

## Biosimilars: Developments and Life Cycle Planning under the Biologics Price Competition and Innovation Act



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# New Regulatory Approval Pathway for Biosimilars

- The Biologics Price Competition and Innovation Act (BPCIA) establishes a new regulatory approval pathway for biosimilars
- Intended to be a major cost-containment mechanism of the Patient Protection and Affordable Care Act of 2010
- Provides for approval of biological products as biosimilar or interchangeable (termed Section 351(k) applications)
  - i.e., products expected to produce the same clinical effect and, if a multi-dose product, not present any greater safety or efficacy risk in switching from reference product
- Provides that there be no “clinically meaningful differences” with the pioneer biologic product

# 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
    - Supplemental BLAs or slight modifications (undefined by the BPCIA) are not included in the exclusivity period and do not extend it

# New Regulatory Approval Pathway for Biosimilars

- Approval requirements are to be set by FDA, but should include, unless FDA waives them, the following:
  - Analytical studies demonstrating the biosimilar is highly similar to the reference product
  - Animal studies
  - A clinical study sufficient to demonstrate safety, purity, and potency
  - Other information showing that the biosimilar uses the same mechanism of action, route of administration, dosage form, and strength
- Exclusivity periods are provided for the first approved biosimilar commercially marketed
- Patent challenge provisions are significantly different from those under Hatch-Waxman for generic drugs, requiring “negotiation” of patent disputes and exchanges of patent information prior to instituting patent litigation

# New Regulatory Approval Pathway for Biosimilars

- REMS requirements are mandated to apply to biosimilars as they may do to the reference pioneer biologic
- Reimbursement for biosimilars is set at average sales price (ASP) plus 6% of the amount determined for the reference pioneer biologic
  - Significant uncertainties regarding appropriate reimbursement approach
- Allows for imposition of user fees to review biosimilars
  - Incorporated in the Biosimilar User Fee Act of 2012, part of the FDA Safety and Innovation Act of 2012, authorizing FDA to collect user fees for biosimilars applications
  - The FDA issued a notice setting out the user fee rates for 2013, ranging from \$195,880 to \$1,958,800, depending on the scope of the application. [77 Fed. Reg. 45634 \(Aug. 1, 2012\)](#)

# 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)

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

- On February 9, 2012, FDA issued three 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 of 2009” (Biosimilars Q&A)
  - “Scientific Considerations in Demonstrating Biosimilarity to a Reference Product” (Biosimilars Scientific Guidance)
  - “Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product” (Biosimilars Quality Guidance)



# FDA Draft Guidance Documents

- Biosimilars Q&A
  - Summarizes statutory requirements for biosimilarity and interchangeability
  - Provides general guidance on content to be included in a 351(k) application
  - Recommends that sponsors meet early with FDA to discuss proposed plan for biosimilar development programs and anticipated study requirements
  - Responds to preliminary exclusivity questions
  - Sets out FDA's current view that comparative animal or clinical data developed using a non-U.S.-licensed product *can* provide evidence that a proposed product is biosimilar to a U.S.-licensed reference product

# FDA Draft Guidance Documents

- Biosimilars Scientific Guidance
  - Sets out three approaches on demonstrating biosimilarity:
    1. A stepwise approach to demonstrating biosimilarity, which can include a comparison of the proposed product and the reference product with respect to structure, function, animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD), clinical immunogenicity, and clinical safety and effectiveness;
    2. The totality-of-the-evidence approach that FDA will use to review applications for biosimilar products; and
    3. General scientific principles in conducting comparative structural and functional analysis, animal testing, human PK and PD studies, clinical immunogenicity assessment, and clinical safety and effectiveness studies (including clinical study design issues).

# FDA Draft Guidance Documents

- Biosimilars Quality Guidance
  - Provides direction on analytical studies relevant to assessing whether proposed biosimilar protein product and reference product are "highly similar"
  - Suggests there may be an opportunity for innovators to argue current technology does not permit for demonstration of "biosimilarity" of a potentially competitive product in manner adequate to gain approval under 351(k), thus necessitating the filing of full biologics license application (BLA)

# Industry Comments on Draft Guidance Documents

- BIO
  - Concerned that animal toxicity or safety data only required in some cases
  - Require biosimilars to have a distinct, non-proprietary name to permit tracking an adverse event
  - Questions how quality comparisons between reference and biosimilar products should be conducted when quality attributes are unstable/change over time
- PhRMA
  - Controllable differences between biosimilars and references should be minimized
  - Limits of state-of-the-art analytical technology should be recognized
  - Require abbreviated approach taken by each applicant to be fully scientifically justified
  - Any data from foreign product trials should be used only to corroborate pivotal data comparing biosimilar to U.S.-approved reference product

# Industry Comments on Draft Guidance Documents

- Amgen
  - Clinical studies are necessary due to complexity and diversity of human biology
  - Acknowledge biosimilars as stand-alone products for purposes of ongoing regulation once they are approved as safe and effective
  - Specify that biosimilar labeling provide all information necessary for physicians and patients to make informed choices
- EMD Serono
  - Take into account not only the size of a protein, but also structural elements, modifications critical to normal biological activity, functional attributes, and the role of living organisms
  - Request further delineation of the term “meaningful” toxicological comparison between the reference and proposed products
  - Elaborate as to what studies and circumstances might allow a biosimilar product to be relieved of any REMS requirements that are applicable to the innovator compound
  - Make clear whether additional "track & trace" provisions are anticipated in future guidance documents

# Industry Comments on Draft Guidance Documents

- GPhA
  - Clinical trials should only be required “if and when the totality of the other evidence is insufficient to establish that the proposed biological product is highly similar to the reference product”
  - Biosimilar manufacturer should not be required to provide more data than they originator did
  - There should be regulatory consistency in the treatment of biosimilars and novel biologics
  - Any sponsor demonstrating its biosimilar has met the comparability standard, as a scientific matter, relative to the chosen reference product should have the option of an interchangeability designation at the time of initial approval
  - FDA may not need to require clinical immunogenicity studies because it can be argued that an immunological response with a biosimilar is no more likely, and may be less likely, than with the reference product

## Other Industry Responses to Draft Guidance Documents

- Challenge by Abbott Laboratories 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
- In comments on this Citizen Petition, the Washington Legal Foundation has urged FDA to delay any approvals of applications for biosimilars for products approved before March 2010 until FDA responds to Abbott's petition. See Pharma. Law & Industry Report (Feb. 22, 2013).
- 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

## Other Industry Responses to Draft Guidance Documents

- Efforts by pioneer manufacturers toward State enactments of substitution requirements for prescription of biosimilars
  - Including imposition of patient and prescriber notification requirements; allowing pharmacy dispensing of interchangeable biosimilars unless the prescriber indicates otherwise (e.g., Virginia proposed legislation, see [Pharma. Law & Industry Rep.](#), March 6, 2013; rejection by Mississippi of restrictions, see [Inside CMS](#), at 17, Feb. 21, 2013)
- Possible litigation challenges to marketing of biosimilars
  - Cf. Endo's false advertising complaint against Actavis alleging false marketing of its generic product as AB-rated to the pioneer Endo drug product, Opana ER. [Endo Pharmaceuticals, Inc. v. Actavis, Inc.](#), D.N.J. (filed Dec. 11, 2012)



## Major Topics Not Addressed in FDA Draft Guidance Documents

- Naming – assignment of unique, non-proprietary names (i.e., generic names) to biosimilars
- Labeling – inclusion of limitations on indications; inclusion of statements on interchangeability
- Interchangeability – determining that a biological product is interchangeable with the reference product
- Clinical trials – size, scope, number, and design
- Number and size of production lots necessary for certain comparative analytical studies
- Regulatory effects of pioneer biologic product drift over time

# Practical Issues Regarding Life Cycle Management

- Significant general uncertainty for R&D in view of the substantial discretion provided to FDA regarding details and standards for submissions and approvals of biosimilars, and absence of comprehensive guidance or regulations
- FDA officials have noted that the Agency has received 50 requests for pre-IND meetings and has held 34, and received 12 IND applications for biosimilars for 12 reference products, notwithstanding that the FDA has not yet issued proposed regulations. (Inside CMS at 20, Jan. 10, 2013)
- Adaptation to a significantly different approach from new drug/biologic development, focusing on analytical characterization data rather than clinical trials directed to showing safety and efficacy
  - See M. McCaughan, *Biosimilars: Inverting the Innovator Development Model*, RPM Report at 10 (March 2012)

# 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
    - Note identification of Teva's recently-approved G-CSF product, 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

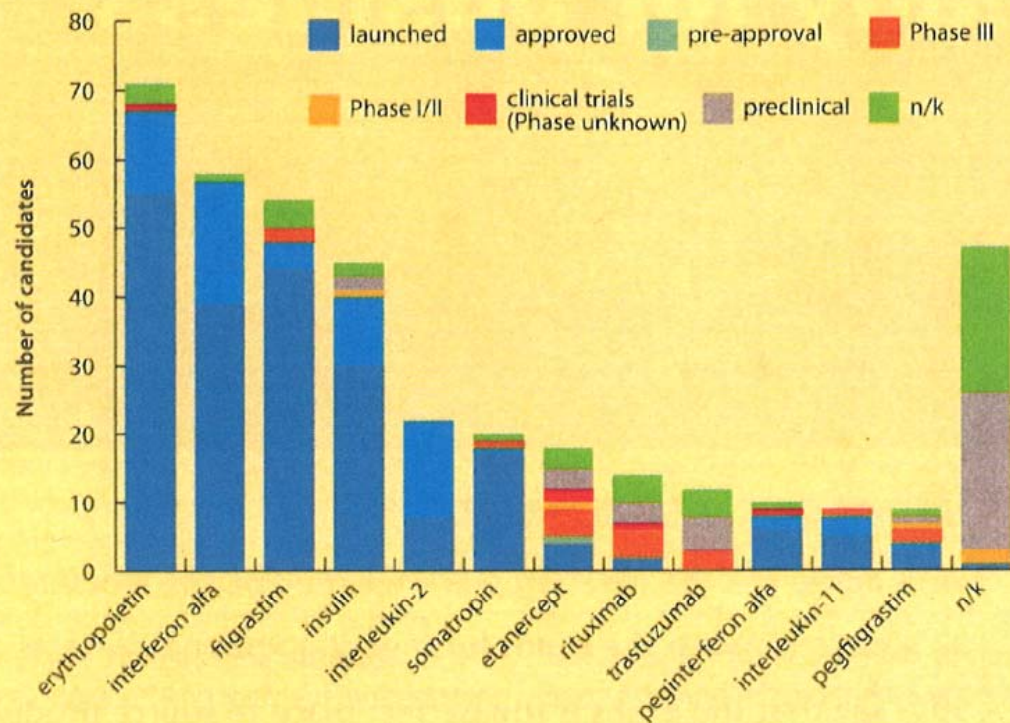
- Whether a label should state that a product has not been deemed biosimilar for all indications of the pioneer product
- Whether a label should affirmatively state that a biosimilar is not interchangeable, unless FDA has so concluded, and that switching is therefore not authorized
- Whether a biosimilar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

# Practical Issues Regarding Life Cycle Management

- Effects on FDA review of European Medicines Agency (EMA) and other non-U.S. approvals of biosimilars
  - See EMA-FDA Report, Interactions between the European Medicines Agency and U.S. Food and Drug Administration, Sept. 2009 – Sept. 2010 (June 2011)
  - Note first application for biosimilar version of a monoclonal antibody (Remicade) filed in EU. (Scrip, Apr. 20, 2012)
  - EU accounts for approximately half of global biosimilar sales, in 2011 totaling only \$400 million; approximately 550 biosimilars are in development worldwide. (Scrip, at 6, Nov. 30, 2012).

# Practical Issues Regarding Life Cycle Management

Figure 1: Biosimilar molecules in development and launched in ROW (not EU, not US, not Japan)



Source: Datamonitor, company reported information

Source: Scrip, at 18 (Sept. 21, 2012)

# Practical Issues Regarding Life Cycle Management

- What potential exists for use of authorized biologic settlement agreements, deriving from the BPCIA's patent negotiation process
  - Continued controversy regarding drug patent litigation settlements (“pay for delay” settlements)
    - Pending Supreme Court decision in [FTC v. Watson Pharmaceuticals](#) (Sup. Ct., Case no. 12-416)
  - See Federal Trade Commission Report, *Authorized Generic Drugs: Short-Term Effects and Long-Term Impact* (August 2011)
  - FTC Staff have noted that a significant potential area of concern regarding biosimilars applications is ensuring that a biosimilar applicant's data package provided to the reference product's owner does not lead to collusion or other anticompetitive consequences. ([Pink Sheet](#), at 1, May 7, 2012)

# 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
- Rebates from pioneer manufacturers may offset the acquisition cost gains experienced by payors from biosimilars



# Practical Issues Regarding Life Cycle Management Development and Marketing

- Likely substantially different competitive market dynamics for biosimilars from that of generic drugs
  - See Federal Trade Commission, *Emerging Health Care Issues: Follow-on Biologic Drug Competition* (June 10, 2009), providing an analysis of the likely nature of competition in a biosimilars market and the significant differences likely compared with the competitive dynamics of the generic drugs market
    - Likely smaller number of entrants
    - Significantly greater cost of applications/testing
    - Likely less reduction in price from that of pioneer biologic
    - Necessity of marketing staff for biosimilars, unlike generic drugs
- Consequent need for sales/marketing staffs and pharmacy education activities

# 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., Sandoz experience with purchaser resistance to Omnitrope (biosimilar somatropin) notwithstanding price advantage (Pink Sheet, Nov. 22, 2010)
- What potential exists for a biologics “evergreening” strategy
  - Use of pioneer biologics modifications to extend exclusivity period
  - Note development by Roche of a new subcutaneous formulation of Herceptin as a response to the potential introduction of biosimilars (Pink Sheet, at 7 – 8, July 11, 2012)

# Impact of Biologics Act on Biopharma Growth and Investment

- Biosimilars regulatory pathway significantly affects biopharma R&D, M&A, investment, and valuation of companies and products
  - Uncertainty of whether and when biosimilars will be approved
  - Uncertainty regarding restrictions affecting substitutability
  - Uncertainty regarding sales and rate of return consequences of biosimilars on pioneer products
  - Uncertainty with respect to reimbursement
  - Uncertainty regarding whether biosimilars approval pathway will be practically viable
- Need to closely monitor and quickly adapt to regulatory and market changes in making biologic product investment and acquisition decisions

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