A review of the FDA approval pathway for biosimilars and a real-world example of the use of infliximab

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Disclosure

- The speaker has no actual or potential conflicts of interest in relation to this presentation

Objectives

- Explain the characteristics of biosimilars and differences between biosimilars and generic drugs
- Describe the regulations and requirements for the approval of biosimilars
- Review utilization of biosimilars in real world practice using infliximab as an example

Approved Tumor Necrosis Factor Inhibitor (TNFi) biosimilars

Reference product	Biosimilar	Approval date	Launch date
infliximab (Remicade®)	infliximab-axxq (Avsola®)	Dec 2019	Jul 2020
	infliximab-qbtx (Ixifi®)	Dec 2017	N/A
	infliximab-abda (Renflexis®)	Apr 2017	Jul 2017
	infliximab-dyyb (Inflectra®)	Apr 2016	Nov 2016
etanercept (Enbrel®, Enbrel Mini®)	etanercept-ykro (Eticovo®)	Apr 2019	Unknown
	etanercept-szzs (Erelzi®, Erelzi Sensoready®)	Aug 2016	Delayed by patent litigation

Reference product	Biosimilar	Approval date	Anticipated launch date
adalimumab (Humira®)	adalimumab-aacf (Idacio®)	Dec 2022	Jul 2023
	adalimumab-aqvh (Yusimry®)	Dec 2021	Jul 2023
	adalimumab-fkjp (Hulio®)	Jul 2020	Jul 2023
	adalimumab-afzb (Abrilada®)	Nov 2019	Jul 2023
	adalimumab-bwwd (Hadlima®)	Jul 2019	Jul 2023
	adalimumab-adaz (Hyrimoz®)	Oct 2018	Sep 2023
	adalimumab-adbm (Cyltezo®) -interchangeable	Aug 2017	Jul 2023
	adalimumab-atto (Amjevita®)	Sep 2016	Jan 2023

Purple Book Database of Licensed Biological Products. FDA. Database last updated Jan 6, 2022. Accessed Jan 12, 2023. https://purplebooksearch.fda.gov/
The Center for Biosimilars® Biosimilar Approvals. AJMC Last Updated Feb 16, 2022. Accessed Feb 20, 2023. https://www.centerforbiosimilars.com/biosimilar-approvals
Drugs@FDA: FDA-Approved Drugs. FDA. Accessed Apr 14, 2023. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

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Overview of biosimilars

Biologic products

- Biologic products are large, complex molecules made from living sources (bacteria, yeast, and animal cells) that are utilized to treat many diseases (psoriasis, inflammatory bowel diseases [IBD], Crohn's disease [CD], ulcerative colitis [UC], arthritis, kidney conditions, diabetes, and cancer)
- Due to the complexity of the structures of biologics, they are more complicated to purify, process, and manufacture
- Biologics contain slight variations from batch to batch. The protein produced by cultured cells is influenced by cell features, environment, and nutrients
- Types of biologics approved by the Food and Drug Administration (FDA) include therapeutic proteins, monoclonal antibodies, insulin, vaccines, and allergenic products

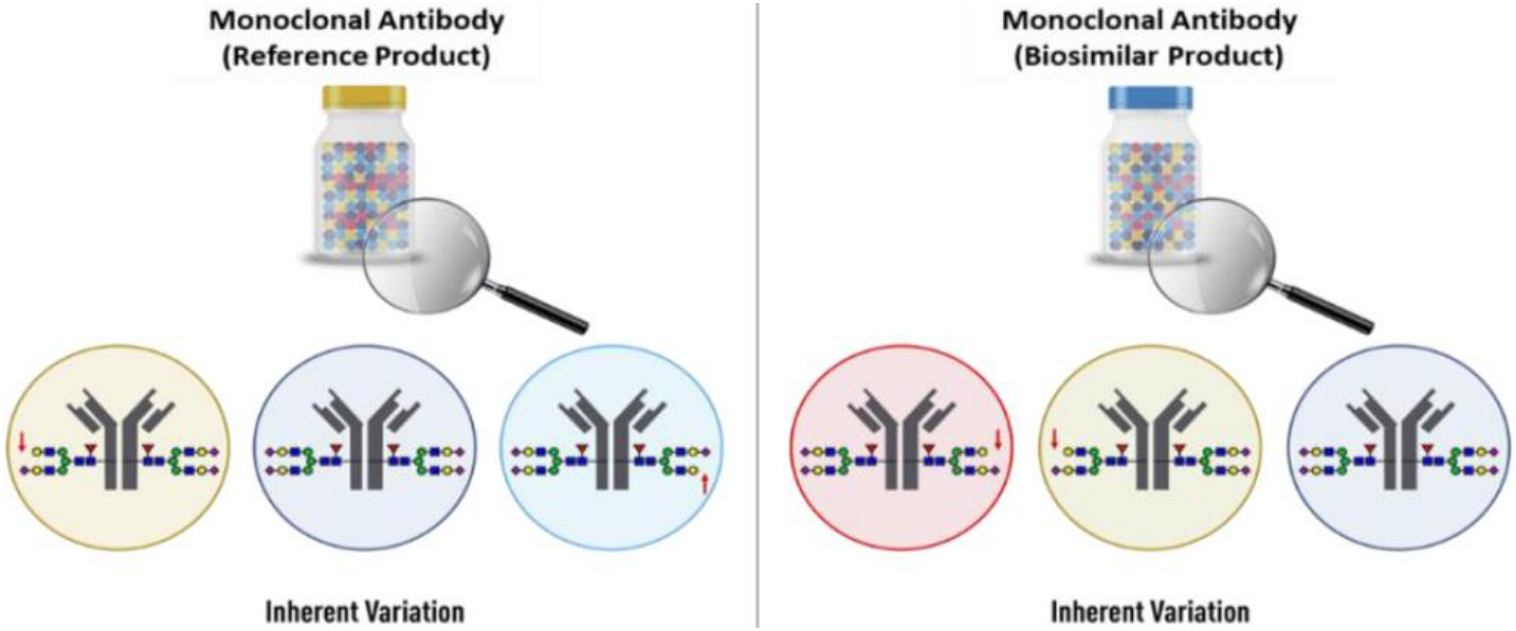
Overview for Health Care Professionals. FDA. Content current as of Dec 13, 2022. Access Dec 26, 2022. https://www.fda.gov/drugs/biosimilars/overview-health-care-professionals
Overview of Biosimilar Products. FDA. Access Dec 26, 2022. https://www.fda.gov/media/151058/download
Blandizzi C et al. Clin Ther. 2017;39(5):1026-1039.

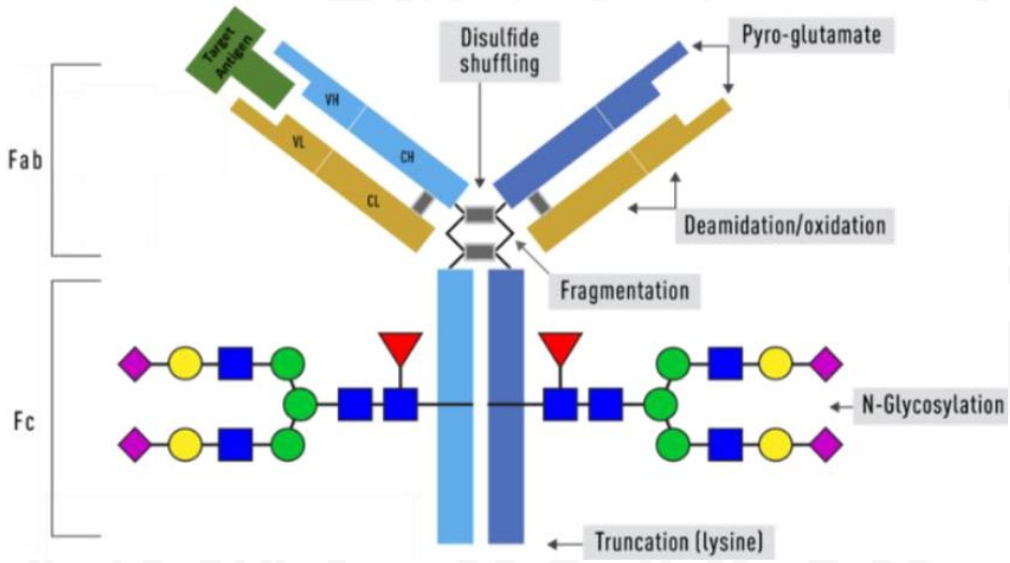
Biosimilar products

- Biosimilars are biologic products that are highly similar to their reference products (existing FDA-approved biologics)
  - Reference products cannot be copied exactly, and slight variations exist in each batch or dose. However, there are no clinically meaningful differences between biosimilars and reference products
- Biosimilars are made with the same types of living sources as the reference product. Biosimilars have the same strength, dose, route of administration, efficacy, and potential side effects as the reference product
- Interchangeable biosimilars are biosimilars that meet additional requirements
- Can be prescribed in patients that have used reference products or treatment naïve patients
- Biosimilars provide accessibility to more treatment options and lower costs through competition

Overview for Health Care Professionals. FDA. Content current as of Dec 13, 2022. Access Dec 26, 2022. https://www.fda.gov/drugs/biosimilars/overview-health-care-professionals
Overview of Biosimilar Products. FDA. Access Dec 26, 2022. https://www.fda.gov/media/151058/download

Inherent variations in biologics





- Inherent variations observed in both reference and biosimilar products (indicated by red arrows) are caused by post-translational modifications, which can be a consequence of manufacturing process operations or storage conditions
- Gray text boxes and arrows are examples of different types of inherent variation in monoclonal antibodies

Adapted from: Biosimilars Info Sheet. Variation in Biological Products. FDA. Accessed Dec 28, 2022. https://www.fda.gov/media/154915/download

Naming for reference and biosimilar products

- FDA designates a nonproprietary name to biologics to facilitate safe use and pharmacovigilance
  - Core name followed by a unique, distinguishing 4-letter suffix
- Some reference products approved prior to this naming convention may not have a suffix, but all biosimilars and interchangeable biosimilars have suffixes.
- Example:

Reference product	Biosimilar products
• infliximab (Remicade®)	• infliximab-axxq (Avsola®) • infliximab-dyyb (Inflectra®) • infliximab-qbtx (Ixifi®) • infliximab-abda (Renflexis®)

Biosimilars Info Sheet Level 2: Regulatory and Scientific Concepts. Prescribing Biosimilar and Interchangeable Biosimilar Products. FDA. Accessed Dec 26, 2022. https://www.fda.gov/media/154917/download
Purple Book Database of Licensed Biological Products. FDA. Database last updated Jan 6, 2023. Accessed Jan 12, 2023. https://purplebooksearch.fda.gov/

Suffixes for biologic products

- A biosimilar application should include up to 10 proposed suffixes composed of 4 lowercase letters in the order of their preferences
- The proposed suffix should: be unique, devoid of meaning, 4 lowercase letters of which at least 3 are distinct, nonproprietary, attached to the core name with a hyphen, and free of legal barriers that would restrict its usage
- Some existing biosimilar product names do not fit the current rules, because they were released before the rules were finalized.
  - Etanercept-szzs has only 2 distinct letters in the suffix.
  - Filgrastim-sndz: suffix is meaningful and refers to the manufacturer (Sandoz)

FDA. Nonproprietary Naming of Biological Products. Guidance for Industry. Published Jan 2017. Accessed Mar 15, 2023. https://www.fda.gov/files/drugs/published/Nonproprietary-Naming-of-Biological-Products-Guidance-for-Industry.pdf
Nancy J. Globus. Center for Biosimilars. Alphabet Soup: The Story Behind Biosimilar Nonproprietary Name Suffixes. The Center for Biosimilars®. Published Aug 8, 2020. Accessed Mar 17, 2023. https://www.centerforbiosimilars.com/view/alphabet-soup-the-story-behind-biosimilar-nonproprietary-name-suffixes
Purple Book Database of Licensed Biological Products. FDA. Last updated Mar 14, 2023. Accessed Mar 17, 2023. https://purplebooksearch.fda.gov/

Comparisons of biosimilars and generic drugs

- Biosimilars and generic drugs have the same strength, dosage form, route of administration, efficacy and side effects as reference products or brand-name drugs

Biosimilars	Generic drugs
• Large complex molecules; mixture of protein with many slight variations • Manufactured from living systems; reference biologics cannot be copied exactly • Information can be found in the Purple Book • Same labeling as reference product is not required	• Structures are smaller and simpler than biologics • Generally synthesized from chemicals; active ingredients are the same as in the brand-name drugs • Information can be found in the Orange Book • Label is the same as in the brand-name drug

Generic Drug Facts. FDA. Content current as of Nov 1, 2021. Accessed Dec 26, 2022. https://www.fda.gov/drugs/generic-drugs/generic-drug-facts
Overview of Biosimilar Products. U.S. Food and Drug Administration. Access Dec 26, 2022. https://www.fda.gov/media/151058/download
Purple Book Database of Licensed Biological Products. FDA. Database last updated Dec 15, 2022. Accessed Dec 26, 2022. https://purplebooksearch.fda.gov/
Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. FDA. Current through December 2022. Accessed Dec 26, 2022. https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm

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Regulations and requirements for the approval of biosimilars

Biologics Price Competition and Innovation Act of 2009

- Allows application of a biological product based on its similarity to a licensed biological product (the reference product). Application must demonstrate that:
  - The biological product is biosimilar to a reference product based upon data derived from studies
  - Same mechanism of action, route of administration, dosage form, and strength as the reference product
- Allows products to be determined to be interchangeable if:
  - The biological product is biosimilar to the reference product and can be expected to produce the same clinical result as the reference product in any given patient
  - Switching between the biologic and reference product does not produce greater risk in terms of safety or diminished efficacy than the risk of using the reference product without such switch

Biologics Price Competition and Innovation Act of 2009 (Sections 7001-7003) of the Patient Protection and Affordable Care Act (Public Law No. 111-148). Congress.gov. Accessed May 22, 2023. https://www.congress.gov/bill/111th-congress/house-bill/3590
Biosimilar Regulatory Approval Pathway. FDA. Accessed Dec 27, 2022. https://www.fda.gov/media/154914/download

Regulatory approval pathways

Reference product

- Approved in a standalone 351(a) biologics license application (BLA)
- Applications must provide all data to demonstrate safety and effectiveness. Generally, applications include data from clinical trials conducted in the relevant patient populations for each indication that the manufacturer is seeking approval for.

Biosimilar product

- Abbreviated approval pathway (351(k) pathway)
  - This pathway was created for time and cost saving in the development of biologics without compromising safety and effectiveness. The goal is to demonstrate biosimilarity between the biosimilar and reference product, instead of establishing safety and effectiveness of the biosimilar independently.

Biosimilar Regulatory Approval Pathway. Biosimilars Info Sheet Level 1: Foundational Concepts. FDA. Accessed Dec 27, 2022. https://www.fda.gov/media/154914/download
Implementation of the Biologics Price Competition and Innovation Act of 2009. FDA. Content current as of Feb 2016. Accessed Dec 27, 2022. https://www.fda.gov/drugs/guidance-compliance-regulatory-information/implementation-biologics-price-competition-and-innovation-act-2009

Regulatory approval pathways (continued)

Reference product

- Standalone 351(a) BLA

Analytical
Animal
Clinical pharmacology
Clinical safety and efficacy study for each indication

Biosimilar product

- 351(k) pathway (abbreviated approval pathway)

Analytical
Animal
Clinical pharmacology
Comparative clinical studies

Adapted from: Biosimilars Info Sheet Level 1: Foundational Concepts. Biosimilar Regulatory Approval Pathway. FDA. Accessed Dec 27, 2022. https://www.fda.gov/media/154914/download

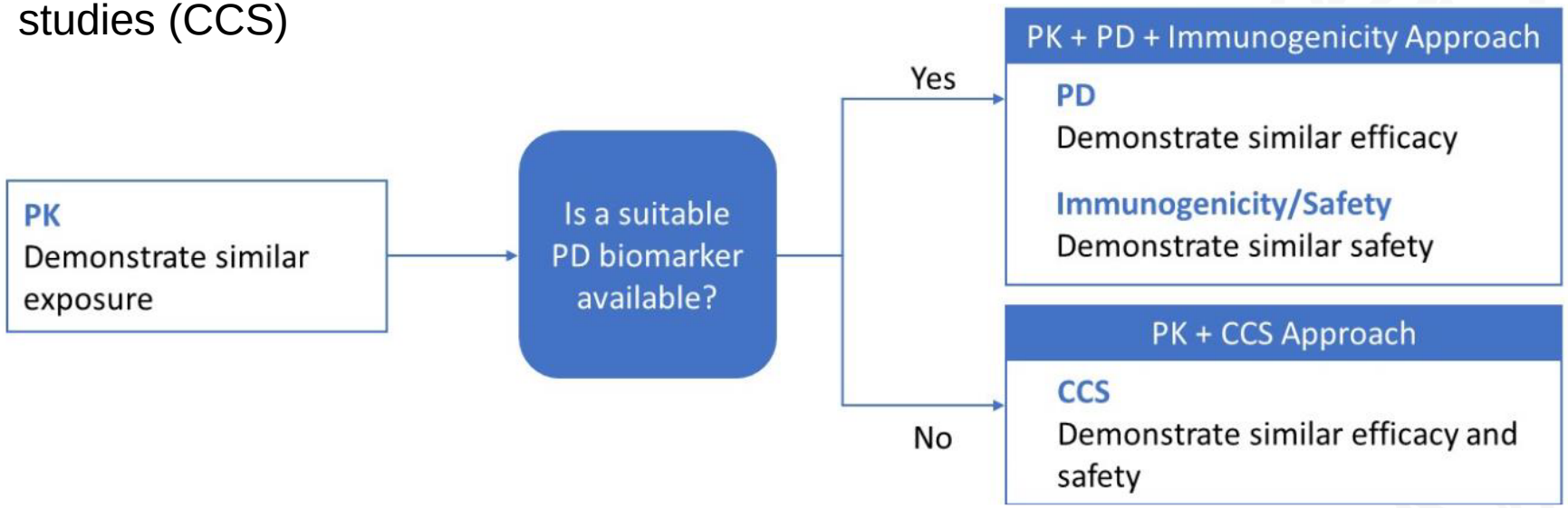
Studies required for biosimilarity

Type of studies	Demonstrate biosimilarity between the biosimilar and reference product
Analytical studies	Provide data to support the structural and functional similarity
Animal studies	Provide toxicology or pharmacology data
Clinical pharmacology studies	Metabolism, efficacy, and immunogenicity assessment
Additional clinical studies	Address remaining uncertainty after the completion of other studies; rule out clinically meaningful differences from the reference product

Adapted from: Biosimilar Regulatory Review and Approval. FDA. Accessed Apr 17, 2023. https://www.fda.gov/media/151061/download
Biosimilars Info Sheet Level 2: Regulatory and Scientific Concepts. Comparative Clinical Studies. FDA. Accessed Apr 17,2023. https://www.fda.gov/media/154916/download

Clinical studies

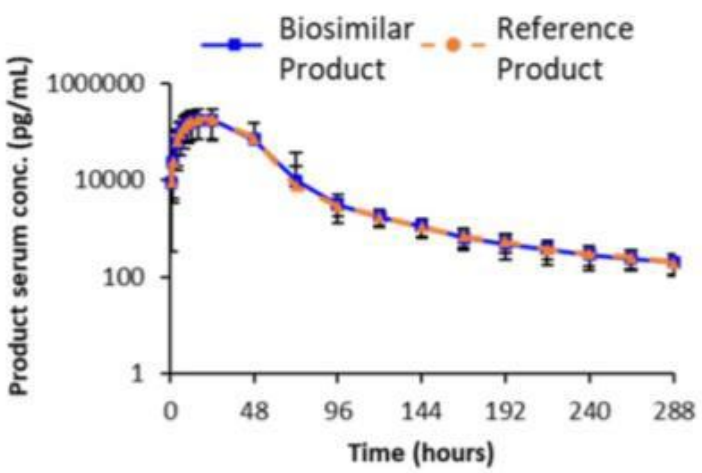
- Evaluate the similarity between biosimilar and reference product and ensure there are no clinically significant differences between them
- Clinical studies that evaluate exposure, efficacy, and safety between biosimilar and reference product: pharmacokinetic (PK), pharmacodynamic (PD), immunogenicity, and comparative clinical studies (CCS)



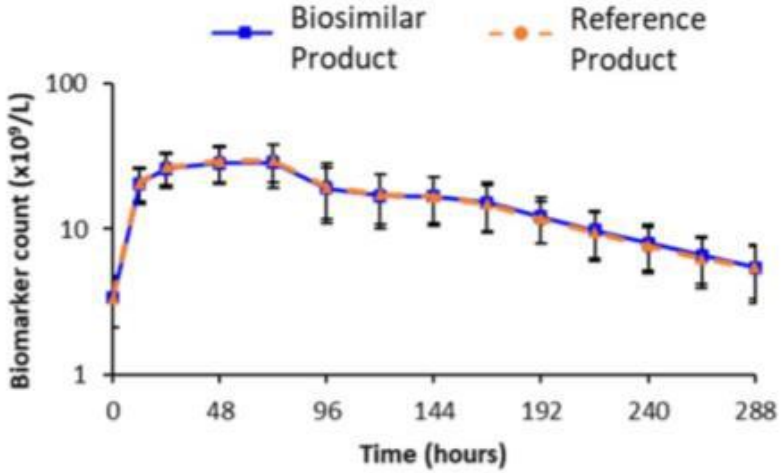
Adapted from Biosimilars Info Sheet Level 2: Regulatory and Scientific Concepts. Comparative Clinical Studies. FDA. Accessed Jan 3, 2023. https://www.fda.gov/media/154916/download

If there is a suitable PD biomarker to evaluate biosimilarity

Similar Exposure



Similar Efficacy



Similar Safety

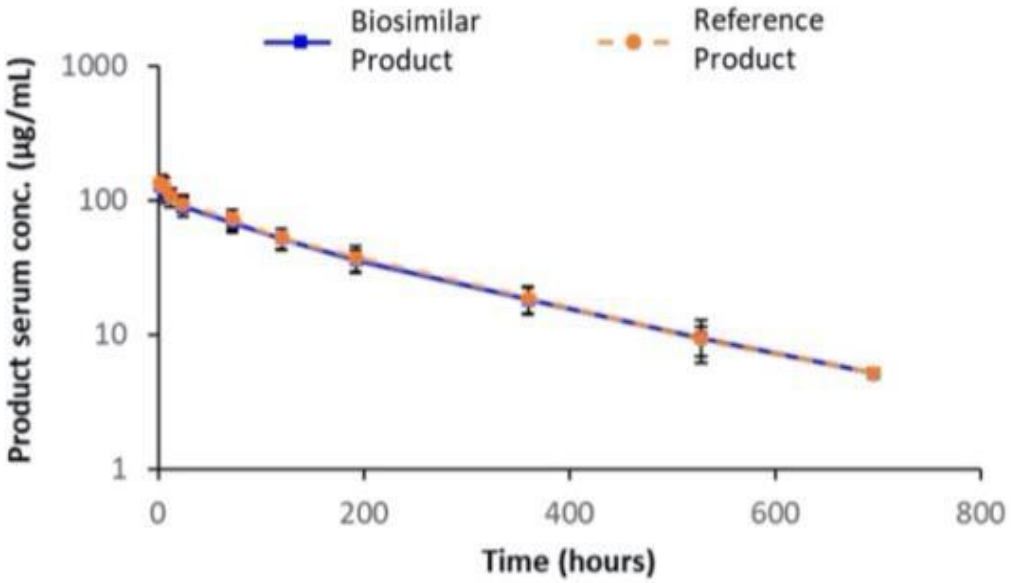
	Biosimilar Product	Reference Product
Immunogenicity	Similar	
Adverse events	Similar	

PK studies + **PD studies** + **Immunogenicity studies**

Adapted from Biosimilars Info Sheet Level 2: Regulatory and Scientific Concepts. Comparative Clinical Studies. FDA. Accessed Jan 3, 2023. https://www.fda.gov/media/154916/download

If there is no suitable PD biomarker to evaluate biosimilarity

Similar Exposure



Similar Efficacy

Similar Safety

	Biosimilar Product	Reference Product
Response rate, n (%)	116/248 (46.8%)	129/256 (50.4%)
90% CI for risk ratio estimate	0.7981–1.0796	
Equivalence margin	0.740–1.350	
Immunogenicity	Similar	
Adverse events	Similar	

PK similarity + **Comparative clinical studies for efficacy and safety (immunogenicity)**

Adapted from Biosimilars Info Sheet Level 2: Regulatory and Scientific Concepts. Comparative Clinical Studies. FDA. Accessed Jan 3, 2023. https://www.fda.gov/media/154916/download

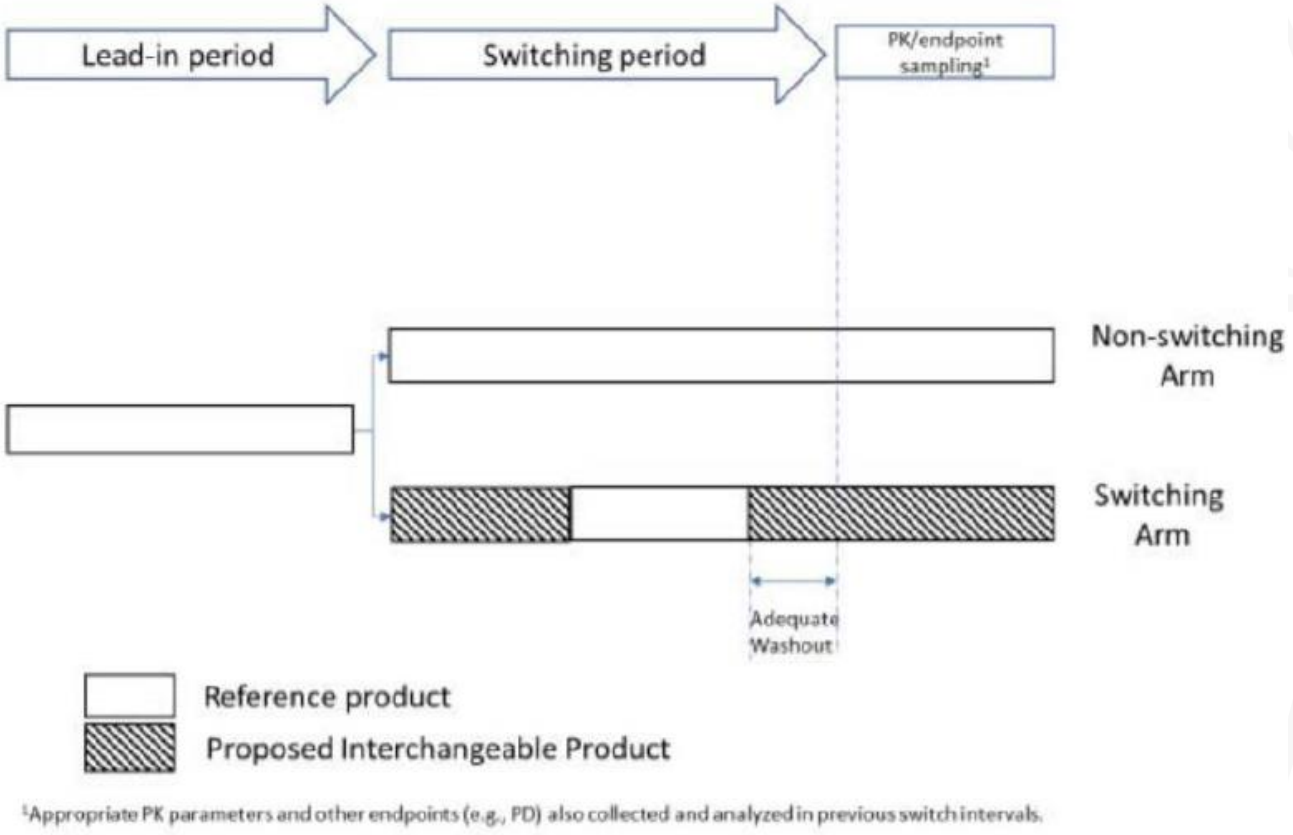
Extrapolation of indications

- It is required that a clinical trial compares a biosimilar to the reference product for at least 1 condition which the reference product is licensed for
- The manufacturer may seek approval for ≥1 or all indications for which the reference product is approved without direct clinical studies in each condition. Must provide adequate scientific justifications to address the following for extrapolation of indications:
  - Mechanism of action in each condition, the PK, immunogenicity, and expected toxicities in each condition and in different patient populations
- Which condition or disease state to conduct a clinical study in? The FDA recommends choosing a condition that is adequately sensitive to allow detecting clinically meaningful differences between the reference and biosimilar product

Bridges SL Jr et al. *Arthritis Rheumatol*. 2018;70(3):334-344.
Biosimilar review and approval. Content current as of Dec 13, 2022. Accessed Jan 10, 2023. https://www.fda.gov/drugs/biosimilars/review-and-approval#indication
Scientific Considerations in Demonstrating Biosimilarity to a Reference Product Published Apr 2015. FDA. Content current as of Apr 24, 2020. https://www.fda.gov/media/82647/download

Interchangeable biosimilar

- Manufacturers provide additional data to support that switching between reference product and interchangeable biosimilar is not associated with increased safety risk or decrease in effectiveness
- Interchangeable biosimilars should not be deemed safer or more effective than other biosimilars without interchangeable status
- Pharmacists may substitute reference product with an interchangeable biosimilar without the intervention of the prescriber, depending on state law



Interchangeable Biological Products. FDA. Accessed Jan 4, 2023. https://www.fda.gov/media/151094/download
Considerations in demonstrating interchangeability with a reference product. Guidance for industry. FDA Content current as of May 6, 2020. Accessed Jan 4, 2023. https://www.fda.gov/media/124907/download
Graph from: Biosimilar and Interchangeable Biosimilars: Review of Scientific Concepts, Case Studies, and Resources. FDA. Program initial release date: Feb 18, 2022. Expiration date: Dec 31, 2024. Accessed Mar 6, 2023. https://www.fda.gov/about-fda/fda-pharmacy-student-experiential-program/biosimilar-and-interchangeable-biosimilars-review-scientific-concepts-case-studies-and-resources

New York State law

- A pharmacist shall substitute a less expensive biological product for a prescribed biological product provided that **ALL** of the following conditions are met:
  - the substituted biological product is either an interchangeable biological product for the prescribed product or the substituted biological product is one for which the prescribed product is an interchangeable biological product
  - the prescriber does not designate that a substitution is prohibited
  - the pharmacist indicates on the label affixed to the immediate container in which the biological product is distributed the name and strength of the product and its manufacturer unless the prescriber states otherwise

Assembly Bill A8519. 2021-2022 Legislative Session. Makes permanent certain provisions of law relating to interchangeable biological products. https://www.nysenate.gov/legislation/bills/2021/a8519
The New York State Senate. Chapter 16 Education. Title 8 The Profession. Article 137, Pharmacy. Section 6816-a. When substitution is required. https://www.nysenate.gov/legislation/laws/EDN/6816-A

New York State law (continued)

- Within 5 business days following the dispensing of a substituted biological product, the dispensing pharmacist or the pharmacist's designee shall communicate to the prescriber the specific product provided to the patient, including the name of the product and the manufacturer
- The communication shall be conveyed to the prescriber by
  - Making an entry that is electronically accessible to the prescriber through an interoperable electronic medical records system, an electronic prescribing technology or a pharmacy record or
  - Using facsimile, electronic transmission or other electronic means
  - If an electronic means described in this paragraph is not available to the pharmacist at the time of communication, the pharmacist may communicate the information by telephone

Assembly Bill A8519. 2021-2022 Legislative Session. Makes permanent certain provisions of law relating to interchangeable biological products. https://www.nysenate.gov/legislation/bills/2021/a8519
The New York State Senate. Chapter 16 Education. Title 8 The Profession. Article 137, Pharmacy. Section 6816-a. When substitution is required. https://www.nysenate.gov/legislation/laws/EDN/6816-A

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Utilization of biosimilars in real-world practice

Process and clinical outcomes of a biosimilar adoption program with infliximab-dyyb

- A pharmacy team at an academic medical center in Massachusetts took the lead in the evaluation, education, and implementation of infliximab-dyyb across the health system
- Sample: patients treated in dermatology, gastroenterology, or rheumatology clinics who had been receiving infliximab for ≥6 months and transitioned to infliximab-dyyb from Mar 2018 to Jun 2019
- Objectives
  - Describe a biosimilar adoption process for large-scale conversion to infliximab-dyyb in patients on infliximab for ≥ 6 months for all indications
  - Characterize cost savings to health systems if patients transition to infliximab-dyyb
  - Evaluate clinical outcomes of adult patients with inflammatory bowel disease (IBD) who transitioned to infliximab-dyyb

Bhat S, et al. J Manag Care Spec Pharm. 2020;26(4):410-416.

Infliximab-dyyb adoption process

Pharmacy team met with providers from dermatology, gastroenterology, and rheumatology department to establish consensus and address clinical concerns.*

Pharmacy team created a monograph for infliximab-dyyb to be presented at pharmacy & therapeutics (P&T) committee meeting.

P&T committee approved the formulary change from infliximab to infliximab-dyyb.

Providers communicated with patients about biosimilar transition and provided educational materials. Nurses were encouraged to call pharmacy to schedule in-person consultations with patients who had questions about infliximab-dyyb.

Pharmacists called each patient to discuss the transition to infliximab biosimilar 2 weeks prior to the first infusion as soon as prior authorization was approved.

*Concerns expressed by providers:

- Appropriate timepoint for biosimilar switch
- Lack of knowledge about financial implications to patients converting to a biosimilar
- Need for patient education to prevent interruptions in workflow
- Extrapolation of indications without clinical evidence

Bhat S, et al. J Manag Care Spec Pharm. 2020;26(4):410-416.

Patients who transitioned to infliximab-dyyb successfully

- 179 patients were identified as receiving infliximab for ≥6 months and eligible to transition to infliximab-dyyb
  - 15 (8%) were ineligible to switch because of insurance denial
  - 7 (4%) received some of their infliximab infusions at other centers
  - 3 (2%) were not deemed to be on a stable infliximab regimen by their providers
  - 3 (2%) refused to transition
  - 151 patients met all criteria for transitioning
    - 146 (97%) transitioned successfully; majority of them were managed by gastroenterology practice. Patients were on infliximab for 27 months before switching on average.
    - 3 discontinued infliximab for alternative treatment option, 1 transferred care for non-switch related reasons, 1 lost to follow-up

Bhat S, et al. J Manag Care Spec Pharm. 2020;26(4):410-416.

Cost savings and clinical outcomes analysis in IBD

- The calculated cost savings for the health system was forecasted to be $500,000 annually.
- In 63 of 75 (84%) eligible patients with IBD transitioned to infliximab-dyyb:
  - Among 40 patients that had Harvey Bradshaw Index (HBI) and Simple Clinical Colitis Activity Index (SCCAI) scores available before and after the switch:
    - 36 (90%) maintained remission
    - 2 (5%) were not in remission on infliximab and attained remission on infliximab-dyyb
    - 1 (2%) in remission on infliximab reported an increased HBI score, although the colonoscopy showed no active CD
  - After transitioning, 5 out of 9 patients who had colonoscopies showed endoscopic remission
  - 32 (51%) continued with the current dose, 24 (38%) required a dose increase, 4 (6%) discontinued due to antibody development or worsening disease, 3 (5%) transferred care or lost to follow-up, as of Oct 2018

Bhat S, et al. J Manag Care Spec Pharm. 2020;26(4):410-416.

Increasing biosimilar utilization at a pediatric center and associated cost savings

- Sample: Patients naïve to IV TNFi therapy (infliximab) and eligible to receive a biosimilar (before Sep 2019: ≥6 years of age with CD or ≥18 years of age with UC; after Sep 2019: ≥6 years of age with UC or CD to reflect change in indication from the FDA)
- Study timeframe: Jul 2019 to Feb 2021 (utilization of infliximab between Jan 2018 to Jun 2019 was documented as baseline data)
- Primary outcome: percentage of eligible patients who initiated biosimilar therapy
- Secondary outcome: patient clinical outcome at 14 weeks, 6 months, and 12 months post first dose to ensure the safety and efficacy of therapy. (Clinical outcome measurements: drug levels, antidrug antibodies, physician global assessment (PGA), therapy switches, and reasons for therapy switches)
- Estimated healthcare cost savings from utilizing biosimilars were calculated by average sales price (ASP) and wholesale acquisition cost (WAC)

Morris GA, et al. Inflamm Bowel Dis. 2022;28(4):531-538.

Process of implementing biosimilars

Education for all stakeholders

- Provide educational materials to providers, patients, the infusion center, and nursing staff to help establish comfort with prescribing and using biosimilars.
- Intervention strategies: division presentations, information sheets, process map to guide providers initiating infliximab, and frequently asked question sheets.

Initiation of prior authorization (PA)

- In outpatient settings: providers requested PA to be completed for a biosimilar on all eligible patients → Insurance specialist completed PA → If biosimilar was denied or nonpreferred drug, a PA request for reference drug was completed
- In inpatient settings: inpatient team consulted clinical pharmacists to determine if a biosimilar could be used→ Pharmacists reviewed patients' coverage and benefits prior to administration to prevent the need to switch to an alternative drug upon discharge

Morris GA, et al. Inflamm Bowel Dis. 2022;28(4):531-538.

Percentage of eligible patients initiated on biosimilar therapy

- Jan 2018 to Jun 2019: 131 patients started infliximab therapy. 1 out of 96 (1%) eligible patients was started on a biosimilar. 35 were ineligible due to age limits
- Jul 2019 to Feb 2021: 106 patients started infliximab therapy
  - 8 were ineligible for a biosimilar due to age limits
  - 23 (23%) started the reference drug
    - 20 due to insurance denials
    - 3 were considered process-related missed opportunities
  - 75 (77%) started a biosimilar

The utilization of biosimilars increased from 1% to 96%

Morris GA, et al. Inflamm Bowel Dis. 2022;28(4):531-538.

Clinical outcomes-drug durability

Patients started on a biosimilar

- 64/75 (85%) had data through 14 weeks post first dose; 60/64 (94%) continued biosimilar therapy and 4 discontinued (2 changed to an alternative due to lack of response, 2 required colectomy)
  - At 6 months, 58/60 (97%) remained on biosimilar (1 with UC required colectomy, 1 with CD developed psoriatic arthritis and changed to ustekinumab)
  - 37/58 had data through 12 months post first dose. 35/37 (95%) remained on biosimilar (2 with CD discontinued biosimilar due to symptoms)

Patients started on the reference drug

- 23/23 had data through 14 weeks post first dose; 20/23 (87%) continued the reference drug. 3 discontinued (2 changed to an alternative due to lack of response, 1 required colectomy)
  - At 6 months, 19/20 (95%) remained on the reference drug (1 with UC required colectomy)
  - 13/19 had data through 12 months post first dose. 13/13 remained on the reference drug

There was no statistically significant difference in drug durability between groups at each timepoint

Morris GA, et al. Inflamm Bowel Dis. 2022;28(4):531-538.

Additional clinical outcomes

Patients started on a biosimilar

- 3 patients developed antidrug antibodies (2 continued biosimilars after dose optimization)
- 76% had moderate or severe physician global assessments (PGAs) at baseline
  - PGAs decreased to 10% at 14 weeks, 5% at 6 months, and 0% at 12 months

Patients started on the reference drug

- No patients developed antidrug antibodies
- 78% had moderate or severe PGAs at baseline
  - PGAs decreased to 12% at 14 weeks, 0% at 6 months and 12 months

There was no statistically significant difference in drug levels, the presence of antibodies, and PGAs between groups at each timepoint

Morris GA, et al. Inflamm Bowel Dis. 2022;28(4):531-538.

Example of estimated healthcare cost savings

- From Jul 2019 to Feb 2021, 575 biosimilar infusions were administered (2821 vials, 5 vials per infusion on average). Estimated total cost savings from using biosimilars: $381,000 ASP; $651,000 WAC
- Cost savings from using infliximab-dyyb:
  - Per infusion: $680 by ASP; $1100 by WAC
  - Estimated annual cost savings for patients on standard induction dosing (500 mg given at 0,2,6 weeks followed by every 8 weeks): $5500 ASP and $8900 WAC per patient per year
- Cost savings from using infliximab-abda:
  - Per infusion: $515 by ASP; $2100 by WAC
  - Estimated annual cost savings for patients on standard induction dosing (500 mg given 0,2,6 weeks followed by every 8 weeks): $4100 ASP and $16,600 WAC per patient per year

Morris GA, et al. Inflamm Bowel Dis. 2022;28(4):531-538.

Barriers to biosimilar adoption

- Concerns about the safety and efficacy of biosimilars
  - Concerns about potential immunogenicity
- Lack of familiarity with the biosimilar development paradigm and regulatory standards for biosimilar approval
  - Concerns about extrapolation of indications and that biosimilars may only have limited clinical data, while the reference product has clinical data in all FDA-approved conditions
- Administrative burden of prescribing biosimilars
  - Prior authorizations may cause delay in treatment
  - Need for lengthy conversations and education with patients about the switch
  - Stocking multiple biosimilars in the same class

Shubow S et al. Clin Pharmacol Ther. 2023;113(1):37-49.
Edgar BS, Cheifetz AS, Helfgott SM, et al. J Manag Care Spec Pharm. 2021;27(8):1129-1135.

Barriers to biosimilar adoption (continued)

- Automatic substitution of interchangeable biosimilars without intervention from providers
  - Especially in patients stabilized on the reference product, the switch may add a layer of uncertainty in the treatment course
  - Some state laws have requirements on notifying prescribers upon substituting biologics
- “Nocebo effect” and lack of awareness and unfavorable perceptions of biosimilars from patients

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Nocebo effect

- Nocebo effect refers to experiencing unexplained, unfavorable therapeutic effects subsequent to a non-medical switch from the reference product to a biosimilar with regaining of the beneficial effects after reinitiating the reference product
- Generally, researchers compared patient reported outcomes on disease activities with objective lab measurements and drug trough levels. If there was no objective data to explain the patient's experienced inefficacy in biosimilar treatment, they considered this effect to be a nocebo effect
- In a systematic review of biosimilar nocebo effects, Odinet and colleagues stated that evidence was insufficient to confirm a biosimilar nocebo effect

Boone NW, et al. Eur J Clin Pharmacol. 2018;74(5):655-661.
Avouac J, et al. Semin Arthritis Rheum. 2018;47(5):741-748.
Odinet JS, Day CE, Cruz JL, Heindel GA. Journal of Managed Care & Specialty Pharmacy. 2018;24(10):952-959.

Overcoming barriers to biosimilar adoption

- Education programs for healthcare professionals and integration of biosimilars into clinical practice guidelines
  - Provide evidence from studies in which patients switched to biosimilars and real-world evidence from postmarketing studies
  - A focus group of providers favored education programs delivered by clinical pharmacists that work at the same institutions, available through a series of grand rounds, and tailored to different specialty departments with clinical data for each disease state
- Streamline PA requirements for biosimilars to remove administrative burden and enable immediate access
  - Provide clarity in the approval criteria for PA and the reasons for denial in response letter

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Overcoming barriers to biosimilar adoption (continued)

- Increased transparency related to formulary placement and biosimilar pricing
  - Real-time benefit checks provide point of care information about patient-specific coverage and costs and inform prescribers whether a PA is required
- Shared decision making and patient education
  - Encourage patients to select FDA-approved biosimilars over lower-cost drugs obtained from an illegitimate source
  - Screen patients at risk for nocebo effects
    - In a qualitative study that interviewed patients who had a non-medical switch from the reference product to a biosimilar in the management of chronic arthritis, the authors concluded that systematic education and communication about the logistics for non-medical switches with all stakeholders were important for avoiding nocebo effects

Shubow S et al. Clin Pharmacol Ther. 2023;113(1):37-49.
Edgar BS, Cheifetz AS, Helfgott SM, et al. J Manag Care Spec Pharm. 2021;27(8):1129-1135.
Jørgensen TS, et al. Arthritis Rheumatol. 2017; 69 (suppl 10). Accessed March 17, 2023. https://acrabstracts.org/abstract/communication-strategies-are-highly-important-to-avoid-nocebo-effect-when-performing-non-medical-switch-from-originator-product-to-biosimilar-product-danish-results-from-applying-the-parker-model-a-q/.

Summary

- Biologic products are large, complex molecules made from living sources, and slight variations exist from batch to batch; biosimilars are biologic products that are highly similar to their reference products. Reference products cannot be copied exactly, but biosimilars have the same strength, dose, route of administration, efficacy and potential side effects as the reference drug
- Examples of studies required for the FDA approval of biosimilars include analytical, animal, clinical pharmacology, and comparative clinical studies
- FDA may approve indications for biosimilars without direct clinical studies if there is at least 1 clinical trial comparing the biosimilar to the reference product for at least 1 condition which the reference product is licensed for

Summary

- NYS law allows pharmacists to substitute interchangeable biosimilars provided that certain conditions are met
- Real-world evidence on adoption of infliximab biosimilars suggests the following:
  - Education of all stakeholders and reducing burden from PA are keys to success
  - Utilization of biosimilars leads to cost savings for health system
  - Utilization of infliximab biosimilars did not produce clinically significant differences in patients' health outcomes compared with the reference drug

Thank you for your participation!

For additional educational opportunities,

please visit the NYSMPEP website

https://nypep.nysdoh.suny.edu/