Biologics and Biosimilars

Emily Marden
Sidley Austin LLP

April 27, 2022

FDLI

Agenda

- What is a Biologic?
- Drug vs. Biologic
- Biologics License Application (BLA) vs. Emergency Use Authorization (EUA)
- What is a Biosimilar?
- Biosimilar Approval Standards
- Interchangeable Biosimilar Approval Standards
- Exclusivity
- Biosimilar Labeling and Substitution
- Nonproprietary Naming of Biologics
- “Deemed to Be a License”
- Overview of Patent Scheme
- State Substitution Laws
- Advertising and Promotion
- The Purple Book Continuity Act

What is a Biologic? – Statutory Definition

- "*Biological product*" narrowly defined by statute

a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

42 U.S.C. § 262(i)

What is a Biologic? – Statutory Definition

1902 Biologics Control Act,	1944 Public Health Service Act	1970 Pub. L. 91-515	1997 FDAMA	2010 BPCIA	2019 Pub. L. 116-94
any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention and cure of diseases of man	any virus, therapeutic serum, toxin, antitoxin, or analogous product, or arsphenamine or its derivatives (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or ~~and~~ cure of diseases or injuries of man	any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or its derivatives (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of diseases or injuries of man	In this section, the term 'biological product' means a~~ny~~ virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or ~~its~~ derivative~~s~~ of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease~~s~~ or condition ~~injuries~~ of human beings ~~man~~	In this section~~,~~: (1) The term "biological product" means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.	In this section: (1) The term "biological product" means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein ~~(except any chemically synthesized polypeptide),~~ or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

What is a Biologic? – Regulatory Definition

(1) A virus is interpreted to be a product containing the minute living cause of an infectious disease and includes but is not limited to filterable viruses, bacteria, rickettsia, fungi, and protozoa.

(2) A therapeutic serum is a product obtained from blood by removing the clot or clot components and the blood cells.

(3) A toxin is a product containing a soluble substance poisonous to laboratory animals or to man in doses of 1 milliliter or less (or equivalent in weight) of the product, and having the property, following the injection of non-fatal doses into an animal, of causing to be produced therein another soluble substance which specifically neutralizes the poisonous substance and which is demonstrable in the serum of the animal thus immunized.

(4) An antitoxin is a product containing the soluble substance in serum or other body fluid of an immunized animal which specifically neutralizes the toxin against which the animal is immune.

(5) A product is analogous:

(i) To a virus if prepared from or with a virus or agent actually or potentially infectious, without regard to the degree of virulence or toxicogenicity of the specific strain used.

(ii) To a therapeutic serum, if composed of whole blood or plasma or containing some organic constituent or product other than a hormone or an amino acid, derived from whole blood, plasma, or serum.

(iii) To a toxin or antitoxin, if intended, irrespective of its source of origin, to be applicable to the prevention, treatment, or cure of disease or injuries of man through a specific immune process.

(6) A protein is any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size. When two or more amino acid chains in an amino acid polymer are associated with each other in a manner that occurs in nature, the size of the amino acid polymer for purposes of this paragraph (h)(6) will be based on the total number of amino acids in those chains, and will not be limited to the number of amino acids in a contiguous sequence.

What is a Biologic?

- Generally, biological products are
  - Therapeutic product
  - Derived from living sources (*e.g.*, humans, animals, microorganisms)
  - A subset of drugs

- "Drug" broadly defined by statute:

  (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and

  (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and

  (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and

  (D) articles intended for use as a component of any article specified in clause (A), (B), or (C).

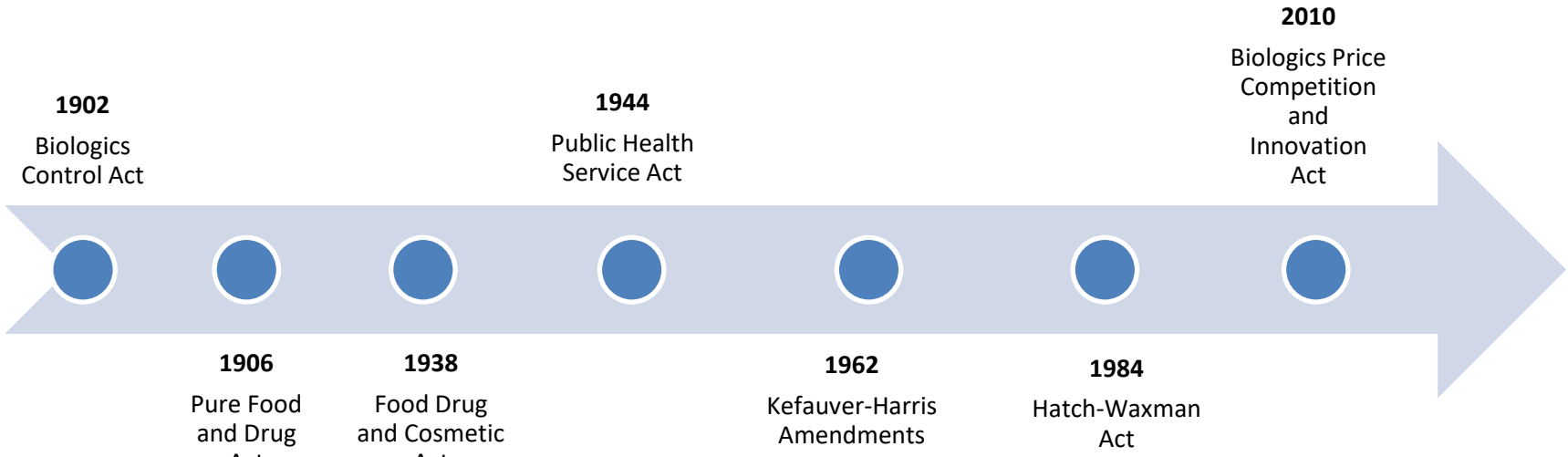
  21 U.S.C. § 321(g)

Drug vs. Biologic

some rules of thumb

Biologics	Drugs
Large molecules	Small molecules
Difficult to characterize	Easier to characterize
Complex to manufacture	Easier to manufacture
Manufactured from a living system	Manufactured through chemical synthesis
Alteration of manufacturing process may change compound	May be possible to alter manufacturing process without changing compound
FDA approval through Biologics License Application (PHSA)	FDA approval through New Drug Application (FDCA)

Drug vs. Biologic



Drug vs. Biologic

- Biologics Control Act of 1902
  - First drug approval statute addressed biologics
  - Passed in response to deaths from tetanus contamination of smallpox vaccine
  - First drug law to require pre-market approval

- Public Health Service Act of 1944 replaced the Biologics Control Act
  - Biological License Application (BLA) requires clinical testing for approval of biologics

- Biologics Price Competition and Innovation Act of 2010
  - Amended definition of biological product to include proteins
  - Created an approval pathway for follow-on biologics (biosimilars and interchangeable)

Drug vs. Biologic

- Pure Food and Drug Act of 1906
  - Came after first biologics legislation
  - Did not include pre-market approval

- Food Drug and Cosmetic Act of 1938
  - Premarket approval, but only required proof of safety

- Kefauver-Harris Amendments of 1962
  - New Drug Application (NDA) requires proof of safety and efficacy in clinical trials
    - Average drug development 8 years (1960) → 14 years (2006)
    - 5,000-10,000 screened compounds → 250 preclinical testing → 5 human clinical trials → 1 FDA approval ($1B per drug estimated)

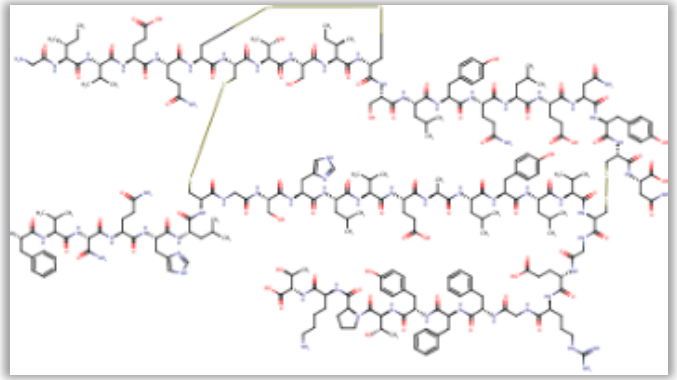
- Hatch-Waxman Act of 1984
  - New approval pathway for generic drugs

Breakout Session

How would FDA categorize a synthetic insulin consisting of 55 amino acids?

(a) Drug

(b) Biological Product



Biologic License Approval Standards

- Biologics license application (BLA) is required for biological products subject to licensure under the PHSA

- FDA shall approve a BLA on the basis of a demonstration that:
  - The biological product at issue is “safe, pure, and potent” and
  - The manufacturing facility “meets standards designed to assure that the biological product continues to be safe, pure, and potent.”

  PHSA Section 351(a)(2)(C)(i); *see also* 21 CFR 601.2(d).

Biologic License Approval Standards

- Congress directed FDA to "take measures to minimize differences in the review and approval of products required to have approved [BLAs] . . . And products required to have approved [NDAs]." 21 U.S.C. § 355 note (Special Rule)

- FDA also considers "substantial evidence" of effectiveness to be necessary to support licensure of a biological product under PHSA Section 351.

> "The term 'substantial evidence' means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof" 21 U.S.C. § 355

FDA, Draft Guidance, Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (Dec. 2019)

Emergency Use Authorization (EUA) Standards

- FDA may authorize the shipment of unapproved drugs, biological products, or medical devices (or unapproved uses of approved products) in the event of an emergency declaration by HHS.

- FDA may authorize the introduction into interstate commerce of such products if it concludes that:
  - an agent referred to in the emergency declaration can cause a serious or life-threatening disease or condition;
  - based on the totality of scientific evidence, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing that disease or condition or a serious or life-threatening disease or condition caused by an approved product or a product marketed under an EUA, and the known and potential benefits of the product when used for that disease or condition outweigh known and potential risks, taking into consideration the material threat of agents identified in the emergency declaration;
  - there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the relevant disease or condition;
  - in the case of an emergency based on the Secretary of Defense's determination that agents exist which may cause or be associated with an imminently life-threatening and specific threat to U.S military forces, the request for emergency use is made by the Secretary of Defense; and
  - any other criteria prescribed by FDA by regulation are satisfied.

21 U.S.C. § 360bbb-3(c).

Breakout Session

Which COVID-19 vaccines were granted EUAs?

(a) Pfizer-BioNTech's COVID-19 Vaccine

(b) Moderna's COVID-19 Vaccine

(c) Janssen's COVID-19 Vaccine

Which COVID-19 vaccines were granted BLAs?

(a) Pfizer-BioNTech's COVID-19 Vaccine

(b) Moderna's COVID-19 Vaccine

(c) Janssen's COVID-19 Vaccine

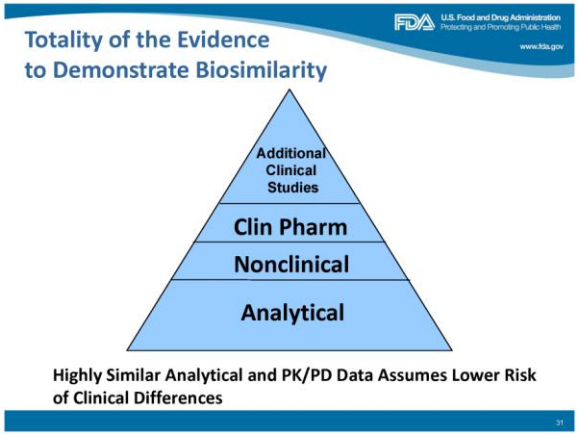
What is a Biosimilar?

- FDA has, to date, approved 35 biosimilar products.
- A biosimilar is a biological product.
  - FDA-approved biosimilars have been compared to an FDA-approved biologic, known as the reference product.
- A biosimilar is "highly similar" to a reference product.
  - For approval, the structure and function of an approved biosimilar are compared to a reference product, looking at key characteristics such as purity, molecular structure and/or bioactivity
- A biosimilar has "no clinically meaningful difference" from a reference product
  - Studies are performed to show that biosimilars have no clinically meaningful differences in safety, purity, or potency compared to the reference product

42 U.S.C. § 262(i)(2)

What is a Biosimilar?

- FDA's guidance describes a "stepwise" inquiry
  - Analytical testing → animal data → human PK and PD studies → clinical immunogenicity assessment → clinical trials
  - Each stage should be designed to eliminate "residual uncertainty" about the biosimilarity of the proposed product
  - At the end, the "totality of the evidence" must show that there are no clinically meaningful differences



FDA, Guidance for Industry, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (Apr. 2015)

Interchangeable Approval Standards

- Additional optional standard beyond biosimilarity

- Biologic is "interchangeable" if (42 U.S.C. § 262(k)(3)):
  - determined to be biosimilar;
  - "can be expected to produce the same clinical result in any given patient as the reference product"; and
  - if administered more than once to an individual, the risk in terms of safety or diminished efficacy of switching between biosimilar and reference product is not greater than the risk of using the reference product without switching

- To assess the safety of switching, manufacturers generally conduct studies in which patients alternate between the reference product and the interchangeable biosimilar and compare those patients to patients who are just being treated with the reference product.
  - The results must show no decrease in effectiveness or increase in safety risk associated with switching.

Interchangeable Biosimilar Product

- Most experts agree that a biosimilar can never be exactly the same as the original
  - Tiny differences in amino acids can produce hugely different immune reactions
- Need to ensure same therapeutic response without new risks
- Most have agreed that FDA should require rigorous testing
- FDA approved the first two interchangeable biosimilars in 2021: Semglee and Cyltezo

FDA NEWS RELEASE

FDA Approves First Interchangeable Biosimilar Insulin Product for Treatment of Diabetes

Availability of Insulin Products Will Help Increase Access and Potentially Lower the Cost of Insulin for People with Diabetes

Share Tweet LinkedIn Email Print

For Immediate Release: July 28, 2021

FDA NEWS RELEASE

FDA Approves Cyltezo, the First Interchangeable Biosimilar to Humira

Second Interchangeable Biosimilar Product Approved by Agency

Share Tweet LinkedIn Email Print

For Immediate Release: October 18, 2021

Exclusivity

- Data Exclusivity for Reference Biologic — 4 years
  - Time after approval of reference during which biosimilars application relying on BLA data may not be filed
- Market Exclusivity for Reference Biologic — 12 years
  - Time after approval of reference during which biosimilar may not enter market
- Market Exclusivity for 1st Interchangeable 1 year
  - Period of time when only 1st interchangeable product may market
  - No market exclusivity for biosimilarity

Biosimilar Labeling

- Issues raised in citizen petitions include whether biosimilar labeling should (1) identify a biosimilar as such; (2) identify the reference product; (3) acknowledge differences in the products' licensed indications; (4) acknowledge the use of extrapolation; (5) include data from studies conducted with the biosimilar; and (6) include clinical data related to the reference product
- In March 2015, FDA adopted a "same labeling" approach for first approved biosimilar Zarxio (filgrastim-sndz)
  - The first five questions were answered "no" and the last was "yes"
  - This was a departure from the draft Scientific Considerations guidance, which was finalized a few weeks later to be consistent with Zarxio
- In March 2016, FDA issued draft guidance on labeling
  - Draft guidance retreats from the Zarxio approach
  - Draft requires a Biosimilarity Statement and opens the door to the inclusion of biosimilar-specific information in narrow circumstances

Biosimilar Labeling

- FDA's final guidance in 2018 continues the approach adopted in draft guidance
  - Recommended inclusion of biosimilarity statement
  - Certain product-specific deviations from reference product label permitted
  - Should include only clinical trial information from trials used to support reference product approval and not clinical trial data used to establish biosimilarity

For example, for the fictitious product NEXSYMEO, the statement should read as follows:

NEXSYMEO (replicamab-cznm) is biosimilar* to JUNEXANT (replicamab-hjxf).

The footnote should appear at the end of the Highlights section (but above the Revision Date) and state the following:

*Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Biosimilarity of [BIOSIMILAR PRODUCT'S PROPRIETARY NAME] has been demonstrated for the condition(s) of use (e.g., indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.

Nonproprietary Naming of Biologics

- One of the most contentious debates regarding biosimilars pertains to their non-proprietary (NP) names
  - Generic industry generally wanted biosimilars and their reference products to have the same NP name (e.g., filgrastim)
  - Innovator industry generally wanted distinct NP names
- FDA tipped its hand in March 2015 with the approval of Sandoz's Zarxio®, which added a suffix to the NP name: filgrastim-sndz
- FDA has issued a proposed rule in August 2015 and final guidance in 2017, explaining that (1) reference products would also use suffixes, and (2) suffixes would be non-meaningful
  - E.g., filgrastim-sndz will become filgrastim-blfm
- FDA's 2017 final guidance decided to apply the four-letter suffixes retrospectively (i.e., previously licensed biological products) but the 2019 draft guidance reversed course such that previously licensed products do not need to be revised to include the suffixes

Breakout Session

What might be FDA's rationales for adding distinguishing four-letter suffixes to biological products?

a. Enhance biological product pharmacovigilance
b. Prevent inadvertent substitution
c. Both (a) and (b)
d. None of the above

The “Deemed to be a License” Provision

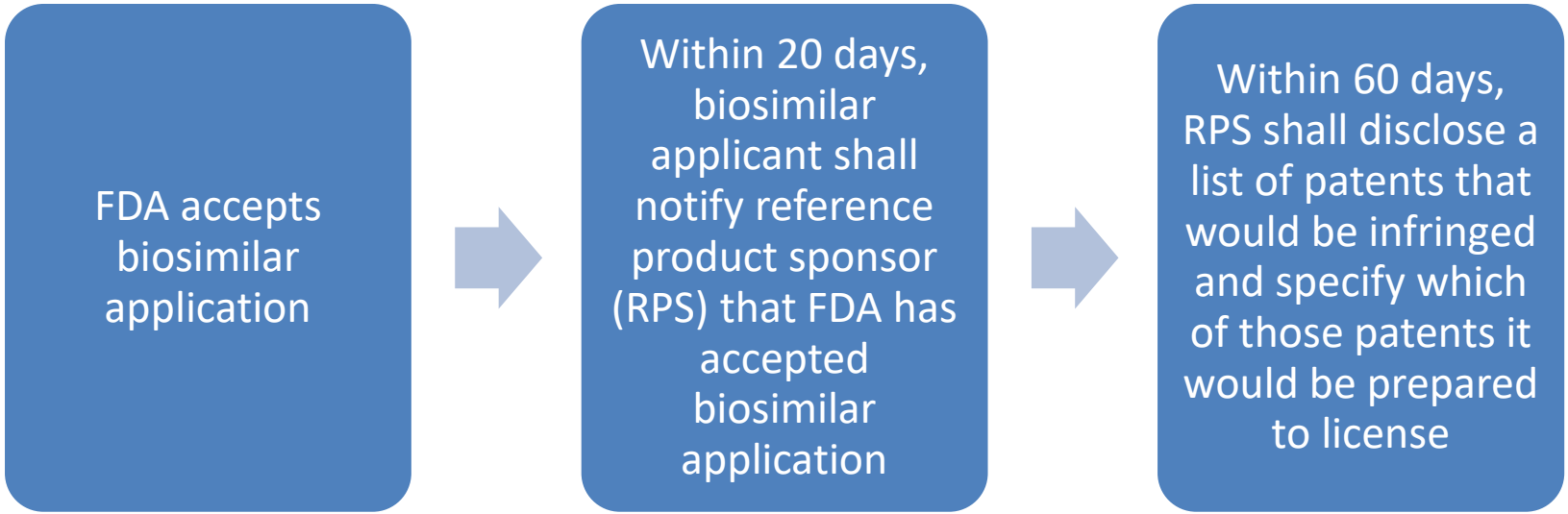
- Some protein products (e.g., insulin and insulin analogs, human growth hormone, pancreatic enzyme, reproductive hormones) historically have been approved in NDAs

- BPCIA amended definition of a “biological product” in the PHSA to include proteins and described procedures for submission of a marketing application for these protein products

- Proposed products: FDA will not approve any application for a biological product under the FDCA after March 23, 2020

- Approved products: An approved marketing application for a biological product under the FDCA will be “deemed to be a license” for the biological product (i.e., approved BLA) under the PHSA on March 23, 2020 and regulated under the PHSA.

Overview of Patent Scheme



See 42 U.S.C. § 262(*l*)

Overview of Patent Scheme

Within 60 days, biosimilar applicant may agree with those claims of infringement; shall either state why the patents are invalid or uninfringed or that it does not intend to begin marketing until they have expired; and shall respond to all license offers

Within 60 days, RPS shall provide detailed contentions supporting its clams of infringement and theories of patent validity

The two parties have 15 days to negotiate the list of patents to be litigated

See 42 U.S.C. § 262(*l*)

Overview of Patent Scheme

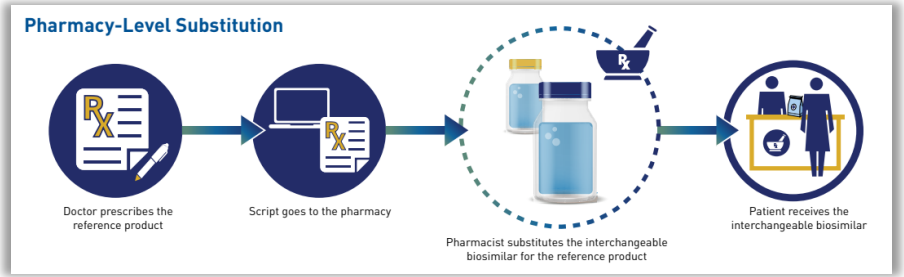
- If no agreement is reached, the parties must exchange lists of patents to be the subject of a patent infringement action
- If the parties reached an agreement on a patent list, then the reference product sponsor shall commence a patent infringement case within 30 days of the agreement
- If the parties did not reach an agreement, then the reference product sponsor shall commence a patent infringement case within 30 days of the exchange of lists
- Within 30 days of being served with the complaint, the biosimilar applicant shall provide FDA with a copy, and FDA shall publish a notice of the complaint in the Federal Register

42 USC 262(*l*)

State Substitution Laws

- An interchangeable biosimilar product may be substituted without the intervention of the health care professional who prescribed the reference product

- This is commonly called pharmacy-level substitution and is subject to state pharmacy laws.

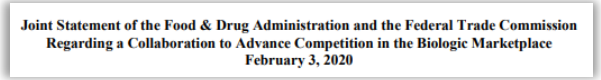


State Substitution Laws

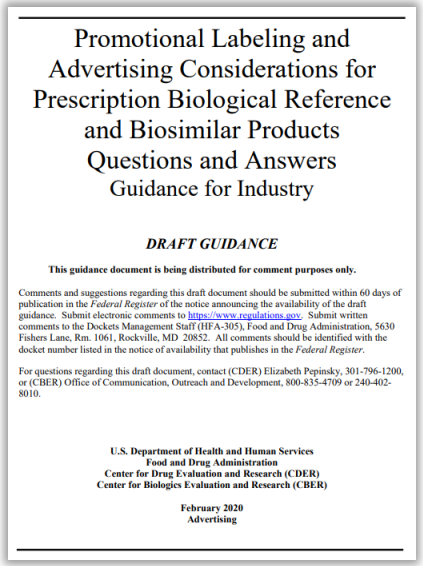
- All 50 states have laws addressing substitution of biosimilars but they have taken different approaches
  - Many states allow a pharmacist to substitute interchangeable biosimilars but with added communication requirements (to prescriber and/or patient)
  - Pharmacist and/or physician may need to retain records of substituted biologic medications for a certain period

Advertising and Promotion

- Part of joint initiative with FTC to deter anti-competitive practices and take action against false or misleading communications about biological products
- Addresses both reference and biosimilar products
- General requirements
  - Truthful and non-misleading
  - Convey information about efficacy and risks in a balanced manner
  - Reveal material facts about product
- Correctly and specifically identify reference and biosimilar products according to FDA-approved labeling
- Comparative claims between reference and biosimilar products:
  - Recommends firms to “avoid presentations that represent or suggest that a licensed biosimilar is not highly similar to the reference product or that a clinically meaningful difference in terms of safety, purity, or potency exists between the reference product and biosimilar”



Joint Statement of the Food & Drug Administration and the Federal Trade Commission Regarding a Collaboration to Advance Competition in the Biologic Marketplace
February 3, 2020



Promotional Labeling and Advertising Considerations for Prescription Biological Reference and Biosimilar Products Questions and Answers
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Elizabeth Pepinsky, 301-796-1200, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

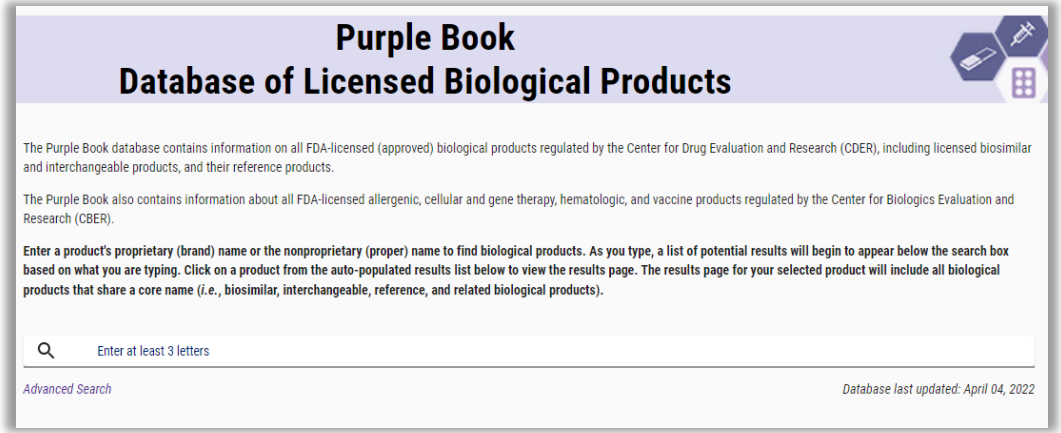
February 2020
Advertising

Advertising and Promotion

- Biosimilars Action Plan – Key Elements:
  - Improving the efficiency of the biosimilar and interchangeable product development and approval process
  - Maximizing scientific and regulatory clarity for the biosimilar product development community
  - Developing effective communications to improve understanding of biosimilars among patients, providers, and payers
  - Supporting market competition by reducing gaming of FDA requirements or other attempts to unfairly delay market competition to follow-on products
- According to FDA, the 2020 Draft Guidance helps ensure that public information surrounding biosimilars and reference products is communicated in a truthful and non-misleading manner

The Purple Book Continuity Act

- Part of the Omnibus Appropriations Bill enacted on December 27, 2020
- Went into effect in June of 2021
- The Purple Book database contains information on all FDA-licensed biological products regulated by CDER and CBER



The Purple Book Continuity Act

- Requires FDA to publish a list of approved biological products, their date of licensure and application number, their licensure and marketing status, and any regulatory exclusivity period
  - Update the list every 30 days

- Imposed a new patent listing requirement
  - Reference product sponsor must provide FDA the list of patents and corresponding expiration dates ("initial list") within 30 days of providing the initial list to a 351(k) applicant
  - Reference product sponsor must also provide FDA any subsequent or supplemental lists, and their corresponding expiration dates, within 30 days of providing the list to a 351(k) applicant

Questions