



Webinar Series: Biosimilars

Biologics Price Competition and Innovation Act of 2009



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Overview

- Biosimilars Series
 - Introduction to the area of biosimilars
 - Explore key developments and trends
- CLE Credit
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- Materials will be made available
fr.com/industries/life-sciences
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**Upcoming Biosimilars
Webinars**

Thursday, February 25

A. The BPCIA Statute and What it Amends

- Public Health Service Act 42 U.S.C. § 262
 - “351(k)” – biosimilar application requirement
 - “351(l)” – patent exchanges procedures
- Patent Statutes 35 U.S.C. § 271
 - 271(e)(2)(c) – new artificial act of infringement

B. Biosimilars and Interchangeable Biosimilars

- **Biosimilarity**
 - Means “highly similar” to the Pioneer product notwithstanding minor differences in clinically inactive components; and where there are no clinically meaningful differences between the biological product and the Pioneer in terms of safety, purity and potency.
- **Interchangeable**
 - Means a biological product found to be Biosimilar; that can be expected to produce the same clinical result as the Pioneer in any given patient; and if the product 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 product and the Pioneer is no greater than the risk of using the Pioneer without such alteration or switch.
 - A Biosimilar found to be interchangeable may be substituted for the Pioneer without the intervention of “the health care provider who prescribed the reference product.”

C. Basic Regulatory Structure

- Pioneer, generic and pediatric exclusivities available.
- Private exchange of patent information.
- Two possible “waves” of pre launch patent litigation.

D. Pioneer Exclusivities

- 12 year marketing exclusivity for new biological structures.
 - If BLA application is filed by same sponsor or manufacturer of the Pioneer product (or a licensor, predecessor in interest or a related party), for a changed biological structure it must also result in a (1) change in indications, route of administration, dosing schedule, dosing form, delivery system, delivery device or strength; or (2) change in safety, purity or potency.
- 4 years of data exclusivity.
- No follow on exclusivity based on clinical trials involving the same biological structure.
- Pediatric exclusivity adds 6 months to 12 year exclusivity; 6 months to 4 year data exclusivity; and 6 months to 7 year Orphan Drug exclusivity.

E. First Interchangeable Exclusivity

- First to obtain an “interchangeable” license for any use receives exclusivity against any subsequent interchangeable license application for any condition of use in Pioneer product until earlier of:
 - one year after commercial marketing by first licensee;
 - or
 - 18 months after court decision (appellate court, if appealed) on all patents or dismissal of action against first licensee;
 - or
 - 42 months after first licensee approval if litigation is still pending, or 18 months after first licensee approval if no “first wave” suit is filed.

F. Biosimilar License Application (351(k))

- Showing of “Biosimilarity” based on data from (1) analytical studies showing “highly similar” to Pioneer (different inactives allowed); (2) animal studies (including toxicity); and (3) clinical studies to demonstrate safety, purity and potency in one or more conditions of use.
- Has same mechanism of action for conditions of use on label (if known), route of administration, dosage and strength of Pioneer product.
- Production facility must meet standards designed to assure product continues to be safe, pure and potent.

G. Interchangeable Biosimilar License

- Must be “Biosimilar” to Pioneer.
- Must also show that (1) Biosimilar can be expected to produce same clinical results as Pioneer in any given patient; and (2) any risk in terms of safety or diminished efficacy from switching between Pioneer and Biosimilar is no greater than using Pioneer without switching.
- Requires separate 351(k) license (FDA yet to provide guidance).

H. Patent “Dance”

- Biosimilar applicant “required” to provide Pioneer with confidential access to Biosimilar application including manufacturing process within 20 days of FDA “acceptance for review.”
- Within 60 days of confidential access Pioneer required to provide Biosimilar applicant with list of patents that could reasonably be asserted; and a designation of patents available for license (“initial Pioneer list”).

H. Patent “Dance”

- Within 60 days of receiving Pioneer patent list, Biosimilar applicant:
 - May provide a list of patents that Biosimilar applicant believes could reasonably be asserted by Pioneer (“initial Biosimilar list”).
 - Shall provide the Pioneer with a claim by claim analysis for each patent listed by the Pioneer or the Biosimilar applicant, of the factual and legal basis as to why patent is invalid, unenforceable or will not be infringed or a statement that Biosimilar applicant does not intend to begin marketing its product before such patent expires.
 - Shall provide Pioneer with a “response” regarding each patent designated by Pioneer as being available for licensing.

H. Patent “Dance”

- Within 60 days of receipt of patent list and claim by claim statement by Biosimilar applicant, Pioneer is required to provide a claim by claim rebuttal on infringement, validity and enforceability for each patent addressed in Biosimilar applicant’s statement.
- After receipt of Pioneer rebuttal, the parties are required to engage in good faith negotiations for up to 15 days to try to arrive at list of patents subject to an infringement action (“negotiated list”).

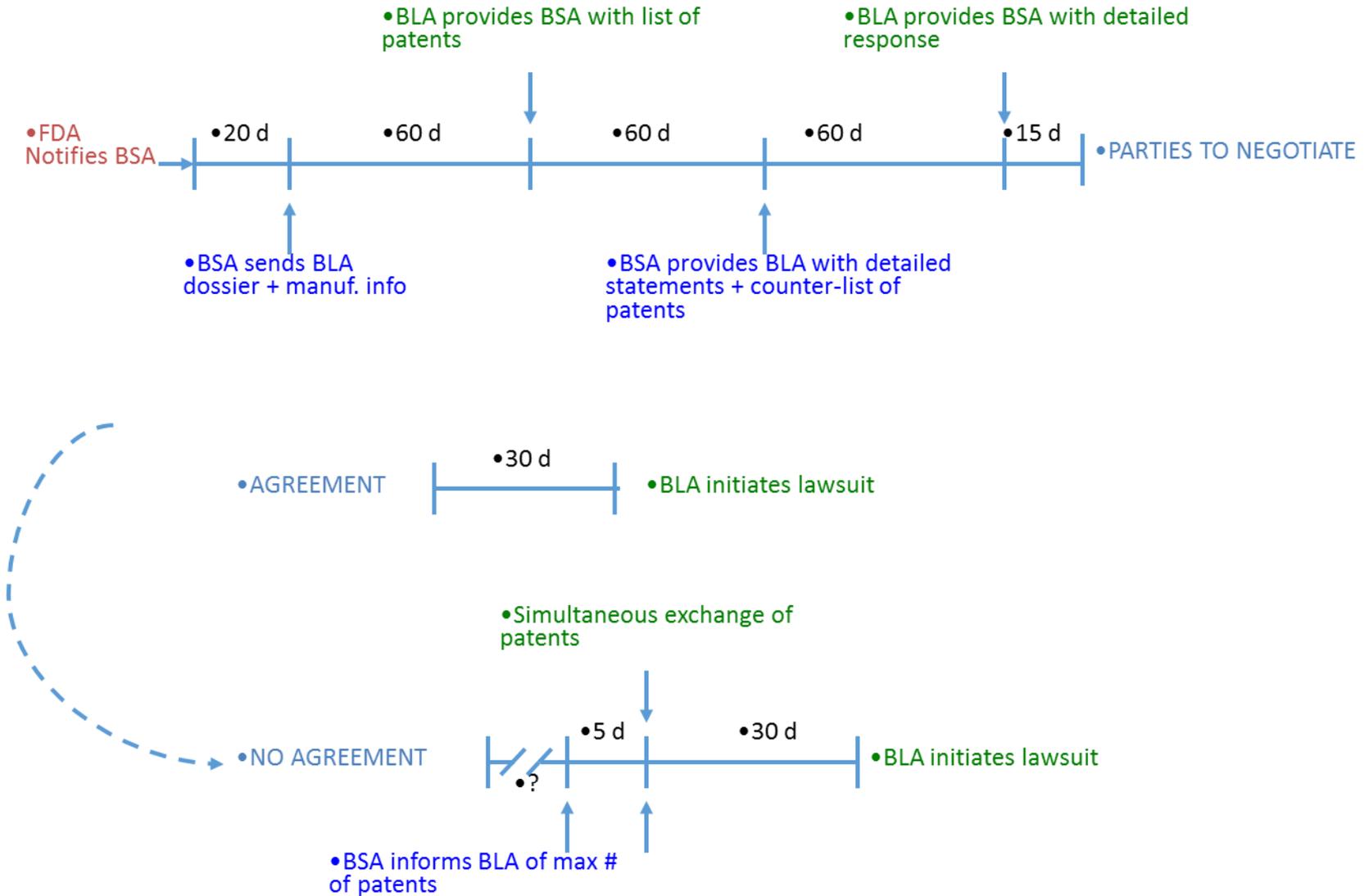
H. Patent “Dance”

- If no resolution of patents after 15 days, patent exchange procedures are triggered:
 - Biosimilar applicant initially notifies Pioneer of the number of patents it will exchange.
 - Within 5 days of receiving Biosimilar applicant’s number, the parties are required to simultaneously exchange lists of patents that each believes should be subject to an infringement action.
 - The number of patents listed by Pioneer cannot be greater than the number notified by Biosimilar applicant unless Biosimilar applicant lists zero patents in which case Pioneer may list one patent.
 - Pioneer must then bring an infringement action within 30 days for each patent on both lists (“exchanged lists”).

H. Patent “Dance”

- If favorable resolution within the 15 days, Pioneer must bring an infringement action also within 30 days for each patent on “negotiated list”:
 - FDA to be notified of infringement action by Biosimilar applicant within 30 days.
 - FDA to publish notice of complaint in Federal Register.

Patent Exchange Time Line



Litigations Involving “Patent Dance”

- No jurisdiction under BPCIA until BLA is accepted for filing by FDA (Sandoz v. Amgen (Enbrel), CAFC 2014).
- Patent Dance is optional (Amgen v. Sandoz (Neupogen), CAFC 2015).

I. 2nd Wave Litigation

Biosimilar Notice of Commercial Marketing and Preliminary Injunction Procedure

- Biosimilar applicant must provide Pioneer with 180 day notice of intent to market commercially.
- Pioneer may seek preliminary injunction (PI) on any patents on the “initial Pioneer list” or “initial Biosimilar list” that are not also included on the “negotiated list” or the “exchanged lists.”
- Both parties required to reasonably expedite discovery in any infringement action seeking PI.

Litigations Involving Notice of Commercial Marketing

- 180 day notice of commercial marketing is mandatory even if patent dance elected (Amgen v. Apotex (Neulasta) S.D.FL 2015).
- 180 day notice of commercial marketing cannot be provided before BLA licensing by FDA (Amgen v. Hospira (Epogen) D.DE 2015; Amgen v. Apotex S.D.FL 2015).

J. Newly Issued/Licensed Patents

- Defined as patent issued/licensed after date of “initial Pioneer list.”
- Within 30 days of issued/licensed patent, Pioneer must supplement its initial list.
- Within 30 days of receiving supplement, Biosimilar applicant must provide statement on claim by claim basis as to non-infringement, invalidity or unenforceability on newly issued/licensed patent.
- Newly issued/licensed patents do not become part of the negotiated/exchanged patent procedures but are subject to Preliminary Injunction procedures.

K. Limitation on DJ Actions

- If Biosimilar applicant provides confidential access to application, no DJ can be brought by either party before the 180 days notice of commercial marketing is received; DJ can only be brought on “PI patent list.”
- If Biosimilar applicant fails to provide (1) claim by claim statement on initial pioneer list (or newly issued patent) within 60 day (or 30 day) time frame; (2) notice of number of to be exchanged patents; (3) notice of complaint to FDA; (4) or 180 day notice prior to marketing, Pioneer can bring DJ on any patent on “initial Pioneer list” and on any newly issued patent.
- If Biosimilar applicant fails to provide access to confidential information Pioneer can bring DJ on any patent that claims biological product or use of product (but not manufacture of product).

L. FAQs

- What happens if Pioneer leaves a patent off its initial patent list?
 - Unless Biosimilar applicant includes the patent on its initial list, Pioneer cannot sue on it prior to launch.
- Can a Pioneer be forced to license its patents?
 - If a Pioneer fails to bring an infringement action within 30 days of (1) a negotiated patent resolution, or (2) following exchange of patent lists where there is no resolution; or
 - If a Pioneer brings an infringement action within 30 days but the suit is dismissed without prejudice or the suit is not prosecuted in good faith.
- What happens if a newly issued/licensed patent is not notified to Biosimilar applicant within 30 days?
 - Patent cannot be litigated prior to Biosimilar launch.

M. What the Pioneer Should Do Now?

- Identify who will receive the biosimilar applicant's confidential information.
- Assess your patent portfolio.
- Strengthen your patent portfolio.
- Establish a reliable updating procedure.
- Review license agreements.

M. What the Pioneer Should Do Now?

Identify Who Will Receive Confidential Info

- Will be the one(s) who decide which patents are infringed, if this requires knowledge of confidential information.
- Criteria set by statute “unless otherwise agreed.”
- Attorneys, not technical people.

M. What the Pioneer Should Do Now?

- One in-house attorney.
 - Not non-attorney unless parties agree.
 - Does not “formally or informally” engage in patent prosecution related to the Pioneer’s product.
 - Issue for small companies.
 - Even in larger company, prosecutors typically collaborate at least informally.
 - Even litigators may occasionally advise prosecutors regarding strategy.
 - May need to hire new in-house attorney for this role.
 - Or rely solely on outside counsel.
- Formally wall the attorney off from all prosecution strategy discussions, even generic.

M. What the Pioneer Should Do Now?

- One or more outside counsel.
 - Can be a team.
 - All attorneys (no patent agents).
 - Include an experienced litigator to manage the process.
 - Include lawyer with appropriate technical savvy.
 - Cannot “formally or informally” engage in patent prosecution related to the pioneer’s product.
 - Not clear if prohibition applies to entire firm.
 - If others in firm handle prosecution related to the product, need a formal wall both ways.

M. What the Pioneer Should Do Now?

- For exclusively in-licensed patent, a representative of the patent owner, **if**:
 - has retained right to participate in litigation, and
 - agrees to confidentiality provisions.

M. What the Pioneer Should Do Now?

- Train the attorney(s):
 - How to find necessary information in BLA applications.
 - Technical details of Pioneer's product and manufacturing.
 - Details of Pioneer's product label.
 - How to interpret claims of all pertinent patents.
 - Results of portfolio analysis (below).

M. What the Pioneer Should Do Now?

Assess Your Patent Portfolio

- Review your own BLA.
- Compile list of all your possibly relevant patents (including exclusively licensed-in):
 - product
 - method of treatment
 - method of manufacture
 - compositions (e.g., target receptor) used in manufacture and quality control
- Determine which claims could arguably be asserted against identical product and methods.
- Decide what information or assays would be needed to establish infringement of each claim.

M. What the Pioneer Should Do Now?

- Predict likely modifications to product or methods.
- Determine which claims could arguably be asserted against those modified products or methods.
- Decide what information or assays would be needed to establish infringement by those modified products or methods.

M. What the Pioneer Should Do Now?

- Analyze enforceability issues for each claim:
 - Validity
 - Inequitable conduct
 - Standing to sue (licensed-in patents)
 - Clear title
 - Inventorship questions
 - Formalities (maintenance fees, FF license, etc.).
- Determine expiration date for each patent.
- Determine if patent is critical for Pioneer's other product(s).

M. What the Pioneer Should Do Now?

- Predict likely scenarios.
- For each scenario, rank the patents in order of priority for enforcement:
 - Expiration date
 - Difficulty of proving infringement
 - Validity concerns
 - Standing to sue
 - Clear title
 - Importance of patent for other products
- Decide whether to offer license to any of the patents.
- Share the analysis with the selected in-house attorney and outside counsel.

M. What the Pioneer Should Do Now?

- Pursue CON/DIV or reissue of existing patents to secure broader and narrower coverage.
- Predict potential designs-around and determine if they can be patented or exclusively in-licensed.
- Seek ways to patent details of the FDA-required label.
- Sue USPTO for additional PTA pursuant to Wyeth and Japan Tobacco decisions.
- Turn non-exclusive licenses into exclusive with right to enforce.

M. What the Pioneer Should Do Now?

Establish Updating Procedure

- Keep patent list updated:
 - Newly issued to Pioneer
 - Newly issued to Pioneer's licensor
 - Newly in-licensed
 - Other patents, if newly implicated by new information
- Inform in-house attorney and/or outside counsel of any updates.
- Periodically ask biosimilar Applicant to disclose any updates to its biosimilar application at FDA.
- Continue updating until biosimilar Applicant's product launch

M. What the Pioneer Should Do Now?

Review License Agreements

- Establish essential criteria for any license:
 - Who enforces?
 - Is enforcement required?
 - Is consent to sue needed?
 - Who decides which patents to enforce at each stage?
 - What remedy if licensed patent is not enforced?
 - Is licensor's cooperation required?
 - Are sublicenses permitted?
 - Who decides whether to sublicense and what terms?
 - Who decides which patent's term to extend?
 - Who decides who gets access to biosimilar applicant's confidential information?
 - What role does licensor play in patent exchange process?

M. What the Pioneer Should Do Now?

- Develop preferred language.
- Review existing licenses for compliance.
- Renegotiate as needed.
- Streamline procedure for getting consent to sue.
 - Default consent?
- Set up procedure to ensure immediate notification of future issued patents within license agreement.

N. What the Biosimilar Applicant Can Do in Advance

- Identify all relevant parties:
 - Pioneer's patents.
 - Patents assigned to others that Pioneer might in-license.

N. What the Biosimilar Applicant Can Do in Advance

- Consider all aspects for searching:
 - Protein name.
 - Amino acid sequences.
 - Nucleic acid sequences.
 - General methods of making the protein.
 - Vectors, promoters, cell lines, purification schemes.
 - Formulations.
 - Methods of treatment or other use.
 - Compositions for manufacture or QC.
 - *In-vivo* and *in-vitro* assays needed to test activity.

N. What the Biosimilar Applicant Can Do in Advance

- Sources of information for Applicants:
 - BLA not available and not subject to FOIA.
 - Pioneer label, scientific publications, known patents.
 - FDA and ex-US health agency websites:
 - HealthCanada (<http://www.hc-sc.gc.ca/index-eng.php>)
 - Pharmaceuticals and Medical Devices Agency, Japan (<http://www.pmda.go.jp/english/about/what.html>)
 - General internet searching.

N. What the Biosimilar Applicant Can Do in Advance

Analyze Freedom to Operate

- For each identified Pioneer patent, assess:
 - Expiration date
 - Validity
 - Enforceability
 - Noninfringement arguments

N. What the Biosimilar Applicant Can Do in Advance

Consider Strategy for Each Identified Patent

- Design around?
- Await expiration?
- Assert noninfringement?
- Assert invalidity?
- Assert unenforceability?

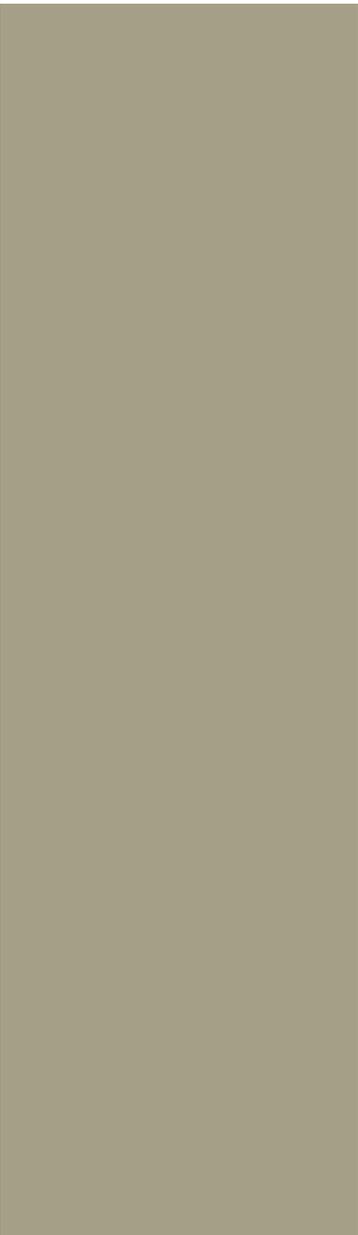
N. What the Biosimilar Applicant Can Do in Advance

Prepare for Patent Exchange

- Prepare list of all patents you want to have included in the first wave.
 - Will be the source of the “initial Biosimilar list.”
- Prepare comprehensive list of all patents you expect will be included on either the “Pioneer patent list” or the “initial Biosimilar list.”
- For each patent on the comprehensive list, prepare claim-by-claim analysis as to why each claim is:
 - invalid or
 - unenforceable or
 - will not be infringed or
 - will have expired before Applicant begins marketing.

Acronyms

- AI – active ingredient
- ACA – Affordable Care Act 2010
- ANDA – abbreviated new drug application
- BPCIA – Biologics Price Competition and Innovation Act of 2009
- BLA – Biologic License Application
- BM – Biomarker
- CAFC – Court of Appeals for the Federal Circuit
- FDA – Food & Drug Administration
- FDASIA – FDA Safety and Innovation Act
- IND – Investigational New Drug
- NCE – New Chemical Entity
- NDA – New Drug Application
- OB – Orange Book
- PHSA – Public Health Service Act
- PMA – Pre-market approval
- PMR – post marketing requirements
- PTE – patent term extension
- PTO – Patent and Trademark Office
- rDNA – recombinant DNA
- RRP – Regulatory Review Period
- SH – Safe Harbor
- S&E – safe and effective
- QIDP – Qualified Infectious Disease Program
- USDA – US Department of Agriculture



Questions?

FISH.

Biosimilars Webinar Series

Mark your calendar!

Upcoming Webinars

Thursday, February 25
1:00 pm EST



Thank you!



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