A Systematic Review of U.S. Biosimilar Approvals: What Evidence Does the FDA Require and How Are Manufacturers Responding?

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ABSTRACT

BACKGROUND: Biosimilars undergo an abbreviated licensure pathway called 351(k), which was created by the Biologics Price Competition and Innovation Act of 2009. This approval process is different from the 351(a) pathway for original biologic approval and, as of August 2017, has been used to approve 5 biosimilars in the United States.

OBJECTIVE: To identify the types and quantities of evidence required by the FDA for biosimilar approval and the corresponding evidence manufacturers have provided in their 351(k) biosimilar approval applications.

METHODS: To collect data for this review, we searched through drug-specific FDA approval documents and approval-related FDA webcasts for approval indications and dates; reference product names; formulations; postmarketing requirements and commitments; evidence used for extrapolation claims; advisory committee votes; and evidence on similarity in analytical and functional characteristics, pharmacokinetics, pharmacodynamics, efficacy, safety, and immunogenicity.

RESULTS: All biosimilars approved in the United States provided a large evidence base to demonstrate similarity in analytical and functional characteristics—3 to 5 clinical studies showed similarity in pharmacokinetics and pharmacodynamics, and 1 to 2 clinical studies demonstrated efficacy. Safety and immunogenicity were evaluated across all clinical studies. All biosimilars were compared with either the U.S.-licensed reference product or the reference product licensed by the European Union. Extrapolation allowed biosimilars to be approved for indications in which clinical studies were not conducted. The few indications for which biosimilars did not share approval with the reference product were due to market exclusivity protection. None of the 5 biosimilars have been approved as interchangeable in the United States.

CONCLUSIONS: The approval process for the first 5 biosimilars on the market in the United States provides a baseline understanding of what type and degree of evidence is required for biosimilar approval.

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What this study adds

- The biosimilar approval pathway relies largely on analytical studies, along with a few clinical studies to assess pharmacokinetics, pharmacodynamics, immunogenicity, safety, and efficacy.
- Key themes in the biosimilar approval pathway include extrapolation, 3-way bridging, and slightly different formulations.

Biologics are used for a wide variety of conditions, from rheumatoid arthritis and psoriasis to various types of cancer.¹ These agents can greatly improve patient quality of life.² However, biologics can be very expensive. Although biologics account for less than 1% of all prescriptions, they amount to 28% of total drug expenditures in the United States.³

In 2010, the Biologics Price Competition and Innovation (BPCI) Act was signed into law, creating the 351(k) approval pathway for biosimilars. By definition, a biosimilar must be “highly similar to the reference product notwithstanding minor differences in clinically inactive components.”⁴ In addition, there should be “no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency of the product.”⁴ Since the 351(k) is an abbreviated pathway compared with the 351(a) approval pathway for biologics (Figure 1), biosimilars require less time and money in development compared with biologics (Table 1).⁴ Importantly, biosimilars are expected to save approximately \$44 billion from 2014 to 2024 in the United States.⁵ The Congressional Budget Office expects cost savings to the federal government to be \$25 billion by 2018.⁶

Although biosimilars are similar in concept to generic drugs, there are key regulatory differences between them. When a branded drug’s patent expires (generally 20 years from the patent’s filing date) and the drug’s market exclusivity protections end, companies that produce generic drugs are encouraged to submit an Abbreviated New Drug Application (505[j]) to the U.S. Food and Drug Administration (FDA) for licensure. Under the Hatch-Waxman Act, these generic applicants only need to establish bioequivalence, without other preclinical or clinical data, to seek FDA approval.⁷ However, bioequivalence is not applicable to biological agents, which are made from living organisms and can have allowable differences. This differentiation explains why biosimilars require extensive analytical data to demonstrate high similarity, which often results in longer

What is already known about this subject

- Biosimilars are relatively new to the U.S. market; as of this writing, there are 5 licensed biosimilars, with 3 on the market.
- The biosimilar approval pathway is different from the approval pathways for biologic reference products and generics.

FIGURE 1 Difference Between Pathways: 351(a) Versus 351(k)

Extracted from Christl L. Overview of the regulatory pathway and FDA's guidance for the development and approval of biosimilar products in the U.S.³²

development time and higher development costs for biosimilars compared with generics (Table 1).⁴ In addition, market exclusivity is longer for a biologic compared with a small molecule drug. Specifically, market exclusivity for a biologic is 12 years, whereas market exclusivity for a small molecule drug is 5 years.^{8,9}

Another major difference between a generic drug and a biosimilar is in the substitution of the branded/reference products. Automatic generic substitution is commonly performed at the point of sale for brand versus generic drugs unless otherwise specified by a prescriber. Biosimilars and their reference products, however, are not automatically interchangeable. The FDA issued its first draft guidance on interchangeability in January 2017. Currently, 27 states have passed legislation to allow the substitution of biosimilars for biologics if the biosimilar is approved as interchangeable.¹⁰ These state laws differ in how long pharmacists have to notify prescribers, whether pharmacists must notify patients, and how long pharmacists have to retain records of such substitutions. For example, Arizona's law (enacted May 2016) allows pharmacists to substitute a biosimilar for its reference product as long as pharmacists notify the prescriber within 5 days. This time frame differs from a 24-hour notification requirement in North Dakota's law (enacted June 2013).¹⁰ However, until the FDA approves a biosimilar as interchangeable, no biosimilar can be automatically substituted for its reference product by pharmacists.

Although the BPCI was signed in 2010, it was not until 2015 that the FDA granted its first biosimilar approval. As of August 2017, there have been 5 biosimilars approved by the FDA in the United States: Zarxio (filgrastim-sndz), Inflectra (infliximab-dyyb), Erelzi (etanercept-szzs), Amjevita (adalimumab-atto), and

TABLE 1 Differences in Development Time and Cost Among Chemical, Generic, Biological, and Biosimilar Drugs

	Chemical Drugs ³³	Generic Drugs ³³	Biological Drugs ^{34,35}	Biosimilar Drugs ³⁶
Development time	7-10 years	1-3 years	10-15 years	8-10 years
Development cost	~\$800M	\$1M-2M	\$1,200M-2,500M	\$100M-200M

Note: Costs are in U.S. dollars.

Renflexis (infliximab-abda). Of these, only 3 are currently on the market: filgrastim-sndz, infliximab-dyyb, and infliximab-abda.

The first few years of biosimilar entry into the U.S. market have been challenging. There has not been a significant price drop or substantial increase in patient access, as previously predicted. Instead, initial experience with the first 3 biosimilars has shown a price reduction ranging from 15% to 19% in a market with 1 biosimilar and 35% in a market with 2 biosimilars for the same biologic.¹¹⁻¹³ This is in comparison with a price reduction of 57%-74% that is seen with generic medicines, although price reduction varies based on factors such as the number of generic entrants into the market.¹⁴ Furthermore, patent disputes and litigation have contributed to delays in biosimilar launches.^{15,16}

There are also other products, such as Basaglar (insulin glargine) and Granix (tbo-filgrastim), that are not officially biosimilars in the United States but are very similar to Lantus (insulin glargine recombinant) and Neupogen (filgrastim). Insulin glargine and tbo-filgrastim are not officially biosimilars because neither were approved through the 351(k) biosimilar approval pathway. Instead, tbo-filgrastim was approved before the 351(k) pathway was available.¹⁷ Meanwhile, since all insulin products are licensed under section 505 of the Food, Drug and Cosmetic Act, insulin glargine was approved under the 505(b)(2) pathway, a hybrid pathway between a full New Drug Application 505(b)(1) and an Abbreviated New Drug Application 505(j) pathway.¹⁸

While biosimilars are a fairly new concept in the United States, other countries have had longer biosimilar experience. Since the European Union's (EU) first biosimilar approval in 2006, its safety surveillance system has not recognized any differences in the rate, as well as the severity, of adverse events between biosimilars and their reference products.¹⁹ In addition, price reductions have ranged from 30% for anti-tumor necrosis factor drugs, 60% for granulocyte colony-stimulating factor drugs, and up to 66% for erythropoietin, leading to increased patient access to these biologics.²⁰ South Korea is also pushing forward with biosimilars. Of its 7 approved biosimilar products, only 2 are approved and available in the United States.

FIGURE 2 Flow Diagram

FDA=U.S. Food and Drug Administration.

South Korea expects its biosimilar market to grow to \$130 million by 2019, with a 22% global share by 2020.²¹

The U.S. biosimilar market is still young. A better understanding of the extensive and rigorous process that goes into biosimilar development and approval will better inform our decisions regarding these products. The objective of this systematic review was to identify the types and quantities of evidence required by the FDA for biosimilar approval and describe how biosimilar manufacturers have responded to the FDA requirements.

Methods

The methodology of this systematic review was adapted from the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines. For data collection, we searched the Drugs@FDA website for drug-specific approval documents and the FDA advisory committee meeting website

for advisory committee meeting materials and webcasts for the 5 FDA-approved biosimilars from January 2015 through June 2017.^{22,23} Search terms included the following: *Zarxio*, *filgrastim-sndz*, *Inflectra*, *infliximab-dybb*, *Amjevita*, *adalimumab-atto*, *Erelzi*, *etanercept-szsz*, *Renflexis*, and *infliximab-abda*. All documents submitted by the biosimilar manufacturers to the FDA, letters from the FDA to the biosimilar manufacturers, and review documents during the FDA advisory committee meetings that were available on the Drugs@FDA website were considered eligible for review. Titles were screened first. If a biosimilar of interest was identified, the entire document or webcast was reviewed. Documents were excluded if they included similar or duplicative content to previously included documents (Figure 2).

Extracted data included the following: approval indications and dates; reference product names; formulations; postmarketing requirements and commitments; evidence used for

TABLE 2 Indications, Dosage Formulations, Extrapolation, and Advisory Committee Vote for Biosimilars^{11-13,15,16,37-45}

Biosimilar (Approval Date; Date on Market) and Its Reference Product (Approval Date) ^a	Indications	Formulations		Extrapolation	Advisory Committee Vote (Favor: Against Licensure)
		Biosimilar	Reference Product		
Zarxio [filgrastim-sndz] (3/6/15; 9/3/15) <i>Neupogen</i> [filgrastim] (2/20/91)	1. Decrease incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer agents associated with a significant incidence of severe neutropenia with fever 2. Reduce time to neutrophil recovery and duration of fever following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia 3. Reduce duration of neutropenia and neutropenia-related clinical sequelae (e.g., febrile neutropenia) in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy following bone marrow transplantation 4. Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis 5. Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia <i>Reference product indication for which biosimilar was not approved by FDA:</i> 1. Increase survival in patients acutely exposed to myelosuppressive doses of radiation (hematopoietic syndrome of acute radiation syndrome)	Injection: 300 mcg/0.5 mL in a single-dose prefilled syringe with BD UltraSafe Passive Needle Guard	Injection: 300 mcg/0.5 mL in a single-dose prefilled syringe with an UltraSafe Needle Guard	Clinical study done in breast cancer patients undergoing 6 cycles of TAC. Extrapolated to 4/6 other indications due to demonstration of: <ul style="list-style-type: none"> MOA: 4/5 approved indications relate to level of neutrophils in peripheral blood. 1/5 approved indications relates to level of CD34+ stem cells in peripheral blood. Binding of filgrastim to granulocyte colony-stimulating factor receptor on cells is the first step of filgrastim-mediated neutrophil differentiation and proliferation, as well as in CD34+ stem cell mobilization. Analytical and functional characteristics related to the MOA were similar between filgrastim-sndz and filgrastim. Biosimilarity (analytical, PK, immunogenicity, safety profiles) to filgrastim. 	14:0
		Injection: 480 mcg/0.5 mL in a single-dose prefilled syringe with BD UltraSafe Passive Needle Guard	Injection: 480 mcg/0.5 mL in a single-dose prefilled syringe with an UltraSafe Needle Guard		
			Injection: 300 mcg/0.5 mL in a single-dose vial		
			Injection: 480 mcg/0.5 mL in a single-dose vial		
Inflectra [infliximab-dyyb] (4/5/16; 10/17/16) <i>Remicade</i> [infliximab] (08/24/98)	1. CD (adult and pediatric patients aged 6 or older) 2. UC in adults 3. RA 4. AS 5. PsA 6. PsO in adults <i>Reference product indication for which biosimilar was not approved by FDA:</i> 1. Pediatric UC	100 mg of lyophilized infliximab-dyyb in a 20 mL vial for intravenous infusion	100 mg of lyophilized infliximab in a 20 mL vial for intravenous infusion	Clinical studies done in RA and AS. Extrapolated to 4/7 other indications due to demonstration of: <ul style="list-style-type: none"> MOA of infliximab-dyyb (binding and neutralization of soluble and membrane TNF-α, which is similar to infliximab). Biosimilarity (analytical, PK, immunogenicity, safety profiles) to infliximab. 	21:3

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extrapolation claims; advisory committee votes; and evidence on similarity in analytical and functional characteristics, pharmacokinetics (PK), pharmacodynamics (PD), efficacy, safety, and immunogenicity. It should be noted that whereas postmarketing requirements are required by statute or

regulation, postmarketing commitments are not.²⁴ Evidence from animal studies were not extracted because, if available, they were only briefly mentioned in advisory committee meetings. Extracted data were then collected and reported in this review.

TABLE 2 Indications, Dosage Formulations, Extrapolation, and Advisory Committee Vote for Biosimilars^{11-13,15,16,37-45} (continued)

Biosimilar (Approval Date; Date on Market) and Its Reference Product (Approval Date) ^a	Indications	Formulations		Extrapolation	Advisory Committee Vote (Favor: Against Licensure)
		Biosimilar	Reference Product		
Erelzi [etanercept-szsz] (8/30/16; expected earliest 2018) <i>Enbrel [etanercept]</i> (11/02/98)	1. RA 2. JIA in patients 2 years or older 3. PsA 4. AS 5. PsO in patients 18 years or older <i>Reference product indication for which bio-similar was not approved by FDA:</i> 1. PsO in patients between 4 and 17 years	Injection: 25 mg/0.5 mL in a single-dose prefilled syringe with BD UltraSafe Passive Needle Guard	Injection: 25 mg/0.5 mL in a single-dose prefilled syringe	Clinical studies done in PsO. Extrapolated to 4/6 other indications due to demonstration of: <ul style="list-style-type: none"> MOA (etanercept-szszs and etanercept's MOA are TNF-α binding and neutralization). Biosimilarity (analytical, PK, immunogenicity, safety profiles) to etanercept. 	20:0
		Injection: 50 mg/mL in a single-dose prefilled syringe with BD UltraSafe Passive Needle Guard	Injection: 50 mg/mL in a single-dose prefilled syringe		
		Injection: 50 mg/mL solution in single-dose prefilled Sensoready Pen	Injection: 50 mg/mL solution in single-dose prefilled SureClick Autoinjector		
			Injection: 25 mg lyophilized powder in a multiple-dose vial for reconstitution		
Amjevita [adalimumab-atto] (9/23/16; expected earliest 2018) <i>Humira [adalimumab]</i> (12/31/02)	1. RA in adults 2. JIA in patients 4 years or older 3. PsA in adults 4. CD in adults 5. UC in adults 6. PsO in adults 7. AS in adults <i>Reference product indication for which bio-similar was not approved by FDA:</i> 1. Pediatric CD 2. Hidradenitis suppurativa 3. Uveitis 4. JIA in patients 2 to <4 years	Injection: 40 mg/0.8 mL in a single-use prefilled SureClick autoinjector	Injection: 40 mg/0.8 mL in a single-use prefilled pen	Clinical studies done in RA and PsO. Extrapolated to 5/11 other indications due to demonstration of: <ul style="list-style-type: none"> Similar MOA for adalimumab-atto and adalimumab. Specifically, the primary MOA for RA, JIA, AS, PsA, and PsO, and likely MOA in CD and UC is inhibition of binding of sTNF to cell-surface receptors and through binding tmTNF, inhibiting subsequent signal transduction and adhesion molecule expression. There are additional likely and plausible MOA in CD and UC. Biosimilar was similar to reference product structurally and functionally related to all above MOA. Biosimilarity (analytical, PK, immunogenicity, safety profiles) to reference product. 	26:0
			Injection: 40 mg/0.4 mL in a single-use prefilled pen		
		Injection: 40 mg/0.8 mL in a single-use prefilled glass syringe	Injection: 40 mg/0.8 mL in a single-use prefilled glass syringe		
			Injection: 40 mg/0.4 mL in a single-use prefilled glass syringe		
		Injection: 20 mg/0.4 mL in a single-use prefilled glass syringe	Injection: 20 mg/0.4 mL in a single-use prefilled glass syringe		
			Injection: 10 mg/0.2 mL in a single-use prefilled glass syringe		
			Injection: 40 mg/0.8 mL in a single-use glass vial for institutional use only		

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TABLE 2 Indications, Dosage Formulations, Extrapolation, and Advisory Committee Vote for Biosimilars^{11-13,15,16,37-45} (continued)

Biosimilar (Approval Date; Date on Market) and Its Reference Product (Approval Date) ^a	Indications	Formulations		Extrapolation	Advisory Committee Vote (Favor: Against Licensure)
		Biosimilar	Reference Product		
Renflexis [infliximab-abda] (04/21/17; 07/25/17) <i>Remicade</i> [infliximab] (08/24/98)	1. CD (adult and pediatric patients aged 6 or older) 2. UC in adults 3. RA 4. AS 5. PsA 6. PsO in adults <i>Reference product indication for which biosimilar was not approved by FDA:</i> 1. Pediatric UC	100 mg of lyophilized infliximab-abda in a 20 mL vial for intravenous infusion	100 mg of lyophilized infliximab in a 20 mL vial for intravenous infusion	N/A	N/A

^aReference product is shown in italics.

AS = ankylosing spondylitis; CD = Crohn's disease; CD34+ = hematopoietic progenitor cell antigen; FDA = U.S. Food and Drug Administration; JIA = juvenile idiopathic arthritis; MOA = mechanism of action; N/A = not available; PK = pharmacokinetic; PsO = plaque psoriasis; PsA = psoriatic arthritis; RA = rheumatoid arthritis; TAC = docetaxel, doxorubicin, and cyclophosphamide; TNF- α = tumor necrosis factor- α ; sTNF = soluble TNF- α ; tmTNF = transmembrane TNF- α ; UC = ulcerative colitis.

Results

The search on Drugs@FDA and of other FDA advisory committee meeting materials yielded 96 documents (Figure 2). Of these documents, 44 were excluded following initial title screening. The remaining 52 documents were then selected for full-text review. The 12 medical, pharmacology, and clinical pharmacology biopharmaceutics reviews were excluded because the important points that were covered in the advisory committee meetings were duplicated in summary reviews and presentation slides from manufacturers. A total of 40 documents were included in the final review.

Of the 5 FDA-approved biosimilars, only infliximab-abda did not have review documents on Drugs@FDA at the time of this study, with the exception of an approval letter and label. A summary of the evidence that the biosimilar manufacturers submitted to the FDA to seek licensure and information that the FDA provided from their review process is provided in Tables 2 and 3.

Table 2 presents information regarding dates of approval versus market entry, indications, formulations, extrapolation, and advisory committee votes. Filgrastim-sndz was the first biosimilar to gain FDA approval (March 2015), followed by infliximab-dyyb (April 2016), etanercept-szss (August 2016), adalimumab-atto (September 2016), and infliximab-abda (April 2017). Only 3 of these biosimilars were available on the U.S. market at the time of this review: filgrastim-sndz (September 2015), infliximab-dyyb (October 2016), and infliximab-abda (July 2017). Postmarketing requirements and commitments for each biosimilar can be found in the Appendix (available in online article).

The 5 biosimilars were approved for all of the same indications as their reference products except for a few indications (Table 3). These exceptions occurred because the reference product had orphan drug marketing exclusivity over these indications or because the reference product had not yet been approved for the indication at the time of biosimilar approval.

In general, clinical studies were conducted in 1 or 2 indications. Biosimilarity for other indications was then extrapolated based on demonstrating that the biosimilar was similar to the reference product in functional characteristics relevant to the understood mechanisms of action for these indications. Extrapolation was also supported by the demonstration of similar analytical characteristics, PK, immunogenicity, and safety profiles between the biosimilar and its reference product.

The formulations that the 5 biosimilars were approved for were the same or similar to those of the reference products (Table 2). There were some differences: Adalimumab-atto was approved for an autoinjector pen instead of a prefilled pen, as with the original reference product, and the prefilled syringe formulation of etanercept-szss had an additional needle guard. The 5 biosimilars did not always have as many formulations as the reference products.

Only etanercept-szss and adalimumab-atto had postmarketing requirements, which were related to treatment in pediatric patients (Appendix, available in online article). All biosimilars except infliximab-dyyb had postmarketing commitments, which were generally related to additional analytical testing. Infliximab-dyyb did not have postmarketing requirements or commitments.

TABLE 3 Efficacy, Safety/Immunogenicity, PK/PD, and Analytical/Functional Evidence for Biosimilars³⁷⁻⁴⁰

Biosimilar	Efficacy	Safety/Immunogenicity	PK/PD	Analytical/Functional
Zarxio [filgrastim-sndz]	<p>1 efficacy trial:</p> <p>R, DB, AC (n=204) in breast cancer patients undergoing 6 cycles of TAC comparing 5 mcg/kg, SC, multiple dose filgrastim-sndz to U.S.-filgrastim. Primary endpoint and result: difference in DSN in cycle 1 (90% CI)=0.04 days (-0.21, 0.28).</p>	<p>Same key efficacy clinical trial (n=214 for safety and immunogenicity).</p> <p>Safety endpoints and results: descriptive statistics were similar in major safety events (TEAEs, related TEAEs, SAEs, related SAEs, fatal TEAEs, related fatal TEAEs); common AEs (musculoskeletal pain, injection site reaction); and hypersensitivity (anaphylactic reaction, hypersensitivity).</p> <p>Immunogenicity endpoint and result: No patients developed ADA.</p> <p>Other clinical studies also demonstrated similar safety and immunogenicity results.</p>	<p>5 clinical studies:</p> <ol style="list-style-type: none"> 1. Substudy from key efficacy clinical trial (n=54). 2. R, DB, 2WC trial (n=28) in HS comparing 10 mcg/kg SC single dose filgrastim-sndz to U.S.-filgrastim. 3. R, DB, 2WC trial (n=28/dose) in HS with 2 dose groups, comparing 2.5 and 5 mcg/kg SC single and multiple (7-day) dose filgrastim-sndz to EU-filgrastim. 4. R, DB, 2WC trial (n=24) in HS, comparing 1 mcg/kg SC single dose filgrastim-sndz to EU-filgrastim. 5. R, DB, 2WC trial (n=32) in HS, comparing 10 mcg/kg SC single and multiple dose filgrastim-sndz to EU-filgrastim. <p>PK endpoints and results: similar AUC and Cmax.</p> <p>PD endpoints and results: similar ANC and CD34+.</p>	<p>The following quality attributes were deemed highly similar between filgrastim-sndz, U.S.-filgrastim, and EU-filgrastim:</p> <p>primary structure, bioactivity, protein content, receptor binding, clarity, subvisible particles, secondary and tertiary structure, high molecular weight variants/aggregates, oxidized species, covalent dimers, partially reduced species, formyl methionine 1 species, sequence variants: histidine → glutamine, aspartate → glutamate, threonine → aspartate, succinimide species, phosphoglucuronoylation, acetylated species, N-terminal truncated variants, norleucine species, deamidated species, and stability profiles.</p>
Inflectra [infliximab-dyyb]	<p>2 efficacy trials:</p> <ol style="list-style-type: none"> 1. R, DB, PG 54-week clinical study (n=606) of patients with active RA despite MTX use to receive infliximab-dyyb and EU-infliximab. Primary endpoint and result: estimated difference in ACR20 response at week 30 (90% CI)=2% (-5%, +9%) 2. R, DB, PG 54-week clinical study (n=250) of patients with active AS. Primary endpoint was PK. Secondary endpoint and result: estimated difference in ASAS20 response at week 30 (95% CI)=-4% (-16%, +8%) 	<p>803 subjects (patients and HS) exposed to at least 1 dose of infliximab-dyyb. Descriptive statistics were similar in TEAEs, SAEs, and AEs leading to discontinuation. The most common TEAEs were infections.</p> <p>Immunogenicity endpoints and results:</p> <p>4 deaths: 2 on infliximab-dyyb and 2 on EU- infliximab</p> <p>7 cases of anaphylaxis on infliximab-dyyb vs. 7 on EU-infliximab; did not increase following transition from EU-infliximab to infliximab-dyyb</p> <p>Incidence of ADA similar between infliximab-dyyb and EU-infliximab. ADA incidence remained unchanged following transition from EU-infliximab to infliximab-dyyb</p>	<p>3 clinical studies:</p> <ol style="list-style-type: none"> 1. 3-way PK bridging/similarity study in HS: R, DB, 3-arm, PG single dose study (N=71/arm). 2. PK study in AS patients: R, DB, 2-arm, PG, multiple dose study (N=125/arm). 3. Comparative clinical study in RA patients: R, DB, PG study (N=606). <p>PK endpoints and results: similar AUC and Cmax.</p>	<p>The following quality attributes were deemed highly similar between infliximab-dyyb, U.S.-infliximab, and EU-infliximab: primary structure, bioactivity, (TNF-α binding and neutralization), purity, Fc receptor binding, protein content, subvisible particles, higher order structure (second structure), biologic analysis and MOA exploration, high molecular weight variants/aggregates, and physicochemical analysis.</p> <p>Highly critical quality attributes include amino acid identity and in vitro TNF-α neutralization and binding.</p>

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Except for infliximab-dyyb and infliximab-abda, the advisory committee vote to approve the biosimilar was unanimous. For infliximab-dyyb, the vote was 21:3. Infliximab-abda did not have an advisory committee meeting or vote.

Table 3 lists information regarding efficacy, safety, immunogenicity, PK, PD, and analytical evidence required to approve 4

of the biosimilars. Table 3 does not include information for infliximab-abda because, at the time of this review, documents for infliximab-abda were not available on Drugs@FDA. For each biosimilar, there were no more than 2 efficacy trials that compared the biosimilar to either the U.S.- or EU-licensed reference product, with the number of participants ranging

TABLE 3 Efficacy, Safety/Immunogenicity, PK/PD, and Analytical/Functional Evidence for Biosimilars³⁷⁻⁴⁰ (continued)

Biosimilar	Efficacy	Safety/Immunogenicity	PK/PD	Analytical/Functional
Erelzi [etanercept-szszs]	<p>2 efficacy trials:</p> <p>R 52-week clinical trial (n=531) in PsO patients comparing etanercept-szszs vs. EU-etanercept (50mg SC twice per week followed by 50 mg SC once per week)</p> <p>2 treatment periods:</p> <p>TP 1: week 0 to 12. Primary endpoint and results: estimated difference in PASI75 at week 12 (90% CI)=-2.3 (-8.63, 4.08)</p> <p>TP 2: week 12 to 30, comparing efficacy of continued treatment arm vs. repeated switches between etanercept and etanercept-szszs. Comparable PASI response between continued etanercept and etanercept-szszs and no impact of switching on PASI response in patient pools that underwent multiple switches</p>	<p>747 subjects (patients and HS) exposed to at least 1 dose of etanercept-szszs.</p> <p>Descriptive statistics were similar in TEAEs, SAEs, and AE leading to discharge. Most common AEs were infection. There was 1 death in the EU-etanercept treatment group (cardiopulmonary death).</p> <p>Immunogenicity endpoints and results:</p> <p>No immunogenicity concerns for etanercept-szszs vs. etanercept. No cases of anaphylaxis. 5% of EU-etanercept treatment group were ADA positive but only transiently.</p>	<p>4 clinical studies of up to 3 months each in healthy volunteers:</p> <ol style="list-style-type: none"> 1. Compare etanercept-szszs vs. U.S.-etanercept in 57 HS 2. Compare etanercept-szszs vs. EU-etanercept in 54 HS 3. Compare etanercept-szszs vs. EU-etanercept in 54 HS 4. Compare etanercept-szszs administration autoinjection vs. prefilled syringes in 51 HS <p>Comparative clinical study in PsO subjects (n=531) also demonstrated similar PK profile between etanercept-szszs and EU-etanercept.</p> <p>PK endpoints: similar Cmax and AUC</p>	<p>The following critical quality attributes were deemed highly similar between etanercept-szszs, U.S.-etanercept and EU-etanercept: primary structure; higher order structure (there are some incorrect disulfide bond variants present that are detectable in vitro; however, these will refold correctly under physiological condition); TNF-α neutralization; content; FcRn binding; product related impurities; and stability.</p>
Amjevita [adalimumab-atto]	<p>2 efficacy trials:</p> <ol style="list-style-type: none"> 1. R, DB, PG 26-week clinical trial (n=526) in RA patients comparing 40 mg SC Q2W+MTX adalimumab-atto to U.S.-adalimumab. Primary endpoint and result: estimated difference in ACR20 at week 24 (90% CI)=-0.4% (-6.8%, 6.1%) 2. R, DB, PG (weeks 1-16 of 48-week trial) clinical trial (n=350) in PsO patients comparing 80 mg SC day 1 then 40 mg SC Q2W from week 2 adalimumab-atto to EU-adalimumab. Primary endpoint and result: difference in % improvement in PASI (90% CI)=-2.2% (-6.6%, 2.2%) 	<p>1,076 subjects (patients and HS) exposed to at least 1 dose of adalimumab-atto. Descriptive statistics were similar in AEs, SAEs, withdrawal due to AEs, infections, malignancies, liver enzyme elevations, injection site reactions, anaphylaxis, and death. No increase in AEs after single transition from EU-adalimumab to adalimumab-atto.</p> <p>Immunogenicity endpoints and results: descriptive statistics were similar in ADA and neutralizing antibodies.</p>	<p>3 clinical studies:</p> <ol style="list-style-type: none"> 1. Same as efficacy study in RA patients 2a. Same as efficacy study in PsO patients 2b. Continuation (week 16 to 48) of efficacy study in PsO patients. Patients on EU-adalimumab were re-randomized to adalimumab-atto so 3 treatment arms of 40 mg SC Q2W were compared: (a) adalimumab-atto → adalimumab-atto; (b) EU-adalimumab → adalimumab-atto; and (c) EU-adalimumab → EU-adalimumab 3. R, PG, single-dose, 3-way PK bridging study (n=203) in HS, comparing 40 mg SC in adalimumab-atto, U.S.-adalimumab, and EU-adalimumab <p>PK endpoints and results: similar Cmax and AUC</p>	<p>The following quality attributes were deemed highly similar between adalimumab-atto, U.S.-adalimumab, and EU-adalimumab: primary structure, bioactivity, purity, Fc receptor binding, protein content, higher order structure, biologic analysis and MOA exploration, high molecular weight variants/aggregates, physicochemical analysis, and general properties.</p> <p>High criticality quality attributes include primary sequence, apoptosis inhibition, and TNF-α binding.</p>

2WC=2-way crossover; AC=active-control; ACR20=American College of Rheumatology scale that measures 20% improvement in RA; ADA=antidrug antibodies; AE=adverse event; ANC=absolute neutrophil count; AS=ankylosing spondylitis; ASAS 20=Assessment in Ankylosing Spondylitis Response criteria, scale that measures 20% improvement in AS; AUC=area under curve; CD34+=hematopoietic progenitor cell antigen; CI=confidence interval; Cmax=maximum concentration; DB=double-blinded; DSN=duration of severe neutropenia; EU=European Union; HS=healthy subjects; MOA=mechanism of action; MTX=methotrexate; PASI=Psoriasis Area Severity Index; PD=pharmacodynamics; PG=parallel group; PK=pharmacokinetics; PsO=plaque psoriasis; Q2W=every 2 weeks; R=randomized; RA=rheumatoid arthritis; SAE=serious adverse event; TAC=docetaxel, doxorubicin, and cyclophosphamide; TEAE=treatment-emergency adverse event; TNF- α =tumor necrosis factor- α ; TP=treatment period.

from 200 to 600 in each study and a duration of 26-54 weeks. Each trial had different endpoints depending on the indication studied. Of all the biosimilars, etanercept-szszs was the only one to have a switchover study conducted when assessing efficacy. Safety and immunogenicity endpoints and results were similar between all biosimilars and their reference products. Participants who were exposed to at least 1 dose of the biosimilar were included in the safety analysis.

There were 3-5 PK/PD studies for each biosimilar, which is more than the number of efficacy trials for each biosimilar (Table 3). The PK/PD studies compared the biosimilar with the U.S.- and EU-licensed reference products.

A large number of analytical and structural studies were done for all biosimilars to examine the high similarity in quality attributes between the biosimilar and the U.S.- and EU-licensed reference products. These studies assessed primary structure, higher order structure, purity, protein content, bioactivity, stability profiles, receptor binding, and other tests related to the mechanism of action.

Discussion

The biosimilar approval process in the United States is still evolving. The experience with the first 5 biosimilars will shape the future of the biosimilar approval process, as well as how biosimilars are adopted. This review uncovered the following key points in the U.S. biosimilar approval process:

1. *The types of evidence that the FDA focused on when approving biosimilars ranged from many analytical studies to fewer clinical studies.*⁴ It is important to understand that the goal of the biosimilar approval pathway is not to demonstrate similar efficacy for each indication that the biosimilar is seeking licensure. Instead, the goal is to use a “totality-of-the-evidence approach” to demonstrate the high similarity between the biosimilar and the reference product in terms of safety, purity, and potency.⁴
2. *All manufacturers used 3-way bridging when seeking FDA approval for their biosimilars.* Three-way bridging is a method that allows a sponsor to use comparative animal or clinical data from a product not licensed by the United States to indirectly demonstrate high similarity between the biosimilar and the U.S. reference product, thereby scientifically justifying the relevance of the comparative data. Analytical, PK, and/or PD data can be used as bridging data.²⁵
3. *Biosimilars were approved for many indications by extrapolation.* For example, clinical studies were conducted in rheumatoid arthritis and ankylosing spondylitis for infliximab-dyyb and extrapolated to 4 additional indications: Crohn’s disease, ulcerative colitis, psoriatic arthritis, and plaque psoriasis. Extrapolation allows a biosimilar to be approved for indications in which clinical studies are not conducted, as long as they provide adequate scientific justification. This scientific justification often includes the mechanism of action in each

indication for which licensure was sought, the PK and immunogenicity in different patient populations, and the toxicity profile for each indication and patient population.⁴

4. *The majority of formulations that the biosimilars were approved for were very similar to, or the same as, those of the reference products.* However, there were minor discrepancies, such as the autoinjector pen for adalimumab-atto instead of a prefilled pen and the additional needle guard for etanercept-szszs. Notably, the FDA draft guidance on interchangeability warns against the approval of biosimilars for formulations that are not identical to the reference product because they are not as likely to receive interchangeable status.²⁵
5. *The 5 biosimilars were not approved for all indications for which their reference products were approved.* The 2 reasons for not approving for all indications were (a) the reference product was granted a new indication after the approval of the biosimilar, and (b) some of the reference product’s indications were protected by orphan drug marketing exclusivity. For example, filgrastim gained FDA approval for hematopoietic syndrome of acute radiation syndrome after the approval of filgrastim-sndz.²⁶ Similarly, the indication to treat pediatric plaque psoriasis was not granted to etanercept until after the approval of its biosimilar etanercept-szszs.²⁷ Alternatively, infliximab-dyyb and infliximab-abda were approved for all indications of infliximab, except for pediatric ulcerative colitis, for which infliximab has orphan drug marketing exclusivity until September 2018.²⁸ In the same manner, adalimumab-atto was approved for all but 4 indications for which adalimumab has orphan drug marketing exclusivity: pediatric Crohn’s disease, juvenile idiopathic arthritis in the specific population aged 2 to less than 4, hidradenitis suppurativa, and uveitis.²⁸
6. *None of the 5 biosimilars were approved for interchangeability, since the FDA has not yet finalized this process.* Thus far, the FDA has said that interchangeability would mean that the biosimilar produces the same clinical effect as its reference product in any given patient and that the substitution between the biosimilar and the reference product is “without the intervention of the healthcare provider who prescribed the reference product.”²⁵ In its draft guidance, the FDA requires data from the switching study (or studies) to demonstrate that safety and efficacy of the biosimilar would not be significantly different had the switch not been done.²⁵ Moreover, according to the draft guidance, while the demonstration of biosimilarity allows the use of a product not licensed by the United States, the FDA recommends against the use of a non-U.S. comparator to establish interchangeability in these switching studies. Another important note regarding these switching studies is that the FDA recommends involving actual patients instead of healthy subjects.²⁵

In this review, we also identified a major barrier to biosimilar uptake: the long gap between the date of FDA approval and the date of market entry by the biosimilar. For example, the launch dates for adalimumab-atto and etanercept-szszs are facing significant delays because of pending litigation related to patent protection challenges from the manufacturers of the reference products.^{15,16} Despite approval in the third quarter of 2016, those 2 biosimilars are not expected to be available on the U.S. market until at least 2018.^{15,16}

Meanwhile, filgrastim-sndz and infliximab-dyyb were not marketed until 6 months after their approval dates. This delay was the result of a requirement in which the biosimilar manufacturer must give the reference product manufacturer 180 days notice before commercial marketing.²⁹ This notice had to be given after the biosimilar's FDA approval,³⁰ until June 2017, when the Supreme Court ruled that the notice could be given before the biosimilar's FDA approval.²⁹ Thus, this notification requirement should not delay future biosimilar launches.

Another change that may help speed up the process is the requirement that FDA advisory committee meetings be part of the approval process for only the first biosimilar of each reference product, as announced by the FDA in September 2016.³¹ Subsequent biosimilars, unless there are specific issues, would not be required to have an advisory committee meeting. This change is why infliximab-abda, the second approved biosimilar to its reference product, was the only biosimilar that did not have an advisory committee meeting.

Strengths and Limitations

This review systematically approached the collection and synthesis of data, which contributed to the completeness of the results. However, there was a limited number of approved biosimilars to work from, and one of the biosimilars, infliximab-abda, had no supporting documents.

Conclusions

Biosimilars are relatively new to the U.S. market. The abbreviated 351(k) approval pathway for biosimilars requires extensive analytical characterization, as well as examination of pharmacokinetics, pharmacodynamics, immunogenicity, safety, and efficacy to establish biosimilarity. Questions remain regarding what evidence the FDA will require to establish interchangeability.

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DISCLOSURES

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APPENDIX Postmarketing Requirements and Commitments for Biosimilars³⁷⁻⁴¹

Biosimilar	Postmarketing Requirements and Commitments
Zarxio [filgrastim-sndz]	<p><i>Commitment:</i></p> <p>(Due May 2016) Enhance the control strategy of ... by development, validation, and implementation of an analytical method to assess ... concentration for release or in-process testing of drug product.</p> <p>(Due May 2020) Implementation of analytical test for release to assess ... concentration in the drug product.</p> <p>(Due May 2016) Confirm stability of drug product in 5% glucose at concentrations ranging from 5 mcg/mL to 15 mcg/mL of in the presence of 2 mg/mL human serum albumin, in glass bottles, polyvinyl chloride and polyolefin IV bags, and polypropylene syringes. Testing will include potency and subvisible particles.</p> <p>(Due May 2018) To readjust the ... bioburden limit of ... for the ... drug substance based on process capability from 10 batches of product.</p> <p>(Due August 2017) Establish bioburden and endotoxin action limits for ... after data from more than 10 batches are available and provide the limits in an annual report.</p> <p>(Due May 2016) Conduct studies to support the worst-case hold times ... at scale from a microbiology perspective.</p> <p>(Due May 2016) To update the stability program for prefilled syringe drug product to include syringe force measurements, glide force, and functional testing of the needle safety device. The update to the stability program will include establishment of appropriate specifications and verification activities for these attributes.</p>
Inflectra [infliximab-dyyb]	None
Erelzi [etanercept-szsz]	<p><i>Requirement:</i></p> <p>(Due December 2019) Develop a presentation that can be used to accurately administer to pediatric patients who weigh less than 63 kg.</p> <p><i>Commitment:</i></p> <p>(Due December 2017) Adequately assess levels of hydrophobic variants, including wrongly bridged disulfide bond variants. For TNF-α neutralization, etanercept-szsz and U.S.-etanercept did not meet statistical criteria for equivalence; the average mean potency of etanercept-szsz was higher than for U.S.-etanercept. It seemed that U.S.-etanercept had wrongly bridged disulfide bonds (a hydrophobic variant) but that these bonds would refold in vivo. Additional data in an in vitro system using mild redox conditions that mimic the in vivo environment showed this was the case—a reduction of levels of wrongly bridged disulfide bonds and restoration of potency.</p> <p>(Due September 2017) Repeat microbial retention study using a more suitable surrogate solution.</p> <p>(Due October 2019) Measure break loose, glide force (BLGF) for prefilled syringes.</p> <p>(Due October 2017) Confirm injection depth (needle length exposed for injection), audible feedback (occurrence of second click), and visual feedback (plunger fills the window and stops moving).</p> <p>(Due September 2016) Transport validation to assess mechanical stress on the new folding box.</p>
Amjevita [adalimumab-atto]	<p><i>Requirement:</i></p> <p>Assessment for treatment of:</p> <p>(Due December 2020) Pediatric UC (aged 5-17 years).</p> <p>(Due September 2021) Pediatric CD (aged 6-17 years).</p> <p>(Due September 2021) JIA in 2 to <4 years.</p> <p>(Due September 2021) Develop a presentation that can be used to accurately administer Amjevita to pediatric patients who weigh <15 kg.</p> <p><i>Commitment:</i></p> <p>(Due July 2017) Perform a drug product shipping study using the approved commercial shipping lane to evaluate the impact of shipment on product quality.</p> <p>(Due December 2016) Perform supplemental method validation and introduce a nonreduced CE-SDS test into the integrated control strategy for drug substance manufacture. Submit the analytical procedure, validation report, proposed acceptance criterion, and data used to set the acceptance criteria that will be provided in a CBE-0 supplement.</p>

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APPENDIX Postmarketing Requirements and Commitments for Biosimilars³⁷⁻⁴¹ (continued)

Biosimilar	Postmarketing Requirements and Commitments
Renflexis [infliximab-abda]	<p><i>Commitment:</i></p> <p>(Due January 2018) Implement a test for FcγRIIa binding affinity into the drug substance release specification.</p> <p>(Due January 2018) Implement the reducing CE-SDS purity test into the drug substance and drug product release specification.</p> <p>(Due March 2018) Re-evaluate and establish final in-process...limits...In addition, provide the qualification test data for the...samples.</p> <p>(Due October 2019) Re-evaluate and establish final endotoxin limits for the... sucrose, pH 6.2 solution, and... polysorbate 80 solution.</p> <p>(Due November 2017) Repeat the container closure integrity test validation for the SB2 drug product using a positive control with a defect size of no more than...microns.</p> <p>(Due December 2017) Qualify an in-process...method and establish an in-process...limit for the...of the SB2 drug product manufacturing process.</p> <p>(Due December 2017) Conduct endotoxin, bioburden, and sterility test method qualification study using 1 additional batch of SB2 drug product manufactured according to the commercial drug product manufacturing processes.</p> <p>(Due November 2017) Conduct the...determination study of the...with 2 additional lots of SB2 drug product.</p>

Note: The ellipses represent items that were blacked out in the FDA documents.

CBE-0= changes being effected; CD= Crohn's disease; CE-SDS= capillary electrophoresis-sodium dodecyl sulfate; FcγRIIa=low affinity immunoglobulin gamma Fc region receptor II-α; FDA= U.S. Food and Drug Administration; IV= intravenous; JIA= juvenile idiopathic arthritis; SB2= Samsung's proposed infliximab biosimilar; TNF-α= tumor necrosis factor-α; UC= ulcerative colitis.