

The Patenting and Regulatory Aspects of Biosimilars



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The Patenting and Regulatory Aspects of Biosimilars

- Introduction to Biosimilars
- What is patentable from a Biosimilar R&D project?
- How are patents covering the biosimilar analyzed and/or avoided during the R&D period
- What are the patent concerns associated with marketing a Biosimilar
- The U.S. Biosimilar regulatory framework

Biosimilars - Background

- Why are we discussing Biosimilars now?
 - Biosimilars have been marketable in Europe since 2005
 - 18 biosimilars marketed
 - 93 in the pipeline
 - Biosimilars have been marketable in S. Korea since 2009
 - 3 biosimilars marketed
 - Framework for approval of Biosimilars in U.S. has been in place since 2010

Biosimilars - Background

- Several significant reasons Biosimilars are “in the news”
 - Global Biosimilars market accounted for approx. \$1.3B in revenue in 2013
 - Anticipated to increase to approx. \$35B by 2020
 - “Patent Cliff” for pioneer biologics– opens market to biosimilar products
 - Ten biologics to lose patent protection over next four years
 - Loss of revenue attributable to Patent Cliff approx. \$60B
 - This summer FDA accepted first two applications for marketing approval for biosimilars

Biosimilars and Abbreviated Approval Pathway

- The Biologics Price Competition and Innovation Act (“BPCIA”, “the Biosimilars Act”)
 - empowers FDA to allow market access to biosimilar products
 - Provides abbreviated process for approval of drugs biosimilar to a reference drug
 - FDA cannot grant marketing approval of biosimilar for 12 years after marketing approval of reference drug
 - Exchange of patent information - to be discussed later

Patenting Biosimilars

- Is the idea of patenting biosimilars internally contradictory?
 - Granting a patent requires proof that the invention is
 - Novel (i.e., new, previously unknown)
 - Non-obvious (i.e., not readily derived from existing knowledge)
 - The applicant for the patent must prove that the invention is not identical or very similar to what is known
 - In contrast...

Patenting Biosimilars

- Applicant for license to market a biosimilar must demonstrate to FDA that biosimilar is
 - “Highly similar to the reference product notwithstanding minor differences in clinically inactive components”
 - “No clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency.”
- If a biosimilar drug is “highly similar to” and has “no clinically meaningful differences” over a known drug, what is there to patent?

Patenting Biosimilars

- Two likely sources of patentable inventions
 - Improvements to formulation that do not impart “clinically meaningful differences”
 - Improved formulation properties
 - Storage stability
 - Flowability
 - Change of excipients
 - Solubility
 - Improved manufacturing process
 - Different cell line
 - Altered nucleic acids
 - Altered culture conditions
 - Improved purification
 - Improved sterilization

Steering a Clear Course

- What about Patents Owned by Others?
- Freedom to Operate
 - A patent provides the right to exclude, not the right to practice
 - What is the correct approach to the patents of the innovator pharmaceutical manufacturer?
 - Understand the state of the art
 - Understand the relevant patent portfolio of the innovator pharmaceutical manufacturer
 - Seek analysis of proposed biosimilar in view of the patent claims of others

Steering a Clear Course

- The Safe Harbor Provision (35 USC §271(e)(1))
 - Immunizes certain activities from patent infringement
 - Obtaining information required to be submitted to FDA for marketing approval
 - Obtaining information required to be submitted to FDA to maintain marketing approval
- R&D outside the U.S.
 - Extraterritorial loophole (*Bayer v. Housey*)
 - Importation into the U.S. of information that would be infringing if generated in the U.S. is not infringement

BPCIA – Patent Dance

- The BPCIA mandates a multi-step information exchange and negotiation between the Reference Product Sponsor and the Biosimilar Applicant regarding which patents cover the Reference Product Sponsor's product and the Biosimilar Product Applicant's Product
 - mechanism is complex
 - several rounds of confidential information exchange directly between Reference Product Sponsor and Biosimilar Applicant
 - two separate litigation cycles
 - strict timing and sequence

BPCIA – Patent Dance

- The “Patent Dance” begins with:
- **Step 1** – Transmission of Biosimilar Application
 - The Biosimilar Product Applicant submits its application for license to market to FDA
 - Celltrion – Remsima (Biosimilar of Janssen Remicade)
 - Sandoz – Zarzio (Biosimilar of Amgen Neupogen)
- **Step 2** – Reference Product Sponsor’s Paragraph 3(A) Patent List
 - A list of all patents for which the Reference Product Sponsor believes a claim of infringement could reasonably be asserted

BPCIA – Patent Dance

- **Step 3 – Biosimilar Applicant’s Paragraph 3(B) Patent List**
 - **May Provide** - A list of all patents for which the Biosimilar Applicant believes a claim of infringement could reasonably be asserted
 - **Shall Provide** - A claim by claim analysis of non-infringement of each patent on Reference Product Sponsor’s list (invalid, unenforceable or not infringed); or
 - A statement by the Biosimilar Applicant that it does not intend to commercially market an infringing product before the relevant patent expires

BPCIA – Patent Dance

- **Step 4 – Reference Product Sponsor’s Response**
 - Answers Biosimilar Applicant’s statements regarding patent invalidity
- **Step 5 – Patent Resolution Negotiations**
 - Reference Product Sponsor and Biosimilar Applicant shall negotiate to agree on which patents are the subject of an action for patent infringement

BPCIA – Patent Dance

- **Step 6/7** – Patent Resolution and Infringement Suit
 - If no agreement – infringement suit on any or all of patents on Reference Product Sponsor's list
 - If agreement – infringement suit on those patents the two parties agreed are infringed

Biosimilar License Strategy

- Biologics License Application (BLA)
- Regulated by 21 CFR 600 – 680
- BLA is submitted by
 - any legal person or entity who is engaged in manufacture, or
 - an applicant for a license who takes responsibility for compliance with product and establishment standards.
- Requirements
 - Applicant information
 - Product/Manufacturing information
 - Pre-clinical studies
 - Clinical studies
 - Labeling

Teva's Granix®

- In early 2010 Teva applies to FDA to market “biosimilar” version of Amgen’s Neupogen
 - traditional application route via a Biologics License Application (BLA) with supporting clinical data. Amgen files a patent infringement claim in the US Federal Court against Teva trying to block the move
 - Teva seeks declaration from the same court that its product does not infringe Amgen's patents
- Note that the application was filed prior to BPCIA – thus no 351(k) abbreviated Biosimilar pathway

Biosimilars and Biobetters

- A biological product related to an already approved biological product
 - superior in one or more product characteristics
- The term “Biobetter” became popular in the context of BPCIA
- Faced with rigorous requirements for biosimilarity and interchangeability in the BPCIA applicants may choose to develop Biobetters

New Regulatory Approval Pathway for Biosimilars

- FDA is granted substantial flexibility in determining approval standards for biosimilars, including whether and what type of clinical studies will be required and what differences in approval process from the Biologics License Application (BLA) process are appropriate
- Grants 12 years of data exclusivity to pioneer manufacturers
 - 12 year exclusivity barring FDA approval of a Section 351(k) application is determined from “the date on which the reference product was first licensed”
 - An application cannot be submitted to FDA until 4 years after the date on which the BLA for the reference product was first granted
- New biosimilar applications are subject to 10-month review timelines under the Biosimilar User Fee Act included in the FDA Safety and Innovation Act (FDASIA) of 2012

Issues Regarding New Regulatory Approval Pathway

- What is a biosimilar, and how similar to the reference product must a biosimilar be, to be (1) approved and (2) considered interchangeable
- What scope of data is necessary, if any, to show biosimilarity
- The scope of innovator modifications to a product that can provide a basis for additional exclusivity
- Effect of manufacturing process differences on showing biosimilarity
- When and under what parameters is reimbursement available

Issues Regarding New Regulatory Approval Pathway

- Naming issues for biosimilars (proprietary/unique or generic)
 - Effect on drug safety reporting/recalls
 - Effect on reimbursement
- Whether a biosimilar needs to provide data in connection with all approved indications of the reference product
- Whether a biosimilar can be better than the reference product (“biobetters”); if so, in what way (safety/efficacy/usability)

FDA Draft Guidance Documents - Helpful, But Silent on Major Questions

- FDA has issued five draft guidance documents intended to facilitate the submission of marketing applications for biosimilars
 - “Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act (February 2012)
 - “Scientific Considerations in Demonstrating Biosimilarity to a Reference Product” (February 2012)
 - “Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product” (February 2012)
 - “Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product” (May 2014)
 - “Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act” (August 2014)

FDA Purple Book – Biologics Exclusivities

- “Purple Book” – FDA “Lists of Licensed Biological Products With Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations” (September 2014)
- Similar in purpose to Orange Book for new drugs
- Lists the following information:
 - date a biologic was licensed under Section 351(a)
 - whether FDA evaluated the biologic product for reference product exclusivity under Section 351(k)(7)
 - whether a biologic licensed under Section 351(k) has been determined by FDA to be biosimilar or interchangeable with a reference biologic product
- How FDA will calculate when a product is first licensed, or the effect of later structure modifications to the product, remain at issue

Initial Biosimilars 351(k) Applications

- First two 351(k) applications:
 - Sandoz (July 2014) for biosimilar version of Amgen's Neupogen
 - Celltrion (August 2014) for biosimilar version of J&J's Remicade
- Note: challenge by Abbott Laboratories [now AbbVie] to FDA biosimilar approval process, by a Citizen Petition (April 2, 2012)
 - Requests that FDA confirm it will not accept for filing or approve any biosimilar application for Humira as the reference product
 - Asserts any approval would necessarily use and disclose Abbott's trade secrets and that such disclosure would constitute a taking under the Fifth Amendment that requires just compensation
- Arguments similar to those advanced by Pfizer in its Citizen Petition (May 13, 2004), opposing approval of a 505(b)(2) application by Sandoz for Omnitrope, a human growth hormone product, rejected on other grounds by FDA by letter dated May 30, 2006

Practical Issues Regarding Life Cycle Management Naming and Labeling

- Naming – whether unique non-proprietary names must be assigned by FDA to biosimilars
 - Safety issues – avoiding prescribing confusion with pioneer biologic
 - Avoiding product liability misallocation of responsibility
 - Tracking issues – enabling proper pharmacovigilance/recalls/investigations by FDA
 - Potential adverse effects on biosimilar utilization/substitution/interchangeability
- Potential options regarding non-proprietary naming
 - Pharmacy groups' concerns with use of unique suffixes in processing and fulfilling prescriptions
 - Possible use of unique prefixes (e.g., WHO proposal to modify INN names)
 - Note identification of Teva's G-CSF product, approved through a BLA, as tbo-filgrastim, distinguishing it from the pioneer product, filgrastim. (Pink Sheet, at 9, Sept. 3, 2012)

Practical Issues Regarding Life Cycle Management Naming and Labeling

- Labeling issues

- Whether a label should state that a product has not been deemed biosimilar for all indications of the pioneer product
- Whether a label should affirmatively state that a biosimilar is not interchangeable, unless FDA has so concluded, and that switching is therefore not authorized
- Whether a biosimilar label should state that substitution is only authorized with the consent of the prescribing physician
- Scope of labeling of “biobetters”

Practical Issues Regarding Life Cycle Management Payment and Reimbursement

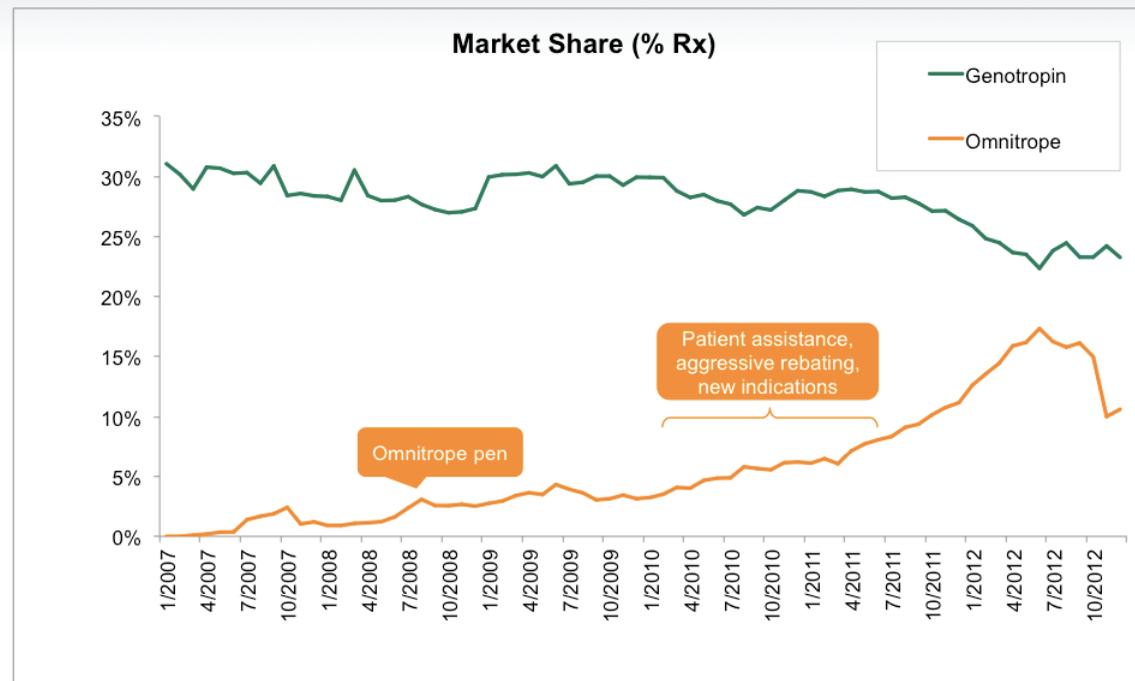
- Effect of reimbursement treatment of the pioneer biologic of approval of a biosimilar, and of biosimilars themselves
 - Absence of express treatment of biosimilars in the BPCIA under Medicare Parts B and D, Medicare Drug Pricing Program, Medicaid, 340B program
 - Whether biosimilars will constitute “multi-source drugs”
 - Whether each biosimilar for a particular reference product will have its own reimbursement rate, or will the data be pooled for a common rate
- Will payors require additional data regarding efficacy or safety for certain products, e.g., biosimilar monoclonal antibodies
- Effect of determination of interchangeability / non-interchangeability on reimbursement
- Effect on reimbursement of different INN or generic name from that of the reference product
- Whether possible rebates from pioneer manufacturers may offset the acquisition cost gains by payors from biosimilars

Practical Issues Regarding Life Cycle Management

- What degree of cost reduction/difference with pioneer biologic will be needed to drive purchasing
 - Potential purchaser/payor concerns regarding interchangeability and safety/efficacy (potency)
 - E.g., initial Sandoz experience with purchaser resistance to Omnitrope (biosimilar somatropin) notwithstanding price advantage (See Pink Sheet, Nov. 22, 2010 and M. Harper, “What Will Happen When Biotech Drugs Go Generic?” Forbes, June 13, 2014)
- What potential exists for a biologics “evergreening” strategy (product modifications to extend exclusivity period)
- Continued uncertainty of biosimilars approval pathway significantly affects strategy of biopharma R&D and investments and M&A valuation of products and companies

Practical Issues Regarding Life Cycle Management

Omnitrope vs. Genotropin share



data: Bloomberg, accessed August 5, 2013. Share erosion calculated comparing H1-2010 vs. H1-2012

2014-04-14 Biosimilars Impact Framework_graphs and price

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