Biologics and Biosimilars

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What is a Biologic?

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What is a Biologic?

- Simply stated: a medical product derived from living organisms

What is a Biologic?

- Legal definition: “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?

- Legal definition: “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.”

Drugs vs Biologics

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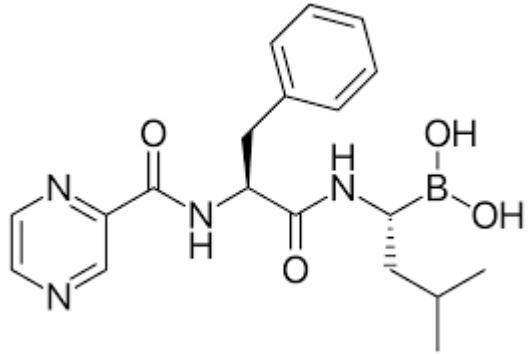
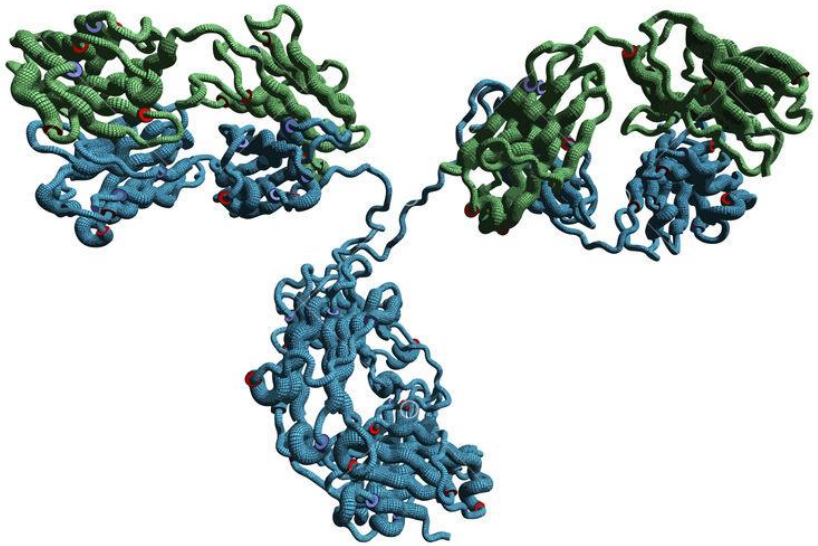
Drugs vs Biologics

Small Molecule Drugs:



Biologic Drugs:



BLA Approval Standards

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BLA Approval Standards

Biologics License Applications (BLA):

- Seeks permission to introduce a biologic into the market
- Similar to an NDA but slightly different in terms of their application content and submission requirements
- A pre-license inspection of the facility is generally required before a BLA is approved

What is a Biosimilar?

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What is a Biosimilar?

Biosimilar or Biosimilarity means:

- The biological product is **highly similar** to the reference product notwithstanding minor differences in clinically inactive components

- There are **no clinically meaningful differences** between the biological product and the reference product in terms of safety, purity, and potency of the product

“Highly Similar”

What does “highly similar” mean?

- Minor differences between the references and proposed biosimilar in clinically inactive components are acceptable
  - For example, the stabilizer or buffer

- To demonstrate that a biosimilar product is highly similar to the reference product, perform extensive analysis and compare the structure and function of the reference product and the proposed biosimilar
  - Results from these comparative tests, along with other information, must demonstrate that the biosimilar is highly similar to the reference product

“No Clinically Meaningful Differences”

How do you demonstrate that there are “no clinically meaningful differences”?

- Analytical studies demonstrating that the biological product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components
- Animal studies, including an assessment of toxicity
- A clinical study or studies assessing immunogenicity, pharmacokinetics (PK), and, in some cases, pharmacodynamics (PD) and may also include a comparative clinical study

An application for an interchangeable product must also include information or data demonstrating that:

- The proposed interchangeable product is expected to produce the same clinical result as the reference product in any given patient
- For a product administered more than once to an individual, switching between the proposed interchangeable product and the reference product does not increase safety risks or decrease effectiveness compared to using the reference product without such switching between products

Interchangeable Approval Standards

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Interchangeable Approval Standards

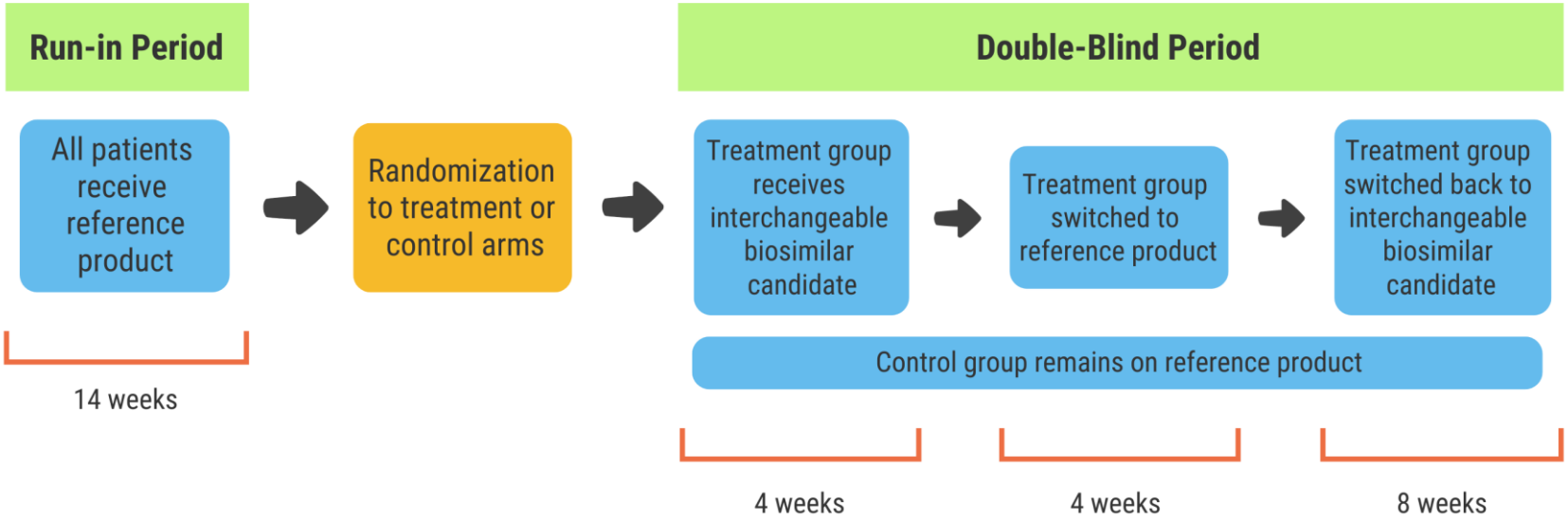
Interchangeable or Interchangeability:

- The biological product is biosimilar to the reference product;
- It can be expected to produce the same clinical result as the reference product in any given patient
  - Data and information necessary to demonstrate this "may vary depending on the nature of the proposed interchangeable product"
- For a product administered more than once, the safety and reduced efficacy risks of alternating or switching are not greater than with repeated use of the reference product without alternating or switching

Benefit of interchangeability:

- The interchangeable product may be substituted for the reference product without authorization of the health care provider
- Potential for exclusivity

Chart. A Sample Outline for an Interchangeability Study [a,b]

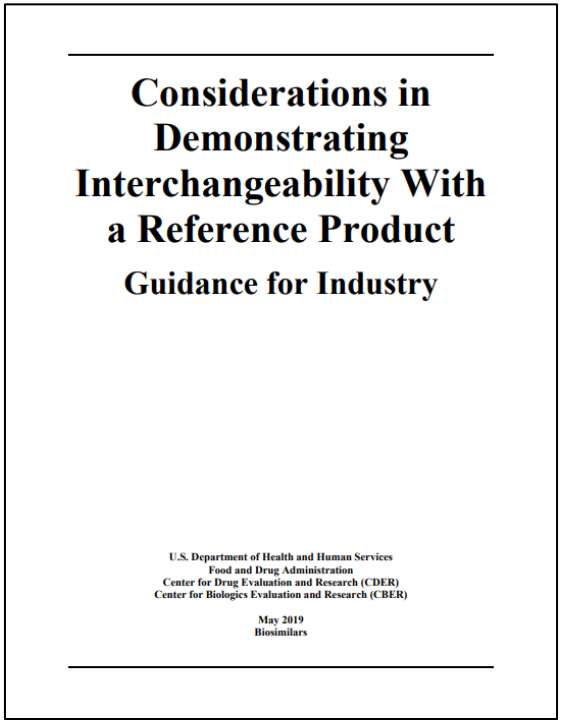


[a] Dose administration must be based on approved label and specific indication.

[b] In the study conducted by Boehringer Ingelheim, investigators followed this model but extended the trial to 48 weeks. After the double-blind period, patients in the treatment group continued on the biosimilar and those in the control group remained on reference product.

Source: Boehringer Ingelheim

FDA's Draft and Final Guidance

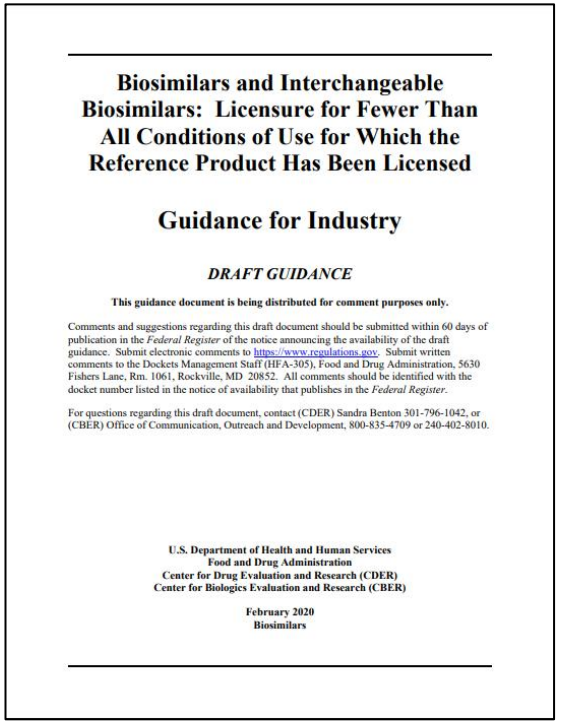


Considerations in Demonstrating Interchangeability With a Reference Product

Guidance for Industry

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)

May 2019
Biosimilars



Biosimilars and Interchangeable Biosimilars: Licensure for Fewer Than All Conditions of Use for Which the Reference Product Has Been Licensed

Guidance for Industry

DRAFT GUIDANCE

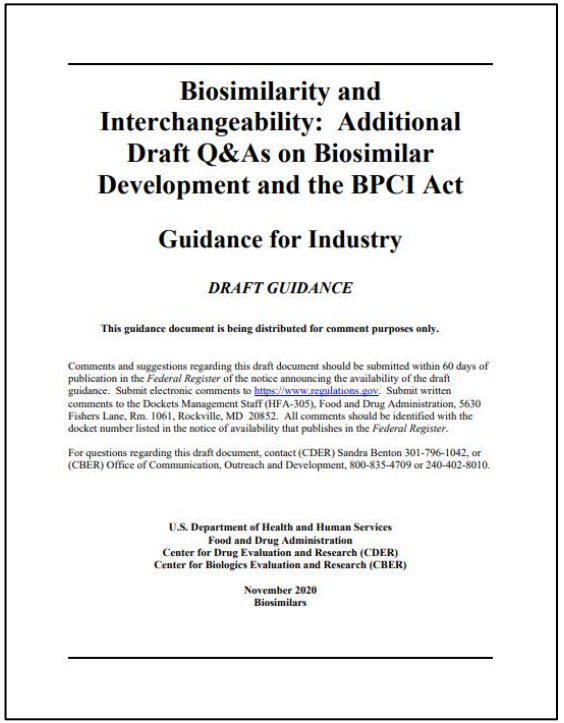
This guidance document is being distributed for comment purposes only.

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) Sandra Benton 301-796-1042, 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
Biosimilars



Biosimilarity and Interchangeability: Additional Draft Q&As on Biosimilar Development and the BPCI Act

Guidance for Industry

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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)

November 2020
Biosimilars

Exclusivity (Biologic and Interchangeable)

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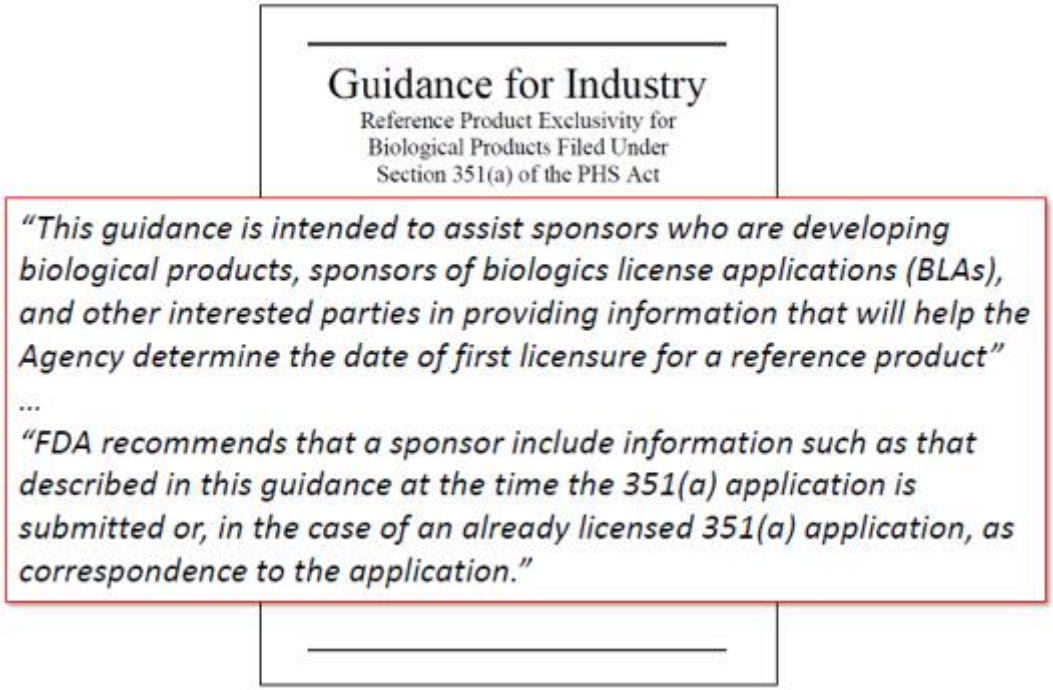
Exclusivity (Biologic)

Reference Product Exclusivity:

- Biosimilar applications may not be:
  - Submitted until 4 years after first licensure of reference product
  - Approved until 12 years after first licensure of reference product
- These exclusivity periods “shall not apply to”:
  - Supplement for reference product
  - Subsequent application filed by same sponsor or “a licensor, predecessor in interest, or other related entity” for:
    - A nonstructural change that results in a new indication, route or administration, dosing schedule, dosage form, delivery system, delivery device, or strength; or
    - A structural modification that does not result in a change in safety, purity, or potency

FDA's August 2014 Draft Guidance



Draft Guidance: Recommended Content of Exclusivity Submissions

1. List of “all licensed biological products that are structurally related” to product for which exclusivity is sought
2. Identify products listed in #1 for which the sponsor or any related entities are the “current or previous license holder”
3. Describe structural differences between products identified in #2 and product for which exclusivity is sought
4. Include evidence of change in safety, purity, or potency between products identified in #2 and proposed product, including a description of how described structural differences “relate to” these changes

Draft Guidance: “Related Entity”

- FDA proposes to interpret “licensor” to include “entities that continue to retain . . . rights to intellectual property that covers the biological product”
- FDA will determine “related entity” status based on:
  - Ownership and control of companies, or
  - Engagement in “certain commercial collaborations” relating to development of the product(s) at issue

Draft Guidance: Other Key Provisions

- Structural Modification: Draft refers to “any” differences in amino acid sequence, glycosylation patterns, tertiary structures, post-translational events (including pegylation), and infidelity of translation or transcription
- Results in a Change in Safety, Purity, or Potency:
  - Determination will be made on case-by-case basis and “generally” will need to be based on data
  - “The supporting information provided should include measurable effects (typically demonstrated in preclinical or clinical studies and shown by relevant methods such as bioassays) clearly describing how the modification resulted in a change in safety, purity, or potency compared to the previously licensed product.”

Exclusivity (Interchangeable)

The first to obtain an “interchangeable” license receives exclusivity against any subsequent interchangeable license application for any condition of use in Pioneer product until:

1. one year after commercial marketing by first licensee; or
2. 18 months after court decision (appellate court, if appealed) on all patents or dismissal of action against first licensee; or
3. 42 months after first licensee approval if litigation is still pending, or 18 months after first licensee approval if no suit is filed (i.e., where 1st licensee fails to market)

Biosimilar Labeling

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Biosimilar Labeling

FDA's guidance aligns with the labeling policy for small molecule generics – very similar to the drugs they reference

But different from small molecule generics by requiring biosimilar labeling to include a biosimilarity statement

Biosimilar Labeling

Some Labeling Requirements Specific to Biosimilar Products:

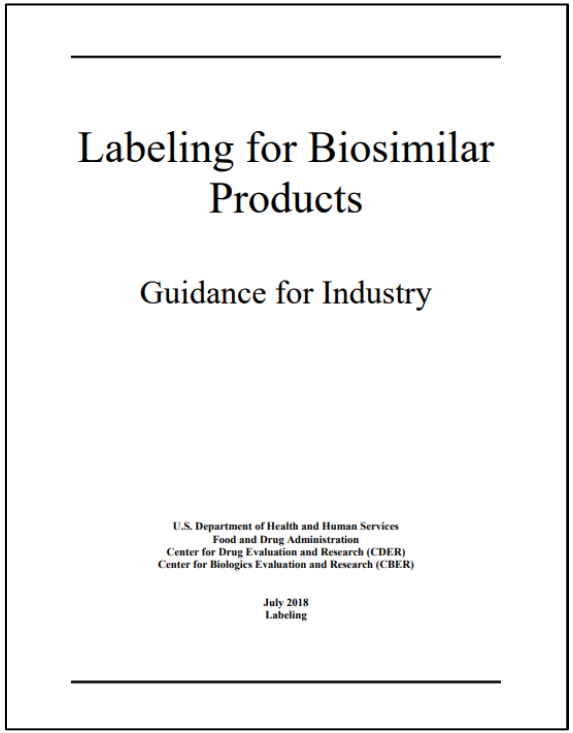
1. Information specific to the biosimilar: administration, preparation, storage, or safety information

2. Must list the biosimilar product's proper name when referencing the drug substance, but may use either proprietary or proper name elsewhere

3. Exclude language directed towards a specific, non-licensed condition of use if a biosimilar product will be licensed for "fewer than all conditions of use . . . for which the reference product is licensed," but include these other conditions if they are needed to ensure safe use of the product

4. The initial U.S. approval in the "Highlights" section of the biosimilar label should list the year that the biosimilar product was licensed

Biosimilar Labeling



Labeling for Biosimilar Products

Guidance for Industry

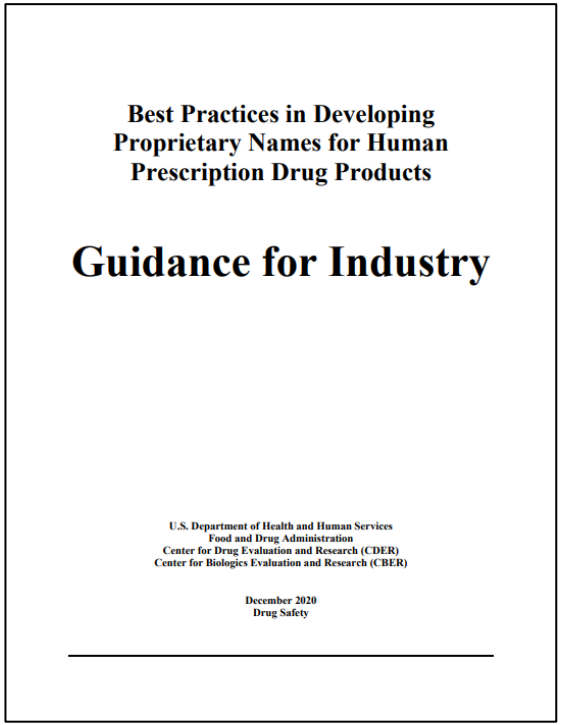
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

July 2018
Labeling

Nonproprietary Naming

Nonproprietary Naming

“Selecting a proprietary name is a critical element in drug product design and development because end users may rely, in part or in whole, on the proprietary name to identify which product, among thousands of available products, is intended for or used by a particular patient.”


Best Practices in Developing Proprietary Names for Human Prescription Drug Products

Guidance for Industry

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)

December 2020
Drug Safety

Nonproprietary Naming

- Some of FDA's recommendations are:
  - Avoid names that are similar in spelling or pronunciation to existing names
  - Do not incorporate any reference to an inert or inactive ingredient
  - For combination products, do not suggest the name of less than all active ingredients
  - Avoid names that incorporate the U.S. Adopted Name stems, which are intended to indicate a trait of a drug that may apply to others
    - Ex. "vir-" used for antivirals
  - Refrain from reusing the name of a discontinued drug product
  - Do not choose a name that is difficult to pronounce

“Deemed to be a License”

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“Deemed to be a License”

On March 23, 2020, certain NDAs were deemed BLAs.

- **March 23, 2010** – FDA enacted the BPCIA, which included a provision that stated that any applications for biological products approved as NDAs would be “deemed to be” BLAs as of March 23, 2020
- **December 2018** – FDA published a guidance interpreting the “Deemed to be a License” provision of the BPCIA, providing sponsors with details regarding the statutes and specifics for certain types of applications
- **September 24, 2019** – FDA posted a preliminary list of approved NDAs that would be converted to BLAs
- **March 23, 2020** – Approved marketing applications for a biological product were deemed to be an approved BLA and regulated under the PHS Act. Sponsors can now seek approval of products that are biosimilar to (or interchangeable with) these transitioned products

Overview of Patent Scheme

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Hatch-Waxman and BPCIA

Hatch-Waxman

- Abbreviated pathway for small molecule pharmaceuticals
- Technical act of infringement
- Notice Letter based on patents identified by Originator

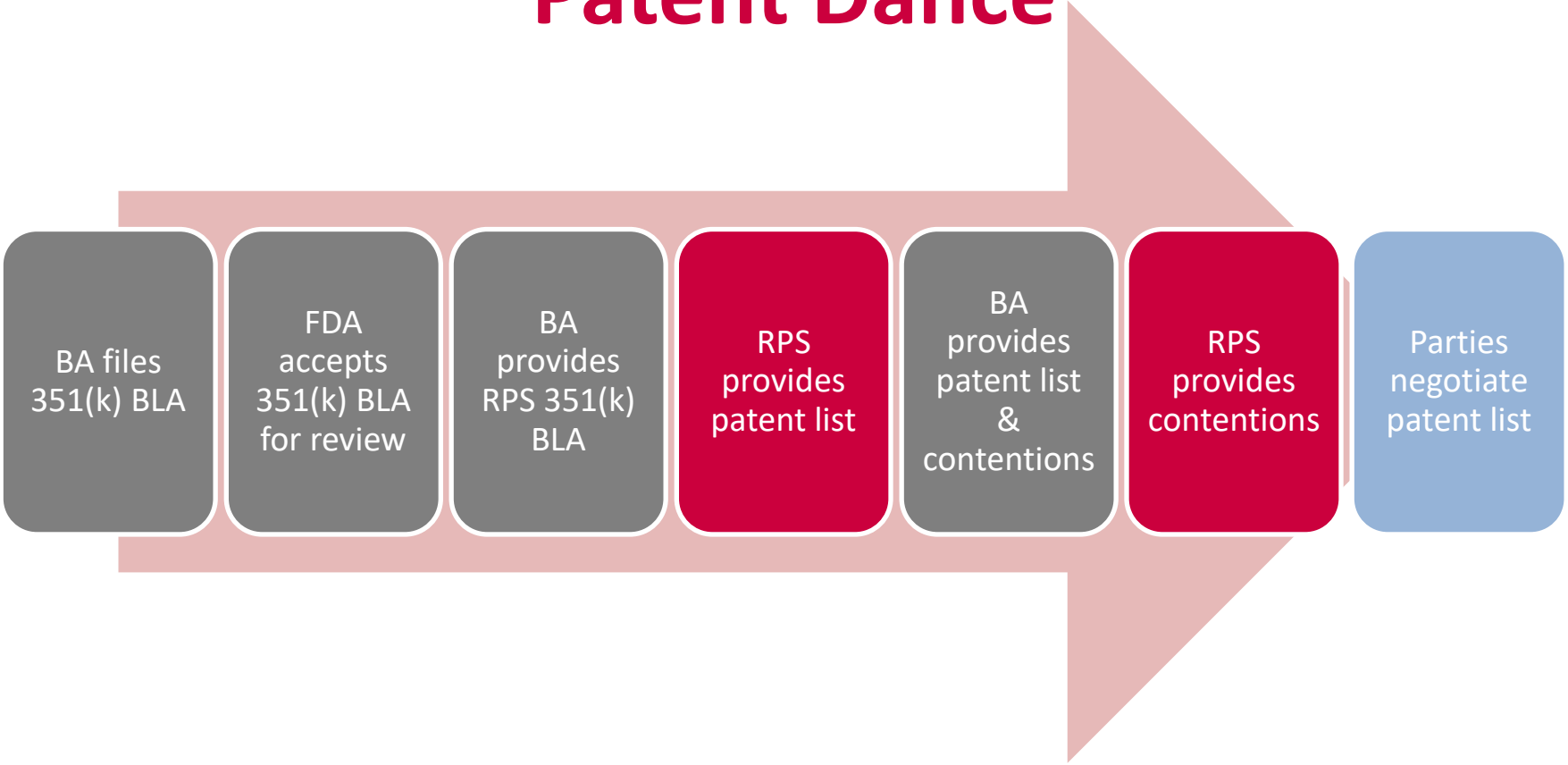
- Patents limited to product/method of use
- Originator initially controls number of asserted patents

BPCIA

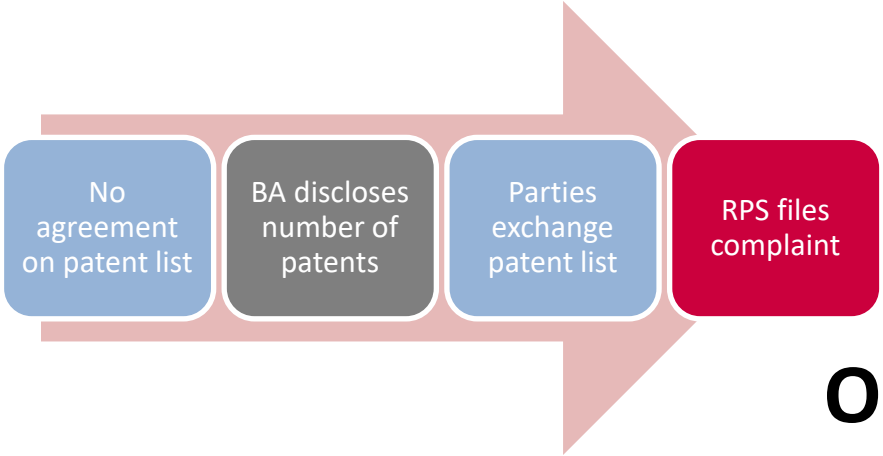
- Abbreviated pathway to follow-on biologics (biosimilars and interchangeables)
- Technical act of infringement
- Detailed Statement based on patents identified by RPS

- Manufacturing patents may be litigated
- aBLA applicant controls number and timing of asserted patents

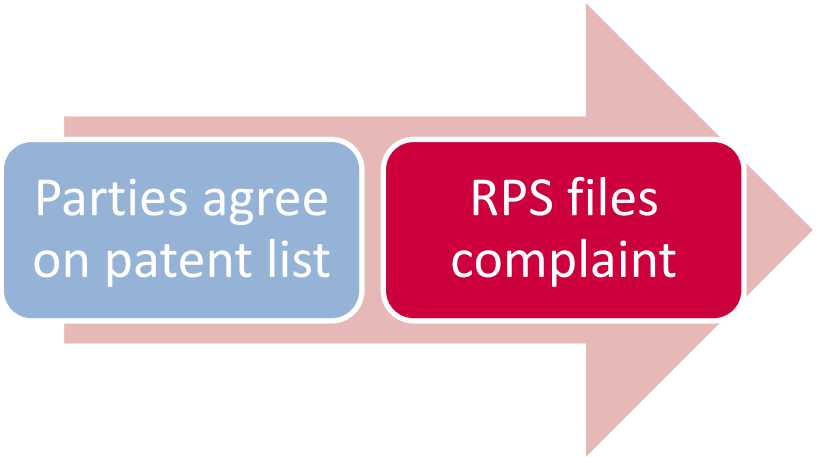
Patent Dispute Process
"Patent Dance"



Patent Dispute Process
"Patent Dance"



OR



Sandoz, Inc. v. Amgen, Inc. (S. Ct. June 12, 2017)

- Sandoz files aBLA for biosimilar to Amgen's Neupogen® (filgrastim).
- Amgen (RPS) *not* entitled to an injunction compelling disclosure of aBLA
  - Statute specifies "remedy" – Amgen can seek an immediate declaratory judgment patent action under Sec. 262(*l*)(9) – this is the "sole remedy"
  - Amgen got control over the timing/content of patent litigation because Sandoz failed to provide the aBLA/manufacturing information
- Remanded to Federal Circuit to determine state law remedies
- On remand, Federal Circuit panel unanimously ruled that the BPCIA preempts any state law remedies that would compel biosimilar applicants to comply with the patent dance provisions.

Patent Dispute Process
Late phase litigation

- Applicant provides Notice of Commercial Marketing. 42 U.S.C. § 262 (*l*)(8)(A)
- Late phase litigation: Before the first commercial marketing, the reference product sponsor ("RPS") may seek a preliminary injunction prohibiting the commercial manufacture or sale of the biosimilar product until the court decides issues of patent validity, enforcement, and infringement

Notice of Commercial Marketing

- The subsection (k) applicant ***shall provide*** notice to the reference product sponsor (RPS) not later than 180 days before the date of the first commercial marketing of the biological product ***licensed under subsection (k)***

- Supplemental applications *do not* trigger a new notice requirement and waiting period. *Genentech, Inc. v. Immunex Rhode Island Corp*., 964 F.3d 1109 (Fed. Cir. Jul. 6, 2020)

- Failure to Provide Notice of Commercial Marketing
  - RPS may bring Declaratory Judgment action for patent infringement, validity, or enforceability 42 U.S.C. § 262(*l*)(9)(B))

State Substitution Laws

State Substitution Laws

A product approved as an interchangeable may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product

- But, not all states have laws permitting substitution

State Substitution Laws

Requirements can differ among the states:

Washington:

A pharmacist must dispense an interchangeable biosimilar if:

1. It is in stock;
2. It has a lower wholesale price than the prescribed biologic and is in stock;
3. The prescriber did not specify in the prescription that substitution is prohibited; and
4. The patient or patient's representative does not ask for the prescribed biologic.

Wyoming:

A pharmacist may dispense an interchangeable biosimilar if:

1. The prescriber has not indicated otherwise.

Advertising and Promotion

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Advertising and Promotion

1. Biosimilars Action Plan
2. FDA/FTC Collaboration to Advance Competition
3. Draft Guidance, Promotional Labeling and Advertising Considerations for Prescription Biological Reference and Biological Products

Biosimilars Action Plan

- Announced in July 2018
- Intended to increase market competition without undermining incentives to invest in research
- Four key areas:
  1. Improving the efficiency of the biosimilar and interchangeable product development and approval process
  2. Maximizing scientific and regulatory clarity for the biosimilar product development community
  3. Developing effective communications to improve understanding of biosimilars among patients, clinicians, and payors
  4. Supporting market competition by reducing gaming of FDA requirements or other attempts to unfairly delay generic competition

FDA/FTC Collaboration

FDA and FTC issued a joint statement that identified four goals to help combat anti-competitive practices in relation to biosimilars:

1. coordinate to promote greater competition in biosimilar markets
2. work together to deter behavior that impedes access to samples of the reference biological product that are required for testing and development of follow-on products
3. take actions against false or misleading communications about biologics, including biosimilars
4. review patent settlements involving biologics, including biosimilars, for antitrust violations

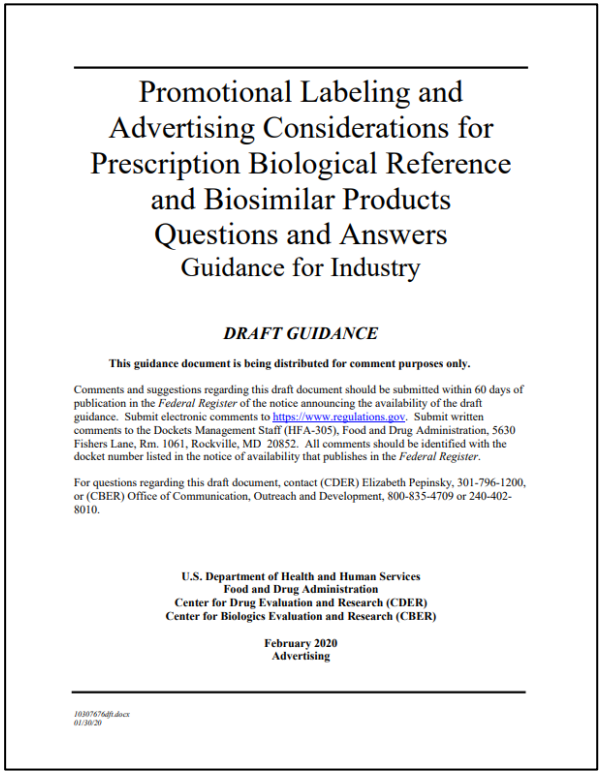
FDA/FTC Collaboration

The agencies were concerned with false or misleading statements comparing biological reference products and biosimilars, and the potentially negative misperceptions about the safety and efficacy of biosimilars

The agencies “intend to take appropriate steps to address companies” who are engaged in such practices

FDA's February 2020 Draft Guidance

"Promotional labeling and advertising must be truthful and non-misleading, convey information about a drugs efficacy and its risks in a balanced manner, and reveal material facts about the drug."



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

Guidance for Industry

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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

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FDA's February 2020 Draft Guidance

A determination of whether something is truthful and non-misleading is a fact-specific inquiry that should consider the following:

1. How information is presented
2. The type and quality of the data relied on to support the presentation
3. Contextual and disclosure considerations

FDA's February 2020 Draft Guidance

Requirements:

1. Promptly update materials based on new safety information or information related to reduced effectiveness

2. Ensure the information correctly identifies the products to which it applies

3. Refer to a biosimilar's label to incorporate relevant data

4. Make sure information in promotional materials that that was not previously in the label is consistent with the labeling and is truthful and non-misleading

FDA's February 2020 Draft Guidance

Examples of promotional materials that are false and misleading include representing or suggesting that:

1. a reference product is safer or more effective than its biosimilar product;
2. a biosimilar is safer or more effective that its reference product;
3. a biosimilar is not highly similar to its reference product.

The Purple Book Continuity Act

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The Purple Book

What is the Purple Book?

- A database maintained by FDA of approved biologic drugs
- Similar to the Orange Book for drug products

The Purple Book Continuity Act

- Requires FDA to list patents in the Purple Book

- But only patents that have *already been asserted* in BPCIA litigation

The Purple Book Continuity Act

- How has this changed the landscape?
  - First biosimilar mover still goes in blind
  - Subsequent litigants have a sense of the patent landscape, but different patents can be asserted

Questions

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