]

The guidance does not provide any indication on how the agency plans to handle labeling of interchangeable products. The BPC believes that ideally, the label should include a statement of whether the biosimilar is interchangeable with the reference product and/or other biosimilars on the market.

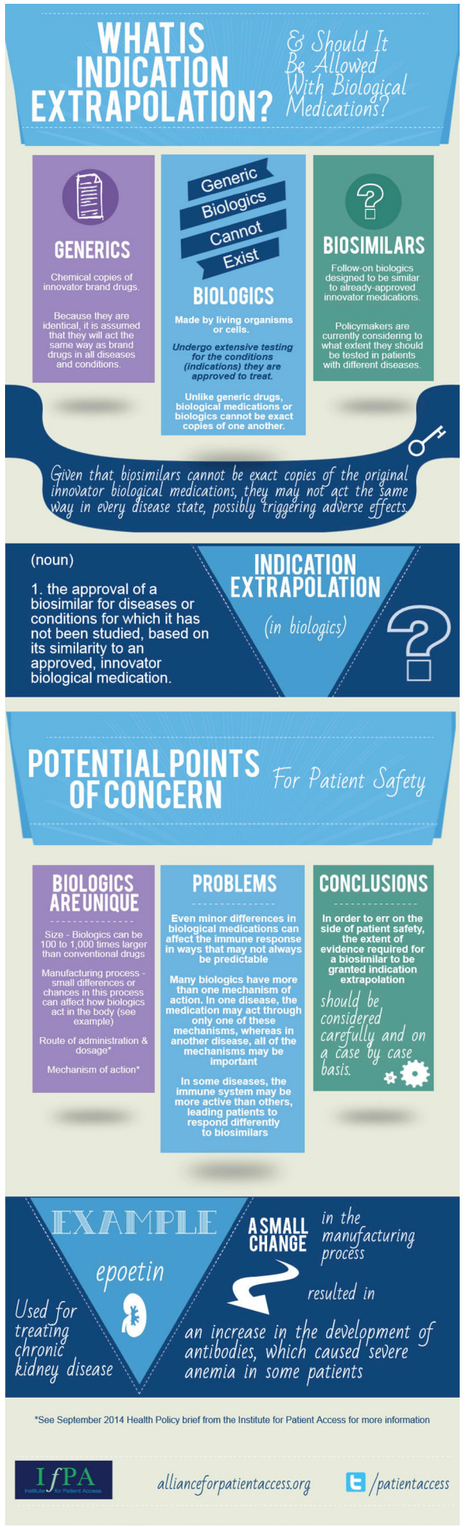
A biosimilar's approval as interchangeable would remove any federal objection to pharmacists automatically substituting it for an originator biologic without prescriber involvement. However, U.S. states regulate the practice of pharmacy and thus substitution procedures.[74]

CHANGING AND SUBSTITUTION

Prescribers will find that there is considerable overlap in use of the terms "changing" (also referred to as "switching" or "transitioning") and "substitution." However, substitution is commonly associated with pharmacy level action, as in "automatic substitution," while changing frequently refers to action at the prescriber level.[75,76] In addition, switching typically refers to transitioning back and forth between medications.[77]

Whether changing by a prescriber or substitution by a pharmacist, either action requires great care.[78] For example, about a third of all patients starting on an intravenous immunoglobulin (IVIG) preparation typically experience an adverse event.[79] Changing a patient who is stable on one IVIG preparation to a new preparation incurs another level of risk.[80,81]

Increasingly, states are enacting laws permitting pharmacists to substitute interchangeable biosimilars automatically. As of publication, 45 states have passed these laws into legislation.[82] However, under most of these laws, the pharmacist must communicate with the prescriber regarding each substitution, identifying the product the patient received so that the patient record



is accurate.[74]

Examples include a Delaware law that requires pharmacists to inform the prescribing physician within 10 days when an FDA-approved interchangeable product is substituted for a prescribed originator biologic.

Massachusetts requires pharmacists to record such substitutions in an interoperable electronic health record (EHR) and inform the prescriber.[84]

MOST COUNTRIES IN EUROPE PROHIBIT PHARMACY LEVEL SUBSTITUTION OF BIOLOGICS.[85]

Only recently have governments in Europe explored measures to promote the use of biosimilars.[86,87] The Netherlands and Finland have supported physician-directed changing.[88] Despite authorizing automatic substitution, France has not yet implemented the 2014 law permitting substitution without physician approval.[89]

EMA does not evaluate the products for safety in repeated switching back and forth, as FDA will do for interchangeable complex biosimilars.[90] EMA recommends only biosimilars to the European Commission for approval, not interchangeable biosimilars. In Europe, the term "interchangeable" typically refers to physician-directed changing of drugs, not U.S.-style pharmacist-directed substitution.

Biosimilar manufacturers in Europe and the U.S. have begun switching trials to determine the efficacy and safety of moving an existing patient already stable on an originator reference biologic to its intended biosimilar.[91]

Until an interchangeable product is approved and available as a treatment option, the impact of substitution with interchangeable products is yet to be seen.

SAFETY AND MONITORING:

GUARDING PATIENTS

Though not all differences between biologics and biosimilars matter, for some patients, such differences can have profound, untoward effects. For these patients, their immune systems may react to biologic products differently, potentially resulting in diminished efficacy, side effects or adverse events.[31]

IMMUNOGENICITY

When it occurs, immunogenicity typically involves the body's production of anti-drug antibodies, which can lower a biologic's bioavailability.[92] These antibodies can also bind to a biologic's active region, blocking its binding in such a manner that the antibodies' downstream effects are neutralized. The responses could be asymptomatic or could be severe producing a serious adverse event.[93] Formulation changes, administration routes or packaging can also cause immunogenicity issues.[94]

Providing a compelling example of immunogenicity are biologics that replace factor VIII (FVIII) in hemophilia A patients. One study found neutralizing antibodies, the therapy's principal complication, in 19% of healthy individuals, 34% of patients without FVIII inhibitors, 39% of patients after successful immune tolerance induction therapy and 100% of patients with FVIII inhibitors.[95]

To ensure a biosimilar is no more immunogenic than its originator reference biologic, FDA requires biosimilar manufacturers to submit one or more studies of comparability, i.e., equivalency. FDA has advised manufacturers to conduct these studies in a "sensitive" immunocompetent population, in which it is possible to detect any clinically meaningful differences in efficacy, safety, or immunogenicity.[96] Refer to FDA draft interchangeability guidance for additional information.

FDA does not require such studies to compare two biosimilars, nor does the law provide for interchangeable substitution at the pharmacy level between two biosimilars.[18,73,96] Further, because there is no legal or regulatory bar to prescribers transitioning patients from one biosimilar for

another, the lack of FDA-reviewed comparability studies should be an important consideration.[97]

Meanwhile, individual patients – prior to administration of a biologic – may have pre-existing antibodies that could affect a biologic's efficacy, safety or immunogenicity.[96]

The presence of antibodies could be associated with prior biologic treatments, including the dosage pattern or frequency for such treatments. Some may be present in the absence of any prior use of a biologic. Tests are available to quantify neutralizing anti-drug antibodies.[99]

PHARMACOVIGILANCE

Adverse drug events (ADEs) may be rare and immune reactions, if any, are usually within safe limits. However, the complexity of biologic drugs and their sensitivity to manufacturing conditions require robust, precise pharmacovigilance.[100] This is true for any new biologic, but particularly for biosimilars, because of the limited number and small population size of clinical trials used in their approvals.[67]

Experience in Europe with both originator and biosimilar erythropoietin drugs illustrates the need for effective pharmacovigilance. Between 1998 and 2003, an increase in pure red cell aplasia (PRCA) occurred among patients given an erythropoietin as a subcutaneous injection following a formulation change. In 2007, the increase in PRCA, attributable to subcutaneous delivery of erythropoietin biosimilar, was noticed after extensive use. The adverse events were found to be linked to packaging and delivery. The manufacturer changed the formulation, packing and delivery guidelines, subsequently recommending intravenous administration only.[101]

Monitoring patient experience with a biologic must extend over the long term given the considerable time lag that can occur between administration and the appearance of a serious reaction. Once again, the European PRCA cases provide an example. The median time from receiving the medication to an immune response was 11 months with a range of three to 90 months.[102]

MONITORING

Safety monitoring in the U.S. primarily relies on two types of signal detection: spontaneous reporting systems (SRS) like the FDA Adverse Event Reporting System (FAERS), and active surveillance (AS) systems such as the agency's new Sentinel System. In addition, manufacturers may conduct additional monitoring, often as a condition of drug approval. These can include patient registries, bioassays, postmarketing clinical trials and risk minimization activities.[103]

Consumers, including patients and caregivers, and health care professionals voluntarily report medication errors or ADEs either to the manufacturer or FDA via the MedWatch website. Manufacturers must relay any ADE reports they receive directly to FDA, also via MedWatch.[104]

FDA uses the reports to signal the need for evaluation using much larger databases. However, there is no certainty that the drug in question caused an adverse event included in FAERS. In fact, FDA does not require a causal connection with the drug to file a report. Reports also do not always contain enough information to evaluate an event.

According to the Institute for Safe Medication Practices (ISMP), only 46% of serious reports from manufacturers are reasonably complete, meaning they contained the patient's age, gender and event date, all factors that could be important during analysis. Upon revision, the share of reasonably complete reports from manufacturers only reached 62%. On the other hand, of the handful of reports directly coming from consumers and health care professionals, 85% were reasonably complete.[105]

FDA's Sentinel System queries diverse automated health care data holders – like electronic health record systems, administrative and insurance claims databases, and registries – to evaluate possible safety issues.[106] Instead of waiting for reports, FDA can "go out and get that information" on 178 million Americans, according to FDA's Center for Drug Evaluation and Research Director, Janet Woodcock, M.D.[107]

NAMING

Critical to safe use are distinguishable names for all biologics, including biosimilars. FDA has proposed giving each biologic, whether an originator or a biosimilar, a distinguishable name. In January 2017, FDA issued final guidance calling for distinguishable names for all biologic medicines.[108]

FDA's final guidance states that all biological products will bear a nonproprietary name that is a combination of a core name and a four-letter suffix, devoid of meaning.

This policy is important for patients and physicians because distinguishable naming is essential for pharmacovigilance, patient safety and transparency.

The agency is continuing to consider the nomenclature for interchangeable biosimilars. Recognizing the possibility of such changes are unlikely, the concerns remain that the random suffixes called for in this guidance will not allow FDA to easily achieve its goal of pharmacovigilance and the prevention of inadvertent substitution. As physicians who routinely prescribe biologic medicine, we believe a "meaningful" suffix is needed. A suffix that reflects the manufacturer of the medicine would be immediately recognizable and would facilitate prompt, accurate adverse event reporting by patients and physicians to the correct manufacturer and that manufacturer's mandated reporting to FDA. The BPC appreciated FDA's careful consideration of this important issue.

As the medical community gains real-world experience using these new medicines, the BPC looks forward to working with the agency to amend policies where we can achieve greater patient benefit and safety, including potentially evolving to a meaningful suffix.

Meaningful suffixes are important in medicine.
That's why 80% of doctors prefer them for biosimilar naming as well.

The FDA is considering naming biosimilar medicines with a random code versus a more recognizable name. In a recent SERMO* poll, representing over 500 physicians across multiple specialties, 80% of physicians prefer a "meaningful suffix." Physician groups across the country call for biosimilar names that are easily distinguished and recognized. For more information go to biologicsprescribers.org.

*SERMO is the largest global social network exclusively for doctors.

In November 2016, the BPC released findings of a SERMO poll representing physicians across multiple specialties.[109] Overwhelmingly, 80% of physicians preferred a meaningful four-letter suffix that noted the biosimilar manufacturer's name, versus a random four-letter suffix.

Only 8% of physicians preferred a suffix devoid of meaning, while 12% had no preference.

Sharing the same non-proprietary name of the chemically-based brand and generic drug frequently leads to misreporting in FAERS.[110]

When generics enter the market, reports still largely arrive on the originator brand product. In a study by the ISMP, when generic competition capturing significant market share became available for six of eight chemical originator drugs, the number of reports attributed to the originator brand products did not decrease significantly. This was despite a steep decrease in the number of dispensed prescriptions of the originator brand product.[111]

SETTINGS OF USE

Making the use of distinguishable names all the more imperative for biologics is their use in medical settings like hospitals and outpatient clinics, as well as through retail and mail pharmacies. Both the medical and pharmacy settings incorporate different tracking, unique identifier and reporting systems.[103]

For example, shared non-proprietary names could lead hospital and clinic pharmacies, where most biologics use occurs, to treat a biosimilar like a generic drug. This could lead to inappropriate and unintended substitution of one biosimilar for another, while also misidentifying them in order entry and electronic medical record systems as the originator biologic.[103]

Retail and mail pharmacies can fall back on unique reimbursement national drug codes (NDC), in the event of shared non-proprietary names. However, NDC codes will be of little use in dispensing the biosimilar intended by the prescriber because prescribers rarely use or have ready access to NDC codes.[103]

Given the nature of our setting-dependent drug identification systems, biologic drugs actually require more than distinguishable non-proprietary names. Multiple or redundant unique product identifiers would promote accurate attribution in the event of errors or ambiguity.[103,111]

For example, like the NDC code in the retail and mail pharmacy, the medical setting benefits from unique HCPCS codes, especially in view of the FDA's Sentinel System's reliance on reimbursement codes.[112] CMS has required the addition of manufacturer identifiers to biosimilar J-codes for this purpose.[113] Matching these codes with ICD-10 codes for medical treatment related to an adverse event or error would provide investigators with a rich source of valuable information.[114,115]

Further, due to varying international naming conventions, suffixes that do not have meaning in English may have meaning in other languages, which could create confusion. For instance, a patient from Europe traveling to the U.S. could be taking a medicine without a clear designation, making it difficult for a U.S. health care provider to identify and administer the correct medicine. FDA and EMA are working to address this lack of agreement in naming.

CONCLUSION:

REALIZING THE BIOSIMILAR PROMISE

Biosimilars are relatively new in the U.S., however they have been revolutionizing treatment for patients with serious illnesses worldwide for more than a decade, with the EMA approving the first biosimilar in 2006.[116] To date, more than 44 biosimilars are available in Europe in at least eight therapeutic areas[117] and globally, there are more than 350 biosimilars in development.[28]

As health care costs continue to rise, biosimilars increase patient access by providing new therapeutic options with potential cost savings to the health care system.

Biosimilars have great potential, however, the foundation of their success depends on a sound regulatory and clinical practice framework – one recognizing that biosimilars are not generics but rather a new category of biologics.

This will require distinguishable and meaningful names, complete labels, specific prescribing information, prescriber involvement in any changing and substitution and strong pharmacovigilance and monitoring programs.

Having read this introductory handbook, prescribers should consult their professional societies for more in-depth clinical information by specialty and look to the BPC for updated education about biosimilars. Together, we will realize the promise biosimilars have to treat our patients for years to come.

GET INVOLVED

For more information on biosimilars, or if you are interested in joining the Biologics Prescribers Collaborative, please visit:
www.biologicsprescribers.org
or email leadership@biologicsprescribers.org
Follow us on Twitter ***@BioPrescribers***.

APPENDIX:

ADDITIONAL RESOURCES

KEY TERMS

FDA definitions for key biosimilar terms are as follows:

Biosimilar Product means a biological product submitted in a 351(k) application that has been shown to be highly similar to the reference product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity and potency of the product (see section 351(i)(2) of the PHS Act).[108]

Core Name means the component shared among an originator biological product and any related biological product, biosimilar product, or interchangeable product as part of the proper names of those products. Two examples of a core name are filgrastim and epoetin alfa.[108]

Interchangeable Product means a biological product that has been shown to meet the standards described in section 351(k)(4) of the PHS Act and may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product (see section 351(i)(3) of the PHS Act).[108]

Nonproprietary Name means a name unprotected by trademark rights that is in the public domain. It may be used by the public at large, both lay and professional.[108]

Originator Biological Product means a biological product submitted in a BLA under section 351(a) of the PHS Act (i.e., a stand-alone BLA) that is not a related biological product.[108]

Proper Name means the nonproprietary name designated by FDA in the license for a biological product licensed under the PHS Act.[108]

Proprietary Name means the trademark or brand name.[108]

Reference Product means the single biological product licensed under section 351(a) of the PHS Act against which a biological product is evaluated in a 351(k) application (section 351(i)(4) of the PHS Act).[108]

Related Biological Product means a biological product submitted in a BLA under section 351(a) of the PHS Act (i.e., a stand-alone BLA) for which there is a previously licensed biological product submitted in a different section 351(a) BLA that contains a drug substance for which certain nomenclature conventions (e.g., United States Adopted Names (USAN) Guiding Principles) would be expected to provide for use of the same drug substance name.[108]

INDEX OF APPROVED BIOSIMILARS

The Biologics Prescribers Collaborative appreciates FDA's careful deliberation before approving biosimilar applicants. As of November 2018, there are 15 approved biosimilars, with additional approvals expected. For further information, please reference the Purple Book on FDA's site.

Biosimilar Product *(Proprietary Name)*	FDA Approval Date	U.S. Launch Date	FDA Approved Indications
filgrastim-sndz **Biosimilar: Zarxio (Sandoz)** **Reference biologic: Neupogen (Amgen)**	**March 2015**	**September 2015**	• 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 • Patients with severe chronic neutropenia *Source: FDA 119*
infliximab-dyyb **Biosimilar: Inflectra (Celltrion)** **Reference biologic: Remicade (Janssen)**	**April 2016**	**November 2016**	• Adult patients and pediatric patients (ages six years and older) with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy • Adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy • Patients with moderately to severely active rheumatoid arthritis in combination with methotrexate • Patients with active ankylosing spondylitis (arthritis of the spine) • Patients with active psoriatic arthritis • Adult patients with chronic severe plaque psoriasis *Source: FDA 120*
etanercept-szzs **Biosimilar: Erelzi (Sandoz)** **Reference biologic: Enbrel (Amgen)**	**August 2016**	**TBD**	• Moderate to severe rheumatoid arthritis, either as a standalone therapy or in combination with methotrexate (MTX) • Moderate to severe polyarticular juvenile idiopathic arthritis in patients ages two and older • Active psoriatic arthritis, including use in combination with MTX in psoriatic arthritis patients who do not respond adequately to MTX alone • Active ankylosing spondylitis (an arthritis that affects the spine) • Chronic moderate to severe plaque psoriasis in adult patients (18 years or older) who are candidates for systemic therapy or phototherapy *Source: FDA 121*
adalimumab-atto **Biosimilar: Amjevita (Amgen)** **Reference biologic: Humira (AbbVie)**	**November 2016**	**TBD**	• Moderately to severely active rheumatoid arthritis • Active psoriatic arthritis • Active ankylosing spondylitis (an arthritis that affects the spine) • Moderately to severely active Crohn's disease • Moderately to severely active ulcerative colitis • Moderate to severe plaque psoriasis *Source: FDA 122*
infliximab-abda **Biosimilar: Renflexis (Samsung Bioepis / Merck)** **Reference biologic: Remicade (Janssen)**	**April 2017**	**July 2017**	• Who have had an inadequate response to conventional therapy • Adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy • Patients with moderately to severely active rheumatoid arthritis in combination with methotrexate • Patients with active ankylosing spondylitis (arthritis of the spine) • Patients with active psoriatic arthritis • Adult patients with chronic severe plaque psoriasis *Source: FDA 123*

INDEX OF APPROVED BIOSIMILARS

Biosimilar Product *(Proprietary Name)*	FDA Approval Date	U.S. Launch Date	FDA Approved Indications
adalimumab-adbm **Biosimilar: Cyltezo (Boehringer Ingelheim)** **Reference biologic: Humira (AbbVie)**	**August 2017**	**TBD**	• Adult patients with moderately to severely active rheumatoid arthritis • Moderately to severely active polyarticular juvenile idiopathic arthritis in patients 4 years of age and older • Adult patients with active psoriatic arthritis • Adult patients with active ankylosing spondylitis • Adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy • Adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine • Adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy *Source: FDA 124*
bevacizumab-awwb **Biosimilar: Mvasi (Amgen/Allergan)** **Reference biologic: Avastin (Genentech)**	**September 2017**	**TBD**	• Patients with metastatic carcinoma of the colon or rectum in combination with intravenous 5-fluorouracil–based chemotherapy • Patients with metastatic colorectal cancer who have progressed on a first-line bevacizumab product-containing regimen • First-line treatment of unresectable, locally advanced, recurrent or metastatic non–squamous non–small cell lung cancer in combination with carboplatin and paclitaxel • Treatment of glioblastoma with progressive disease in adult patients following prior therapy as a single agent • Treatment of metastatic renal cell carcinoma in combination with interferon alfa • Treatment of persistent, recurrent, or metastatic carcinoma of the cervix in combination with paclitaxel and cisplatin or paclitaxel and topotecan *Source: FDA 125*
trastuzumab-dkst **Biosimilar: Ogivri (Mylan/Biocon)** **Reference biologic: Herceptin (Roche)**	**December 2017**	**TBD**	• Adjuvant treatment of HER2-overexpressing node positive or node negative (EP/PR negative or with one high risk feature) breast cancer • As a single agent or in combination with paclitaxel for HER2-overexpressing metastatic breast cancer • In combination with cisplatin and capecitabine or 5-fluorouracil for the treatment of patients with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease *Source: FDA 128*
infliximab-qbtx **Biosimilar: Ixifi (Pfizer)** **Reference biologic: Remicade (Johnson & Johnson)**	**December 2017**	**TBD**	• Adult patients and pediatric patients (6 years of age and older) with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy • Adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy • Patients with moderately to severely active rheumatoid arthritis in combination with methotrexate • Patients with active ankylosing spondylitis (arthritis of the spine) • Patients with active psoriatic arthritis • Adult patients with chronic severe plaque psoriasis *Source: FDA 129*
epoetin alfa-epbx **Biosimilar: Retacrit (Pfizer/Hospira)** **Reference biologic: Epogen/ Procrit (Amgen)**	**May 2018**	**November 2018**	Treatment of anemia due to: • Chronic Kidney Disease (CKD) in patients on dialysis and not on dialysis • Zidovudine in patients with HIV-infection • The effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of unplanned chemotherapy • Reduction of allogeneic RBC transfusions in patients undergoing elective, noncardiac, nonvascular surgery *Source: FDA 130*

INDEX OF APPROVED BIOSIMILARS

Biosimilar Product *(Proprietary Name)*	FDA Approval Date	U.S. Launch Date	FDA Approved Indications
filgrastim-aafi **Biosimilar: Nivestym (Pfizer)** **Reference biologic: Neupogen (Amgen)**	**July 2018**	**October 2018**	• Patients with cancer receiving myelosuppressive chemotherapy or induction and/or consolidation chemotherapy for AML • Patients with cancer undergoing bone marrow transplantation • Patients undergoing autologous peripheral blood progenitor cell collection and therapy • Patients with congenital neutropenia • Patients with cyclic or idiopathic neutropenia *Source: FDA 131*
pegfilgrastim-jmdb **Biosimilar: Fulphila (Mylan/ Biocon)** **Reference biologic: Neulasta (Amgen)**	**June 2018**	**July 2018**	• Patients with cancer receiving myelosuppressive hemotherapy to decrease the incidence of infection, as manifested by febrile neutropenia • Patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically signigicant incidence of febrile neutropenia. *Source: FDA 132*
adalimumab-adaz **Biosimilar: Hyrimoz (Sandoz)** **Reference biologic: Humira (AbbVie)**	**October 2018**	**TBD**	• Adult patients with rheumatoid arthritis • Pediatric patients (4 years of age and older) with juvenile idiopathic arthritis • Adult patients with psoriatic arthritis • Adult patients with ankylosing spondylitis • Adult patients with adult Crohn’s disease • Adult patients with moderately to severely active ulcerative colitis • Adult patients with moderate to severe chronic plaque psoriasis *Source: FDA 133*

INDEX OF APPROVED BIOSIMILARS

Biosimilar Product *(Proprietary Name)*	FDA Approval Date	U.S. Launch Date	FDA Approved Indications
pegfilgrastim-cbqv **Biosimilar: Udenyca (Coherus Biosciences)** **Reference biologic: Neulasta (Amgen)**	**November 2018**	**TBD**	• Patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia to decreace the incidence of infection, as manifested by febrile neutropenia *Source: FDA 134*
rituximab-abbs **Biosimilar: Truxima (Celltrion/ Teva)** **Reference biologic: Rituxan (Roche)**	**November 2018**	**TBD**	• Adult patients with relapsed or refractory, low grade or follicular, CD20-positive B-cell NHL as a single agent • Adult patients with previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy • Adult patients with non-progressing (including stable disease), low-grade, CD20 positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine and prednisone (CVP) chemotherapy *Source: FDA 135*

REFERENCES

1. The comments of the Biotechnology Industry Organization on India's draft national IPR strategy as prepared by the sectoral innovation council in IPR, PROPOSED, Biotechnology Industry Organization, 2012, available at https://www.bio.org/sites/default/files/files/BIO%20Comments%20to%20India%27s%20National%20IP%20Strategy.pdf, accessed May 4, 2018.

2. Biologic Medicines in Development 2013 Report, Pharmaceutical Research and Manufacturers of America, 2013, available at http://www.phrma.org/sites/default/files/pdf/biologics2013.pdf, accessed May 4, 2018.

3. What Are "Biologics" Questions and Answers, United States Food and Drug Administration, 2015, available at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133077.htm, accessed May 4, 2018.

4. The big story behind synthetic human growth hormone, National Museum of American History, October 18, 2012, available at http://americanhistory.si.edu/blog/2012/10/human-growth-hormone.html, accessed May 4, 2018.

5. Winearls, C. G., Recombinant human erythropoietin: 10 years of clinical experience, Nephrology Dialysis Transplantation, 1998, 13 [Suppl 2]: 3–8, available at http://ndt.oxfordjournals.org/content/13/suppl_2/3.long, accessed May 4, 2018.

6. Foote, M. A. and Boone, T., Biopharmaceutical drug development: A case history, in Walsh G. and Murphy, B., eds., Biopharmaceuticals, an industrial perspective, 1999, pp. 109-123, available at http://link.springer.com/chapter/10.1007/978-94-017-0926-2_4, accessed May 4, 2018.

7. Campbell, J., Developing the next generation of monoclonal antibodies for the treatment of rheumatoid arthritis, British Journal of Pharmacology, April 2011, 162(7): 1470–1484, available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3057286/, accessed May 4, 2018.

8. Ledford, H., First cancer-fighting virus approved, Nature, October 29, 2015, 526(7575): 622–623, available at http://www.nature.com/news/cancer-fighting-viruses-win-approval-1.18651, accessed May 4, 2018

9. The impact of biosimilars' entry in the EU market, EMINet, 2011, available at http://ec.europa.eu/DocsRoom/documents/7651/attachments/1/translations/en/renditions/pdf, accessed May 4, 2018.

10. Centers for Medicare and Medicaid Services. 2018 ASP Drug Pricing Files, March 30, 2018, available at https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2018ASPFiles.html, accessed May 14, 2018.

11. Questions and answers on biosimilar medicines (similar biological medicinal products), European Medicines Agency (EMA), 2012, available at http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12WC500020062.pdf, accessed May 4, 2018.

12. Understanding biologic medicines from the cancer patient perspec-tive, American Cancer Society, January 2013, available at http://action.acscan.org/site/DocServer/ACSCAN-Biosimilars-Primer.pdf?do-cID=22449, accessed May 4, 2018. (See Figure 1, p. 5.)

13. Škalko-Basnet, N., Biologics: the role of delivery systems in improved therapy, Biologics, March 19, 2014, 8:107-114, available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3964020/, accessed May 4, 2018

14. Sing, R., et al., Past, present, and future technologies for oral delivery of therapeutic proteins, Journal of Pharmaceutical Sciences, July 2008, 97(7): 2497–2523, available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4627499/pdf/nihms573041.pdf, accessed May 4, 2018.

15. 42 USC §262(k)(4)(A) (2010), available at https://www.gpo.gov/fdsys/pkg/USCODE-2010-title42/html/USCODE-2010-title42-chap6A-subchapII-partF-subpart1.htm, accessed May 4, 2018.

16. Information for consumers (Biosimilars), US Food and Drug Administration, August 27, 2015, available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM241718_F, accessed May 4, 2018.

17. Koyfman, H., Biosimilarity and interchangeability in the Biologics Price Competition and Innovation Act of 2009 and FDA's 2012 Draft Guidance for Industry, Biotechnology Law Report, August 2013, 32(4): 238–251, available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3827854/, accessed May 4, 2018.

18. Scientific considerations in demonstrating biosimilarity to a reference product, Guidance for industry, United States Food and Drug Administration, April 2015, available at https://www.fda.gov/downloads/drugs/guidances/ucm291128.pdf, accessed May 4, 2018.

19. FDA approves first biosimilar product Zarxio, U.S. Food and Drug Administration, March 6, 2015, available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&applno=125553, accessed May 4, 2018.

20. Woodcock, J., Biosimilar implementation: A progress report from FDA, Statement before the Committee on Health, Education, Labor and Pensions, U.S. Senate, September 17, 2015, available at https://www.help.senate.gov/imo/media/doc/Woodcock4.pdf, accessed May 4, 2018.

21. US Capitol Capsule: Don't Make Assumptions On Biosimilars Actions, FDA Official Warns, SCRIP, Nov 16, 2016, available at https://scrip.pharmamedtechbi.com/SC030310/US-Capitol-Cap-sule-Dont-Make-Assumptions-On-Biosimilars-Actions-FDAOffi-cial-Warns, accessed May 4, 2018.

22. EMA approves biosimilar insulin, GaBI Online, Generics and Biosimilars Initiative, July 4, 2014, available at http://www.gabionline.net/Biosimilars/News/EMA-approves-biosimilar-insulin, accessed May 4, 2018.

23. Frequently asked questions about therapeutic biological products, United States Food and Drug Administration, July 7, 2015, available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications / TherapeuticBiologicApplictions/ucm113522.htm, accessed May 4, 2018.

24. FDA approves Basaglar, the first "follow-on" insulin glargine product to treat diabetes, United States Food and Drug Administration, December 16, 2015, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/205692Orig1s000TOC.cfm, accessed May 4, 2018.

25. Part B biosimilar biological product payment and required modifiers, available at https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/Part-B-Biosimilar-Biological-Product-Payment.html, accessed May 4, 2018.

26. Medicare Program, Revisions to Payment Policies Under the Physician Fee Schedule and Other revisions to Part B for CY 2016, Final Rule, Federal Register, November 16, 2015 (80)220: 71096-71101,71382, available at https://www.gpo.gov/fdsys/pkg/FR-2015-11-16/pdf/2015-28005.pdf, accessed May 4, 2018.

27. Physician Groups Express Concerns to Congress on CMS Biosimilar Billing Code Decision, Biologics Prescribers Collaborative, December 9, 2015, available at https://biologicsprescribers.org/policy-issues/physician-groups-express-concerns-to-congress-on-cms-biosimilar-billing-code-decision/, accessed May 4, 2018.

28. Winning with biosimilars: Opportunities in global markets, Deloitte, available at https://www2.deloitte.com/content/dam/Deloitte/us/Documents/life-sciences-health-care/us-lshc-biosimilars-whitepaper-final.pdf, accessed May 4, 2018.

29. Blackstone, E. and Fuhr, J., The economics of biosimilars, American Health and Drug Benefits, 2013, 6(8):469-478, available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4031732/pdf/ahdb-06-469.pdf, accessed May 4, 2018.

30. Tsuruta, L.R., et. al., Biosimilars advancements: Moving on to the future. Biotechnology Progress, March 2015, 31:1139-1149, available at https://onlinelibrary.wiley.com/doi/epdf/10.1002/btpr.2066, accessed May 4, 2018.

31. Choy, E., Biosimilar safety considerations in clinical practice, Seminars in Oncology, February 2014, 41(S1):S3-S14, available at http://www.seminoncol.org/article/S0093-7754(13)00211-X/fulltext, accessed May 4, 2018.

32. Lybecker, K. The biologics revolution in the production of drugs. Fraser Institute, July 2016, 1-7, available at https://www.fraserinstitute.org/sites/default/files/biologics-revolution-in-the-production-of-drugs.pdf, accessed May 8, 2018.

33. Morrow T. and Felcone L., Defining the difference: What makes biologics unique, Biotechnology Healthcare, September 2004, 1(4): 2426,2829, available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3564302/pdf/bh0104024.pdf, accessed May 4, 2018.

34. Shih, H. Discovery process for antibody-based therapeutics, in Tabrizi, M., et al., eds. Development of Antibody-Based Therapeutics, Springer, 2012, available at https://www.springer.com/us/book/9781441959539, accessed May 4, 2018.

35. Wurm, F., Production of recombinant protein therapeutics in cultivated mammalian cells, Nature Biotechnology, November 2004, 22(11):1393-1398, available at http://www.nature.com/nbt/journal/v22/n11/pdf/nbt1026.pdf, accessed May 4, 2018.

36. Jeske, W., Update on the safety and bioequivalence of biosimilars – focus on enoxaparin, Drug, Healthcare and Patient Safety, June 10, 2013, 5:133-141, available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3684140/, accessed May 4, 2018.

37. Jenkins, Nigel, Post-translational modifications of recombinant proteins: Significance for biopharmaceuticals, Molecular Biotechnology, June 2008, 39(2):113-118, available at http://link.springer.com/article/10.1007/s12033-008-9049-4, accessed May 4, 2018.

38. Feldman, S., Inflammatory disease: Integrating biosimilars into clinical practice, Seminars in Arthritis and Rheumatism, April 8, 2015, available at http://www.semarthritisrheumatism.com/article/S0049-0172(15)00065-7/abstract, accessed May 4, 2018.

39. Jenkins, N. and Curling, E., Glycosylation of recombinant proteins: Problems and prospects, Enzyme and Microbial Technology, May 1994, 16(5):354-364, available at http://www.sciencedirect.com/science/article/pii/014102299490149X, accessed May 4, 2018.

40. Chartrain, M. and Chu, L., Development and production of commercial therapeutic monoclonal antibodies in mammalian cell expression systems: An overview of the current upstream technologies, Current Pharmaceutical Biotechnology, 2008, 9:447-467, available at https://people.ucsc.edu/~drsmith/migrated/metx270/html/Chartrain%20and%20Chu.pdf.pdf, accessed May 4, 2018.

41. Huang, CJ, A robust method for increasing Fc glycan high mannose level of recombinant antibodies, Biotechnology Bioengineering, 2015 Jun;112(6):1200-9, available at https://onlinelibrary.wiley.com/doi/pdf/10.1002/bit.25534, accessed May 4, 2018.

42. Shi, Helen H. and Goudar, Chetan T., Recent advances in the understanding of biological implications and modulation methodologies of monoclonal antibody n-linked high glycans, Biotechnology Bioengi-neering. 2014; 111:1907-1919, available at http://www.readcube.com/articles/10.1002%2Fbit.25318?r3_referer=wol&tracking_action=preview_click&show_checkout=1&purchase_referrer=onlinelibrary.wiley.com&purchase_site_license=LICE N SE_DENIED_NO_CUSTOME, accessed May 4, 2018.

43. Markovic, I., Chemistry, manufacturing and control issues in production of therapeutic biologic protein products, United States Food and Drug Administration, available at https://ncifrederick.cancer.gov/research/brb/workshops/presentation/12_markovic_4-4-07_reviewed.ppt, accessed May 4, 2018.

44. Siew,A., Drug-delivery systems for biopharmaceuticals, BioPharm International, August 2015, 28(8):14-19, available at http://www.biopharminternational.com/drug-delivery-1, accessed May 4, 2018.

45. Frequently asked questions about therapeutic biological products, U.S. Food and Drug Administration, July 7, 2015, available at https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/ucm113522.htm, accessed May 4, 2018.

46. Kruse, Nanna Aby, Manufacturing process changes, biologic product comparability and post approval changes, European Medicines Agency, April 16, 2015, available at http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2015/05/WC500187356.pdf, accessed May 4, 2018.

47. Thompson, Cheryl A., One IVIG mystery solved, another demands vigilance, AJHP News, February 15, 2012, available at http://www.ajhp.org/content/69/4/271.long?sso-checked=true, accessed May 4, 2018.

48. FDA approves U.S. market return for octagam® following Octaphar-ma's implementation of enhanced safety measures, April 11, 2011, available at https://primaryimmune.org/fda-approves-u-s-market-return-for-octagam%25c2%25ae-following-octapharma%25e2%2580%2599s-implementation-of-enhanced-safety-measures, accessed May 4, 2018.

49. Eleryan, M. et al., Biosimilars: Potential implications for clinicians. Clin Cosmet Investig. Dermatol. 2016: (9)135-142, available at https://www.ncbi.nlm.nih.gov/pubmed/27382321, accessed May 11, 2018.

50. Ramanan, S., Drift, evolution, and divergence in biologics and biosimilars manufacturing, BioDrugs, 2014; 28(4):363-372, available at http://link.springer.com/article/10.1007%2Fs40259-014-0088-z, accessed May 4, 2018.

51. Process validation: General principles and practices, Guidance for industry, January 2011, available at https://www.fda.gov/downloads/drugs/guidances/ucm070336.pdf, accessed May 4, 2018.

52. Ho, K., Quality by Design – Applications and perspectives for biologicals, CHMP Biologics Working Party, European Medicines Agency, available at http://www.ema.europa.eu/docs/en_GB/docu-ment_library/Presentation/2009/10/WC500004218.pdf, accessed May 4, 2018.

53. Hutchinson, N., Understanding and controlling sources of process variation: Risks to achieving product critical quality attributes. BioProcess International, October 16, 2014, available at http://www.bioprocessintl.com/analytical/downstream-validation/understanding-controlling-sources-process-variation-risks-achieving-product-critical-quality-attributes/, accessed May 4, 2018.

54. Chirino, Arthur J and Mire-Sluis, Anthony, characterizing biological products and assessing comparability following manufacturing changes, Nature Biotechnology 22, 1383 - 1391 (2004), available at http://www.nature.com/nbt/journal/v22/n11/full/nbt1030.html, accessed May 4, 2018.

55. Cohen, M., Managing the expanded use of biologics across therapeutic areas: An example from B-cell targeted therapies, American Journal of Managed Care, March 1, 2006, 12:S24-S37, available at http://www.ajmc.com/journals/supplement/2006/2006-03-vol12-n2suppl/mar06-2271ps24-s37/P-1, accessed May 4, 2018.

56. Jahnsen, J. Clincal experience with infliximab Remsima (CT-P13) in inflammatory bowel disease patients. Therap Adv. Gastroenterol. 2016 May: 9(3):322-329, accessed May 4, 2018.

57. Weise, M., et al., Biosimilars: The science of extrapolation, Blood, November 20, 2014, 124(22):3191-3196, available at http://www.bloodjournal.org/content/124/22/3191, accessed May 4, 2018.

58. Nonproprietary naming of biological products, Draft guidance for industry, United States Food and Drug Administration, August 2015, available at http://www.fda.gov/downloads/drugs/guidancecompliance-regulatoryinformation/guidances/ucm459987.pdf, accessed May 4, 2018.

59. FDA approves first biosimilar Zarxio, United States Food and Drug Administration, March 6, 2015, available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&applno=125553, accessed May 4, 2018.

60. Zarxio, Advisory committee briefing materials: Available for public release, submitted by Sandoz to the United States Food and Drug Administration Oncologic Drugs Advisory Committee meeting, January 7, 2015, available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCom-mittee/UCM428782.pdf, accessed May 4, 2018.

61. CHMP Assessment Report for Zarzio. European Medicines Agency, available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000917/WC500046528.pdf, accessed May 4, 2018.

62. Summary Basis of Decision-Inflectra, Health Canada, March 4, 2014, available at https://hpr-rps.hres.ca/reg-content/summary-basis-decision-detailTwo.php?lang=en&linkID=SBD00253, accessed May 4, 2018.

63. Extrapolation of indications in biosimilars: infliximab, GaBI Online, Generics and Biosimilars Initiative, September 1, 2015, available at http://gabionline.net/Biosimilars/Research/Extrapolation-of-indications-in-biosimilars-infliximab, accessed May 4, 2018.

64. Remsima, Assessment Report, Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency (EMA), June 27, 2013, available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002576/WC500151486.pdf, accessed May 4, 2018.

65.FDA, Arthritis Advisory Committee Meeting, BLA 125544, CT-P13, a proposed biosimilar to Remicade® (infliximab), available at https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM484859.pdf, accessed May 8, 2018.

66. Pascal, E., A brave new world for biosimilars — How labeling requirements may impact preemption of product liability claims, Genetic Engineering and Biotechnology News, June 1, 2015, available at http://www.genengnews.com/insight-and-intelligence/a-brave-new-worldforbiosimilars/77900459/, accessed May 4, 2018.

67. Ventola, C., Biosimilars part 2: Potential concerns and challenges for P&T committees, Pharmacy and Therapeutics, June 2013, 38(6):329-335, available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3737987/pdf/ptj3806329.pdf, accessed May 4, 2018.

68. Citizen petition from AbbVie to the U.S. Food and Drug Administration, June 2, 2015, available at http://policymed.typepad.com/files/abbvie---citizen-petition-on-labeling-0615.pdf, accessed May 4, 2018.

69. Callahan, Elizabeth L., Royzman, Irena, Update on FDA's approach to labeling biosimilars like generics, Biologics Blog, Patterson, Belknap, Webb and Tyler, LLP, October 5, 2015, available at https://www.biologicsblog.com/update-on-fdas-approach-to-labeling-biosimilars-like-generics/, accessed May 4, 2018.

70. Labeling for biosimilar products, Draft guidance for industry, United States Food and Drug Administration, March 2016, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM493439.pdf, accessed May 4, 2018.

71. Supplement to Citizen Petition from AbbVie regarding biosimilar labeling, August 13, 2015, ID:FDA-2015P-2000-0007, available at http://www.regulations.gov/#!documentDetail;D=FDA-2015-P-2000-0007, accessed May 4, 2018.

72. Citizen Petition from AbbVie regarding biosimilar labeling, June 2, 2015, ID: FDA-2015-P-2000-0001, available at http://www.regulations.gov/#!documentDetail;D=FDA-2015-P-2000-0001, accessed May 4, 2018.

73. Considerations in Demonstrating Interchangeability With a Reference Product, Draft guidance for industry, United States Food and Drug Administration, January 2017, available at https://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf, accessed May 4, 2018.

74. State laws and legislation related to biologic medications and substitution of biosimilars. National Conference of State Legislatures, January 4, 2016, available at http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologicmedications-and-substitu-tion-of-biosimilars.aspx, accessed May 4, 2018.

75. Experiences with generics, Drugs and money - Prices, affordability and cost containment, World Health Organization, 2003, available at http://apps.who.int/medicinedocs/en/d/Js4912e/3.6.html#Js4912e.3.6, accessed May 4, 2018.

76. Sarpatwari, A., Paying physicians to prescribe generic drugs and follow-on biologics in the United States, PLoS Med. 2015 Mar; 12(3):e1001802, available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4363899/, accessed May 4, 2018.

77. Augustin, M., et al., Biologic therapies: Clinical practice in a changing environment, EMJ Dermatol. 2015;3[1]:38-44, available at https://www.emjreviews.com/dermatology/symposium/biologic-therapies-clinical-practice-in-a-changing-environment/, accessed May 4, 2018.

78. Cherin, P, Management of adverse events in the treatment of patients with immunoglobulin therapy: A review of evidence, Autoimmunity Reviews, September 16, 2015, 15(1): 71–81, available at http://www.ncbi.nlm.nih.gov/pubmed/26384525, accessed May 4, 2018.

79. Palabrica, R., Adverse events of intravenous immunoglobulin infusions: a ten-year retrospective study, Asia Pacific Allergy. October 2013, 3(4): 249–256, available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3826603/, accessed May 4, 2018.

80. Orange, J., Clinical update in immunoglobulin therapy for primary immunodeficiency diseases, Clinical Focus on Primary bioImmunodeficiencies, Immune Deficiency Foundation, March 2011, 14:1-9, available at https://primaryimmune.org/wp-content/uploads/2011/04/Clinical-Update-in-Immunoglobulin-Therapyfor-Primary-Imunonodefi-ciency-Diseases.pdf, accessed May 4, 2018.

81. Ameratunga, R., Increased risk of adverse events when changing intravenous immunoglobulin preparations, Clinical and Experimental Immunology, April, 2004, 136(1): 111–113, available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1809000/, accessed May 4, 2018.

82. Schneider, P. 93% of americans are now covered by biosimilar substitution laws. Alliance for Safe Biologics, available at https://safebiologics.org/2018/04/93-of-americans-are-now-covered-by-biosimilar-substitution-laws/, accessed May 8, 2018.

83. Delaware passes biosimilars substitution law, GaBI Online, Generics and Biosimilars Initiative, April 25, 2014, available at http://www.gabionline.net/Policies-Legislation/Delaware-passes-biosimilars-substitution-law, accessed May 4, 2018.

84. Massachusetts governor signs biosimilars substitution bill, GaBI Online, Generics and Biosimilars Initiative, June 27, 2014, available at http://gabionline.net/Policies-Legislation/Massachusetts-governor-signs-biosimilars-substitution-bill, accessed May 4, 2018.

85. Minghetti, P., The constrained prescription, interchangeability and substitution of biosimilars, Nature Biotechnology, July 8, 2015,33:688-689, available at http://www.readcube.com/articles/10.1038%2Fnbt.3272, accessed May 4, 2018.

86. Assessing biosimilar uptake and competition in European markets, IMS Institute for Healthcare Informatics, October 2014, available at https://www.medicinesforeurope.com/wp-content/uploads/2017/05/IMS-Biosimilar-2017_V9.pdf, accessed May 4, 2018.

87. Renwick, M., et al., Postmarket policy considerations for biosimilar oncology drugs, Lancet Oncology, 17(1): e31 - e38, available at http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(15)00381-2/fulltext, accessed May 4, 2018.

88. Green light for biosimilar switching, European Biotechnology, May 26, 2015, available at https://www.medicinesforeurope.com/wp-content/uploads/2017/03/M-Biosimilars-Overview-of-positions-on-physician-led-switching.pdf, accessed May 4, 2018.

89. Thimmaraju, P.K., Legislations on biosimilar interchangeability in the US and EU – developments far from visibility, GaBI Online, Generics and Biosimilars Initiative, June 1, 2015, available at http://www.gabionline.net/Sponsored-Articles/Legislations-on-biosimilar-interchangeability-in-the-US-and-EU-developments-far-from-visibility, accessed May 4, 2018.

90. Biosimilars, European Medicines Agency, available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general_content_001832.jsp&mid=WC0b01ac0580bb8fda, accessed May 4, 2018.

91. MacDonald, Gareth, Amgen studying what impact switching to 'biosimilar' Aranesp has on patients, BioPharma Reporter, October 29, 2014, available at https://www.biopharma-reporter.com/Article/2014/10/21/Amgen-studying-what-impact-switching-to-biosimilar-Aranesp-has-on-patients,

accessed May 4, 2018.

92. Cai, X., et al., Challenges of developing and validating immunoge-nicity assays to support comparability studies for biosimilar drug development, 2012, 4(17):2169-2177, available at http://www.future-science.com/doi/pdf/10.4155/bio.12.185, accessed May 4, 2018.

93. Shankar, G., et al., Assessment and reporting of the clinical immunogenicity of therapeutic proteins and peptides—Harmonized terminology and tactical recommendations, The AAPS Journal, July2014, 16(4):658–673, available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4070270/, accessed May 4, 2018.

94. Guideline on immunogenicity assessment of biotechnology- derived therapeutic proteins, European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), January 24, 2007, available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003947.pdf, accessed May 4, 2018.

95. Whelan, S., et al., Distinct characteristics of antibody responses against factor VIII in healthy individuals and in different cohorts of hemophilia A patients, Blood, February 7, 2013, 121(6): 1039 – 1048, available at http://www.bloodjournal.org/content/121/6/1039#x-ref-ref-1-1, accessed May 4, 2018.

96. Immunogenicity assessment for therapeutic protein products, Guideline for industry, United States Food and Drug Administration, available at http://www.fda.gov/downloads/drugs/guidancecompliance-regulatoryinformation/guidances/ucm338856.pdf, accessed May 4, 2018.

97. Biosimilars, American College of Rheumatology position statement, March 12, 2015, available at https://www.rheumatology.org/Portals/0/Files/Biosimilars-Position-Statement.pdf, accessed May 4, 2018.

98. van Schie, K. et al., Cross-reactive and pre-existing antibodies to therapeutic antibodies—Effects on treatment and immunogenicity, mAbs, May 11, 2015, 7(4):662-671, available at http://www.tandfonline.com/doi/full/10.1080/19420862.2015.1048411, accessed May 4, 2018.

99. Bendtzen, Immunogenicity of Anti-TNF-α Biotherapies: II. Clinical Relevance of Methods Used for Anti-Drug Antibody Detection, Frontiers in Immunology, April 8, 2015, 6(109):1-5, available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4389574/pdf/fimmu-06-00109.pdf, accessed May 4, 2018.

100. Camacho, L., et al., Biosimilars 101: Considerations for U.S. oncologists in clinical practice, Cancer Medicine, 2014 3(4):889-899, available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4303156/, accessed May 4, 2018.

101. Tighter EU rules on pharmacovigilance for biologicals, GaBI Journal, Generics and Biosimilars Initiative, 2012, available at http://gabi-journal.net/tighter-eu-rules-on-pharmacovigilance-for-biologicals.html, accessed May 4, 2018.

102. Casadevall, I., Immune-response and adverse reactions: PRCA case example, European Medicines Agency, 2009, available at https://pdfs.semanticscholar.org/presentation/5b26/d40f049abb7507fe0388b2a96b05b46ee3f2.pdf, accessed May 4, 2018.

103. Grampp, G. and Felix, T. Pharmacovigilance considerations for biosimilars in the USA, BioDrugs, October 2015, 29(5):309-321, available at https://www.ncbi.nlm.nih.gov/pubmed/26419971, accessed May 4, 2018.

104. Vermeer, N, Traceability of biopharmaceuticals in spontaneous reporting systems: A cross-sectional study in the FDA Adverse Event Reporting System (FAERS) and EudraVigilance databases, Drug Safety, June 15, 2013, 36:617–62, available at https://www.ncbi.nlm.nih.gov/pubmed/23771794, accessed May 4, 2018.

105. QuarterWatch™ (Special Report): A critique of FDA's key drugsafety reporting system, Institute for Safe Medication Practices, January 29, 2015, available at https://www.ismp.org/resources/quarterwatchtm-special-report-critique-fdas-key-drug-safety-reporting-system?id=100, accessed May 4, 2018.

106. Findlay, S., Health policy brief: The FDA's sentinel initiative, Health Affairs, June 4, 2015, available at http://www.healthaffairs.org/healthpolicybriefs/brief.php?brief_id=139, accessed May 4, 2018.

107. Woodcock, J., Another important step in FDA's journey towards enhanced safety through full-scale "active surveillance", FDA Voice, United States Food and Drug Administration, December 30, 2014, available at http://blogs.fda.gov/fdavoice/index.php/2014/12/another-important-step-in-fdas-journey-towards-enhanced-safety-through-full-scale-active-surveillance/, accessed May 4, 2018.

108. Nonproprietary naming of biological products, Final guidance for industry, United States Food and Drug Administration, January 2017, available at https://www.fda.gov/downloads/drugs/guidances/ucm459987.pdf, accessed May 4, 2018.

109. Importance of Meaningful Suffixes, Biologics Prescribers Collaborative, November 2016, available at http://biologicsprescribers.org/resources/importance-of-meaningful-suffixes, accessed May 4, 2018.

110. A critique of a key drug safety monitoring system, QuarterWatch, Institute for Safe Medication Practices, January 28, 2015, available at http://www.ismp.org/quarterwatch/pdfs/2014Q1.pdf, accessed May 4, 2018.

111. Developing systems to support pharmacovigilance of biologic products – Meeting summary, Engelberg Center for Health Care Reform at Brookings, November 15, 2013, available at https://www.brookings.edu/events/developing-systems-to-support-pharmacovigilance-of-biologic-products/, accessed May 4, 2018.

112. Sarpatwari, A., Progress and hurdles for follow on biologics, New England Journal of Medicine, June 18, 2015,372:2380-2382, available at http://www.nejm.org/doi/full/10.1056/NEJMp1504672?af=R&rss=currentIssue, accessed May 4, 2018.

113. Part B Biosimilar Biological Product Payment and Required Modifiers, Centers for Medicare & Medicare Services, December 23, 2015, available at https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/Part-B-Biosimilar-Biological-Product-Payment.html, accessed May 4, 2018.

114. Hatch, O. letter to Slavitt, A., October 22, 2015, available at https://www.finance.senate.gov/imo/media/doc/Letter%20to%20CMS%20on%20Part%20B%20Rule.pdf, accessed May 4, 2018.

115. Biosimilars Forum disappointed with CMS final rule on biosimilar payment and coding, Biosimilars Forum, October 30, 2015, available at http://www.biosimilarsforum.org/news/biosimilars-forum-disappointed-cms-final-rule-biosimilar-payment-and-coding, accessed May 4, 2018.

116. European Medicines Agency recommends approval of first two monoclonal-antibody biosimilars, European Medicines Agency, June 2013, available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/06/news_detail_001837.jsp&mid=WC0b01ac058004d5c1, accessed May 4, 2018.

117. Global Biosimilars Pathways and Clinical Development Activity Infographic, Decision Resources Group, 2014, available at https://decisionresourcesgroup.com/downloads/biosimilars-insights-infographic/, accessed May 4, 2018.

118. FDA's Woodcock to Congress: Pass the GDUFA and BsUFA Reauthorizations, RAPS, March 2017, available at https://docs.house.gov/meetings/IF/IF14/20170302/105631/HHRG-115-IF14-Wstate-WoodcockJ-20170302.PDF, accessed May 4, 2018.

119. Testimony of Janet Woodcock, M.D. Before the United States House of Representatives, March 2017, available at http://docs.house.gov/meetings/IF/IF14/20170302/105631/HHRG-115-IF14-Wstate-WoodcockJ-20170302.PDF, accessed May 4, 2018.

120. Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations, United States Food and Drug Administration, available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411418.htm, accessed May 4, 2018.

121. FDA approves first biosimilar product Zarxio, United States Food and Drug Administration, March 2015, available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&applno=125553, accessed May 4, 2018.

122. FDA approves Inflectra, a biosimilar to Remicade, United States Food and Drug Administration, April 2016, available at https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm494227.htm, accessed May 4, 2018.

123. FDA approves Erelzi, a biosimilar to Enbrel, United States Food and Drug Administration, August 2016, available at https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm518639.htm, accessed May 4, 2018.

124. FDA approves Amjevita, a biosimilar to Humira, United States Food and Drug Administration, September 2016, available at https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm522243.htm, accessed May 4, 2018.

125. Highlights of Prescribing Information, Renflexis, August 2017, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761054Orig1s000lbl.pdf, accessed on May 4, 2018.

126. United States Food and Drug Administration, Highlights of Prescribing Information Cyltezo, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761058lbl.pdf, accessed May 4, 2018.

127. United States Food and Drug Administration, Highlights of Prescribing Information, Mvasi, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761028s000lbl.pdf, accessed May 4, 2018.

128. United States Food and Drug Administration, Highlights of Prescribing Information, Ogivri, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761074s000lbl.pdf, accessed May 4, 2018.

129. United States Food and Drug Administration, Highlights of Prescribing Information, Xifi, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761072s000lbl.pdf, accessed May 4, 2018.

130. United States Food and Drug Administration, Highlights of Prescribing Information, Retacrit, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125545s000lbl.pdf

131. United States Food and Drug Administration, Highlights of Prescribing Information, Fulphila, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761075s000lbl.pdf, accessed August 6, 2018.

132. United States Food and Drug Administration, Highlights of Prescribing Information, Nivestym, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761075s000lbl.pdf, accessed August 6, 2018.

133. United States Food and Drug Administration, Highlights of Prescribing Information, Hyrimoz, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761071lbl.pdf, accessed October 31, 2018.

134. United States Food and Drug Administration, Highlights of Prescribing Information, Udenyca, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761039s000lbl.pdf, accessed November 2, 2018.

135. United States Food and Drug Administration, Highlights of Prescribing Information, Truxima, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761088s000lbl.pdf, accessed November 28, 2018.

THE

BIOSIMILAR PROMISE

bpc BiologicsPrescribers COLLABORATIVE

A PROJECT OF AfPA