THE BIOSIMILAR PROMISE
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, 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.

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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.

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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 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.

The Biologics Prescribers Collaborative
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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.\textsuperscript{1,2}

They come from living cells and many are induced by DNA insertion to create therapeutically valuable proteins, peptides, monoclonal antibodies and viral vectors.

**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.\textsuperscript{4,5,6}

Soon after, more advanced and complex biologics harnessed antibody construction to fight cancer and other diseases like rheumatoid arthritis and multiple sclerosis. In a critical breakthrough, some biologics target the immune system by binding to and inactivating inflammatory-mediating proteins called cytokines.\textsuperscript{7}
Further, a recently launched biologic, the first to use a viral vector, targets cancerous melanoma cells in two ways. The biologic only replicates in the cancer cells, destroying them, and it also stimulates the immune system to attach the cancer cells.\textsuperscript{8}

Exciting disease discoveries and new ways of designing and manufacturing biologics are driving work on 600 more advanced biologics for 200 serious illnesses.\textsuperscript{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.\textsuperscript{9} Costs will be lower, improving access, though not as low as for generics. This is because biosimilars are not generic drugs; they are a new category of biologics.\textsuperscript{10}

Chemically-based generics and their originator brand drugs have relatively simple structures, making identical replication much less complex. However, because living cells make biologics, it is currently impossible for a biosimilar to be an identical copy of its originator biologic.

In addition, biologically-constructed molecules are far larger than the small molecules of chemically-based drugs – by 200 to 1,000 times.\textsuperscript{11} That is one reason why patients receive most biologics by injection or intravenously, instead of in pill form like chemically-based drugs and their generics.\textsuperscript{12} Oral administration would result in the gastrointestinal tract drastically altering a biologic’s structure and configuration.\textsuperscript{13}

**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.\textsuperscript{14}

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

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**THERE CAN BE MINOR DIFFERENCES WITH THE ACTIVE INGREDIENT, BUT THESE DIFFERENCES CANNOT HAVE A CLINICALLY MEANINGFUL EFFECT IN PATIENTS.**\textsuperscript{15}

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.\textsuperscript{16}

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.\textsuperscript{17}

FDA approved the first U.S. biosimilar in March 2015 – Zarxio\textsuperscript{TM} (filgrastim-sndz).\textsuperscript{18} It is a biosimilar to Neupogen\textsuperscript{®} (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.\textsuperscript{19}
As of publication in April of 2017, FDA has approved four biosimilars. See the “Approval” index in a later section for specific details on approved products. FDA has indicated the agency anticipates that at least one biosimilar application per reference product will go before an Advisory Committee panel.

Unlike the U.S., the European Commission approves synthetic insulin follow-on products as biosimilars, as shown in 2014 for Lantus® (insulin glargine).

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.

**REIMBURSEMENT**

The Centers for Medicare & Medicaid Services (CMS) has placed biosimilars of a single reference product into one Healthcare Common Procedure Coding System (HCPCS) code, known as a J-code. As a result, under the 2016 Medicare Physician Fee Schedule, Medicare Part B reimbursement of biosimilars is based on the weighted average of sales prices under each shared HCPCS code. Almost unanimously disagreeing with the CMS policy are Members of Congress, manufacturers of both originator and biosimilar biologics and physician groups. All assert that 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.

By prioritizing price over all other product features, the CMS proposal would also deter innovation and may discourage manufacturers from investing in new indications, according to physician groups.

Despite important differences between products, the groups add that hospitals and payers also could easily prefer the lowest cost biosimilar at any given time, reducing choice and potentially encouraging inappropriate non-medical switching back and forth between one biologic/biosimilar and another.

In the U.S. alone, the cost savings from using biosimilars in comparison to the original biologic 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.
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 originator 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 more than 200. In addition, 250 tests – five times those used for a chemical drug – are required to validate potency, quality and purity.32

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.34

The cell line, reproducing at high volume, utilizes the new, inserted DNA to manufacture and then secrete the desired protein for collection.35 While
in-solution, before purification, the protein’s structure folds over itself, changing its three dimensional shape.\textsuperscript{36}

Further, while in-solution, molecular modifications occur, including the attachment of sugars, as well as other changes.\textsuperscript{37,38}

\textbf{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.\textsuperscript{39} The production process must therefore achieve a therapeutically optimal ration of these sugars, called glycans.\textsuperscript{40}

For example, different numbers of attached mannose – a ringed sugar molecule – cause variability in a product’s clinical efficacy.\textsuperscript{41}

Uncontrolled, these levels can lead to wide variation in the clearing of protein-based biologics from the body.\textsuperscript{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.\textsuperscript{43}

They also constitute yet another reason for injecting instead of orally administering biologics.\textsuperscript{44}

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\textbf{ALTERATION OF BIOLOGIC PRODUCTS CAN ALSO OCCUR DUE TO INTENTIONAL PROCESS CHANGES OVER TIME.} \textsuperscript{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.\textsuperscript{46}

In 2010, a manufacturer withdrew an intravenous immune globulin (IVIG) product upon detecting a higher-than-normal rate of thrombotic and thromboembolic events. A manufacturing process alteration had unintentionally increased the coagulation factor X\textsubscript{a}, which caused the events.\textsuperscript{48} The manufacturer and FDA developed a scientific method to measure factor X\textsubscript{a} levels, permitting the product’s market return.\textsuperscript{49}

In addition, biologic products can change because of “drift,” an unintended, unexplained or unexpected trend away from intended process or product targets.\textsuperscript{50} Experienced biologics manufacturers minimize drift with strong process
controls and a sophisticated ability to modulate processes to meet product specifications consistently.\textsuperscript{51,52}

**CONTROL**

Variation occurs in all drug production process and manufacturers work to understand, monitor and control processes within ranges that maintain product quality, efficacy and safety.\textsuperscript{53} Biologics manufacturers need to monitor hundreds of process parameters against proven acceptable ranges.\textsuperscript{54}

Biologics manufacturers must maintain product consistency largely by controlling process consistency, batch-to-batch.\textsuperscript{55} They know from clinical and other studies the impact specific process variations, such as changing molecular rations, may have on a product.\textsuperscript{56}
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.\(^{57}\)

**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.

Very likely, the agency will approve extrapolated indications for diseases that share the same pathophysiology as the disease state in the actual clinical study.\(^{58}\) FDA has acknowledged the distinct possibility of approving biosimilars for fewer indications than their originator reference products.\(^{59}\)

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\(^{60}\)

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.\(^{61}\)

However, Health Canada approved Inflectra™ (infliximab), a biosimilar (or, in Canada, subsequent entry biologic) for Remicade® (infliximab) for all indications except those related to inflammatory bowel diseases (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 rely, as does IBD in part, on another mechanism of action, soluble and membrane-bound tumor necrosis factor–alpha (TNFa).\(^{62}\)

On the other hand, the European Medicines Agency (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.”\(^{64}\)

**LABELING**

Ideally, the results of studies comparing a biosimilar with its originator reference product would be included in the full prescribing information that is part of a biosimilar’s label.\(^{65,66,67}\)

However, when FDA approved the biosimilar Zarxio (filgrastim-sndz), 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.\(^{68}\)

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.

FDA slightly changed course on biosimilar labeling in a draft guidance issued March 2016. The agency said, when clinical studies or data derived from studies with the originator) reference product are described in biosimilar product labeling, the (originator) reference product’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 reference product.

In so doing, the agency was unmoved by arguments that biosimilar labeling should include a concise description of pertinent data supporting licensure of the biosimilar. Still, it did agree 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 reference product.

As of March 2017, FDA has not yet issued a final guidance for labeling.

INTERCHANGEABILITY

The law establishing the biosimilar pathway also provided for approval of interchangeable biosimilars. FDA issued draft guidance on biosimilar interchangeability in January 2017. BPCIA requires and the 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.”

FDA’s draft guidance outlines additional specifics to demonstrate interchangeability including applicant’s data, switching studies and scientific justification for indication extrapolation.

The guidance does not provide any indication on how the agency plans to handle labeling of interchangeable products. 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 reference product without prescriber involvement. However, U.S. states regulate the practice of pharmacy and thus substitution procedures.

SWITCHING AND SUBSTITUTION

Prescribers will find that there is considerable overlap in use of the terms “switching” and “substitution.” However, substitution is commonly associated with pharmacy level action, as in “automatic substitution,” while switching frequently refers to action at the prescriber level. In addition, switching typically refers to changing back and forth between medications.

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

Increasingly, states are enacting laws permitting pharmacists to substitute interchangeable biosimilars automatically. 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.

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 reference biologic product.\textsuperscript{80} Massachusetts requires pharmacists to record such substitutions in an interoperable electronic health record (HER) and inform the prescriber.\textsuperscript{81}

**MOST COUNTRIES IN EUROPE PROHIBIT PHARMACY LEVEL SUBSTITUTION OF BIOLOGICS.\textsuperscript{82}**

Only recently have governments in Europe explored measures to promote the use of biosimilars.\textsuperscript{83,84} The Netherlands and Finland have supported physician-directed switching.\textsuperscript{85} Despite authorizing automatic substitution, France has not yet implemented the 2014 law permitting substitution without physician approval.\textsuperscript{86}

EMA does not evaluate the products for safety in repeated switching back and forth, as FDA will do for interchangeable biosimilars.\textsuperscript{87} 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.\textsuperscript{88}

Until an interchangeable product is approved and available as a treatment option, the impact of substitution with interchangeable products is yet to be seen.
Though not all differences between biologics, including 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.

**IMMUNOGENICITY**

When it occurs, immunogenicity typically involves the body’s production of neutralizing antibodies, which can lower a biologic’s bioavailability. These antibodies can also bind to a biologic’s active region, neutralizing its effects, or to the body’s own counterpart to the biologic with the same result. The responses could be without symptoms or as severe as a clinically meaningful serious adverse event. Formulation changes, administration routes or packaging can also cause immunogenicity issues.

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.

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. 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. However, because there is no legal or regulatory bar to prescribers switching one biosimilar for another, the lack of
FDA-reviewed comparability studies should be an important consideration before substitution.94 Meanwhile, individual patients – prior to administration of a biologic – may have pre-existing antibodies that could affect a biologic’s efficacy, safety, or immunogenicity.95 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.96

**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.97 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.96

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, during clinical trials of one of the first biosimilars, a PRCA increase attributable to subcutaneous delivery occurred. The manufacturer changed the formulation and guidelines, subsequently recommending intravenous administration only.98

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.99

**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, post marketing clinical trials and risk minimization activities.100 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.

**CONSUMERS ORIGINATE 51% AND HEALTH CARE PROFESSIONALS 48% OF THE ADES REPORTS, NEARLY ALL OF WHICH ARE INITIALLY MADE TO MANUFACTURERS WHO IN TURN MUST SUBMIT THEM TO FDA.**

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 casual 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, 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.\textsuperscript{102}

FDA’s Sentinel System queries diverse automated healthcare data holders – like electronic health record systems, administrative and insurance claims databases, and registries – to evaluate possible safety issues.\textsuperscript{103} 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.\textsuperscript{104}

**NAMING**

Critical to safe use are distinguishable names for all biologics, including biosimilars. FDA and the World Health Organization have proposed giving each biologic, whether an originator or a biologic, a distinguishable name.\textsuperscript{105} In January 2017, FDA issued final guidance calling for distinguishable names for all biologic medicines.\textsuperscript{106}

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 still has not proposed distinguishable naming nomenclature for interchangeable biosimilars.

However, the Collaborative remains concerned that the random suffixes called for in this guidance will not allow FDA to achieve its goal of
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.
pharmacovigilance and the prevention of inadvertent substitution. As physicians who routinely prescribe biologic medicine we believe a memorable 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. BPC appreciated FDA’s careful consideration of this important issue. As the medical community gains real-world experience using these new medicines, the Collaborative 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.

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

Only eight percent of physicians preferred a suffix devoid of meaning, while 12 percent had no preference.

Sharing the same non-proprietary name of the chemically-based brand and generic drug frequently leads to misreporting in FAERS. When generics enter the market, reports still largely arrive on the originator brand product. In a study by the Institute for Safe Medication Practices, 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.

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.

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.

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.

Given the nature of our settling-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.

For example, like the NDC code in the retail and mail pharmacy, the medical setting would significantly benefit from unique Healthcare Common Procedure Coding System (HCPCS) J-codes, especially in view of the FDA Sentinel System’s reliance on reimbursement codes. CMS is requiring the addition of manufacturer identifiers to biosimilar J-codes for this purpose. 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.
CONCLUSION:
REALIZING THE BIOSIMILAR PROMISE

Biosimilars are relatively new in the United States, however they have been revolutionizing treatment for patients with serious illnesses worldwide for over a decade, with the EMA approving the first biosimilar in 2006. To date, more than 20 biosimilars are available in Europe in at least eight therapeutic classes and globally there are over 350 biosimilars in development.

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.

Transparent and full information must serve as the foundation for the confident use of biosimilars by patients and prescribers.

This requires distinguishable names, complete labels, specific prescribing information, prescriber involvement in any switching 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 Biologics Prescribers Collaborative 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).\(^{106}\)

**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.\(^{106}\)

**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).\(^{106}\)

**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.\(^{106}\)

**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.\(^{106}\)

**Proper Name** means the nonproprietary name designated by FDA in the license for a biological product licensed under the PHS Act.\(^{106}\)

**Proprietary Name** means the trademark or brand name.\(^{106}\)

**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).\(^{106}\)

**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.\(^{106}\)
INDEX OF APPROVED BIOSIMILARS

The Biologics Prescribers Collaborative appreciates FDA’s careful deliberation before approving biosimilar applicants. As of publication (April 2017), only four approved biosimilars exist, however, additional approvals are expected. FDA indicated to Congress in a BsUFA hearing in March 2017 that the agency is working on 64 biosimilar development programs for 23 reference biologics\textsuperscript{116} and that nine companies have publicly announced submission of 13 applications for proposed biosimilar products to FDA.\textsuperscript{117} For additional information, please reference the FDA’s Purple Book\textsuperscript{118} on FDA’s site.

<table>
<thead>
<tr>
<th>Biosimilar Product (Proper Name)</th>
<th>Proprietary Name</th>
<th>Biosimilar</th>
<th>Reference Product</th>
<th>Approved Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>filgrastim-sndz</td>
<td>Zarxio</td>
<td>Sandoz</td>
<td>Neupogen (Amgen)</td>
<td>• patients with cancer receiving myelosuppressive chemotherapy;</td>
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<td></td>
<td>• patients with acute myeloid leukemia receiving induction or consolidation chemotherapy;</td>
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<td>• patients with cancer undergoing bone marrow transplantation;</td>
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<td>• patients undergoing autologous peripheral blood progenitor cell collection and therapy;</td>
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<td>• patients with severe chronic neutropenia</td>
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<tr>
<td>infliximab-dyyb</td>
<td>Inflectra</td>
<td>Celltrion</td>
<td>Remicade (Johnson &amp; Johnson)</td>
<td>• 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;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy;</td>
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<td></td>
<td>• patients with moderately to severely active rheumatoid arthritis in combination with methotrexate;</td>
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<td></td>
<td>• patients with active ankylosing spondylitis (arthritis of the spine);</td>
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<td>• patients with active psoriatic arthritis;</td>
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<td></td>
<td></td>
<td>• adult patients with chronic severe plaque psoriasis</td>
</tr>
<tr>
<td>etanercept-szzs</td>
<td>Erelzi</td>
<td>Sandoz</td>
<td>Enbrel (Amgen)</td>
<td>• moderate to severe rheumatoid arthritis, either as a standalone therapy or in combination with methotrexate (MTX);</td>
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<td></td>
<td></td>
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<td>• moderate to severe polyarticular juvenile idiopathic arthritis in patients ages two and older;</td>
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<td>• active psoriatic arthritis, including use in combination with MTX in psoriatic arthritis patients who do not respond adequately to MTX alone;</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>• active ankylosing spondylitis (an arthritis that affects the spine); and</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• chronic moderate to severe plaque psoriasis in adult patients (18 years or older) who are candidates for systemic therapy or phototherapy</td>
</tr>
<tr>
<td>adalimumab-atto</td>
<td>Amjevita</td>
<td>Amgen</td>
<td>Humira (AbbVie)</td>
<td>• moderately to severely active rheumatoid arthritis;</td>
</tr>
</tbody>
</table>
REFERENCES


11. Understanding biologic medicines from the cancer patient perspective, American Cancer Society, January 2013, available at http://action.acscan.org/site/DocServer/ACSCAN-Biosimilars-Primer.pdf?docId=22448, accessed January 22, 2016. (See Figure 1, p. 5.)


January 18, 2016.


THE BIOSIMILAR PROMISE