Biosimilars: Draft FDA Guidance and Emerging Legal Challenges
Navigating FDA's Approval Pathway, Patent Issues, and the Complexities of Exclusivity

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Biosimilars: Draft FDA Guidance and Emerging Legal Challenges

October 23, 2012

Presented by
Kevin E. Noonan and Howard W. Levine
BPCIA Legislation & FDA Guidance
The Biologics Price Competition and Innovation Act of 2009 (“BPCIA”)

- The BPCIA signed into law on March 23, 2010, amended
  - § 351 of the PHSA (42 U.S.C. § 262)
  - § 271(e) of the Patent Act
  - Created a statutory framework for FDA approval of new product as “biosimilar” to or “interchangeable” with “reference” products
  - Grants agency discretion in implementing approval pathway
  - Specifies procedures for filing patent infringement actions, preliminary injunctions and declaratory judgment actions
Outline of the BPCIA

- Changes to PHSA § 351(i) (42 U.S.C. § 262(i))
  - Provides new and amended definitions

- New PHSA § 351(k) (42 U.S.C. § 262(k))
  - Provides regulatory pathway for biosimilar/interchangeable products
  - Provides RP exclusivity

- New PHSA § 351(l) (42 U.S.C. § 262(l))
  - Provides patent litigation process
BPCIA Benefits

- Allows for “biosimilar” products
- Allows for “interchangeable” products
- Provides ~ 1 year exclusivity period for first approved “interchangeable” product
- Provides 12 year exclusivity period for RP
- Allows biosimilar applicant to file application 4 years after RP is first licensed
- Potential for FDA guidance
**BPCIA Definition of “Biological Product”**

- 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.

- FDA definition of “protein” (FDA Q&A at 13):
  - “[A]ny alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size”
  - “Compounds greater than 40 amino acids in size will be scrutinized to determine whether they are related to a natural peptide of shorter length and, if so, whether the additional amino acids raise any concerns about the risk/benefit profile of the product.”
“Biosimilar” Products

“Biosimilar” defined in statute:

- “(A) that the biological product is *highly similar* to the reference product notwithstanding minor differences in clinically inactive components; and

(B) 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.”

42 U.S.C. § 262(i)(2)

- “Clinically meaningful differences could include a difference in the expected range of safety, purity, and potency of the proposed and reference products” (Scientific Considerations at 8.)

- *Non-clinically meaningful differences* could include “slight differences in rates of occurrence of adverse events between the two products.” (Scientific Considerations at 8.)
Factors FDA Will Consider to Determine Whether Biosimilar Is “Highly Similar”

- Expression System
- Manufacturing Process
- Assessment of Physiochemical Properties
- Functional Activities
- Receptor Binding and Immunochemical Properties
- Impurities
- Reference Product and Reference Standards
- Finished Drug Product
- Stability
Factors FDA Will Consider to Determine Whether Biosimilar Is “Highly Similar”

- Comparison between the putative biosimilar and one reference biologic drug including:
  - Analytical studies that demonstrate putative biosimilar is "highly similar" to reference biologic
  - Animal studies on (at least) toxicity
  - Human clinical trials to assess immunogenicity, pharmacodynamics/ pharmacokinetics

- Data supporting biosimilarity includes:
  - "[A] clinical study or studies [] that are sufficient to 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 for the biological product."
Factors FDA Will Consider to Determine Whether Biosimilar Is “Highly Similar”

- In addition to biosimilarity
  - Biosimilar and reference product use the same mechanism of action (if known)
  - Conditions of use for biosimilar be the same as those previously approved for reference product
  - Identical route of administration, dosage form and strength as approved reference product
  - Biosimilar prepared in a facility that meets standards that insure biosimilar is safe, effective and pure
Guidance for Industry

Scientific Considerations in Demonstrating Biosimilarity to a Reference Product

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Guidance for Industry

Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product

**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 comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5600 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 at 301-796-2500.

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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 2012
Biosimilarity

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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 2012
Biosimilarity
FDA Guidance on Establishing Biosimilarity

Communication With FDA is Essential

- “FDA encourages sponsors to consult extensively with the Agency after completion of comparative structural and functional analysis (before finalizing the clinical program), and throughout development as needed.” (Scientific Considerations at 7-8.)

- “FDA also advises sponsors intending … to meet with FDA to present their product development plans and establish a schedule of milestones that will serve as landmarks for future discussions with the Agency. FDA anticipates that early discussions with FDA about product development plans and about the appropriate scientific justifications will facilitate biosimilar development.” (Scientific Considerations at 21.)
FDA Guidance on Establishing Biosimilarity

- “FDA intends to use a risk-based, **totality-of-the evidence** approach to evaluate all available data and information submitted in support of the biosimilarity of the proposed product.” (Scientific Considerations at 8.)
- “The type and amount of analyses and testing that will be sufficient to demonstrate biosimilarity will be determined on a product-specific basis.” (Scientific Considerations at 8.)
  - “[M]any product-specific factors can influence the components of a product development program intended to establish that a proposed product is biosimilar to a reference product. Therefore, FDA will ordinarily provide feedback on a case-by-case basis on the components of a development program for a proposed product.” Scientific Considerations at 21.
FDA Guidance on Establishing Biosimilarity

- **Structural and Functional Characterization**
  
  - “The more comprehensive and robust the comparative structural and functional characterization . . . the more useful such characterization will be in determining what additional studies may be needed.” *Scientific Considerations* at 7.
  
  - Primary structures, such as amino acid sequence
  
  - Higher order structures, including secondary, tertiary, and quaternary structure (including aggregation)
  
  - Enzymatic post-translational modifications, such as glycosylation and phosphorylation
  
  - Other potential variants, such as protein deamidation and oxidation
  
  - Intentional chemical modifications, such as PEGylation sites and characteristics” (*Scientific Considerations* at 9.)
FDA Guidance on Establishing Biosimilarity

- **Animal data:** “The sponsor should then consider the role of animal data in assessing toxicity and, in some cases, in providing additional support for demonstrating biosimilarity and in contributing to the immunogenicity assessment.” (Scientific Considerations at 7.)

  - **Animal Toxicity Studies:** “As a scientific matter, animal toxicity data are considered useful when, based on the results of extensive structural and functional characterization . . . Animal toxicity studies are generally not useful if there is no animal species that can provide pharmacologically relevant data for the protein product.” (Scientific Considerations at 11.)

  - **Animal Immunogenicity Studies:** “Animal immunogenicity assessments generally do not predict potential immunogenic responses to protein products in humans. However, when differences in manufacturing (e.g., impurities or excipients) between the proposed product and the reference product may result in differences in immunogenicity, measurement of anti-protein antibody responses in animals may provide useful information relevant to patient safety.” (Scientific Considerations at 12.)

  - **Animal PK and PD Measures:** “Under certain circumstances, a single-dose study in animals comparing the proposed product and reference product using PK and PD measures may contribute to the totality of evidence that supports a demonstration of biosimilarity.” (Scientific Considerations at 12.)
FDA Guidance on Establishing Biosimilarity

- Human Studies
  - “In general, the clinical program for a 351(k) application must include a clinical study or studies (including an assessment of immunogenicity and PK or PD) sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product, as set forth in the PHS Act. The scope and magnitude of clinical studies will depend on the extent of residual uncertainty about the biosimilarity of the two products after conducting structural and functional characterization and possible animal studies.”

(Scientific Considerations at 12.)
FDA Guidance on Establishing Biosimilarity

- Human Studies (cont.)
  - **PK / PD studies:** “We have determined that both PK and PD studies . . . *generally will be expected* to establish biosimilarity, unless a sponsor can scientifically justify that an element is unnecessary.” (*Scientific Considerations* at 13.)
  - **Clinical immunogenicity studies:** “[A]t least one clinical study that includes a comparison of the immunogenicity of the proposed product to that of the reference product *will generally be expected.*” (*Scientific Considerations* at 14.)
FDA Guidance on Establishing Biosimilarity

- Human Studies (cont.)
  - Comparative clinical safety and effectiveness data
    - “If there are residual uncertainties about the biosimilarity of the two products after conducting structural and functional studies, animal toxicity studies, human PK and PD studies, and clinical immunogenicity assessment, the sponsor should then consider what comparative clinical safety and effectiveness data may be adequate.” (Scientific Considerations at 7.)
    - “Clinical studies should be designed such that they can demonstrate that the proposed product has neither decreased nor increased activity compared to the reference product.” (Scientific Considerations at 17.)
FDA Guidance on Establishing Biosimilarity

- What must be assessed:

  **Binding Antibody**
  - Titer
  - Specificity
  - Relevant Isotype Distribution
  - Time Course of Development
  - Persistence
  - Disappearance
  - Association with clinical sequelae

  **Neutralizing Antibody**
  - (all Binding Antibody points)
  - Plus neutralizing capacity to all relevant functions
  - Uptake and catalytic activity
  - Neutralization for replacement enzyme therapeutics

- Immunogenicity assays developed and validated for biosimilar and reference product
Bioanalytical assay for PK analysis (5 – 8 months)
- Reagent preparation (3 – 4 months) – May have reagents from release testing
- Method development and validation (2 – 4 months)

Immunogenicity testing assay (6 – 9 months)
- Reagent preparation (3 – 4 months) – may have reagents from release testing
- Method development and validation (3 – 5 months)
Canonical Timeline

- Cell based assays for functional activity (11 – 15 months)
  - Selection of the assay procedure (1 month)
  - Breeding of cell lines and feasibility study (2 – 3 months)
  - Final selection of cell line and reference antibodies (2 – 3 months)
  - Optimization and final development of assay (4 – 6 months)
  - GLP validation (2 months)

(If reagents and cell lines are available, applicant could save up to 6 months)
“Interchangeable” Products

“Interchangeable” means:

– Biosimilar to RP and

– Can be expected to produce the same clinical result as the RP in any given patient, and

– For a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the RP is not greater than the risk of using the RP without such alteration or switch.

42 U.S.C. § 262(k)(4)
“Interchangeable” Products

- What’s the benefit for “interchangeability”?  
  - The interchangeable product “may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.”
  - A biosimilar product cannot be switched for RP without doctor intervention

- FDA has not yet issued guidance on Interchangeability
  - “At this time it would be difficult as a scientific matter for a prospective biosimilar applicant to establish interchangeability in an original 351(k) application. . . . FDA is continuing to consider the type of information sufficient to enable FDA to determine that a biological product is interchangeable with the reference product.” Q & A at 11-12.

42 U.S.C. § 262(i)(3)
“Interchangeable” Products

- Exclusivity for first approved “interchangeable” product
  - No subsequent FOB can be found to be interchangeable until earlier of
    - 1 year after first commercial marketing of first interchangeable FOB
    - 18 months after final court decision or dismissal with or without prejudice on patents involved in suit against first interchangeable FOB
    - 42 months after approval of first interchangeable FOB if patent litigation is still ongoing within the 42 month period or 18 months after such approval if no patent suit was filed against first interchangeable FOB

42 U.S.C. § 262(k)(6)
Reliance on Non-US Licensed Product Comparisons

“In general, a sponsor needs to provide information to demonstrate biosimilarity based on data directly comparing the proposed protein product with the reference product. . . However, under certain circumstances, a sponsor may seek to use data derived from animal or clinical studies comparing a proposed protein product with a non-U.S. licensed product . . . In such a case, the sponsor should provide adequate data or information to scientifically justify the relevance of this comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the U.S.-licensed reference product.” (Quality Considerations at 9.)
Extrapolating to Other Indications

“If the proposed product meets the statutory requirements for licensure as a biosimilar product under section 351(k) . . . the potential exists for the proposed product to be licensed for one or more additional conditions of use for which the reference product is licensed. However, the sponsor will need to provide sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for each condition of use for which licensure is sought.” (Scientific Considerations at 19; Q & A at 9.)
RP Exclusivity

- **12 year exclusivity for RP**
  - The RP is entitled to 12 years exclusivity starting from the date when the RP was first licensed by the FDA
  - Potential for 6 additional months of pediatric exclusivity

- **No additional exclusivity for:**
  - Supplemental BLA
  - A new BLA filed by same RPS (or related entity) for
    - A change that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device or strength; or
    - A modification to the structure of the biological product that does not result in a change in safety, purity, or potency

42 U.S.C. § 262(k)(7)
Potential additional exclusivity for new BLA if

- Change involves a modification in structure that results in a change in safety, purity or potency compared to the previously approved biologic product

If modified BLA results in new RP

- Pending FOB applicant may have to resubmit application (FOB may only be evaluated against 1 RP)
  
  42 U.S.C. § 262(k)(5)(A)

- Offers real opportunity for additional exclusivity
  
  • Investigate potential avenues for structural change
  
  • How much of a change in safety (including side effects), purity or efficacy is required?
Litigating Under the BPCIA
1. Biosimilar applicant provides application to RPS
2. RPS and Biosimilar applicant identify potentially relevant patents
3. RPS and Biosimilar applicant “negotiate” final list of patents to actually litigate
4. 180 days before 1\textsuperscript{st} commercial marketing Biosimilar applicant must notify RPS, who may file for preliminary injunction
5. RPS and Biosimilar can negotiate alternative to patent exchange process
BPCIA Litigation ≠ Hatch Waxman

• No orange book listing
  – Biosimilar applicant has burden of identifying relevant patents during development work
  – Negotiated list of patents in suit

• No limitation on types of patents to assert
  – Hatch-Waxman limited to listing patents covering the active ingredient, formulations, and method of use patents
  – BPCIA allows RPS to assert any patent that a claim of patent infringement “could reasonably be asserted”

• No 30 month stay upon filing suit

• No 180 day exclusivity period for 1st filed biosimilar application
Patent Litigation and FDA Approval

• Patent litigation process cannot start until four years after RP is first licensed
• Patent litigation process does not stay FDA approval of biosimilar application
  – Even if Biosimilar applicant indicates it will not market until after patent expiry, FDA can still approve application
• Only way to stop biosimilar product from coming onto the market is injunction from the court

- Biosimilar files Application
- Biosimilar Application accepted by FDA
- Biosimilar provides confidential info to RPS
  - RPS provides patent list to Biosimilar
  - RPS & Biosimilar negotiate final list of patents to litigate
    - Agreement reached
      - yes: RPS files complaint
      - no: Biosimilar identifies number of patents that can be asserted
        - yes: Simultaneous exchange of patent lists
          - 5 days
        - no: RPS files complaint
          - 30 days
- 180 days before Biosimilar commercialization must notify RPS
- 20 days
- 60 days
- 60 days
- 15 days
- 30 days
- 60 days
Confidential Disclosure of Biosimilar Application

- Confidential information
  - Within **20 days** after Biosimilar applicant receives notice that application has been accepted for review, Biosimilar applicant “shall provide”:
    - Copy of the application
    - Information that describes the process used to manufacture the biological product and
    - “May provide” other information requested by the RPS

42 U.S.C. § 262(l)(2)
Confidential Disclosure of Biosimilar Application

- **Access to confidential information** 42 U.S.C. § 262(l)(1)(B)
  - One in-house RPS lawyer who does not prosecute patents related to RP
  - Outside counsel who do not prosecute patents related to RP
  - Owner of patent if not RPS and agrees to be bound by confidentiality provisions

- **Limitation on disclosure** 42 U.S.C. § 262(l)(1)(C),(D), (F)
  - No disclosure to anyone else without prior written consent
    - Includes RPS employees, outside experts, or other outside counsel
  - Information only used to determine identify relevant patents that “a claim of patent infringement could reasonably be asserted”
  - Confidentiality provisions govern until court enters protective order
Confidential Disclosure of Biosimilar Application

• **Penalties for improper disclosure** 42 U.S.C. § 262(l)(1)(H)
  
  – Improper disclosure is presumed to cause Biosimilar applicant “irreparable harm”
  
  – Court “shall enter” immediate injunctive relief appropriate and necessary to remedy violation
Patent Exchange Process

Biosimilar files Application

? → Biosimilar Application accepted by FDA

→ 20 days → Biosimilar provides confidential info to RPS

RPS provides patent list to Biosimilar

→ 60 days → Biosimilar provides RPS with patent list and detailed statement

RPS & Biosimilar negotiate final list of patents to litigate

→ 15 days → RPS provides Biosimilar with detailed statement

Agreement reached

yes → 30 days → RPS files complaint

no → Biosimilar identifies number of patents that can be asserted

→ 5 days → Simultaneous exchange of patent lists

→ 30 days → RPS files complaint

180 days before Biosimilar commercialization must notify RPS
RPS List of Patents

• Within **60 days** after receiving copy of Biosimilar application RPS “shall provide”:
  
  – “A list of patents for which the reference product sponsor believes a claim of *patent infringement could reasonably be asserted* ” and
  
  – “Identification of the patents . . . that the reference product sponsor would be *prepared to license* to the” Biosimilar applicant

• RPS must list their own patents as well as patents owned by third parties that could reasonably be asserted

42 U.S.C. § 262(l)(3)(A)
RPS List of Patents

• Duty to supplement patent lists
  – Reference product sponsor must notify Biosimilar applicant of newly issued/licensed patents (for which a claim of patent infringement could be reasonably asserted) within 30 days of issuance/licensing
    42 U.S.C. § 262(l)(7)

• RPS’s failure to list patents
  – If RPS fails to list patents or supplement list then owner of that patent “may not bring an action under this section for infringement of the patent with respect to the biological product”
    35 U.S.C. § 271(e)(6)(C)
  – Could RPS file an action under 35 USC § 271(a) after Biosimilar product on market or a DJ action if launch is imminent?
Biosimilar files Application

? -> Biosimilar Application accepted by FDA

20 days -> Biosimilar provides confidential info to RPS

60 days -> RPS provides patent list to Biosimilar

60 days -> Biosimilar provides RPS with patent list and detailed statement

RPS & Biosimilar negotiate final list of patents to litigate

15 days -> RPS provides Biosimilar with detailed statement

60 days -> Agreement reached

no -> Biosimilar identifies number of patents that can be asserted

5 days -> Simultaneous exchange of patent lists

30 days -> RPS files complaint

yes -> RPS files complaint

30 days -> 180 days before Biosimilar commercialization must notify RPS
Within **60 days** after receiving patent list from RPS, Biosimilar applicant “shall provide”:

- A *detailed statement* that describes, on a claim by claim basis, the factual and legal basis of the opinion . . . that [each listed] patent is invalid, unenforceable, or will not be infringed” or

- “A statement that the [Biosimilar] applicant does not intend to begin commercial marketing of the biological product before the date that such patent expires;” and

- Response regarding any licensing offer

Biosimilar applicant “may provide”:

- “A *list of patents* for which the . . . [Biosimilar] applicant believes a claim of *patent infringement could reasonably be asserted*”

Patent Exchange Process

Biosimilar files Application → Biosimilar Application accepted by FDA → 20 days → Biosimilar provides confidential info to RPS → 60 days → RPS provides patent list to Biosimilar → 60 days → Biosimilar provides RPS with patent list and detailed statement

RPS & Biosimilar negotiate final list of patents to litigate → 15 days → RPS provides Biosimilar with detailed statement → 60 days

Agreement reached

- yes → RPS files complaint → 30 days
- no → Biosimilar identifies number of patents that can be asserted → 5 days → Simultaneous exchange of patent lists → 30 days → RPS files complaint

180 days before Biosimilar commercialization must notify RPS
RPS Detailed Statement

• Within **60 days** after receiving list and detailed statement from Biosimilar applicant RPS “shall provide”:
  
  – “A **detailed statement** that describes . . . on a claim by claim basis, the factual and legal basis of the opinion of the [RPS] that [each listed] patent will be infringed” by the Biosimilar and
  
  – “A **response**” to any allegation by the Biosimilar applicant that patents are invalid or unenforceable

42 U.S.C. § 262(l)(3)(C)
Patent Exchange Process

Biosimilar files Application

? -> Biosimilar Application accepted by FDA

20 days -> Biosimilar provides confidential info to RPS

60 days -> RPS provides patent list to Biosimilar

60 days -> Biosimilar provides RPS with patent list and detailed statement

RPS & Biosimilar negotiate final list of patents to litigate

15 days -> RPS provides Biosimilar with detailed statement

60 days

Agreement reached

yes -> RPS files complaint

30 days

no -> Biosimilar identifies number of patents that can be asserted

5 days -> Simultaneous exchange of patent lists

30 days

RPS files complaint

180 days before Biosimilar commercialization must notify RPS
Duty to Negotiate Prior to Filing Suit

- **15 days** for RPS and Biosimilar applicant to negotiate in good faith upon list of patents for litigation
  - Patents to litigate selected from patents identified during exchange period

  42 U.S.C. § 262(l)(4)

- If RPS and Biosimilar agree, RPS must file suit on agreed upon patents within 30 days

  42 U.S.C. § 262(l)(6)

- If no agreement reached follow alternative procedures

  42 U.S.C. § 262(l)(5)
**Patent Exchange Process**

1. **Biosimilar files Application**
   - Question mark

2. **Biosimilar Application accepted by FDA**
   - 20 days

3. **Biosimilar provides confidential info to RPS**
   - 60 days

4. **Biosimilar provides RPS with patent list and detailed statement**
   - 60 days

5. **RPS & Biosimilar negotiate final list of patents to litigate**
   - 15 days

6. **Agreement reached**
   - Yes:
     - **Biosimilar identifies number of patents that can be asserted**
     - 5 days
     - **Simultaneous exchange of patent lists**
     - 30 days

   - No:
     - **RPS files complaint**

7. **180 days before Biosimilar commercialization must notify RPS**

8. **RPS files complaint**
Duty to Negotiate Prior to Filing Suit

- No agreement on patent list
  - If the RPS and Biosimilar applicant do not agree on patents for litigation within 15 days then:
    - Biosimilar applicant “shall notify” RPS of number of patents it will provide to RPS
    - Five days later RPS and Biosimilar simultaneously exchange
      - List of patents RPS believes should be in suit
      - List of patent Biosimilar believes should be in suit
    - RPS list cannot exceed number of patents identified by Biosimilar
    - Except if Biosimilar provides no patents, then RPS can list one patent

42 U.S.C. § 262(l)(5)
Infringement Actions

• Infringement action when no agreement on patent list
  – Upon completion of exchange RPS “shall bring an action for patent infringement with respect to each patent that is included on such lists”

  42 U.S.C. § 262(l)(6)(B)

• How often will RPS and Biosimilar not agree on the list of patents to be litigated?
Remedies for Timely Lawsuit

- RPS is entitled to mandatory permanent injunction against infringement if:
  
  (a) Suit filed within 30 days,
  
  (b) Final judgment of infringement from which no appeal can be taken (excluding certiorari to the Supreme Court), and
  
  (c) FDA has yet to approve Biosimilar because of 12 year exclusivity

  • Depending on when Biosimilar filed application RPSs may need to litigate quickly

  35 U.S.C. § 271(e)(4)(D)

- Might obtain permanent injunction under eBay if (a)-(c) not met
Limitations on Remedies

- RPS’s remedy for infringement shall be limited to a reasonable royalty if:
  - Suit was filed after the 30 day period, or
  - Suit was filed within 30 day period, but was dismissed without prejudice or was not prosecuted to judgment in good faith


- Airtight complaint and personal jurisdiction are of paramount importance
Preliminary Injunctions

• Biosimilar applicant must give RPS 180-day notice before date of first commercial marketing of Biosimilar

• After receiving 180-day notice, and before commercial marketing by Biosimilar, RPS may seek a preliminary injunction with respect to any patent
  – Identified during patent exchange but Biosimilar applicant excluded from the list of patents to litigate

• RPS and Biosimilar applicant have a duty to cooperate in expediting discovery for purposes of preliminary injunction

  42 U.S.C. § 262(l)(8)
Declaratory Judgment Actions-Permitted

• Declaratory judgment actions are permitted in very specific circumstances

• **Timing:**
  
  – RPS and Biosimilar applicant *cannot file* DJ actions until 180 days before 1st commercial marketing if Biosimilar applicant provides RPS with copy of Biosimilar application

  42 U.S.C. § 262(l)(9)(A)

  – If Biosimilar applicant does *not* provide copy of Biosimilar application, RPS *may* file DJ action before the 180 day period

  42 U.S.C. § 262(l)(9)(A),(C)
Declaratory Judgment Actions-Permitted

- RPS **can file** DJ on any patent on list it provided to Biosimilar applicant if Biosimilar applicant fails to:
  - Complete exchange of patent information or
  - Provide detailed statement, or
  - Notify FDA that RPS filed suit, or
  - Provide the required notice of first commercial marketing

  42 U.S.C. § 262(l)(9)(B)

- RPS **can file** DJ on any patent that “claims the biological product or a use of the biological product” if Biosimilar applicant fails to provide the Biosimilar application to the RPS
  - No DJ on process patents

  42 U.S.C. § 262(l)(9)(C)
Could There Be Three Rounds of Litigation?

• Round 1: Initial suit after the patent exchange process
• Round 2: Preliminary injunction 180 days before 1st commercial marketing on patents exchanged but not litigated
• Round 3: Traditional 271(a),(b), and/or (c) suit after commercial launch of Biosimilar product on new patents
Take Home Points

• RPS and Biosimilar should create an “advance team”
  – In-house lawyer
  – In-house technical expert
  – Outside counsel
  – Outside technical expert

• Don’t skimp on your detailed statement
  – Draft with your “advance team” a thorough detailed statement
Take Home Points-RPS

• Identify ahead of time designated in-house counsel to receive confidential information

• Identify ahead of time patents you own and third parties own that a claim of patent infringement could reasonably be asserted – create “internal” Orange Book

• Communicate with Third Party patent owners before you receive Biosimilar application
  – Do you take a license
  – Do you renegotiate license terms
  – Determine if you are obligated to assert licensed patents against infringers
Take Home Points-RPS

- Do you want to propose alternative to patent exchange process
- Identify “best” patent to litigate in event Biosimilar applicant tries to limit infringement suit
- Request relevant information from Biosimilar applicant, including samples or site visit
- Consider negotiating personal jurisdiction with Biosimilar applicant
- File a properly pled complaint to avoid dismissal
- Plan for preliminary injunction well in advance of 180-day trigger
  - Which patents will you assert at PI stage
Take Home Points-Biosimilar Applicant

• Identify ahead of time patents owned by RPS and third parties that a claim of patent infringement could reasonably be asserted
  – Can you license from a third party before you file application

• Do you file application early or late in 12-year exclusivity period
  – If file early, you may have the opportunity to be 1st approved interchangeable
  – If file late, you may preclude RPS from obtaining injunction
Take Home Points-Biosimilar Applicant

- Do you want to propose alternative to patent exchange process
- Develop “detailed statement” of non-infringement, invalidity, and unenforceability well before patent exchange starts
- Consider contesting personal jurisdiction
- Weigh pros and cons of litigating only one patent, some patents, or all patents
- Comply with all regulations to avoid DJ action
Long Term Predictions

- Changing biosimilar patent strategy: drift towards trade secrets to avoid disclosing manufacturing secrets and enjoy statutory exclusivity instead
- Prior User Rights defense from AIA also incentives trade secret protection for manufacturing methods
- *Prometheus v. Mayo* – way too early impact predictions, but may foreclose certain method claims
- *Myriad* – broad "product of nature" preclusion could have negative effects on biologic drugs
Less Reliance on Patent Exclusivity

- Strong likelihood that the combination:
  - Non-specific guidances;
  - Reduced scope of patent protection;
  - Possibility of protecting manufacturing methods by asserting prior user rights defense; and
  - Complex litigation provisions of the law

- provide incentives for biologic drug innovators to rely more heavily on the market exclusivity provisions of the Act than on patents
Statutory Exclusivity

- Prohibits biosimilar filings until 4 years after reference product is licensed
- Prohibits biosimilar approval until 12 years after reference product is licensed
Safeguarding intellectual property and maximizing biologic patent life through a robust biosimilars patent portfolio strategy
Less Reliance on Patent Exclusivity

- What will be the relevance of patents in the future of Biosimilars?
- If innovators eschew patenting altogether
- What must be shared:
  - How the biologic was made
  - Characterization of the biologic (with the FDA)
- But NOT the cell itself
- Advantages:
  - Obstacles to biosimilar applicants
  - Avoiding biosimilars litigation under the statute
Universities and Startups

- "If Patents Become Irrelevant in a Biosimilars Future, What About University Patents and Startups?"
- Statutes:
  - BPCIA
  - Hatch-Waxman Act
  - Bayh-Dole
- Biotech patenting plays a vital role in early development, especially licensing, but then is de-emphasized for later state development
- Startups have become the feeder for new technologies for large pharmaceutical companies
- Startups could flounder if patents become less important in biologics development

www.patentdocs.org, Dec. 21, 2011
Of course…

- The importance of patent protection cannot be understated or minimized

- But patent exclusivity might not hold the preeminent role it does with small molecule drugs
Questions?
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