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# *The New Biosimilars Act*

## *Overview of the Legislation and IP Implications*

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# Introduction

- Overview of political, legislative and regulatory climate that led to the new biosimilars pathway
- Analysis of the provisions of Biologics Price Competition and Innovation Act of 2009
  - signed into law March 23, 2010
- New biosimilars legislation vs. Hatch-Waxman Act
- Implications for IP

# Political/Legal/Regulatory Climate

- Political Climate
  - Strong incentives to establish biosimilars pathway in the U.S.
  - Pressure from Government and Consumer Advocacy Groups
    - Biopharmaceuticals are increasing component of Medicare/Medicaid costs
    - Top 5 Medicare expenditures are biologicals
    - EPO alone = $2B
    - Cost comparison:
      - Traditional small molecule drug = $2/day
      - Typical biologic = $44/day

# Political/Legal/Regulatory Climate

- Political Climate
  - Pressure from industry
    - More than 500 biologics in clinic
    - Almost 1/3 of all new drug approvals will be biologics
    - Patents of first generation biologics have expired or are expiring
    - Total sales of off-patent biologics >$20B

- Legal Climate
  - Biosimilars legislation was part of broader healthcare reform legislation
  - Both Senate and House passed competing bills in Fall of 2009
  - Senate version passed House March 21, 2010
    - Biosimilars provisions untouched by Reconciliation Bill
  - Signed into law on March 23, 2010

# Political/Legal/Regulatory Climate

- Regulatory Climate
  - Although legislation passed, *still no formal regulatory framework* for approval of biologics in U.S.
  - Will likely take at least two years after passage of legislation before FDA will establish regulatory framework

# Biologics Price Competition and Innovation Act

Proposed legislation recognizes *two classes of biosimilar products*:

1. Biological products that are "*biosimilar*" to a reference biological product

2. Biological products that are "*interchangeable*" with a reference biological product

# Biologics Price Competition and Innovation Act

- "**Biosimilar**" = a biological product that "is *highly similar to the reference product* notwithstanding minor differences in clinically inactive components" and for which "there are *no clinically meaningful differences* between the biological product and the reference product *in terms of the safety, purity and potency* of the product."

# Biologics Price Competition and Innovation Act

- "**Interchangeable**" - a biological product is interchangeable with the reference product only if:
  - (i) It *meets the criteria for being biosimilar* to the reference product;
  - (ii) It can be expected to produce the *same clinical result* as the reference product *in any given patient*; and
  - (iii) The risk in terms of safety or diminished efficacy in *alternating or switching* between use of the biological and the reference product is not greater than the risk of using the reference product without such alteration or switch

# Biologics Price Competition and Innovation Act

- **Biosimilar vs. Interchangeable**
  - Only biosimilar products that meet the higher interchangeability standard are eligible for *market exclusivity*
  - Only interchangeable products can be *substituted* for the reference product without the intervention of the healthcare provider who prescribed the reference product
  - Biosimilar products are deemed to contain a *new active ingredient*; but not interchangeable products

# Biologics Price Competition and Innovation Act

- ***Requirement for clinical studies***
  - Any application for biosimilar must include "a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics/pharmacodynamics
    - But FDA has discretion to deem unnecessary
  - Biological product must use same mechanism of action and same route of admin., be for same condition(s) for use, and have same dosage form and strength as reference product
- FDA *required* to approve application if applicant demonstrates biological product is either biosimilar to or interchangeable with reference product

# Biologics Price Competition and Innovation Act

- **Market exclusivity for biosimilar applicant**
  - Only granted to first *interchangeable* biological product
  - Prevents other *interchangeable* products from entering market for defined period (e.g. 1 year from commercial marketing)
  - However, other *biosimilar* products can be approved during that period.

# Biologics Price Competition and Innovation Act

- **Periods of exclusivity (earlier of):**
  - *1 year after first commercial marketing* of first interchangeable product; or
  - *18 months after final court decision* on all patents in suit in action against applicant for first interchangeable product *or after dismissal* of such an action; or
  - *42 months after approval* of first interchangeable product if applicant that submitted product was sued and *litigation is still ongoing* within 42-month period; or
  - *18 months after approval* of first interchangeable product *if applicant has not been sued*.

# Biologics Price Competition and Innovation Act

- **Data Exclusivity for Innovator**
  - Reference product sponsor entitled to 12 years of data exclusivity
    - No application for any biosimilar can be *approved* prior to the date that is *12 years* after the reference product was first licensed
    - No biosimilar application can be *submitted* to the FDA until *4 years* after the reference product was licensed
    - *Not applicable* for license for *supplement* for reference product or *subsequent application filed by same sponsor* of reference product for change in indication, route of administration, dosing schedule, dosage form, delivery system, delivery device or strength, or modification of structure of product (*limitations on life-cycle management*)
      - Includes structural modification if no change on safety, purity or potency

- **FDA Guidance Documents**
  - Legislation specifically authorizes FDA to issue guidance documents that can be general or specific (e.g., product class)
  - Failure to issue guidance document cannot delay consideration of a biosimilar application

# Biologics Price Competition and Innovation Act

- **Guidance Documents**
  - FDA not obligated to issue guidance document, but if does, must contain criteria that the FDA will use to determine whether a biological product is highly similar to or interchangeable with reference product
  - *FDA permitted to indicate in a guidance document that "the science and experience, as of the date of such guidance . . . does not allow approval of an application for a license for [a particular] product or product class*
  - In a recent statement to Congress, the FDA stated that the science and experience is not yet to the point where it can approve *any* biological product as *interchangeable* with a reference product
- **Naming**
  - House bill specifically requires biological product approved as biosimilar to have unique name that distinguishes it from the reference product and any other biologicals licensed as biosimilars

# Biologics Price Competition and Innovation Act – The Patent Face-off

1. ***Biosimilar Notice*** -Biosimilar applicant must provide copy of biosimilar application to reference product sponsor, *including how product manufactured (w/in 20 days of application being accepted)*

2. ***Patent Notice*** - Reference product sponsor must then provide biosimilar applicant with list of patents owned or exclusively licensed by sponsor that sponsor reasonably believes would be infringed if biosimilar made or sold in U.S. Must also identify patents willing to license (60 days)

# Biologics Price Competition and Innovation Act– The Patent Face-off

3. **Applicant Patent Notice** – Biosimilar Applicant may (but not required to) provide reference product sponsor with own list of sponsor's patents for which applicant believes sponsor could claim infringement. At minimum, applicant must provide claim-by-claim statement for patents in sponsor's list why applicant believes invalid/not infringed or a statement that applicant not going to market until sponsor's patents expire (60 days)

4. **Sponsor Response** – Sponsor provides detailed statement why patents are valid and infringed (60 days)

# Biologics Price Competition and Innovation Act– The Patent Face-off

5. ***Requirement to Negotiate*** - on patents to be litigated (15 days)

6. ***Identification of patents to be litigated*** – Applicant indicates number to litigate then parties exchange lists. KEY – number identified by sponsor cannot exceed number proposed by applicant

7. ***Litigation*** – sponsor must bring suit within 30 days of exchange of lists

8. ***Requirement to update*** – if new patent issues or is licensed, sponsor must update list and applicant must provide statement

# Biologics Price Competition and Innovation Act– The Patent Face-off

9. ***Potential forfeiture of rights*** – if patent should have been included in list but is not, patent owner will forfeit right to action against biosimilar product on that patent

# Biologics Price Competition and Innovation Act

- ***Notice of Commercial Marketing***
  - Legislation requires biosimilar applicant to provide notice to reference product sponsor at least 180 days before first commercial marketing

- ***Limitation on Declaratory Judgment Actions***
  - Neither party can initiate a declaratory judgment action before the notice of commercial marketing is provided

# Biologics Price Competition and Innovation Act

- Eventual phase out of 505(b) route for biologics
  - No longer able to submit an application for biological product under section 505 of FDCA,
    - Exception: where application is for product in class for which a biological product has already been approved under 505(b) and the application is submitted either before enactment of biosimilars legislation or not later than 10 years after enactment
    - But no 505(b) application can be submitted if reference product approved under this act is available
  - 10 years after enactment, all 505(b) approvals switch to 351 approvals (PHS Act)

# Biologics Price Competition and Innovation Act

- Pediatric Exclusivity
  - Six additional months → 12 yrs 6 mos and 4 yrs 6 mos

# Biosimilars Act vs. Hatch-Waxman

***Biosimilars***

- No requirement for structural identity
- Process of making is critical → applicant must disclose to sponsor
- Clinical studies required
- 12 yrs of data exclusivity
- Dev. costs $80M-$100M
- Bioequivalence not req.

***Hatch-Waxman 505(j)***

- Structural identity required
- Method of making much less relevant → cannot list process patents in OB
- Limited clinical studies (Only need Phase 1 – no efficacy)
- 5 yrs data exclusivity
- Dev. costs about $5M
- Must show bioequivalence

# Biosimilars Act vs. Hatch-Waxman

| ***Biosimilars*** | ***Hatch-Waxman 505(j)*** |
| --- | --- |
| – No substitution unless interchangeable | – Automatic substitution (if AB) |
| – No Orange Book (Exchange of Patent Lists) | – Orange Book |
| – No stay of FDA approval | – Stay possible |

# Common Innovator Strategies to Delay Generic Entry to Market

- Massive patent portfolios around blockbusters
- Patent litigation
- Patent Life Cycle Management
  - small modification improves safety, purity and/or potency justifying new 12 yr period of exclusivity
    - Example – Aranesp (Amgen) → modification of 2 sugar residues
- Settlement agreements
  - House bill required filing with FTC → not adopted
- "Biobetter" launched before expiration of patents on original product
  - Shift to new product
  - Loss of market share for generic companies
  - Example: Aranesp → 15-30% price premium over first generic products

# Unique IP Issues for Biosimilars

- Trade Secret Issue
  - Under Hatch-Waxman, method of making API generally not relevant to ANDA filing
  - Biosimilars legislation *requires* biosimilar applicant to disclose manufacturing process to reference product sponsor
    - Applies to applicant pursuing either biosimilar or interchangeable biologic
    - Forced disclosure of potentially valuable trade secret
  - Sponsor's process patents more likely to be subject of litigation

# Unique IP Issues for Biosimilars

- Less Patent Certainty
  - No "Orange Book" for biosimilars
  - Proposed legislation allows parties to determine patents to be litigated
  - Greater need for applicant to determine patent landscape

- "Patent Protection Gap"
  - Hatch-Waxman requires generic drug to be essentially same as reference drug
    - Difficult for ANDA challenger to avoid claims on active
  - Biosimilar product only needs to be *"highly similar"* to reference product and have *"no clinically meaningful differences"*
    - Arguably allows for minor differences in primary structure

# Unique IP Issues for Biosimilars

- "Patent Protection Gap"
  - Potential for biosimilar applicant to obtain abbreviated approval by relying on prior approval of reference product sponsor, while at same time avoiding patents protecting reference product
    - Initial patents on API generally provide strong protection
    - Generic protection more difficult for biologics
      - Biologics generally hundred – to thousand-fold larger than small molecule drugs
        - » More opportunities to design around
      - Written Description/Enablement requirements hinder broad claims
- Example
  - Follow on product with nonconservative amino acid substitutions may be "highly similar" and have no "clinically meaningful differences", but fall outside scope of claims on reference product

# Unique IP Issues for Biosimilars

- Criticality of Process/Platform Patents
  - Example: Antibodies
    - Phage Display/Xenomouse
    - Humanization
    - Fc Engineering
    - Cell Lines
    - Cabilly II

# Unique IP Issues for Biosimilars

- Patent Life-Cycle Management will be critical to innovators
  - Follow-on patents will be essential to extend innovator's exclusivity
  - Initial patents will likely expire early in life of commercial product and before end of exclusivity period
  - Innovators will need to be proactive in seeking patent protection for formulations, new methods of treatment, dosing regimens, etc.

- Biosimilar applicants will want to identify potentially relevant patents sooner rather than later
  - Including patents of innovator AND third-parties
  - Increases ability to design around before too far down development path
  - Reexamination as means to gain some certainty

# Predicting the Impact of Biosimilars on the Biopharm Industry

- Convergence of Bio and Pharma
  - Roche/Genentech
  - AZ/MedImmune
- Blurring of Innovator vs. Generic distinction
  - Companies will pursue both
- Cost and Clinicals will favor Big Pharma, Big Bio, and Big Generic
- Fewer generic entries, less price erosion for innovators

# Biosimilars

Thank you

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