Biologics and Biosimilars

Introduction to Drug Law and Regulation
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Christopher M. Mikson, M.D.
Partner
DLA Piper LLP (US)

500 Eighth Street, NW
Washington, DC 20004

1650 Market Street
Philadelphia, PA 19130

T +1 215 656 3380
christopher.mikson@dlapiper.com
dlapiper.com

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Agenda

Biologics and Biosimilars

A. What is a Biologic?
B. Drug vs. Biologic
C. Biologics License Application (BLA) Approval Standards
D. What is a Biosimilar?
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F. Interchangeable Approval Standards
G. Exclusivity
H. Biosimilar Labeling and Substitution
I. Nonproprietary Naming of Biologics
J. "Deemed to Be a License"
K. Overview of Patent Scheme

A. What is a Biologic?

- "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).

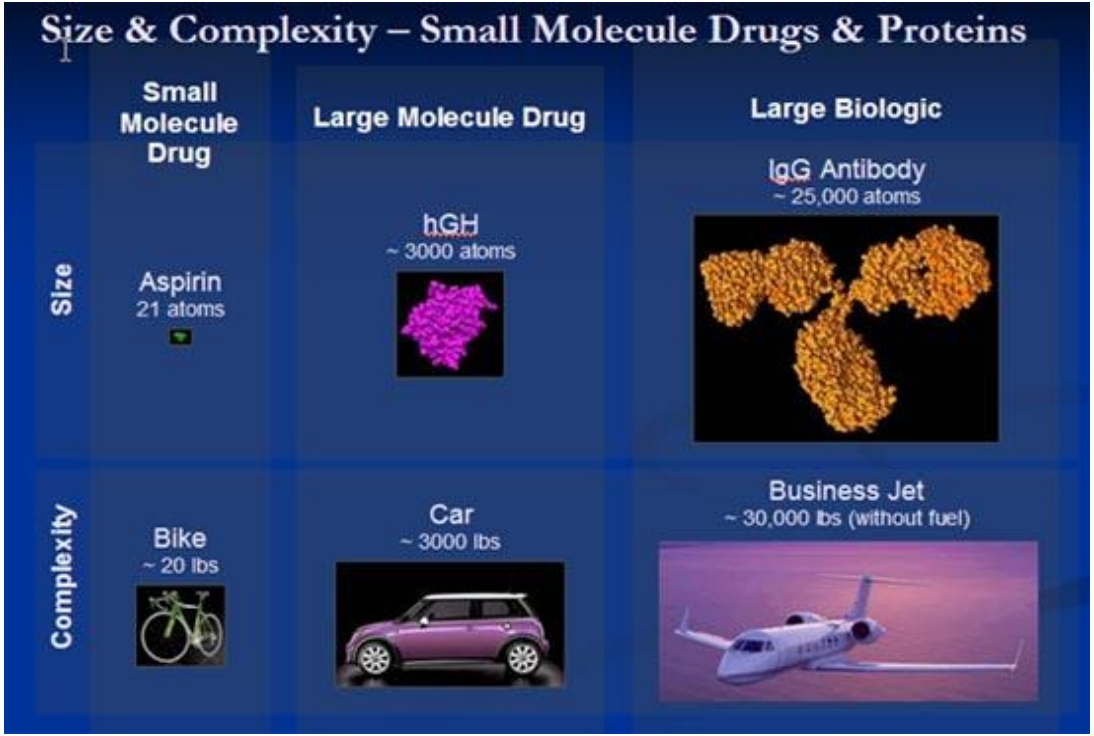
  21 U.S.C. § 321(g)

A. What is a Biologic?

- Therapeutic product derived from living sources
- *e.g.*, humans, animals, microorganisms
- "*Biological product*" narrowly defined by statute
- *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.*

  42 U.S.C. § 262(i)

B. Drug vs. Biologic



B. Drug vs. Biologic

Comparison of Drug and Biologic Legislation

BIOLOGICS		DRUGS
Biologics Control Act	1902	
	1906	Pure Food and Drug Act
	1938	Food Drug and Cosmetic Act
Public Health Service Act	1944	
	1962	Kefauver-Harris Amendments
	1984	Drug Price Competition and Patent Term Restoration Act ("Hatch-Waxman")
Biologics Price Competition and Innovation Act (BPCIA)	2010	

B. 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

B. 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) required 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

B. Drug vs. Biologic

- "Generic" Drugs
  - Same active ingredients as original formulation
  - Within acceptable "bioequivalent" range as original
  - State laws allow substitution by pharmacists
  - Market already established
- Prior to 1984, relatively few generics were being approved
  - In 1983, 35% of branded drugs faced generic competition after patent expiration
  - In 1983, average generic market entry after patent expiration was 3 years

B. Drug vs. Biologic

- Hatch-Waxman enacted in 1984 to incentivize generic drugs

- Abbreviated New Drug Application ("ANDA")
  - New approval pathway for generic drugs
  - Obviates clinical trials by citing innovator's test data
  - ANDA approved if generic establishes bioequivalence
  - ANDA can rely on original formulation's clinical trial information

B. Drug vs. Biologic

- Patent Provisions
  - Safe harbor (for research)
  - Patent term restoration (up to 5 years)
  - Specific procedures for patent litigation involving generics (filing of ANDA triggers litigation procedures)
- Exclusivity
  - » Market exclusivity for first generic (180 days)
  - » Data exclusivity for innovator (3-5 years)

B. Drug vs. Biologic

- H-W Created the modern generic drug industry
  - Sales: $1B (1984) → $59B (2007)
  - Generic Rx: 13% (1984) → 84% (2012)
- Most drugs now face generic competition when patents expire
  - Generics: 35% (1983) → virtually 100% (2012)
  - Average price of generic 80-85% less (2014)
- But no “generic” biologics
  - Because Hatch-Waxman only amended FDC Act

B. Drug vs. Biologic

Regulatory Hurdles for Biologics

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	• Can alter manufacturing process without changing compound
• FDA approval through Biologics License Application	• FDA approval through New Drug Application

C. Biologics License Application (BLA) Approval Standards

- Biological products are a subset of drugs
  - Both are regulated under the FDC Act
  - Only biological products are licensed under the PHS Act
- Biological products (like other drugs), can be studied in clinical trials in humans under an investigational new drug application (IND)
  - If the data generated by the studies demonstrate that the product is safe and effective for its intended use, the data are submitted as part of a marketing application

C. Biologics License Application (BLA) Approval Standards

- Biologics license application (BLA) is required for biological products subject to licensure under the PHS Act
- FDA must determine that the product, the manufacturing process, and the manufacturing facilities meet applicable requirements to ensure the continued safety, purity and potency of the product
  - Safety and purity assessments must consider the storage and testing of cell substrates that are often used to manufacture biologics
  - A potency assay is required due to the complexity and heterogeneity of biologics

D. What is a Biosimilar?

- Congress tried for years to enact something like H-W for biologics
- Debate over interchangeability
  - Most experts agree that a biosimilar can never be exactly the same as the original
  - Need to ensure same therapeutic response without new risks
- Debate over period of exclusivity
  - What period of time is reasonable to incentivize innovation?

D. What is a Biosimilar?

- Biosimilars bills proposed in 110th Congress (2007-2009)
  - H.R. 1038, S. 623 (Waxman, Schumer) - Access to Life-Saving Medicine Act
  - H.R. 1956 (Inslee) - Patient Protection and Innovative Biologic Medicines Act
  - S. 1695 (Kennedy) - Biologics Price Competition and Innovation Act
  - H.R. 5629 (Eshoo, Barton) - Pathway for Biosimilars Act
  - S. 1505 (Gregg, Burr, Coburn) - Affordable Biologics for Consumers Act
- Biosimilars bills proposed in 111th Congress (2009-2011)
  - H.R. 1427 (Waxman) – Promoting Innovation and Access to Life-Saving Medicine Act
  - H.R. 1548 (Eshoo) – Pathway for Biosimilars Act

D. What is a Biosimilar?

- Policy Differences in Proposed Legislation
  - Interchangeability
    - Waxman → Yes
    - Eshoo → Not until final guidance from FDA
  - Market exclusivity for reference compound
    - Waxman → 3-5 years
    - Eshoo → 12-14 years

D. What is a Biosimilar?

- Biologics Price Competition and Innovation Act of 2009
  - Biosimilars Legislation Passed in 111th Congress
  - Contained in Affordable Care Act
- Signed into law on March 23, 2010
- Allows submission of biosimilar application for approval of a biologic that is "biosimilar" or "interchangeable" with an already licensed biologic
- Sets specific limitations and procedures for patent litigation arising from a biosimilar application

D. What is a Biosimilar?

- BPCIA consists of two main parts
  - Regulatory provisions
    - 42 U.S.C. § 262(i)
    - 42 U.S.C. § 262(k)
    - 42 U.S.C. § 262(k)(6) & (7)
  - Patent litigation provisions
    - 42 U.S.C. § 262(l)

E. Biosimilar Approval Standards

- What does it mean to be "biosimilar"? (42 U.S.C. § 262(i)(2)))
  - the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and
  - there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency of the product
- Generally based on data from (42 U.S.C. § 262(k)(2)(A)(i)(I)))
  - analytical studies
  - animal studies (including the assessment of toxicity); and
  - one or more clinical studies that demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought

F. 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
- First interchangeable biologic gets market exclusivity (42 U.S.C. § 262(k)(6))

F. Interchangeable Approval Standards

- 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

G. 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

H. Biosimilar Labeling and Substitution

- Interchangeability – FDA determination
  - The BPCIA states, "the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product" (42 U.S.C. § 262(i)(3))
- Substitution – Pharmacist determination under state law
  - "Substitution" is when a patient presents an Rx for one drug or biologic (usually branded) and the pharmacist fills it with another (generic drug or interchangeable biologic)
- Switching – Physician action in practice of medicine
- FDA's finding of interchangeability does not preempt state substitution laws or the medical judgment of the treating physician in switching

I. Nonproprietary Naming of Biologics

- FDC Act and PHS Act require label of drug to state drug's "established" or "proper" name, respectively
- In practice, and by agreement among various member organizations on the United States Adopted Name Council, this means the USAN name
- There has been debate over whether reference biologic and biosimilar should have
  - Distinguishable but related names
  - Identical nonproprietary names
  - BPCIA made no changes to existing protocol

J. "Deemed to Be a License"

- BPCIA addressed fact that some biologics have been historically approved under the FDC Act
  - Amended definition of a "biological product" in PHS Act to include a "protein (except any chemically synthesized polypeptide)"
  - 10 year transition period to change approval from FDC Act to PHS Act
- FDA Guidance, *Interpretation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009* (December 2018)
  - BPCIA provided FDA will not approve any application for a biological product under FDC Act after March 23, 2020
  - Biologics approved under FDC Act as NDAs or ANDAs were replaced by BLAs under section 351(a) or 351(k) of PHS Act effective March 23, 2020

K. Overview of Patent Scheme

"The Patent Dance"

- Information Exchange
  - Provision of application and exchange of patent information (42 U.S.C. § 262(l)(2)-(3))
- First Wave
  - Patent resolution negotiations, failure of such negotiations, and "immediate" infringement action (42 U.S.C. § 262(l)(4)-(6))
- Newly issued or licensed patents (42 U.S.C. § 262(l)(7))

K. Overview of Patent Scheme

"The Patent Dance"

- Second Wave
  - Notice of commercial marking and preliminary injunctions (42 U.S.C. § 262(l)(8))
- Limitations
  - Declaratory judgment actions (42 U.S.C. § 262(l)(9))

K. Overview of Patent Scheme Issues

- Compared to H-W Patent Litigation –
  - Complicated patent information exchange
    - No public patent listing (Orange Book) in place
    - Purple Book does not provide patent information
      - Reference must bring suit within 30 days after exchange
      - Limitations on injunctions and declaratory judgments based on conduct in information exchange
- Statutory provisions concerning notice and information exchange have been litigated in a number of cases.

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Thank You!

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