

Food and Drug Administration guidances on biosimilars: an update for the gastroenterologist

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Abstract: The management of inflammatory bowel disease (IBD), a significant cause of morbidity in the United States (US), has been revolutionized over the last two decades by the introduction of biologic therapies. These include antitumor necrosis factor α (TNF- α) agents. Since 2016, five biosimilar TNF- α inhibitors have been approved by the US Food and Drug Administration (FDA) for use in the treatment of IBD. The FDA has published a series of guidance documents related to the evaluation, licensing, and approval of biosimilars. The aim of this review is to provide an overview of these FDA guidances and the issues associated with biosimilars in the US.

Keywords: biologic, biosimilar, reference product, regulatory guidance, US Food and Drug Administration

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Introduction

Inflammatory bowel disease (IBD), the major forms of which are ulcerative colitis (UC) and Crohn's disease (CD), affects approximately 3.1 million (1.3%) adults in the United States (US).¹ Traditional treatment options for IBD include corticosteroids, 5-aminosalicylates, and immunomodulators; however, the introduction of biologic therapies well over a decade ago for the management of IBD has had a profound clinical impact.² Biologic therapies approved by the US Food and Drug Administration (FDA) for the treatment of IBD (indicated for UC and CD) include antitumor necrosis factor (TNF) agents, such as infliximab and adalimumab; and anti-integrin agents, such as vedolizumab.² More recently, the FDA approved an anti-interleukin agent, ustekinumab, for the treatment of moderately to severely active CD.³ Further biologics and other novel drugs for managing IBD are in clinical development.⁴

Since April 2016, five biosimilars (three for infliximab and two for adalimumab) have been approved by the FDA for indications that include

the treatment of IBD. A biosimilar is a biologic product that 'is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and there are no clinically meaningful differences between the biologic product and the reference product in terms of safety, purity, and potency'.⁵ Regulatory bodies require demonstration of biosimilarity for a proposed biosimilar and its reference product *via* a rigorous but abbreviated⁶ pathway.⁷ Anticipation of increased competition from biosimilars entering European markets has resulted in overall price reductions in biologic product classes in the European Economic Area; for example, the total market price per treatment-day for anti-TNF agents decreased by 10% (price per treatment day in 2016 \div price in year before biosimilar entrance), with greater reductions ($\geq 15\%$) observed in other established biologic therapy areas.⁸ Greater competition from biosimilars in European Union countries has also increased total market volume uptake of all established biologic therapies, which is contributing to a rise in patient access.⁸ Biosimilars may, therefore, address unmet clinical needs by potentially allowing more patients to

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receive biologic therapies, facilitating earlier initiation, and increasing biologic treatment continuity.⁷ Projected biosimilar savings for US payers may be more difficult to evaluate, due to US market variables. A recent report estimated that biosimilars will lead to a reduction of \$54 billion (range \$24 billion to \$150 billion) in direct spending on biologic drugs from 2017 to 2026.⁹

The FDA has published a series of guidance documents related to the evaluation, licensing, and approval of biosimilars. The aim of this review is to provide an overview of these FDA guidances and discuss the associated clinical considerations in the US.

Current status of biosimilars in the US

To date, a total of nine biosimilar agents have been licensed by the FDA; namely, six TNF- α inhibitors, one granulocyte colony-stimulating factor (G-CSF), one vascular endothelial growth factor A inhibitor, and one human epidermal growth factor receptor 2 inhibitor (Table 1¹⁰⁻¹²). Further biosimilar candidates, such as CHS-1701 (Coherus; TNF- α inhibitor; reference product, infliximab, Remicade; Janssen, Horsham, PA) and MYL-1401H (Mylan/Biocon; G-CSF; reference product, pegfilgrastim, Neulasta; Amgen, Thousand Oaks, CA) are currently undergoing FDA review. Many (>60) additional biosimilar candidates are at various stages of biologic product development.¹³

Biologics Price Competition and Innovation Act

Requirements for the approval and licensing of complex biopharmaceuticals are specified in Section 351(a) of the Public Health Services Act (PHSA), whereas Section 351(k) of the PHSA contains approval and licensure requirements for biosimilars.⁷ The Biologics Price Competition and Innovation Act (BPCIA), which is part of the Patient Protection and Affordable Care Act, was passed to facilitate the entry of biosimilar drugs into the market. The BPCIA addresses regulatory issues pertaining to the approval of biosimilars [42 U.S.C., Section 262(k)],⁵ and specific patent resolution issues [42 U.S.C., Section 262(l)].^{5,14} The BPCIA amends the PHSA to create an abbreviated approval pathway for a Biologics License Application (BLA) for biologic products that are highly similar to an FDA-approved

biologic reference product (i.e. biosimilars). This licensure pathway, often referred to as the 351(k) pathway, permits the evaluation of a biosimilar candidate by comparing it with a single reference product, provided that the biosimilar candidate has the same mechanism of action, route of administration, dosage forms, and potency as the reference product⁵⁻⁷ (Figure 1). The BPCIA also creates what is commonly known as the ‘patent dance’, establishing the steps and schedule during which the biosimilar applicant and reference product sponsor exchange information (which is not available in the public domain) regarding the abbreviated approval pathway for a BLA.¹⁴

FDA guidances

The FDA has published a series of guidance documents on biosimilars to assist with the implementation of the BPCIA^{7,15} (Table 2¹⁶⁻²⁶).

Reference product exclusivity

The draft guidance¹⁶ reiterates what the BPCIA legally requires on biologic reference product exclusivity; specifically, approval of an application for a biosimilar may not be made effective until 12 years after the date of first licensure of the reference product.⁵ In addition, a 351(k) application for a biosimilar may not be submitted for review (to the FDA) until 4 years after the date of the first licensure of the reference product.⁵

Scientific considerations for demonstrating biosimilarity

The FDA recommends a stepwise, risk-based approach using the totality of the evidence when comparing the biosimilar candidate with the reference product.^{7,17} The reference product with which the proposed biosimilar is compared must be a US-licensed product [under Section 351(a) of the PHSA]. The stepwise approach should include extensive structural analyses, functional assays, animal testing, human pharmacokinetic (PK) and pharmacodynamic (PD) studies (if there are relevant measures), and a clinical immunogenicity assessment. Animal toxicity studies may be useful if uncertainties remain after structural and functional studies, or if data from studies or marketing experience outside the US with the same proposed product (formulation and route of administration) are not available. If any residual uncertainty over biosimilarity remains thereafter,

Table 1. Biosimilars currently approved by the FDA.

Biosimilar (brand name; manufacturer)	Approval date	Reference product (brand name; manufacturer)	Action	Indications
Filgrastim-sndz (Zarxio; Sandoz Princeton, NJ)	March 2015	Filgrastim (Neupogen; Amgen Thousand Oaks, CA)	G-CSF	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
Etanercept-szszs (Erelzi; Sandoz Princeton, NJ)	August 2016	Etanercept (Enbrel; Amgen Thousand Oaks, CA)	TNF- α inhibitor	PsPL (m-s) RA, active (m-s) \pm MTX JIA (m-s) in patients aged ≥ 2 years PsA, active in combination with MTX AS, active
Infliximab-dyyb (Inflectra Celltrion, Incheon, Republic of Korea for Hospira (a Pfizer Company), Lake Forest, IL)	April 2016	Infliximab (Remicade; Janssen Horsham, PA)	TNF- α inhibitor	RA, active (m-s) AS, active CD, active (m-s) Pediatric CD, active (m-s) in patients aged ≥ 6 years UC, active (m-s) PsA, active PsPL (m-s)
Infliximab-abda (Renflexis; Merck & Co., Whitehouse Station, NJ Samsung Bioepis Incheon, Republic of Korea)	April 2017	Infliximab (Remicade; Janssen Horsham, PA)	TNF- α inhibitor	RA, active (m-s) CD, active (m-s) Pediatric CD, active (m-s) in patients aged ≥ 6 years UC, active (m-s) AS, active PsA, active PsPL (chronic severe)
Infliximab-qbtz (Ixifi; Pfizer New York, NY)	December 2017	Infliximab (Remicade; Janssen Horsham, PA)	TNF- α inhibitor	RA, active (m-s) + MTX CD, active (m-s) Pediatric CD, active (m-s) in patients aged ≥ 6 years UC, active (m-s) AS, active PsA, active PsPL (chronic severe)
Adalimumab-atto (Amjevita; Amgen Thousand Oaks, CA)*	September 2016	Adalimumab (Humira; AbbVie North Chicago, IL)	TNF- α inhibitor	RA, active (m-s) \pm MTX JIA (m-s) in patients aged ≥ 4 years \pm MTX PsA, active \pm nonbiologic DMARDs AS, active CD, active (m-s) UC, active (m-s) PsPL (m-s)
Adalimumab-adbm (Cyltezo; Boehringer Ingelheim Ridgefield, CT) [†]	August 2017	Adalimumab (Humira; AbbVie North Chicago, IL)	TNF- α inhibitor	RA, active (m-s) \pm MTX or nonbiologic DMARDs PsPL (m-s) JIA (m-s) \pm MTX CD, active (m-s) \pm nonbiologic DMARDs UC, active (m-s) PsA, active AS, active

(continued)

Table 1. (continued)

Biosimilar (brand name; manufacturer)	Approval date	Reference product (brand name; manufacturer)	Action	Indications
Bevacizumab-awwb (Mvasi; Amgen Thousand Oaks, CA/Allergan Thousand Oaks, CA)‡	September 2017	Bevacizumab (Avastin; Genentech South San Francisco, CA)	VEGF inhibitor	Nonsquamous non-small cell lung cancer in combination with carboplatin and paclitaxel Metastatic colorectal cancer in combination with 5-fluorouracil-based chemotherapy Glioblastoma Metastatic renal cell carcinoma in combination with interferon α Persistent, recurrent, or metastatic carcinoma of the cervix in combination with paclitaxel and cisplatin, or paclitaxel and topotecan
Trastuzumab-dkst (Ogivri; Mylan Zurich, Switzerland/Biocon Zurich, Switzerland)	December 2017	Trastuzumab (Herceptin; Genentech South San Francisco, CA)	HER2 antagonist	Adjuvant breast cancer Metastatic breast cancer Metastatic gastric cancer

*Not currently available in the United States (US) market (launch expected in 2023).¹⁰

†Not currently available in the US market due to patent litigation.¹¹

‡Not currently available in the US market (launch expected in 2019).¹²

AS, ankylosing spondylitis; CD, Crohn's disease; DMARD, disease-modifying antirheumatic drug; FDA, US Food and Drug Administration; G-CSF, granulocyte colony-stimulating factor; HER2, human epidermal growth factor receptor 2; JIA, polyarticular juvenile idiopathic arthritis; m-s, moderate to severe; MTX, methotrexate; PsA, psoriatic arthritis; PsPL plaque psoriasis; RA, rheumatoid arthritis; TNF- α , tumor necrosis factor α ; VEGF, vascular endothelial growth factor; UC, ulcerative colitis.

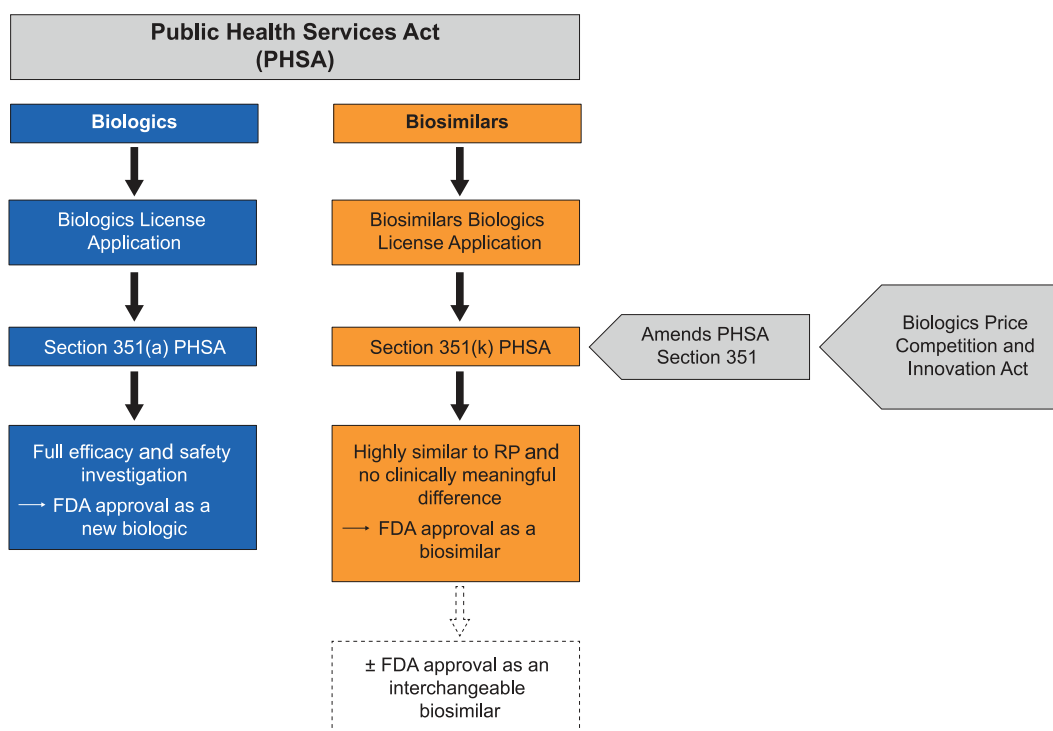


Figure 1. FDA approval pathway for biosimilars. FDA, US Food and Drug Administration; RP, reference product [i.e. 351(a) approved biologic].

Table 2. FDA guidances on biosimilars.

Title	Issue date	Status	Reference
Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act	August 2014	Draft	16
Scientific Considerations in Demonstrating Biosimilarity to a Reference Product	April 2015	Final	17
Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product	April 2015	Final	18
Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009	April 2015	Final	19
Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009	May 2015	Draft	20
Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants	November 2015	Final	21
Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product	December 2016	Final	22
Labelling for Biosimilar Products	March 2016	Draft	23
Nonproprietary Naming of Biological Products	January 2017	Final	24
Considerations in Demonstrating Interchangeability With a Reference Product	January 2017	Draft	25
Statistical Approaches to Evaluate Analytical Similarity	September 2017	Draft	26
See also FDA website. ¹⁵ FDA, US Food and Drug Administration; PHS, Public Health Services.			

an additional comparative clinical study (or studies) of efficacy and safety may be required to further evaluate whether there are any clinically meaningful differences between the biosimilar candidate and the reference product.¹⁷ It is likely that studies of human safety and immunogenicity would be required to contribute to the overall evidence, as these parameters cannot be predicted outside of a clinical study (i.e. using sensitive assays, appropriate patient population, adequate duration of exposure and follow up, etc.).²⁷ Due to the relatively small patient populations in the clinical equivalence studies, immune response may not be captured adequately in the approvals data; thus, ongoing pharmacovigilance will be required to ensure safety.²⁸ Furthermore, PD efficacy markers often do not exist for many monoclonal antibodies; thus, again, clinical trials would be required.²⁷ A biosimilar applicant may be able

to demonstrate biosimilarity even though there are formulation or minor structural differences, as long as they provide sufficient data to demonstrate that the differences are not clinically meaningful in terms of safety, purity, and potency, and the proposed biosimilar product otherwise meets the statutory criteria for biosimilarity¹⁷ (Figure 2²⁹).

Extrapolation is a core concept for the regulatory approval of biosimilars: it refers to the approval of a biosimilar for one or more of the indications held by its reference product, even though that biosimilar was not studied in a comparative clinical trial in all of those indications.³⁰ The biosimilar applicant must provide sufficient scientific justification, in the context of the totality of evidence, for extrapolating clinical data to support a determination of biosimilarity for each indication for which licensure is sought.¹⁷

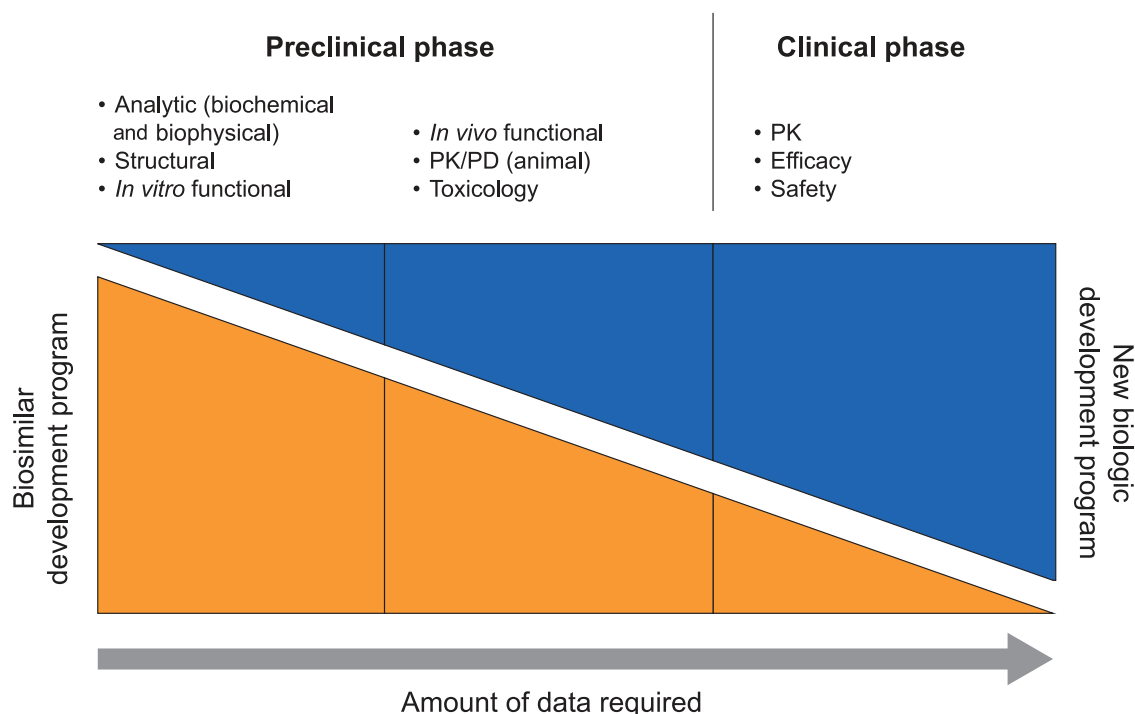


Figure 2. Development of biosimilar *versus* reference product.²⁹

New biologic *versus* biosimilar drug development. In contrast to the development program for a new biologic, the preclinical phase of the biosimilar development program is more comprehensive. Conversely, fewer data are required for the clinical phase of the biosimilar development program as a result of establishing adequate similarity between the reference biologic product and the biosimilar in the preclinical evaluation phase. Toxicology studies differ between a biosimilar development program and a new biologic development program. In contrast to a new biologic development program, a biosimilar development program might contain at least one toxicology study, assessing safety, pharmacokinetic (PK), immunogenicity and any pharmacodynamic (PD) effects. Safety pharmacology, reproductive toxicity, genetic toxicity and carcinogenicity studies are not routinely required in a biosimilar development program.²⁹

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The totality of evidence approach was applied in the FDA application for ABP-501,³¹ (adalimumab-atto, approved as Amjevita; Amgen³²), a biosimilar TNF- α inhibitor to the reference product adalimumab (Humira; AbbVie North Chicago, IL³³). The data package supporting biosimilarity was composed of analytical, nonclinical, PK, and clinical data; and included results from two phase III studies [the first study was carried out in patients with moderately to severely active plaque psoriasis, and the second study was carried out in patients with moderately to severely active rheumatoid arthritis (RA)], in which clinical equivalence to the reference product was demonstrated.³⁴ Scientific justification for extrapolation of biosimilarity to other indications that were not studied in the ABP-501 development program was made.³¹ The FDA approved adalimumab-atto as biosimilar across all eligible

indications of the adalimumab reference product, which included moderately to severely active polyarticular juvenile idiopathic arthritis (children aged ≥ 4 years), active psoriatic arthritis, active ankylosing spondylitis, adult moderate to severe CD and moderate to severe UC, as well as moderate to severe chronic plaque psoriasis and moderately to severely active RA.³⁴ However, adalimumab-atto (Amjevita) will not be launched in the US market until 2023, as outlined in a recent patent settlement with AbbVie,¹⁰ but is expected to be available in the European Union from October 2018 (EU brand name Amgevita).³⁵

Quality considerations in demonstrating biosimilarity

Recommendations provided in the guidance on quality considerations concern the scientific and

technical information on analytical studies for the chemistry, manufacturing, and controls (CMC) section of a marketing application for a proposed biosimilar under section 351(k) of the PHSA.¹⁸ Robust characterization of the proposed biosimilar is required to demonstrate that it is highly similar to the reference product, and should include comparative physicochemical and functional studies with the reference product.¹⁸

Common questions and answers and formal FDA meetings

The FDA has issued two questions and answers (Q&A) guidance documents; one provides answers to common questions from biosimilar product sponsors, applicants, or other interested parties,¹⁹ and a second Q&A document provides direction on previously unanswered questions concerning biosimilarity or interchangeability, requirements for submission of a BLA, and requirements regarding product exclusivity.²⁰ Another guidance document discusses considerations for any type of formal meeting (e.g. face to face meeting, teleconference, videoconference) between the FDA and biosimilar product sponsors or applicants that relates to the development of a biosimilar biologic product.²¹ It summarizes the principles of good meeting management practices, and describes standardized procedures for requesting, preparing, scheduling, conducting, and documenting such formal meetings.²¹

Clinical pharmacology

The clinical pharmacology guidance describes concepts and approaches related to clinical pharmacology testing for biosimilars.²² It includes the role of clinical pharmacology in demonstrating biosimilarity, critical considerations in clinical pharmacology studies supporting biosimilars, developing clinical pharmacology data to support biosimilars, and the utility of simulation tools in study design and data analysis. Clinical pharmacology studies are part of the stepwise process supporting the demonstration that there are no clinically meaningful differences between the proposed biosimilar and its reference product. These studies may also address any residual uncertainties following analytic evaluation, and may support a selective targeted approach to the design of any subsequent clinical study (or studies) needed to support the demonstration of biosimilarity.²²

Labelling for biosimilar products

This guidance describes the FDA's recommendations for biosimilar product labelling.²³ It includes approaches to product identification, content presentation, and specific sections of biosimilar product labelling, as well as how to revise biosimilar product labelling (e.g. to update safety information, additional conditions of use), and how to submit labelling.

Naming of nonproprietary biologic products

The guidance on the naming of nonproprietary biologic products describes the current FDA approach to designating the proper name for originator biologic products, related biologic products, and biosimilar products.²⁴ The guidance discusses prospective and retrospective naming of biologic products submitted or licensed, respectively, under section 351(a) of the PHSA, as well as naming of proposed biosimilars submitted under section 351(k) of the PHSA. The nonproprietary name is composed of a core name plus an arbitrary four-letter lowercase suffix attached with a hyphen; for example, infliximab-dyyb (Inflectra, Celltrion, Incheon, Republic of Korea for Hospira (a Pfizer Company), Lake Forest, IL) is a biosimilar to the reference product infliximab (Remicade; Janssen). The use of distinguishable nonproprietary names for biologic products is intended to facilitate pharmacovigilance by tracking adverse events to a specific manufacturer, which allows surveillance systems to detect safety signals throughout the life cycle of a product.²⁴ The use of a suffix is also intended to minimize inadvertent substitution of any such products that have not been determined to be interchangeable (see below), and to enable accurate product identification by health care professionals in terms of ordering, prescribing, dispensing, record keeping, and pharmacovigilance.²⁴

Demonstrating interchangeability with the reference product

As well as describing the requirements for biosimilarity, the BPCIA contains further criteria for biologics that are deemed to be interchangeable with the reference product.⁵ The requirements for demonstrating interchangeability are additional to those for demonstrating biosimilarity. To meet the conditions for interchangeability, the proposed interchangeable biologic product must be biosimilar to the reference product; be

‘expected to produce the same clinical result as the reference product in any given patient’; and ‘for a biologic product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biologic product and the reference product is not greater than the risk of using the reference product without such alternation or switch’.⁵

An example of an interchangeability study is VOLTAIRE-X [ClinicalTrials.gov identifier: NCT03210259]. It is a 58-week randomized, double-blind, parallel-arm, multiple-dose, active comparator trial to investigate PK, safety, immunogenicity, and efficacy of BI 695501 (adalimumab-adbm, Cyltezo; Boehringer Ingelheim Ridgefield, CT) *versus* the reference product (adalimumab, Humira; AbbVie) in patients with moderate to severe chronic plaque psoriasis, and is due to be completed in July 2019.³⁶

The FDA is currently evaluating what additional data would be needed to meet the interchangeability criteria.³⁷ Under the BPCIA, and as stated by the FDA, an interchangeable product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product; however, the FDA expects that a biosimilar product will be prescribed specifically by the health care provider and will not be able to be substituted for a reference product at the pharmacy level.³⁸ The FDA’s ‘Purple Book’, a resource for pharmacists, lists biologic products, including any biosimilar and interchangeable biological products, licensed by the FDA under the PHSa.³⁸ It also contains the date of licensure for a product, states whether a biologic has been deemed by the FDA to be biosimilar or interchangeable with a given reference product, and lists the proprietary (i.e. brand) and nonproprietary (i.e. generic) names.

The draft FDA guidance on interchangeability with a reference product includes a description of information needed to support the demonstration of interchangeability, as well as considerations in the design and analysis of supporting switching studies.²⁵ Switching studies, an essential component of the draft interchangeability guidance, are required to determine if alternating between a biosimilar and its reference product two or more times has any impact on the safety or efficacy of the treatment. The FDA expects that applications

generally will include data from a switching study or studies in one or more appropriate conditions of use for which the reference product is licensed.²⁵

The FDA guidance also states that a non-US licensed comparator (reference) product would not be appropriate generally in a switching study.²⁵ Per FDA guidance: ‘Rather than being used only as a control, the comparator (reference) product in a switching study is used in both the active switching arm and the control non-switching arm. Switching studies are designed to assess whether one product will affect the immune system’s response to the other product, once the switch occurs, and whether this will result in differences in immunogenicity or PK profiles.’ A non-US licensed comparator product may have subtle differences to the proposed interchangeable product (e.g. specific structural features, such as acidic variants or deamidations, or the presence of impurities), and multiple exposures to each product during switching may prime the immune system to recognize these differences and increase the overall immune response, even though these differences may not preclude a demonstration of biosimilarity.²⁵ Per FDA guidance: ‘There is uncertainty as to whether the results observed using a non-US licensed comparator product would also be observed if a US-licensed reference product had been used instead’.

The FDA draft guidance also states that postmarketing data from a licensed biosimilar product generally would not be sufficient to support a demonstration of interchangeability, without corresponding data from an appropriately designed switching study or studies. However, on some occasions, postmarketing data may be helpful in describing the real-world use of the biosimilar product, including certain safety data related to patient experiences in some switching scenarios.²⁵ Furthermore, if interchangeability of a biosimilar product has been demonstrated for a particular condition of use for which the reference product is licensed, the FDA may also permit extrapolation of the data for one or more additional licensed conditions of use, provided scientific justification for such extrapolation is demonstrated.²⁵

Statistical approaches to evaluate analytical similarity

This draft guidance describes the type of information a sponsor should obtain about the structural/physicochemical and functional attributes of the

reference product, how that information is used in the development of an analytical similarity assessment plan, and the statistical approaches recommended for evaluating analytical similarity.²⁶ It is a companion document to the guidance on quality considerations in demonstrating biosimilarity (described above).¹⁸

The FDA recommends using a three-step, risk-based approach in the analytical similarity assessment of quality attributes of the biosimilar candidate.²⁶ These steps are determination of the quality attributes that characterize the reference product in terms of its structural/physicochemical and functional properties; ranking of these quality attributes according to their risk of potential clinical impact; and evaluation of these attributes/assays according to one of three tiers of statistical approaches (equivalence testing, quality ranges, or visual comparisons) based on a consideration of risk ranking, as well as other factors (e.g. level of the attribute, assays used to assess the attribute, type of attributes/assays).²⁶ The FDA also recommends that a four-stage analytical assessment plan is designed ‘to identify and address all factors that could impact the determination about whether the proposed biosimilar is highly similar to the reference product’. Factors that may need to be considered include differences in age of the lots produced at testing, multiple testing results, assay performance, and differences in attributes considered acceptable.²⁶

Guidances from non-US regulatory bodies

The basic principles governing regulatory approval of biosimilar candidates for the FDA, European Medicines Agency (EMA),^{39,40} and World Health Organization (WHO)⁴¹ are broadly similar.⁷ The EMA created the first guidelines for evaluating proposed biosimilars in 2005 and approved the first biosimilar in 2006; since then, it has approved the highest number of biosimilars worldwide (36 at the time of writing⁴²). It has been estimated that biosimilar medicines in the European Union have generated more than 700 million patient-days of clinical experience;⁴³ consequently, the EMA has gathered substantial experience in their use and safety.³⁹ EMA guidelines specify that the reference product must be licensed in the European Economic Area (which consists of the 28 EU Member States plus Iceland, Liechtenstein, and Norway), with some exceptions permissible but requiring justification and

bridging studies.⁴⁰ The EMA does not make recommendations on interchangeability of a biosimilar with a reference product, and substitution policies are within the remit of the EU Member States.³⁹ EMA guidelines do state that if biosimilarity has been demonstrated in one indication, extrapolation to other indications of the reference product could be acceptable with appropriate scientific justification.⁴⁰ For example, the European Public Assessment Report (EPAR) for the biosimilar infliximab (Inflectra; Hospira UK Ltd Hurley, Maidenhead, UK) allowed extrapolation to all of the six indications for which the reference product infliximab (Remicade) was approved, even though clinical trials were conducted only in RA and ankylosing spondylitis.⁴⁴ WHO attempted to harmonize the evaluation of biosimilar candidates, and WHO guidelines followed the scientific principles and requirements of the EMA.⁷ Other highly regulated countries such as Australia,⁴⁵ Canada,⁴⁶ Japan,⁴⁷ and South Korea⁴⁸ have issued guidance documents and regulations for biosimilars that are largely consistent with those of the EMA or WHO.⁷ It should be noted that the lack of global harmonization of regulatory requirements for biosimilars has enabled the approval of ‘biomimics’ in some regions, such as Latin America and India. Biomimics, or intended copies, are copies of licensed biologics that have been approved without the stringent comparative evaluations with the reference product that is required by regulatory bodies, and cannot, therefore, be considered as biosimilar.⁴⁹

Considerations with FDA guidances

The FDA guidance documents relating to naming and interchangeability of biosimilars are somewhat contentious, and have generated debate and comment. The FDA naming convention (i.e. core name + four-letter arbitrary suffix) for biologic products, including biosimilars, is viewed by some stakeholder groups (including representatives of the US Congress) as unnecessary and confusing.⁵⁰ In the US, supporters of the four-letter suffix argue that a biosimilar should not be treated like a generic product with regard to a naming convention, and that it is important to know exactly which drug a patient has been prescribed for pharmacovigilance purposes.⁵⁰ Opponents claim the suffix may lead to medical errors and obstruct appropriate drug substitution,⁵⁰ which could occur if health care professionals were under the misconception that differences in the suffixes

Table 3. Features of United States (US) state legislation related to substitution of biosimilars.⁵³

Commonly included provisions	Details
FDA approval	The biosimilar product under consideration must be FDA approved as 'interchangeable' (NB: none of the biosimilars currently licensed in the US have been approved by the FDA as interchangeable)
Prescriber decision	The prescriber can prevent the substitution by stating 'dispense as written' (or similar notation)
Communication with prescriber	The pharmacist must communicate with the prescriber regarding the allowable substitution
Notify patient	The patient must be notified that a switch has been made; patient consent required in some states
Records	The pharmacist and physician must retain records of the substituted biosimilar
Immunity	Immunity is provided by some states for pharmacists who make substitutions in compliance with state law
Lists	Publicly accessible or web-based list of permissible interchangeable products must be provided and maintained by the state
Costs or pricing	Pharmacists must explain the cost or price of the biologic and interchangeable biosimilar Some states require that any authorized or allowable substitution must have lowest cost

FDA, US Food and Drug Administration.

implied clinically meaningful differences between the biosimilar and the reference product.⁵¹ Support for the use of a shared nonproprietary name generally comes from biosimilar industry groups, whereas groups advocating for innovator reference products would prefer a naming scheme that distinguishes between the reference product and the biosimilar.⁵¹ A less controversial naming system is used in the European Union. Specifically, EMA guidance states that the trade name, international nonproprietary name (INN; a WHO drug-naming system used since the 1950s), and batch number should be used to identify and trace biologic medicines for safety monitoring.³⁹

The concept of interchangeability is also causing some confusion, and many US clinicians do not realize that demonstrating interchangeability is a separate and additional criterion to that of demonstrating biosimilarity. To quote biosimilars expert, Dr Robert M. Rifkin: 'Interchangeability, in the biosimilar regulatory context, sets a higher bar than the test for biosimilarity, and it requires more

data'.⁵² Approval of a biologic product as a biosimilar enables a manufacturer to market that product, whereas a designation of interchangeability allows a pharmacist to switch from the reference product to its interchangeable biosimilar product without the involvement of the original prescriber. This is subject to US state law; although only the FDA can approve a product as interchangeable, individual states control the act of pharmacy-based substitution.⁵³ At the time of writing, 35 US states (plus Puerto Rico) had passed legislation addressing biosimilar interchangeability.⁵³ The specifics vary but several key features are common across state laws (Table 3⁵³). However, none of the manufacturers of the biosimilars currently approved by the FDA has applied for interchangeability. Interchangeability is a potential driver of the adoption, profitability, and sustainability of biosimilars.⁵⁴ Notwithstanding, formulary decisions may actually dictate whether a patient's insurance plan will only cover a biosimilar (even if it is not deemed interchangeable) in the current environment.

The FDA draft interchangeability guidance was released for public consultation from January to May 2017 and received 52 comments in total, mainly concerning issues related to switching studies and requirements for interchangeability.⁵⁵ Many comments came from pharmaceutical manufacturers.⁵⁵ Physician groups, including the American Gastroenterological Association (AGA), also expressed a number of concerns.⁵⁶ The AGA sent a letter detailing several comments to the FDA that included suggestions for measures to enhance patient safety, involvement of gastroenterologists with appropriate disease expertise when interchangeable products are reviewed for FDA approval, and ensuring prescribing physicians are empowered with the ability to prevent nonmedical switching from a reference product to an interchangeable product.⁵⁷

Physicians have also expressed concern over switching to a biosimilar product in well-managed patients who are already being treated successfully with a biologic reference product;⁵⁸ thus, biologic treatment-naïve patients are likely to be targeted by physicians for treatment with a biosimilar agent. Nevertheless, real-world and emerging clinical trial data from other countries on switching from the infliximab reference product (Remicade) to a biosimilar infliximab, CT-P13 [EU brand name Remsima; Celltrion Incheon, Republic of Korea (US brand name Inflectra)], have been favorable; there were no concerns relating to safety or efficacy in patients with ankylosing spondylitis, RA, or IBD.⁵⁹ A further study carried out in Norway, NOR-SWITCH [ClinicalTrials.gov identifier: NCT02148640] ($N = 482$), reported that switching from reference product infliximab to the biosimilar CT-P13 was not inferior to continued treatment with the reference product, according to a prespecified noninferiority margin of 15%; disease worsening occurred in 53 (26%) patients in the reference product infliximab group and in 61 (30%) patients in the CT-P13 group [per protocol set; adjusted treatment difference -4.4% , 95% confidence interval (CI) $-12.7, 3.9$].⁶⁰ Subgroup analysis in NOR-SWITCH showed that disease worsening in patients with CD occurred in 14 patients (21.2%) receiving reference product infliximab *versus* 23 patients (36.5%) receiving biosimilar infliximab CT-P13 (adjusted treatment difference -14.3% , 95% CI $-29.3, -0.7$).⁶⁰ The frequency of adverse events and serious adverse events was similar between treatment groups. Secondary loss of response (i.e.

patients who respond initially but show loss of response over time) is also an area that requires further study in the context of switching to a biosimilar. A recent review by Moots and colleagues examined data from 53 switching studies involving biosimilars (approved and candidates), and reported that there were generally no differences in efficacy and safety data between patients who switched and those who did not.⁶¹ The report highlighted the fact that switching data are not transferable between different biosimilars for the same reference product, which will need to be considered if switching from one biosimilar to a second biosimilar is an option. Also, differences in the incidence or type of adverse events upon switching must be examined, and Moots and colleagues suggest that a national pharmacovigilance database should be created to monitor biosimilar safety and collect benefit/risk data on switching in all patients. It is recommended that the decision to switch a patient from a reference product to a biosimilar should be made on a case by case basis, after considering the underlying disease, patient characteristics and comorbidities, type of reference product, and patient willingness to switch.⁶¹ Tracking the switch from the reference product to its biosimilar is of the utmost importance, and patients and physicians must be informed when these switching decisions are made. There is concern that insurers or pharmacy benefits managers could effectively cause or incentivize switching to a biosimilar by changing their formularies and not offering the biologic reference product. Also, if a patient changes health insurance provider, different biosimilars may be covered by the new policy.

The concept of extrapolation of indications for a biosimilar (i.e. granting regulatory approval of the biosimilar for one or more licensed indications of its reference product without conducting clinical trials specifically in those disease states) is proving difficult for some health care professionals to accept. For example, a survey of gastroenterologists reported that the majority of respondents were reluctant to accept data from clinical trials conducted in rheumatologic conditions as being valid for IBD.⁵⁸ However, regulatory decisions regarding extrapolation across indications for a biosimilar are based on the totality of evidence provided in the regulatory submission for that individual biosimilar application (i.e. the entire data set), including analytical, functional and nonclinical studies, as well as clinical data.³⁰ Regulatory approval of extrapolation across indications is

made on a case by case and indication by indication basis, rather than as a consequence of biosimilar candidate approval for a single indication.³⁰

An evolving clinical landscape

Changes to the therapeutic landscape will undoubtedly occur with the increased use of biosimilars, as greater patient access to these agents will facilitate more effective and earlier therapy in a particular disease, and perhaps permit individualized therapeutic planning.⁶² Competition among biosimilar developers may stimulate further efforts to determine the best use of a given therapy in a specific disease, and lower drug prices may raise standards by pushing for increased innovations in new drugs.⁶² Cost will be a key issue in influencing the acceptance of biosimilars in the market.⁶³ For example, the price regulator in Norway was offered a significant discount (>60%) for biosimilar infliximab (Remsima, marketed by Orion Pharma (Espoo, Finland) in Scandinavia; Inflectra, marketed by Hospira/Pfizer in the US), and due to Norway's national tender agreements with one manufacturer per drug molecule, biosimilar infliximab has now achieved 95% market share since its launch in December 2013.⁶⁴ Reimbursement, patient assistance programs, co-pays, and formulary status for biosimilars will all have to be determined by payers.⁶³ Health insurance companies could use several strategies to increase biosimilar use and reduce prescription drug costs, such as incentivizing patients to switch from their regular reference product by reducing cost sharing for biosimilars, replacing reference products in their formularies with biosimilars, or requiring biologic treatment-naïve patients to start on biosimilars *versus* reference product therapy.⁶³ Health insurance/financial support could be included as part of patient support programs, which are vital to help meet patient needs, and will be of particular importance with the introduction of biosimilars. Such programs may also include injection training, nursing support, peer resources, and patient education. The latter is of specific importance, as patients must have confidence in the efficacy and safety of a biosimilar if they are to feel comfortable using it in place of their regular innovator product (i.e. reference product). A low level of patient awareness of the existence of biosimilars has been reported (6–30%), with gaps in patient knowledge regarding the efficacy and safety of biosimilars.⁶⁵

Lastly, given the considerable annual US expenditure on biologics such as adalimumab and infliximab, the challenge is to improve treatment effectiveness with these agents without increasing treatment costs. Therapeutic drug monitoring for biologicals, including biosimilars, may have a role here, as it can be used to identify patients who are eligible for dose tapering, treatment intensification or cessation, and switching within or out of class.⁶⁶ Therapeutic thresholds have been established for infliximab and adalimumab, and some innovator biologics are offering therapeutic drug monitoring as part of a bundled service. Whether biosimilars will offer similar bundled services remains to be seen, as does whether the same therapeutic drug-monitoring assays that are used with innovator biologics also work with biosimilars. A recently developed enzyme-linked immunosorbent assay for reference product infliximab (Remicade) demonstrated equal reactivity toward its biosimilars (Remsima and Inflectra).⁶⁷ This facilitates the implementation of therapeutic drug monitoring for infliximab biosimilars.

Conclusion

The process for the regulatory approval of biosimilars in the US is relatively new, and only a modest number of biosimilar applications have been filed since the enactment of the BPCIA. Regulatory issues relating to interchangeability may need further clarification. Nevertheless, it is hoped that the availability of biosimilars in the US market will improve patient access to biologic therapies used in the management of chronic inflammatory diseases, including IBD, and oncology. The eventual availability of biosimilars in the US, their subsequent uptake, and impact on clinical practice remain to be seen.

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