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Biosimilars: Emerging Legal Challenges

Navigating FDA's Pathway to Approval, Patent Issues, and the Exclusivity Period

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1pm Eastern | 12pm Central | 11am Mountain | 10am Pacific

Today's faculty features:

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ARNOLD & PORTER LLP

Regulatory Legal Challenges Under the Biologics Price Competition and Innovation Act

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Biosimilars: Emerging Legal Challenges
Strafford Webinar
December 6, 2011

"These new regulations will fundamentally change the way we get around them."

Future Biosimilars Legal Issues

- Legal issues likely to center on:
  - Definitions
  - Standards
  - Statutory discretion and judicial deference afforded the Food and Drug Administration
- Guidance from FDA pending

Single Reference Product

- **Reference Product:** single biological product licensed under subsection (a) of Section 351 of the PHSA against which a biosimilar or interchangeable biological product is evaluated
- Application must contain information to show that the new product and reference product are biosimilar or interchangeable

Relationship to Reference Product and Determination of Biosimilarity

- Biological product and reference product must utilize the ***same mechanism or mechanisms of action*** for ***condition(s) of use prescribed, recommended, or suggested*** in the proposed labeling
- ***Condition(s) of use*** prescribed, recommended, or suggested in the labeling proposed for the biosimilar product ***must have been previously approved*** for the reference product
- Route of administration, dosage form, and ***strength*** of the biological product are the ***same*** as those of the reference product

What is Biosimilarity?

"The term 'biosimilar' or 'biosimilarity', in reference to a biological product that is the subject of an application under subsection (k), means—

(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."

Interchangeability

- "…the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product."
- "….can be expected to produce the ***same clinical result*** as the reference product ***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 reference product is ***not greater*** than the risk of using the reference product without such alternation or switch."
- Role of states in biosimilars substitution

Data Requirements

- Analytical studies demonstrating that the biosimilar product is highly similar to the reference product notwithstanding minor differences in clinically inactive components
- Animal studies, including an assessment of toxicity
- Clinical study or studies, including but not limited to the assessment of immunogenicity and pharmacokinetics or pharmacodynamics, 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 biosimilar product
- ***FDA may determine that one or more of these requirements are unnecessary***

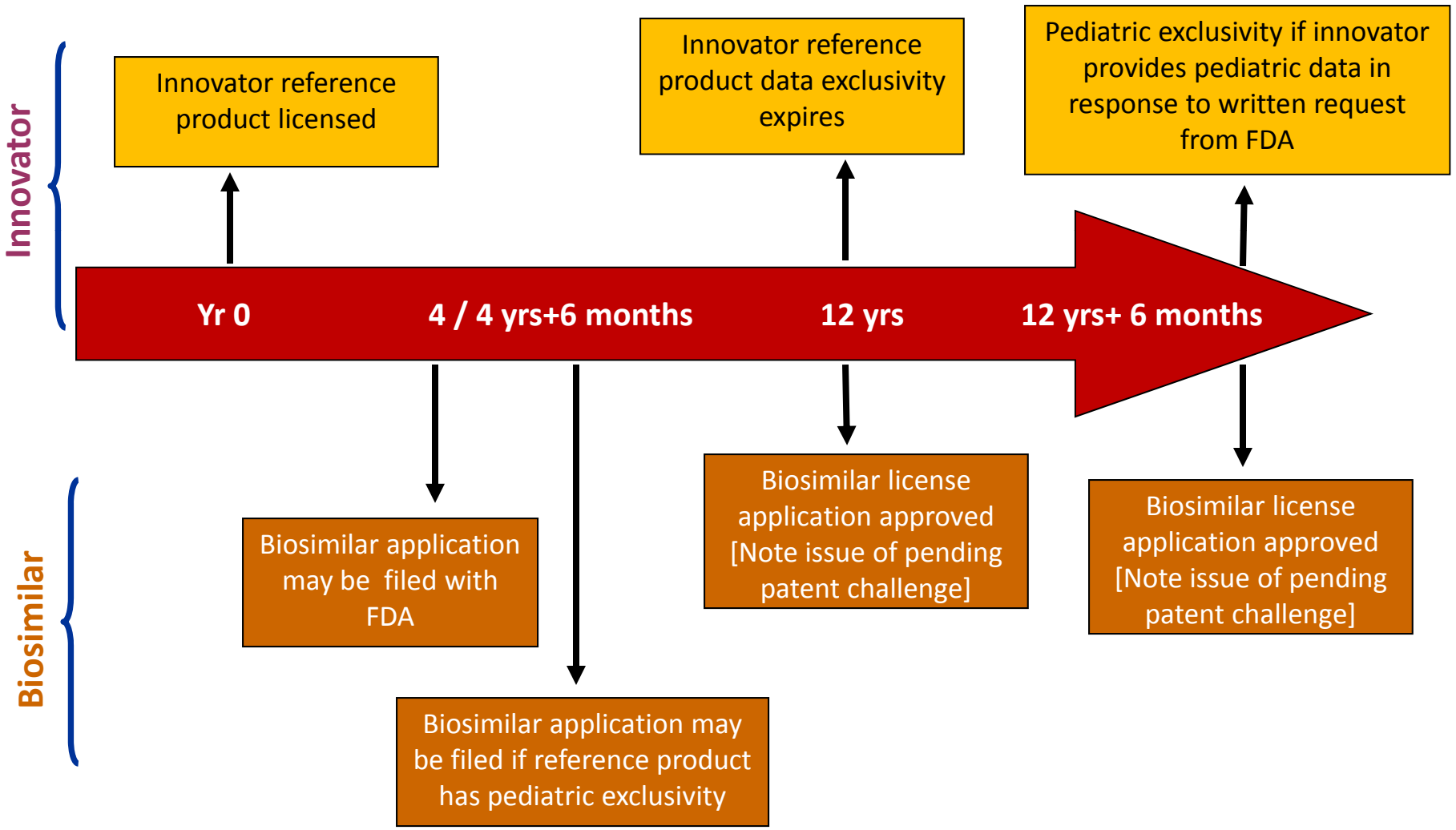
Choice of Pathway and "BioBetters"

- Can biosimilar applicants choose Public Health Service Act Section 351(a) versus (k) pathways?
- Could the new biosimilars framework be used to develop a "biobetter" product, or is the full BLA route the appropriate pathway?

Post-Market Issues

- Risk Evaluation and Mitigation Strategies
  - In general, a REMS may be required if "necessary to ensure that the benefits of the drug outweigh the risks of the drug"
  - Under the BPCIA, the authority of FDA with respect to risk evaluation and mitigation strategies (REMS) under the FDCA applies to biosimilar or interchangeable products "*in the same manner*" it applies to reference products
- Post-market Studies and Pharmacovigilance
- Nomenclature

Reference Product Exclusivity



"Evergreening"

"FIRST LICENSURE.— [12-year exclusivity and 4-year biosimilar application delay] shall not apply to a license for approval of—

(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—

(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

- Only products deemed interchangeable (as opposed to biosimilar) are eligible for exclusivity
- FDA may not approve a second interchangeable product until the earlier of:
  - 1 year after commercial marketing of first interchangeable product
  - 18 months after final court decision or dismissal in patent suit under patent notice provisions
  - 42 months after approval of first interchangeable if sued for patent infringement under patent notice provisions and still ongoing after 42 months
  - 18 months after approval of first interchangeable if not sued under patent notice provisions

Citizen Petitions and Legal Challenges Likely?

- At least three types of challenges are likely
  - General process issues
  - General statutory interpretation/scientific issues
  - Specific product-focused statutory interpretation/scientific issues

- Federal Food, Drug, and Cosmetic Act Section 505(q) does not apply to biosimilar-related citizen petitions
  - Only petitions relating to 505(b)(2) and (j) applications
    - Under 505(q), FDA may not delay approval of a pending application unless necessary to protect the public health.

Questions?

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Patent Challenges Under the Biologics Price Competition and Innovation Act

Anthony J. Fitzpatrick

December 6, 2011

Biologics Price Competition and Innovation Act of 2009

§ 351(l) - Patents

1. Applicant provides its section (k) application to the Reference Product Sponsor (RPS)
2. Confidential Treatment
3. Exchange of Patent Lists
4. Patent Resolution – Good Faith Negotiations
5. Filing of Infringement Action
6. Preliminary Injunctions
7. Declaratory Judgment Action

Applicant Provides Its Application to The RPS:

- No ORANGE BOOK-type patent listing, and no Paragraph (IV) Certification
- FDA accepts §351(k) application for review ➔ **Day 1**
- Within **20 days**

1. Applicant *MUST* provide to the RPS:
   - Complete copy of the §351(k) application; and
   - Information describing process used to manufacture the biological product.
2. Applicant *MAY* provide additional information requested by the RPS.

Confidential Treatment for the Applicant's Information:

- Who Can Have Access To The Applicant's Information?
  - **One or more** Outside Counsel designated by RPS (not involved in patent prosecution relevant or related to reference product)
  - **One** In-House Counsel representing RPS (not involved in patent prosecution relevant or related to reference product)
  - **A** representative of an exclusive licensee who has retained the right to enforce patent or participate in patent litigation (subject to confidentiality)
- Confidential information may only be used to evaluate a claim of infringement
  - May not be included in complaint or pleading
  - If RPS does not file infringement action, RPS must return or destroy confidential information
  - Effect of Violation: injunctive relief

RPS Provides Its List of Patents to The Applicant:

- Not later than **60 days** after receipt of application documents, the RPS *MUST* provide to Applicant:

  1. List of patents for which RPS believes a patent infringement claim could reasonably be asserted ("Paragraph 3(A) List")

  2. Identification of patents on such list the RPS would license to the Applicant

- RPS *CANNOT* sue Applicant for infringement of a patent not included in the Paragraph 3(A) list

  - Important to submit a comprehensive Paragraph 3(A) List

Exchange of Detailed Statements:

- Not later than **60 days** after receipt of the RPS' Paragraph 3(A) List, the Applicant:

  1. *May* provide a list of patents for which the Applicant believes a patent infringement action could be brought ("Paragraph 3(B) List")

  2. *Must* provide a detailed statement that describes:

     - why any of the RPS - identified patents is invalid, unenforceable, or will not be infringed (claim-by-claim analysis); or

     - that the Applicant does not intend to begin commercial marketing of the biological product before the date that such patent expires

  3. *Must* provide a response to the RPS regarding each patent offered for licensing

Exchange of Detailed Statements:

- Not later than **60 days** after receipt of Applicant's response, the RPS *MUST* provide to the Applicant:
  - Detailed statement of factual and legal basis for opinion of infringement, on a claim-by-claim basis
  - Response to any unenforceability/invalidity contentions

“Good faith negotiations” before the Filing of Litigation:

- After receipt of the RPS’ detailed statement, Applicant and RPS *MUST* engage in **good faith negotiations** to agree on which patents shall be the subject of a patent infringement action.

- If agreement is reached within **15 days,** the RPS *Must* file patent infringement action on agreed patent(s) not later than **30 days** of agreement.

If Negotiations Fail:

- **If NO agreement is reached within 15 days**
  - Applicant identifies number of patents that can be asserted Incentive: list all relevant patents to avoid RPS's last minute injunction option
  - Within **5 days**, Applicant and RPS *MUST* exchange their respective lists of patents they believe should included in a patent infringement action ("Paragraph 5 Lists")
  - Not later than **30 days** after the exchange of the lists, the RPS *MUST* bring a patent infringement action
  - **Applicant controls how many patents will be litigated!**
    - » RPS is limited to the greater of one patent or the number of patents disclosed by Applicant.
    - » Patents that appear on both "Paragraph 5 Lists" MUST be included in the suit.
    - » Patents not on a "Paragraph 3 List" may not be included.

Notification and Publication of Complaint:

- Not later than **30 days** after service, the Applicant *MUST* notify the FDA of the infringement action and provide to the FDA a copy of the complaint
- The FDA will publish a notice of the complaint in the Federal Register
- **Notes**:
  - Failure to timely file suit will limit remedies available to RPS
  - Reasonable royalty only
  - Litigation does NOT automatically stay approval process

Notice of Commercial Marketing & Preliminary Injunction:

- Not later than **180 days** before the date of the commercial marketing, Applicant *MUST* provide to the RPS a Notice of Commercial Marketing ("Paragraph 8 Notice").
- RPS *MAY* then seek a **preliminary injunction** prohibiting Applicant from manufacturing or sale of a biological product (until a court decides on patent validity, enforcement and infringement) on any patent that was not asserted in the initial litigation, but was previously identified in the first "RPS list" or in Applicant's list of patents ("Paragraph 3 patent").

Preliminary Injunction, *cont'd*:

Example

- RPS' Paragraph 3(A) List: Patents A, B, C, D, E
- Applicant's Paragraph 3(B) List: Patents F, G
- Patent Infringement Action: Patents A, B, C, D, F, G

  (Paragraph 5 Lists)

  - For Preliminary Injunction Action: Patent E

Declaratory Judgment:

- If Applicant complies with all requirements, neither party can bring a Declaratory Judgment (DJ) action prior to the 180 day marketing notice.
- If Applicant fails to act on a response, RPS may bring DJ action – on any patent listed in the RPS' Paragraph 3(A) List:
  - Failure to exchange list of patents
  - Failure to provide detailed statements on RPS' listed patents
  - Failure to provide notice of commercial marketing
  - Failure to notify FDA of infringement action
- If an Applicant does not disclose its *subsection (k) application* to the RPS, the RPS may bring a DJ action for infringement of "***any*** patent that claims a **biological product** or a **use** of the biological product" and seek injunctive relief against the Applicant, § 351(l)(9)(C).
  - Process/manufacturing patents seem to be excluded

Newly Issued Or Exclusively Licensed Patents:

- For patents issued or exclusively licensed to RPS after the RPS provides the initial list of patents to the Applicant, the RPS *MUST* provide a supplemental list within **30 days** of issuance or licensing
- Then, within **30 days**, Applicant *Must* provide statements on a claim-by-claim basis as to non-infringement, invalidity, and unenforceability.
- Newly issued/licensed patents are not subject to the negotiation/exchange procedure, but can be used for Preliminary Injunction.

IP Considerations – RPS

Evaluate Patent Portfolio Early

- Patent life span (possibility of patent term extension?)
- Evaluate validity, enforceability, and infringement
- Does the claim protect against the biosimilar if the biosimilar is NOT identical to the reference product?
- Seek broad patent protection
- Written description and enablement issues
- Write claims of various scope
- Fix any weaknesses ➔ Consider reissue and reexamination applications
- Obtain claims for methods of producing product
- Obtain claims for testing products
- Consider keeping certain manufacturing information a trade secret
- Process is more important for biological products than small molecules

IP Considerations – Applicant

EARLY Preparation

- Monitor patent activities of RPS
- Monitor patent activities of third parties (RPS may license patents)
- Analyze patent claims ➔ what do the claims cover?
  - Is the biosimilar different enough to fall outside the scope of the RPS' patents?
- Any RPS pending applications for manufacturing and testing methods?
- Any RPS published patent applications that cover the product and could be asserted later by the BLA holder?
- Consider how many patents to identify during the patent exchange period
  - If no patent is identified, the RPS may litigate only on one patent.
  - Risk of preliminary injunction.

Questions?

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(With thanks to my colleague Siegfried J.W. Ruppert, Ph.D., Esq.)