Biologics & Biosimilars

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FDLI Introduction to Drug Law
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FDLI

Overview

- What is a Biologic?
- New additions
- Drug v. Biologic
- Biologic Development
- Emergency Use Authorizations
- Biologics and COVID
- Special Programs
- What is a Biosimilar?
- Biosimilar Approval Standards
- Demonstrating Biosimilarity
- Interchangeable Approval Standard
- Demonstrating Interchangeability
- Biosimilar Labeling
- Biosimilar Substitution
- Exclusivity
- Naming
- Patent Dance
- Advertising and Promotion
- Purple Book

What is a Biologic?

- **Drug+**
- **Drug Definition (FFDCA § 301)**
  - "…articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease…; and…articles…intended to affect the structure or any function of the body…."
- **Biologic Definition (PHSA-42 U.S.C. § 262)**
  - "…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."

New Additions to the Biologic Family

- Historically some **protein-based products** were approved by FDA as drugs (e.g., insulin and insulin analogs, human growth hormone, pancreatic enzymes, reproductive hormones).
- The **2009 Biologic Price Competition and Innovation Act** clarified that protein products, except chemically synthesized polypeptides are biologics.
- The **2020 Further Consolidated Appropriations Act** removed the exclusion for chemically synthesized polypeptides.
- **Now**, all products that previously would have fallen in these categories must submit BLAs rather than NDAs/ANDAs.
- For those products already approved under the drug structure, the approved drug applications are **"deemed to be" a BLA.**
  - This means that follow-on products can no longer pursue ANDAs or 505(b)(2) NDAs but now must pursue biosimilar applications.

Drug v. Biologic

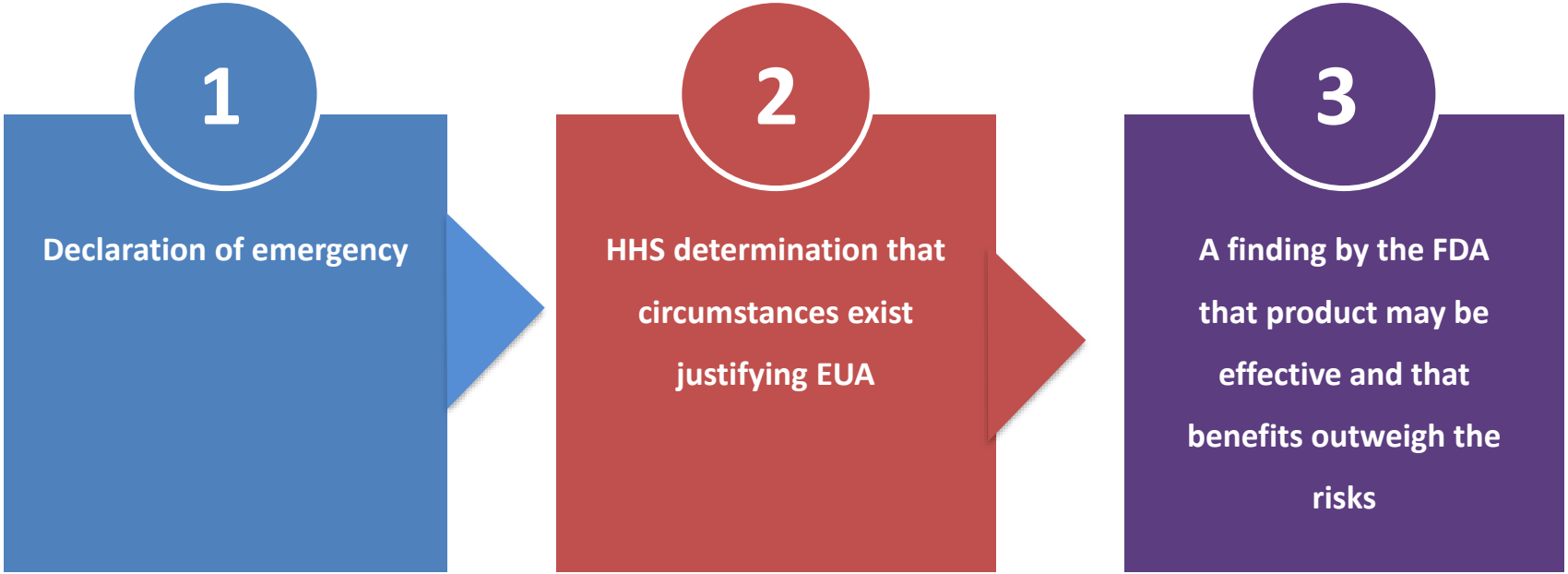
	Drug	Biologic
Authorizing Statute/Regulations	FFDCA 21 C.F.R. 200s-300s	FFDCA & PHSA 21 C.F.R. 200s-300s, and 600s
FDA Center	CDER	CDER or CBER
Composition	Smaller, well-defined chemical structure, chemically synthesized	Complex mixtures, usually natural source
Manufacturing	May not need to be sterile	Usually more complex, usually requires aseptic processing, potential lot release
Application	NDA Safe and effective	BLA Safe, pure, potent
Follow-On Products	Generic (ANDA)	Biosimilar (351(k))
Exclusivity	180 days, 3 years, 5 years	12 years, 12-42 months
Publication	Orange Book	Purple Book

Biologic Development Process

- **Process**
  - Nonclinical → IND → Clinical → BLA → Licensure/Marketing
- **Standard**
  - Product is safe, pure, and potent
  - Manufacturing facility meets standards designed to assure product continues to be safe, pure and potent
- **Parts of a BLA**
  - Nonclinical laboratory studies
  - Clinical studies
  - Compliance statements
  - Description of manufacturing methods
  - Data establishing stability
  - Product samples and lot testing results
  - Specimens of the labels, medication guides, enclosures, and containers
  - Manufacturers
  - Financial certification

Special Note on Emergency Use Authorizations

- Permits the use of unapproved or unapproved uses of drugs, biologics, and medical devices during certain types of emergencies (FFDCA § 564)



Biologics and COVID

Supplements for Approved Premarket Approval (PMA) or Humanitarian Device Exemption (HDE) Submissions During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency (Revised): Guidance for Industry and Food and Drug Administration Staff	05/04/2022
Emergency Use Authorization for Vaccines to Prevent COVID-19: Guidance for Industry	03/31/2022
Nonclinical Considerations for Mitigating Nonhuman Primate Supply Constraints Arising from the COVID-19 Pandemic: Guidance for Industry	02/04/2022
Investigational COVID-19 Convalescent Plasma: Guidance for Industry	01/07/2022
Policy for Certain REMS Requirements During the Tocilizumab Shortage Related to the COVID-19 Public Health Emergency: Guidance for Industry and Health Care Professionals	12/10/2021
FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards	08/30/2021
COVID-19: Master Protocols Evaluating Drugs and Biological Products for Treatment or Prevention: Guidance for Industry	05/17/2021
Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers: Guidance for Industry	05/17/2021
Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency Guidance for Industry: Guidance for Industry	04/14/2021
COVID-19 Container Closure System and Component Changes: Glass Vials and Stoppers Guidance for Industry: Guidance for Industry	03/04/2021
Manufacturing Considerations for Licensed and Investigational Cellular and Gene Therapy Products During COVID-19 Public Health Emergency: Guidance for Industry	01/19/2021
Policy for Testing of Alcohol (Ethanol) and Isopropyl Alcohol for Methanol, Including During the Public Health Emergency (COVID-19): Guidance for Industry	01/19/2021
Review Timelines for Applicant Responses to Complete Response Letters When a Facility Assessment Is Needed During the COVID-19 Public Health Emergency Guidance for Industry: Guidance for Industry	12/21/2020
Assessing COVID-19-Related Symptoms in Outpatient Adult and Adolescent Subjects in Clinical Trials of Drugs and Biological Products for COVID-19 Prevention or Treatment : Guidance for Industry	09/14/2020
Resuming Normal Drug and Biologics Manufacturing Operations During the COVID-19 Public Health Emergency: Guidance for Industry	09/10/2020
Development and Licensure of Vaccines to Prevent COVID-19: Guidance for Industry	06/30/2020
Good Manufacturing Practice Considerations for Responding to COVID-19 Infection in Employees in Drug and Biological Products Manufacturing: Guidance for Industry	06/19/2020
Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency Guidance for Industry: Guidance for Industry	06/16/2020
COVID-19: Developing Drugs and Biological Products for Treatment or Prevention: Guidance for Industry	05/11/2020
COVID-19 Public Health Emergency: General Considerations for Pre-IND Meeting Requests for COVID-19 Related Drugs and Biological Products : Guidance for Industry and Investigators	05/11/2020
Exemption and Exclusion from Certain Requirements of the Drug Supply Chain Security Act During the COVID-19 Public Health Emergency: Guidance for Industry	04/30/2020
Alternative Procedures for Blood and Blood Components During the COVID-19 Public Health Emergency: Guidance for Industry	04/02/2020
Policy for Certain REMS Requirements During the COVID-19 Public Health Emergency Guidance for Industry and Health Care Professionals	03/22/2020

Special Programs

- **Orphan**
- **Expedited Development**
  - Fast Track
  - Breakthrough
  - Priority Review
  - Accelerated Approval
  - Regenerative Therapies (New in the 21st Century Cures Act)
- **Pediatric Studies/Exclusivities**
- **REMS**
- **Post-Marketing Studies**
- **Expanded Access**

What is a Biosimilar?

- Established via **Biologics Price Competition and Innovation Act** (Part of ACA) in 2010
- Definition
  - A biological product that is **highly similar to a reference product notwithstanding minor differences** in clinically inactive components; and
  - There are **no clinically meaningfully differences** between the biological product and the reference product in terms of the safety, purity, and potency of the product.
  - NOT BIOEQUIVALENT
- 39 approved biosimilars for 10 Reference Products

Biosimilar Approval Standard

- Demonstration of biosimilarity based upon:
  - Analytical studies demonstrating high similarity to the reference product;
  - Animal studies; and
  - A clinical study or studies sufficient to demonstrate safety, purity, and potency
- Same mechanism of action, to the extent known for reference product
- Same conditions of use as the reference product
- Same route of administration, dosage form, and strength as the reference product
- Facility meets standards designed to assure safety, purity, and potency

Demonstrating Biosimilarity: Sponsor Approach

- Goal-Demonstrate biosimilarity without independently establishing safety and efficacy
- No one size fits all approach
- Stepwise Approach
  - Structure and function
  - Animal studies
  - Human PK and PD
  - Clinical immunogenicity
  - Clinical safety and effectiveness

Demonstrating Biosimilarity: FDA Approach

- Totality of the Evidence
  - Uses a risk-based approach to evaluate data and information
  - Biosimilar may be approvable even with some differences if data supports that the differences are not clinically meaningful and product meets biosimilarity criteria

Interchangeable Approval Standard

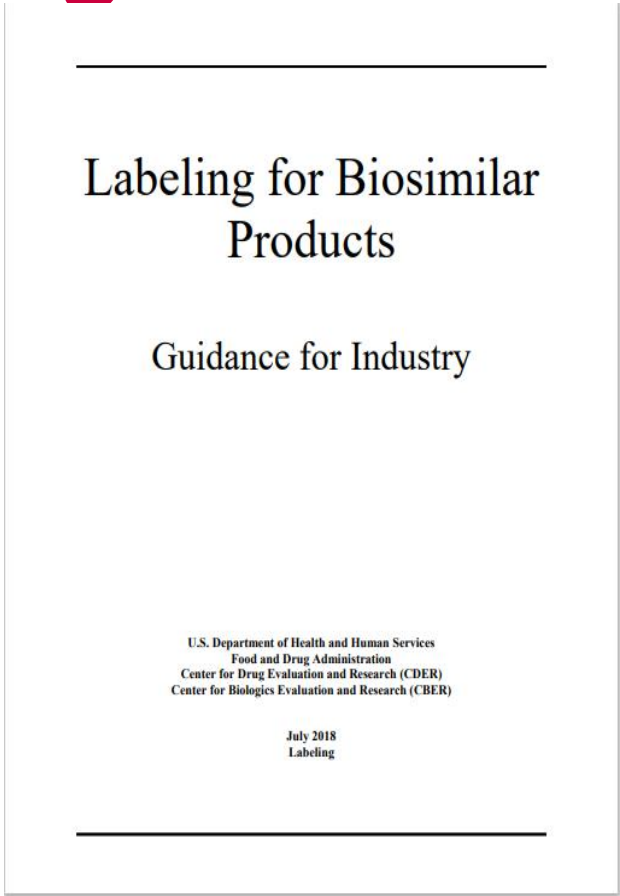
- A biological product that:
  - Is biosimilar
  - Is **expected to produce the same clinical result** as the reference product
  - If administered more than once, the **risk of safety or diminished efficacy of switching between the reference and biosimilar product is not greater than using the reference product without switching**
- May be substituted for the reference product without the intervention of the HCP
- FDA Approach-Totality of the evidence
- Three approved interchangeable biosimilars

Demonstrating Interchangeability

- Data demonstrating the product produces the same clinical result as the reference product
- Data/Information
  - Critical quality attributes
  - Analytical differences
  - Mechanism(s) of action
  - Pharmacokinetics and biodistribution
  - Immunogenicity risk
  - Toxicity
  - Other factor affecting safety or efficacy
  - Switching studies
  - Product presentation (e.g., product design and user interface)
- Role of post-marketing data
- Extrapolation to other conditions of use

Biosimilar Labeling

- Incorporate relevant data/information from the reference product label (with appropriate modifications)
- Information/data regarding the biosimilar product should only be described when it informs safe and effective use (e.g., generally not studies to demonstrate biosimilarity).
- Information should be specific to the condition of use (i.e., a biosimilar may be approved for fewer than all of the reference product's uses) and should not imply broader licensure.
- Specific requirements regarding when to use the biosimilar name, reference product name, and core name.


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

Biosimilar Substitution

- All 50 states
- Substitution laws vary by state
- Generally, though there are exceptions, the product must be **interchangeable**
- Generally, there must be **prescriber/patient notification/communication** of the substitution
- Prescribers generally can **opt to dispense as written**
- Some states provide for pharmacist immunity

Exclusivity

- Reference Product Exclusivity
  - Time
    - **12 years after the date of first licensure**
    - Biosimilar applications may not be submitted until 4 years after the date of first licensure
  - Not all BLA licenses will be a first licensure
- Other Exclusivities
  - Orphan
  - Pediatric
- First Interchangeable Product-Earlier of:
  - 1 year after first commercial marketing
  - 18 months after a final court decision or dismissal of a patent case instituted under the BPCIA
  - 42 months after approval if BPCIA patent litigation is ongoing
  - 18 months after approval if no patent suit is instituted

Proper Naming

- **Core Name + Distinguishing Suffix**
  - Suffix must be devoid of meaning and be four lowercase letters
  - Must not be too similar to any other suffix
- **Intended to:**
  - Facilitate pharmacovigilance
  - Aid in HCP identification of products
  - Minimize inadvertent substitution of non-interchangeable products

The Patent Dance (Per Statute)

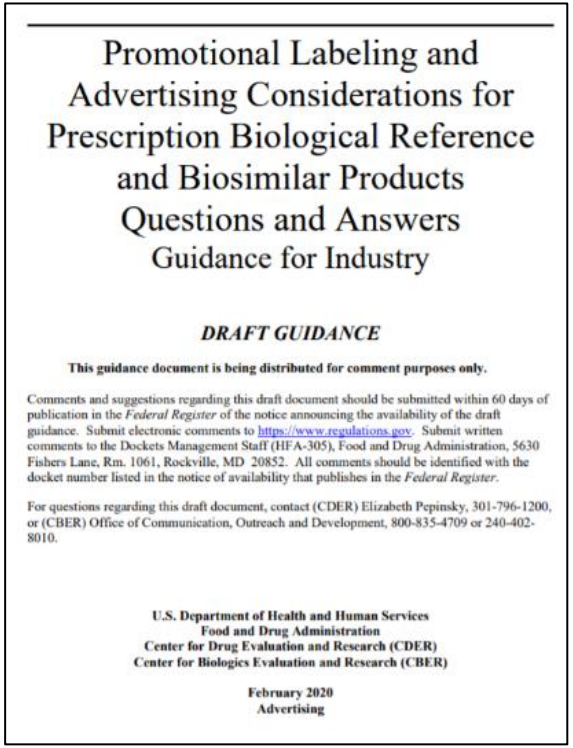
- Biosimilar sponsor provides the reference product sponsor a copy of the application and manufacturing information
- Parties trade lists of infringed/non-infringed patents and the basis for their belief
- Parties negotiate which patents will be the subject of an infringement action
- Biosimilar sponsor must provide notice of intent to market no less than 180 days before first commercial marketing
  - Notice triggers ability to bring actions on additional patents
  - Notice not required for reference product sponsor action if biosimilar applicant discontinues the dance
- No FDA stays

The Patent Dance (Following Supreme Court Decision)

- Patent dance is NOT mandatory
  - If biosimilar applicant does not dance (or discontinues dance), reference product sponsor may bring action
- 180 day notice may be given before licensure

Advertising & Promotion

- **Accurate identification of product(s)** when presenting information in promotional materials for reference products or biosimilar products (or both)
  - Follow the FDA approved labeling
- Biosimilar products **may present data/ information used to support biosimilarity** even if not in FDA approved label if consistent with the label
- **May not make representations/suggestions that there are clinically meaningful differences between a reference product and a biosimilar** (either better or worse)
- **May not create an impression that a biosimilar is interchangeable** if it has not been approved as such



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)

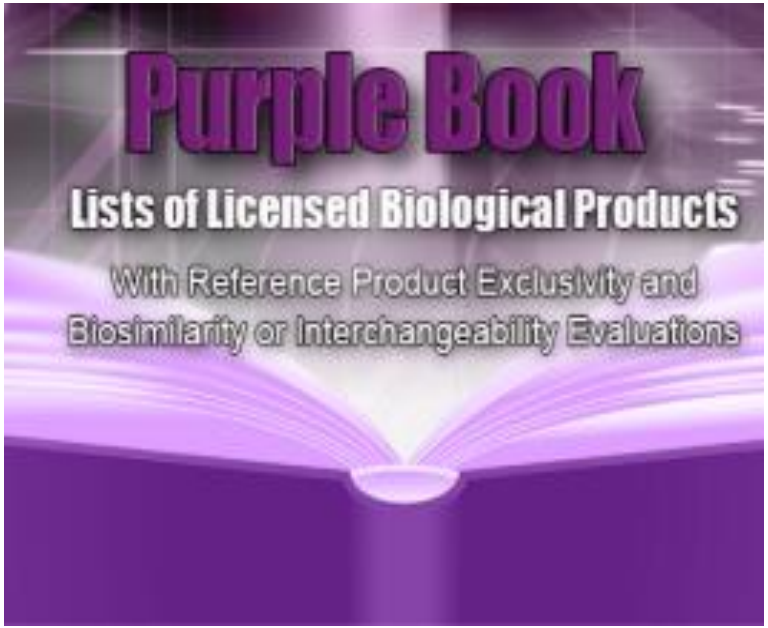
February 2020
Advertising

Advancement of Competition

- **FDA Biosimilar Action Plan (2018)**
  - Improve efficiency of biosimilar development/approval
  - Maximize scientific and regulatory clarity
  - Develop effective communication to improve biosimilar understanding
  - Support market competition by reducing gaming of FDA requirements/unfair competition delays
- **FDA/FTC Joint Statement Regarding a Collaboration to Advance Competition in the Biologic Marketplace (Feb. 2020)**
  - Coordinate to promote greater competition (e.g., education and public outreach)
  - Work together to deter behavior that impedes access to samples for biosimilar development
  - Take appropriate action against false or misleading communications
  - FTC review of patent settlements for antitrust violations

Purple Book

- Searchable database with information on all FDA licensed biologics
- **Biological Product Patent Transparency** passed in 2020
  - Required expanded categories of data to be listed in the purple book by FDA.
  - Required disclosure of patent information to FDA within 30 days of patent dance disclosure.



Questions?

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