# BIOSIMILARS IN THE UNITED STATES – UPDATE ON FDA IMPLEMENTATION AND OTHER CURRENT ISSUES

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# Agenda



1. BPCIA Overview
2. FDA Developments - Purple Book, Draft Guidances, Abbott Petition, FDA Review of Applications
3. Challenges to Promotion and Marketing

# BPCIA Overview

# Biologics Price Competition and Innovation Act of 2009



- BPCIA passed as Title VII, Subtitle A of the Patient Protection and Affordable Care Act, Pub. L. No. 111-148, 124 Stat. 119, §§ 7001-03.
- Signed into law on March 23, 2010.
- Effects a large and rapidly growing market

# BPCIA Overview



- Amends the PHS Act by adding:
  - Section 351(k) – licensure requirements for biologics as either: Biosimilar or Interchangeable
  - Section 351(l) – patent infringement disputes

# Key Provisions



- Approval pathway and data requirements
- Interchangeability
- Exclusivity
- Drug to biologic transition
- Patent issues

# Biosimilar Pathway



- Highly similar to the reference product notwithstanding minor differences in clinically inactive components.
- No clinically meaningful differences from reference in terms of safety, purity, and potency
- FDA permitted but not required to give product-specific guidance

# Interchangeability



- Defined as "may be substituted for the reference product without the intervention of the health care provider who prescribed the product"
- FDA may approve as interchangeable if:
  - Biosimilar
  - Expected to produce the same clinical result in any given patient
  - If administered more than once, risk of alternating or switching is not greater than using reference alone
- It's a very high standard

# Reference Product Exclusivity

- No 351(k) application can be filed until four years after the date the reference product was first licensed.
- No 351(k) application can be approved until 12 years after the date the reference product was first licensed.
- Pediatric Exclusivity – Four- and 12-year periods can be extended for six months each.

# Reference Product Exclusivity - Limitations

- RP Exclusivity does not apply to:
  - (i) a supplement for the biological product that is the reference product; or
  - (ii) a subsequent application filed by the same sponsor or manufacturer of the biological product that is the reference product (or a licensor, predecessor in interest, or other related entity) for—

# Reference Product Exclusivity - Limitations

- (I) a change (not including a modification to the structure of the biological product) that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength; or

- (II) a modification to the structure of the biological product that does not result in a change in safety, purity, or potency.

# Interchangeable Product Exclusivity

- First 351(k) applicant to obtain FDA approval as interchangeable is eligible for marketing exclusivity.
- Subsequent applications for interchangeable product cannot be approved for one year.
- Does not prevent approval of biosimilar products based on the same reference product.
- Interchangeable exclusivity can be shortened or forfeited.

# Drug to Biologics Transition



- Historically, FDA regulated some biologics as drugs, e.g., human growth hormone, insulin
- The BPCIA automatically transitions these products to drugs in 2020
- Definition of biologic now includes “protein”
- FDA trying to define protein but industry objected to proposed 40 amino acid limit

# Patent Issues



- Complex scheme for patent litigations
- First cases filed this year
- Not clear how patent litigation will affect development strategies

# FDA Developments

# The Purple Book



- Promised by FDA last December
- Published on the FDA Website September 9th
- Official Name is "Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations"
- The first edition gave exclusivity dates for only three reference products (Neupogen, Perjeta and Granix), but FDA notes that there will be others

# The FDA Draft Guidances



- Three of them released in 2012 – Scientific Considerations in Demonstrating Biosimilarity, Quality Considerations in Demonstrating Biosimilarity and Q and A regarding implementation (biosimilarity v. interchangeability, exclusivity and definition of a biological product).
- Clinical Pharmacology and Exclusivity Released 2014
- Will be others
- No clarity on when they will be finalized

# Abbott Humira Petition



- Abbott April 2012 citizen petition (Docket No. FDA-2012-P-0317)
- Abbott argues that it is unconstitutional for FDA to reference pre-BPCIA BLAs (before 2010) without paying the BLA sponsor "just compensation"
- Doesn't affect post-BPCIA BLAs
- Not clear when FDA will rule

# Status of Biosimilar Applications at FDA



- 36 biosimilars are in the "product development stage" as of mid-December 2013
- Filings have now been acknowledged
- **When will there be an approval?**

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# Marketing and Promotion Challenges

- Naming
- State Substitution Laws
- Marketplace Challenges

# The Naming Question . . . .



- Must each biosimilar have a unique name in order for patients and physicians to easily distinguish between medicines and to track and trace adverse events for such products?

# History



- The "naming question" has been around a long time
- In 2006, PhRMA and BIO asked WHO to use distinct INNs for each biotechnology-derived therapeutic protein produced by different manufacturers.
  - To "accommodate the acknowledged complexity of protein medicinal products and… facilitate safe prescription and dispensing of medicines and preserve patient safety."
- The EU uses different names
- The BPCIA does not address biosimilar product naming.

# Biosimilar Product Maker Position



- Each biological product is clearly identified by its brand name.
- The INN identifies the active substance and is not suitable for product identification.
- Different INNs for biosimilars would confuse physicians.
- Implied inferiority
- The current naming system for biologics works well and should not be dismantled.
- Additional means of identification such as NDC numbers, lot numbers and manufacturer names suffice for pharmacovigilance purposes.

# The Reference Product Maker Position



- Distinct nonproprietary names are based on scientific principles that reflect the complexity of both the molecules and the manufacturing processes.
- Distinct names justified by global experience and necessary for tracking adverse events.
- NDC and lot numbers are not adequate for pharmacovigilance.
- Policy measures that are transparent, scientifically consistent and that encourage accountability will develop trust in biosimilars.

# Naming Question Status



- Heated US debate – letter from Congress, citizen petitions, etc.
- **As with the first biosimilar approval, everyone is waiting for FDA to decide**

# State Substitution Laws



- Although FDA has not approved a biosimilar application – let alone define interchangeability – many states are considering and passing legislation governing the substitution of interchangeable biosimilar biological products.

# 2013 Biosimilar Legislation Scorecard



- Bills introduces in 18 states
- Rejected in 11 states – AZ, AR, CA (vetoed), CO, DE, IL, IN, MD, MS, TX, WA.
- Enacted in 5 states – FL, ND, OR, UT, VA.
- Under consideration in 2 states – MA, PA.

# Typical State Legislation Requirements



- Substitution should occur only when FDA has designated a biologic product as interchangeable.
- The patient should be notified of the substitution.
- The prescribing physician should be notified of the substitution.
- The pharmacist and the physician should keep records of the substitution.

# State Substitution Law Concerns



- Premature
- Confusion
- Undermines Public Confidence

# Marketing and Promotion of Biosimilars

- Not addressed in the BPCIA.
- Traditional rules that apply to other drugs and biologics will apply to biosimilars.
- Promotion must be on-label.
- Limited communication of off-label uses —
  - Peer reviewed articles
  - Unsolicited requests for information
  - Presentations at scientific/medical meetings

# Biosimilar Pathway Will Require Creative Approaches

- Unlike Hatch-Waxman Act structure, biosimilars will generally not be automatically substitutable as are generic drugs.
- Brand name drugs lose 90% of market share in first year of generic competition. This will not happen with biosimilars.
- Need to detail/promote biosimilars as is the case with 505(b)(2) drugs.
- Price differential between reference biologic and biosimilar will be much smaller than is the case with generic drugs.

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