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Biologics and Biosimilars

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Dr. Mona Thompson has no relevant financial relationships to disclose.

Goal. The goal of this lesson is to provide an overview of biologic agents, and the subsequent biosimilar development program. FDA regulations and a general review of four U.S. FDA-approved biosimilars are included.

Objectives. At the completion of this activity, the participant will be able to:

1. define a generic medication, biologic product, biosimilar product, and reference product;
2. demonstrate an understanding of the legislative and regulatory information supporting biosimilar development;
3. compare and contrast generic medications with biosimilar products; and
4. identify approved biosimilar products in the U.S. and their approved indications.

What are Biologics?

Biologic agents have been on the rise in the pharmaceutical industry since the 1980s and have gradually grown more popular and more complex. The term *biologics* generally refers to various products such as vaccines, blood and blood components, and allergenics that are isolated from natural sources. A biologic drug is defined as a *substance that is made from a living organism or its products and is used in the prevention, diagnosis or treatment of cancer and other diseases*. It has long been recognized that many biological products derived from natural sources still show some variability, and the nature of biological products means that there can be variation even within a single batch of product. Manufacturing conditions are critically important and must be tightly controlled throughout the process to ensure the production of a consistent, quality product and to prevent environmental contamination. The introduction of recombinant biotechnology has enabled greater consistency. In addition, modern analytics can allow for better identification of variations between different batches of products, and for robust monitoring of the stability of the product over its shelf life. Today, many biologics are produced utilizing recombinant DNA technology.

Biologic agents tend to be sensitive to light and high temperatures. In comparison to small-molecule drugs, biologics are also more susceptible to contamination such as microbial and viral contamination. Due to their chemical instability, they may be lyophilized or freeze-dried and are often stored under refrigeration. Biologics are generally administered by injection or infusion.

Biologics can be further organized into classes such as monoclonal antibodies, growth hormones, colony stimulating factors (CSFs) and recombinant proteins that work to manage conditions such as autoimmune diseases or genetic disorders. As a class, biologics have had a profound impact on many areas of practice, but primarily in rheumatology, oncology/hematology, and gastroenterology.

Examples of biologics commonly prescribed in these area include epoetin alfa (Procrit®, Epogen®), trastuzumab (Herceptin®), filgrastim (Neupogen®), pegfilgrastim (Neulasta®), infliximab (Remicade®), adalimumab (Humira®), and etanercept (Enbrel®).

Given the intricate process, biologics are costly to manufacture which is reflected in the cost of therapy. For example, the cost of treatment for one year with a biologic agent ranges from $15,000 to $150,000. On average, the daily cost of chemical (small-molecule) drugs is $2.00 versus $45.00 for biologics. Despite the cost, biologic agents have had great financial success. In 2012, five of the top 10 global prescription products were biologics. Monoclonal antibodies (mAbs) have accounted for as much as 19 percent of the global pharmaceutical market and exceeded $140 billion in sales in 2011.

What are Biosimilars?

A biosimilar product is a biological product that is approved based on a showing that is it highly similar to a Food and Drug Administration (FDA)-approved biological product, known as a *reference product*. Generic biologics are not possible as they are not made using the

Table 1
Summary of key differences between biosimilars and small-molecule generics, and comparison to reference product

	Small-Molecule Generic	Biosimilar Medications
Product		
Chemical Structure	Active drug is chemically identical to the reference product	Amino acid sequence is the same; expected slight difference in terms of protein folding and glycosylation
Analytical Characterization	Available techniques to ensure that active drug in the generic product is identical to reference	Final structure can't be defined based on current analytical techniques; therefore degree of structural similarity to reference product is unknown
Manufacturing		
Complexity	Relatively simple; uses organic medicinal chemistry reactions	Very complex; produced in living cells and involves several stages of purification, production, and validation of the final product
Impact of Change in Manufacturing Process	Likely to be negligible; end product identical	Small changes in process can alter final structure and function of the protein
Regulation *Abbreviated Pathway utilized for approval*	Hatch Waxman Act	Biologics Price Competition and Innovation Act of 2009
Indication	Same as reference drug	Varies; dependent on data and determined during approval process

Adapted from NCCN Biosimilars White Paper: Regulatory, Scientific, and Patient Safety Perspectives. *JNCCN*. 2011; 9(4):s10

traditional chemical processes utilized in small-molecule drugs. Hence it is impossible to create an exact replica. Alternatively, the equivalents to biological drugs are called *biosimilars*. Biosimilars are biologic products that have a molecular structure and biological properties that are "highly similar" to the biologic. Regardless of some slight differences, biosimilars produce the same results via the same mechanism of action as the reference biologic at the same dose. In addition to the development of biosimilars, efforts are already underway to develop a new class of follow-on biologics named *biobetters* or *biosuperiors*. Table 1 compares and contrasts biologic agents and biosimilars.

On March 23, 2010, President Obama signed into law the Patient Protection and Affordable Care Act, or the Affordable Care Act. This law contained the Biologics Price Competition and Innovation Act of 2009, or BPCI Act. This act was intended to encourage biosimilar competition while still providing incentives for pharmaceutical innovators to develop new drugs similar to the Hatch-Waxman Act for generic drugs. The BPCI Act provides for 12 years of non-patent market exclusivity for licensed reference products which can be extended for six months for pediatrics. The BPCI Act defined standards for biologics and biosimilars, and created a new abbreviated FDA approval pathway for biosimilars under the Public Health Service Act (PHS Act).

The progress and expansion of biosimilars is of interest for both industry and society as the patents of some key biologics recently expired and many more are going off-patent in the coming years. Because the goal of a biosimilar product development program is to demonstrate biosimilarity between the proposed biosimilar product and a reference product rather than independently establishing safety and efficacy, there is potential cost savings that may be passed on to the consumer. Thus, given the current global socioeconomics regarding patient access to biologics and additional technologic innovations, a shift in pharmaceutical product development is occurring, indicating an increase in biosimilar advancement. It is estimated that the use of biosimilars in practice could result in a cost savings of $44.2 billion in the U.S. healthcare system.

Prior to the availability of biosimilars in the U.S., they were available in the European Union (EU) as early as 2007. Other countries that are approving biosimilars include Canada, Japan, India, and Turkey. Over 700 biosimilar products are reported to be in the development pipeline undergoing various phases of clinical testing.

FDA Regulation of Biosimilars

As mentioned earlier, a *biosimilar* is a biological agent that is highly similar to an FDA-approved biological product, known as a reference product, notwithstanding minor differences in clinically inactive components. These products must have no clinically meaningful differences in regards to the reference product that they emulate when referring to safety, purity, and potency. The European Medicines Agency (EMA) was the first entity to publish guidelines for the production of biosimilars, and became the first to approve a biosimilar product, somatropin (Omnitrope) from the reference

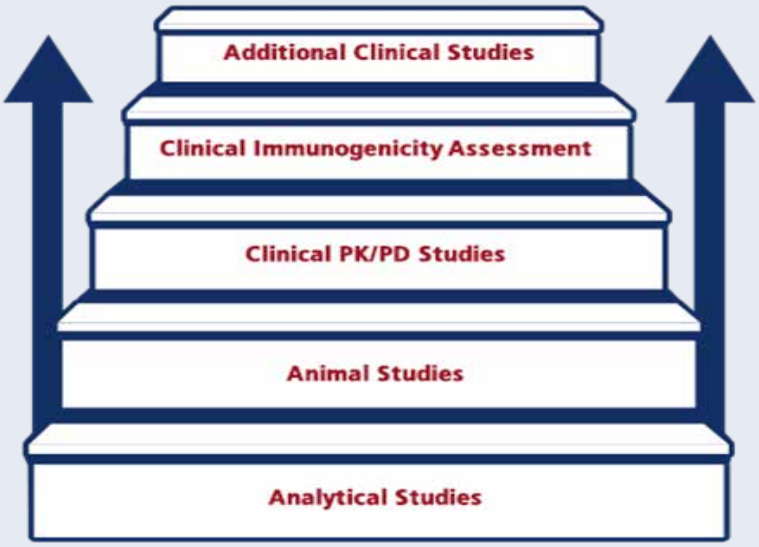
product Genotropin®, just one year later in 2006. In 2010, the EMA approved a biosimilar version of Amgen's Neupogen followed by the first mAb, Inflectra®, a biosimilar of Remicade. As of 2016, EMA has approved 22 biosimilars with two molecules subsequently withdrawn. While the U.S. is lagging behind in biosimilar approval, both the World Health Organization (WHO) and FDA, using the EU's framework, are following suit in releasing guidelines and guidance documents to facilitate approval. There are now eight FDA guidance documents addressing biosimilars.

Biosimilars are approved under the BPCI Act 351k pathway under the PHS Act. Applicants under the 351k path must demonstrate that the new product is similar to the reference product utilizing the same mechanism of action for the proposed conditions of use, and has the same route of administration, dosage form, and strength.

In 2012, FDA issued guidance documents that describe a stepwise approach for industries seeking biosimilar development. The stepwise approach, in order, consists of analytical studies of the product, animal studies testing for safety, clinical PK/PD (pharmacokinetic/pharmacodynamic) studies in humans, and clinical immunogenicity assessment. This concept, termed *totality of evidence*, uses analytical characterization as the foundation to achieve biosimilarity. Figure 1 reviews this stepwise approach.

Based on available data, FDA may also request additional clinical studies. The guidance document allows for extrapolation from the reference drug to biosimilar across indications given sufficient scientific justification. In 2015, FDA released a guidance document related to the labeling and naming of biosimilars calling for the use of the reference product name with a four-letter suffix. The U.S. labels for a biosimilar are the same as for the reference product and do not include information about the biosimilar itself.

Figure 1
FDA Stepwise Approach to Biosimilar Approval



Adapted from *FDA Overview of Biosimilar Agents Continuing Education Powerpoint Presentation*

Biosimilars and Interchangeable Biologic Products

Interchangeability must be supported by data showing that the product is biosimilar to and likely to produce the same clinical results as the reference product. Interchangeable biosimilars must have the availability to be switched for or alternated with the reference product in any given patient without introducing new risks in terms of safety and reduced efficacy. According to FDA, an interchangeable biosimilar product may be substituted for the reference product by a pharmacist without the intervention of the healthcare provider who prescribed the reference product.

FDA has created the *Purple Book* to act as a biologic equivalent of the *Orange Book* which references the small-molecule drugs for therapeutic equivalence, to serve as a resource for reference product exclusivity and interchangeability evaluations for all licensed biological products. The book includes information that is useful to healthcare professionals such as the reference product exclusivity dates, biosimilar status, interchangeability status, and availability. It is important to note that biosimilars and interchangeable biological products are not one in the same. Hence, a biosimilar is not "automatically" interchangeable. To be approved by FDA as interchangeable, the biosimilar must meet a higher standard. However, at the time of writing this lesson, the higher standards required to qualify as interchangeable had not yet been issued by FDA. Like FDA, the BPCI Act describes an interchangeable product as a product that may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product.

At the time of writing, no biosimilars have been designated as interchangeable. The discussion on interchangeability and approval of automatic substitution programs for biosimilars is ongoing, with debates in the literature citing patient safety (i.e., immunogenicity) as the primary concern.

Immunogenicity

Clinical immunogenicity is a focus of safety assessments when analyzing biosimilar products. Due to the nature of biologic products, including monoclonal antibodies,

Table 2
Summary of Select Biosimilars*

Reference Product	Biosimilar	FDA Indication	Product and Cost**
Adalimumab (Humira)	Adalimumab-atto (Amjevita)	Ankylosing spondylitis, Crohn's disease, juvenile idiopathic arthritis, plaque psoriasis, psoriatic arthritis, rheumatoid arthritis, ulcerative colitis	Humira 40 mg/0.8 ml = $2667 Amjevita = not available
Etanercept (Enbrel)	Etanercept-szzs (Erelzi)	Ankylosing spondylitis, juvenile idiopatic arthritis, plaque psoriasis, psoriatic arthritis, rheumatoid arthritis	Enbrel 25 mg/0.5 ml = $667 Enbrel 50 mg/ml = $1333 Erelzi = not available
Infliximab (Remicade)	Infliximab-dyyb (Inflectra)	Ankylosing spondylitis, Crohn's disease, plaque psoriasis, psoriatic arthritis, rheumatoid arthritis, ulcerative colitis	Remicade 100 mg vial = $1404 Inflectra 100 mg vial = $1136
Filgrastim (Neupogen)	Filgrastim-sndz (Zarxio)	Cancer patients 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	Neupogen 300 mcg = $368 Neupogen 480 mcg = $585 Zarxio 300 mcg = $330 Zarxio 480 mcg = $526

*Includes only approved biosimilars discussed in this lesson
**Wholesale list prices available as of 3/1/17

they are capable of eliciting immune responses in humans. An immune response to biologics or biosimilars may lead to altered efficacy or compromised safety. For instance, an immune response may consist of immune complex formation that can result in increased or decreased clearance of the biologic, and neutralization of the activity of the biologic. Immune responses may also result in anaphylaxis, hypersensitivity reactions, and infusion reactions. Subtle changes in manufacturing, purification, or packaging, as well as shipping and storage conditions, have the potential to impact the molecular structure of the biologic product and its immunogenic potential.

Therefore, the goal of the clinical immunogenicity assessment is to evaluate potential differences between the proposed biosimilar product and the reference product in the incidence and severity of human immune responses. FDA requires a comparative assessment of immunogenicity to be incorporated into the design of all clinical studies conducted. Showing there are no clinically meaningful differences in immune response between a proposed biosimilar product and the reference product is an important element in the demonstration of biosimilarity. Additionally, all biosimilars require postmarketing surveillance to track ongoing safety and immunogenicity.

FDA-Approved Biosimilars

Infliximab-dyyb (Inflectra®) is an immunoglobulin G1 (IgG1) chimeric human-murine monoclonal antibody developed as an anti-TNF mAb biosimilar to the original reference product infliximab (INX, Remicade®). Remicade was first approved in 1999 for the treatment of rheumatoid arthritis and has had market exclusivity until now. Infliximab-dyyb has an identical amino acid sequence to infliximab and is produced in the same type of cell line. It also exhibits highly similar *in vitro* and *in vivo* pharmacodynamics, binding specificities and affinities, and other biologic and pharmacologic characteristics.

Infliximab-dyyb has shown equivalent clinical efficacy by multiple response measures to the innovator infliximab in a small number of randomized clinical trials in patients with rheumatoid arthritis (RA) and in patients with ankylosing spondylitis, without any differences detected in immunogenicity or safety between two agents.

The PLANETRA study was designed to assess the efficacy equivalence and to evaluate pharmacokinetics, pharmacodynamics, and overall safety of multiple doses of CT-P13 (now termed infliximab-dyyb) versus INX in active RA patients. Patients meeting inclusion criteria were randomly assigned 1:1 to receive two-hour intravenous infusions of either 3 mg/kg of CT-P13 or INX at weeks 0, 2, 6, and then every eight weeks up

to week 30. Patients also received methotrexate (MTX) 12.5 mg or 25 mg weekly. In this trial, the combination of MTX plus CT-P13 demonstrated equivalent efficacy to MTX plus INX at week 30. There was also no difference in safety or immunogenicity.

Inflectra has been available in South Korea since 2012 and is now available in over 70 countries worldwide. The approved indications for its use will depend on regulatory requirements in each region. In the U.S. (and Europe), this agent is approved for the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and psoriasis, Crohn's disease, and ulcerative colitis.

The NOR-SWITCH study, which was supported by the Norwegian government, was designed as a non-inferiority study over 12 months to evaluate maintenance of efficacy, safety, and immunogenicity following transitioning from reference to biosimilar infliximab (termed Remsima® by EMA), compared with maintaining patients with the reference product in patients with rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease, and chronic plaque psoriasis. Eligible patients on stable treatment for at least six months were randomized to either continue treatment with reference infliximab or to transition to CT-P13 with a primary endpoint of worsening disease. This data, reported in October 2016 at the United European Gastroenterology Week, indicated that after 52 weeks Remsima (CT-P13) is non-inferior to Remicade. The presenters claim that this real-life data validate the ability to switch patients from Remicade to Remsima (termed Inflectra in the U.S.) safely and without disease worsening.

The budget impact of switching patients to CT-P13 for RA alone in the UK, Italy, France, and Germany is estimated to offer a savings of 233 million euros over five years. At the time of writing this lesson, the wholesale list price for infliximab-dyyb 100mg is $1135 versus $1404 for Remicade 100mg. This translates to an average savings of $850 for a 70 kg patient receiving 3-5 mg/kg per dose.

Filgrastim-sndz (Zarxio®). In March 2015, FDA approved its first biosimilar, filgrastim-sndz (Zarxio®), a product available in Europle since 2009. Zarxio has the same mechanism of action, route of administration, strength, and dosage form as Amgen's Neupogen®. Zarxio is a recombinant leukocyte growth factor prescribed to combat a decline in neutrophils, a condition called *neutropenia*, that may predispose an individual to a host of illnesses. Zarxio shares the following five indications with Neupogen: (1) patients with cancer receiving myelosuppressive chemotherapy; (2) patients with acute myeloid leukemia receiving induction or consolidation chemotherapy; (3) patients with cancer undergoing bone marrow transplantation; (4) patients undergoing autologous peripheral blood progenitor cell collection and therapy; and (5) patients with severe chronic neutropenia.

The phase 3 PIONEER trial, a randomized, double-blind, parallel-group, multicenter study was conducted to demonstrate the non-inferiority of Zarxio to Neupogen in the prevention of neutropenic complications in 218 breast cancer patients treated with myelosuppressive chemotherapy. Patients were initially randomized to either Zarxio or Neupogen. Half of the patients remained on the therapy started in the first treatment cycle for the duration of the trial, while the other half of the patients received alternating treatment with either Zarxio or Neupogen starting with the second cycle of chemotherapy. The design was used to assess whether switching therapies during the treatment period has an impact on safety, efficacy, and immunogenicity. Patients enrolled in PIONEER received the biosimilar or the reference drug at a daily dose of 5 mcg/kg body weight via subcutaneous injection starting on day 2 of each chemotherapy cycle until the absolute neutrophil count recovered after nadir or for a maximum of 14 days.

The primary endpoint was duration of chemotherapy-induced severe neutropenia which was defined as number of consecutive days with grade 4 neutropenia. The mean duration of grade 4 neutropenia in cycle 1 was approximately 1.2 days (range of zero to 4 days) in both groups. Upon completion of six cycles of treatment, the predefined non-inferiority criteria (–15 percent) were met, and filgrastim-sndz was deemed noninferior to filgrastim. Additionally, no differences in the rates of treatment-emergent adverse events were observed among the treatment arms in the PIONEER clinical trial and none of the patients in the study developed antidrug antibodies.

Zarxio is available as a 300 mcg or 480 mcg single-dose vial and is administered as a subcutaneous (SC) injection, a short intravenous (IV) infusion over 15 to 30 minutes, or a continuous IV infusion, depending on the indication. Filgrastim-sndz is contraindicated in patients with a history of serious allergic reactions to human granulocyte CSFs, such as filgrastim or pegfilgrastim drugs. Depending on indication, the dose of Zarxio is 5 to 10 mcg/kg/dose for the recommended duration with the identical product label including warnings and precautions as its reference drug Neupogen.

At the time of launch of filgrastim-sndz in the U.S. in September 2015, filgrastim-sndz was priced 15 percent lower than its reference drug filgrastim. At the time of writing this lesson, the wholesale list price of the biosimilar is $330 for 300 mcg dose and $526 for the 480 mcg dose. In comparison, the cost of filgrastim (Neupogen), the originator biologic, is $368 for the 300 mcg dose and $585 for the 480 mcg dose.

Etanercept-szzs (Erelzi™). In August 2016, FDA approved etanercept-szzs (GP2015, Erelzi™), a biosimilar to Enbrel manufactured

by Sandoz, Inc. Originally licensed in 1998, Enbrel, a tumor necrosis factor inhibitor, is approved and used for multiple inflammatory conditions. Like Enbrel, Erelzi is available as an injectable solution in a prefilled syringe or autoinjector (25 mg/0.5 ml or 50 mg/ml) for subcutaneous administration, and has been granted approval for use in the following disease states: (1) moderate to severe rheumatoid arthritis, either as standalone therapy or in combination with MTX; (2) moderate to severe polyarticular juvenile idiopathic arthritis in patients ages two and older; (3) active psoriatic arthritis including use in combination with MTX in psoriatic arthritis patients who do not respond adequately to MTX alone; (4) active ankylosing spondylitis; and (5) chronic moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

The FDA Arthritis Advisory Committee voted unanimously to recommend licensure of GP2015 (Erelzi) after reviewing data from three single-dose PK studies and one comparative study. The PK studies were designed to support PK similarity of GP2015 and U.S.-licensed etanercept, and to demonstrate that PK comparative data generated using EU-approved etanercept could be used to demonstrate the biosimilarity of GP2015 to U.S.-licensed etanercept. FDA reports that the three products met the pre-specified criteria for analytical specificity.

The 52-week, randomized, double-blind, multicenter comparative clinical study was conducted outside the U.S. and consisted of 531 patients with moderate to severe chronic plaque psoriasis. Patients were randomly assigned in a 1:1 ratio to receive 50 mg GP2015 or EU-approved etanerept subcutaneously twice weekly for 12 weeks followed by 50 mg weekly thereafter. Patients who completed the 12-week treatment period 1 and achieved an improvement in the Psoriasis Area Severity Index (PASI) of 50 percent or higher were re-randomized to either continue the initial treatment or undergo predefined switches between the two products at six-week intervals during week 12 to week 30. This was referred to as treatment period 2. Finally, patients continued with the last assigned treatment from week 30 to week 52. Researchers assessed safety and immunogenicity in patients who completed treatment period 2. The primary outcome of PASI 75 at week 12, defined as a reduction in the PASI score of at least 75 percent from baseline, was 73.4 percent in the GP2015 group and 75.7 percent in the etanercept group. In the GP2015 group, 35 patients experienced one or more treatment-related emergent adverse events compared to 37 patients in the etanercept group. Hence, FDA concluded that in totality of evidence, the data submitted by Sandoz show that GP2015 is highly similar to etanercept. At the time of writing, Erelzi is not approved with interchangeable status.

Despite approval, Erelzi has not reached the market at the time of writing this lesson. Amgen has filed a lawsuit against Sandoz claiming the company is wrongly profiting from its research on etanercept. The cost of Enbrel is $667 for a single 25 mg dose and $1333 for a single 50 mg dose.

Adalimumab-atto (Amjevita™). In September 2016, FDA approved the U.S.'s fourth biosimilar, adalimumab-atto (ABP501, Amjevita™). Amjevita was approved as a biosimilar to adalimumab (Humira®, approved in 2002), and is approved for the following indications in adults: (1) moderate to severe active rheumatoid arthritis; (2) active psoriatic arthritis; (3) active ankylosing spondylitis; (4) moderately to severely active Crohn's disease; (5) moderately to severely active ulcerative colitis; (6) moderate to severe plaque psoriasis; and (7) moderately to severely active polyarticular juvenile idiopathic arthritis in patients four years of age and older. When available in the U.S., Amjevita will be supplied for subcutaneous administration in single-use prefilled syringes (20 mg/0.4 ml and 40 mg/0.8 ml) and single-use autoinjectors (40 mg/0.8 ml).

The 26-member FDA committee voted unanimously for approval. The decision was based on data from a single-dose PK study and two clinical trials. The PK study was a three-way comparison of ABP501, U.S.-licensed adalimumab, and EU-approved adalimumab which supported PK similarity. The first clinical trial was a 26-week, randomized, double-blind, parallel group study that included 526 patients with moderately to severely active rheumatoid arthritis who were receiving methotrexate. The study randomly assigned patients in a 1:1 ratio to receive ABP501 or U.S.-licensed adalimumab at a dose of 40 mg subcutaneously every other week. The primary endpoint of the study was the proportion of patients who stayed in the study and achieved an American College of Rheumatology 20 percent response at week 24. The study concluded that there were no meaningful differences in the safety, purity, and potency of the two drugs.

The second clinical trial, consisting of 350 patients, was conducted outside the U.S. and studied patients with moderate to severe plaque psoriasis. Patients either received the EU-approved adalimumab or ABP501. After 16 weeks of treatment with the EU-approved product, patients were randomly assigned to either one transition to ABP501 or continued to receive EU-approved adalimumab through week 48. The transition from EU-approved adalimumab to ABP501 showed no difference in the safety or immunogenicity. This data support the safety of one transition in a non-treatment naïve patient.

According to the FDA statement, despite the data provided by the company addressing scientific justification for extrapolating data to support similarity in other indications (i.e., Crohn's disease and ulcerative colitis), patients and

patient advocates voiced concerns during open public sessions regarding this matter. While many experts advocated for the extrapolation of indications based on the evidence, some felt there was a lack of data. Others have called for the need for post-marketing studies and improved monitoring.

Similar to Erelzi, Amjevita is also being blocked from reaching the market as Abbvie claims its patent protects adalimumab from competition from biosimilar products until 2022. As of March 2017, the cost of a single dose of Humira 40 mg/0.8ml was $2667.

Summary

The development of a U.S. biosimilar program is an important advancement in healthcare as it can potentially improve access to treatment and has been shown to reduce healthcare costs in the EU. Yet, a knowledge and clinical data gap may be present for both healthcare professionals and the lay public. Additional education, clinical experience, and post-marketing data are likely needed before widespread use and confidence in these products are present in the U.S. Even though biosimilars are priced approximately 15 percent lower, this cost savings can be significant over the lifetime of treatment. As biosimilars continue to be approved, we can expect a delay in marketing and availability due to patent protection and legal battles.

The author, the Ohio Pharmacists Foundation and the Ohio Pharmacists Association disclaim any liability to you or your patients resulting from reliance solely upon the information contained herein. Bibliography for additional reading and inquiry is available upon request.

This lesson is a knowledge-based CPE activity and is targeted to pharmacists in all practice settings. Disclosure: The OPF trustees and other individuals responsible for planning OPF continuing pharmacy education activities have no relevant financial relationships to disclose.

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continuing education quiz

Biologics and Biosimilars

1. Biologics have had a profound impact on all the following areas of practice EXCEPT:
   a. gastroenterology. c. oncology/hematology.
   b. neurology. d. rheumatology.

2. Biosimilars are generic biologic agents.
   a. True b. False

3. All of the following are true concerning reference products EXCEPT they:
   a. are an FDA-approved biological product.
   b. have the same mechanism of action of a biosimilar.
   c. have the exact molecular structure as the biosimilar.

4. Which of the following Acts created a new abbreviated FDA approval pathway for biosimilars?
   a. BPCI Act c. Hatch-Waxman Act
   b. Affordable Care Act d. Food, Drug, Cosmetic Act

5. FDA's stepwise approach for industries seeking biosimilar development consists of all of the following EXCEPT:
   a. animal studies.
   b. clinical PK/PD studies in humans.
   c. clinical immunogenicity assessment.
   d. postmarketing studies.

6. Which of the following formats is used to name biosimilars?
   a. Different first letter from reference product
   b. 4-letter prefix + reference product
   c. Reference product + 4-letter suffix

7. According to FDA, an interchangeable biosimilar product may be substituted for the reference product.
   a. True. b. False

Completely fill in the lettered box corresponding to your answer.

1. [a] [b] [c] [d]	6. [a] [b] [c]	11. [a] [b] [c] [d]
2. [a] [b]	7. [a] [b]	12. [a] [b] [c] [d]
3. [a] [b] [c]	8. [a] [b] [c] [d]	13. [a] [b] [c]
4. [a] [b] [c] [d]	9. [a] [b] [c]	14. [a] [b] [c]
5. [a] [b] [c] [d]	10. [a] [b] [c]	15. [a] [b] [c] [d]

❑ **I am enclosing $5 for this quiz made payable to: Ohio Pharmacists Association.**

1. Rate this lesson: (Excellent) 5 4 3 2 1 (Poor)
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   If no, list any unmet_____
3. Was the content balanced and without commercial bias?
   ❑ yes ❑ no If no, why?_____
4. Did the program meet your educational/practice needs?
   ❑ yes ❑ no
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Return quiz and payment (check or money order) to Correspondence Course, OPA, 2674 Federated Blvd, Columbus, OH 43235-4990

8. Which of the following reference books was created by FDA to serve as a resource for licensed biological products?
   a. The *Red Book* c. The *Purple Book*
   b. The *Orange Book* d. The *Pink Book*

9. The goal of clinical immunogenicity assessments is to evaluate potential differences between biosimilar and reference products in the incidence and severity of:
   a. adverse events. c. human immune responses.
   b. contamination.

10. Amjevita, Erelzi and Inflectra are all approved to treat:
   a. cancer. c. Crohn's disease.
   b. rheumatoid arthritis.

11. The PLANETRA study showed there was no difference in safety or immunogenicity between:
   a. Humira and Amjevita. c. Enbrel and Erelzi.
   b. Neupogen and Zarxio. d. Remicade and Inflectra.

12. Zarxio is used to treat:
   a. neutropenia. c. normocytic anemia.
   b. leukocytosis. d. thrombocytopenia.

13. Zarxio is administered by all of the following routes EXCEPT:
   a. IV infusion. c. SC injection.
   b. IM injection.

14. All of the following are approved indications for Erelzi EXCEPT:
   a. Crohn's disease. c. rheumatoid psoriasis.
   b. plaque psoriasis.

15. Amjevita is approved for all the following indications EXCEPT:
   a. rheumatoid arthritis. c. Crohn's disease.
   b. ankylosing spondylitis. d. chronic neutropenia.

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