Biosimilar Naming and Labeling - How Can We Best Promote Patient Safety?

12th Biosimilars Summit - CBI
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January 24, 2017
Momenta: Creating Value through a Diversified Business Strategy

Corporate Info
• Founded in 2001; IPO 2004
• Located in Cambridge, MA
• ~275 employees; >75% in R&D

An Advanced Analytic Platform
• Expertise in high-resolution analytics, biological characterization, and process engineering

Driving Potential in Three Areas
• Complex Generics
• Biosimilars
• Novel Drugs

With a Track Record of Success
• Breakthrough success with
  • 2010 generic Lovenox approval
  • 2015 generic Copaxone approval
Building a Sustainable Biopharmaceutical Company Based on Proven Technology

Complex Generics

Generic LOVENOX® (Enoxaparin Sodium Injection)

Biosimilars

M923 (HUMIRA®)
M834 (ORENCIA®)
Portfolio of development candidates

Novel Drugs

Novel Autoimmune Drugs
M281 (Anti-FcRn)
M230 (SIF3)
hs-IVIg

Physicochemical Analytics

Control of Manufacturing

Biological Characterization

Technology

for the characterization of complex biologic mixtures
Capturing Value Through Scientific Capabilities

**Thorough Structural Characterization**
High resolution physicochemical analytics platform to thoroughly characterize any product

**Control of Manufacturing**
Understanding the nonlinear chemical and biosynthetic reactions that drive production

**Thorough Biological Characterization**
High resolution biology applied pre-clinically and in clinical settings
## A History of Commercial Messaging to Deter Biosimilar Innovation and Competition

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<th>Tactic</th>
<th>Message</th>
<th>Barriers to Competition</th>
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<td>BIO CP - 2003</td>
<td>• Generic biologics are impossible</td>
<td>• Prevent regulatory approval</td>
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<td>• Prevent/deter legislative pathway</td>
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<td>Oppose Biosimilar Pathway – 2007-2010</td>
<td>• Biosimilars are unsafe even if possible</td>
<td>• Prevent/deter pathway</td>
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<td>• Interchangeable biologics are impossible/different</td>
<td>• Incorporate legislative features that prevent/deter use of the pathway</td>
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<td>• Mandatory clinical trials</td>
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<td>Influence FDA Guidance - 2011</td>
<td>• Same messages</td>
<td>• Emphasize differences (e.g., naming)</td>
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<td>• Mandate unnecessary clinical trials</td>
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<td>• Freeze scientific standards for similarity and interchangeability</td>
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<td>AbbVie CP</td>
<td>• Same messages</td>
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<td>Naming Campaign</td>
<td>• Biosimilars are different and raise safety concerns</td>
<td>• Amplifies anti-biosimilar commercial campaign with providers, payers, patients and regulators</td>
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<td>JnJ Citizen Petition</td>
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<td>• Prevents/delays initiation of development</td>
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<td>Restricted Access to Reference Products</td>
<td>• Biosimilar companies are irresponsible</td>
<td>• Prevents/delays initiation of development</td>
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Biosimilars and Interchangeable Biologics

- **Biosimilars**
  - A biological product that is “highly similar” to an FDA licensed reference product,
    - Notwithstanding minor differences in clinically inactive components; and
    - That there are no clinically meaningful differences between the biologic reference product and the biosimilar in terms of safety, purity and potency.

- **Interchangeable Biologics**
  - A *biosimilar product* that can be expected to produce the same clinical result as the reference product in any given patient, and
  - If it is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating between the use of the interchangeable biologic and the reference product is not greater than the risk of using the reference product.
  - Interchangeable biologics may be substituted at the pharmacy without the intervention of a physician.
Biosimilar Development and Approval
Evidence of Biosimilarity and Interchangeability

• Final Guidance Issued – December 2016 – Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product

In evaluating a sponsor’s data to support a demonstration of biosimilarity, FDA will consider the totality of the data and information submitted using a risk-based approach, including data from the structural and functional characterizations, nonclinical evaluations, clinical PK and PD studies, clinical immunogenicity testing and an investigation of clinical safety, and, when appropriate, clinical effectiveness. These data should be collected in a stepwise manner. Especially pertinent to FDA’s clinical pharmacology evaluation are the clinical PK and PD data and immunogenicity and other safety data obtained in conjunction with the clinical pharmacology studies. The need for additional studies at each step in this progressive approach will be determined by the degree of residual uncertainty that remains at each step regarding the similarity of the products and whether the study can address these uncertainties.

• Four levels of Analytical Assessment
  • Insufficient Analytical Similarity
  • Analytical Similarity with Residual Uncertainty
  • Tentative Analytical Uncertainty
  • Fingerprint-like Analytical Similarity
Risks of Unique Naming – A Commercial Differentiation Strategy

• Biosimilars are carefully reviewed and approved by the FDA
  • Biosimilars must be highly similar and have been shown *not to have clinically meaningful differences*
  • Interchangeable biologics must also be demonstrated to be capable of being substitutable at the pharmacy without the need for intervention of a physician
  • Brand drift and manufacturing changes do not require a unique name or special notice – Why? Same rationale applies.

• Unique non-proprietary names can
  • Suggest “meaningful differences” and confuse physicians and patients
  • Impair competition when more reliable means exist for tracking safety events
  • Make it harder to track safety issues associated with product drift or manufacturing changes of all biologics
Pharmacovigilance Could be Impaired by Unique Names

• Balkanization of safety events through unique naming
  • Rare signals across biosimilar products could be missed
  • Doctors could assume safety events are unrelated to the reference product and *vice versa*

• Existing, more robust safety methods could be undermined
  • NDC number and its bar code is used to track and record products at the pharmacy and is unique to the product
  • Manufacturer name is on the product and in pharmacy record
  • Electronic prescribing records are available to all physicians without charge for all products
National ePrescribing Patient Safety Initiative

The Time for ePrescribing is Now.

MEDICATION ERRORS, CONSIDERED PREVENTABLE, HARM 1.5 MILLION PATIENTS – AND OVER 7,000 PEOPLE DIE EACH YEAR.

FREE electronic prescribing... for every physician in America.

The National ePrescribing Patient Safety Initiative (NEPSI) is a joint project of dedicated organizations that each play a unique role in resolving the current crisis in preventable medication errors.

Electronic prescribing (ePrescribing) is a viable solution to counter shortcomings of the current paper-based prescribing processes that are in large part responsible for these errors. However, accessibility and cost barriers have slowed adoption of ePrescribing by providers.
Final FDA Guidance – Non-Proprietary Naming

- Draft Guidance Issued in January 2017
- Updated Draft 2015 Guidance
- Basic Principles
  - Shared Core Name for all biologics
  - Four letter Suffix for each Manufacturer’s biologic (reference or biosimilar)
  - Applies a suffix to all biologics to treat all biologics alike
- Leaves open but states
  - There should be a unique name with clear indication of interchangeability
  - Same suffix? Or Different suffix with Interchangeability designation?
  - Will indication of interchangeability be on both the reference and the interchangeable product?

Example from Guidance
replicamab-cznm
replicamab-hixf

Testimony of Janet Woodcock, M.D., Director, CDER – February 2, 2016

“FDA believes that both reference products and biosimilars should have nonproprietary names (also called a proper name) that include a core drug substance name and, in order to facilitate safe use and pharmacovigilance, an FDA-designated suffix that is unique for each product. The agency is continuing to consider whether the nonproprietary name for an interchangeable product should include a unique suffix or share the same suffix as its reference product.”
Proposing a Suffix for a Biologic

- **Should**
  - 10 proposed suffixes
  - Be four lowercase letters
  - Be unique and nonproprietary
  - Be devoid of meaning
    - Does this undermine or make its use unnecessary?

- **Should Not**
  - Be promotional or make safety or efficacy claims
  - Relate to the Company’s name
  - Include common medical abbreviations that could impact clinical practice
  - Contain or suggest the drug substance name or core name designated by USAN
  - Look to similar to another marketed product and risk medical errors
  - Be too similar to another product’s suffix
Biosimilar Labeling

• FDA Draft Guidance on Labeling for Biosimilar Products – April 4, 2016
• Industry Perspectives
• What to expect in the future
Draft Labeling Guidance

- Guidance, not law or regulation
- Builds on Existing Labeling Rules for Drugs and Biologics
  - Basic Principle
    - Prescription Drug labeling must provide adequate information to enable health care practitioners to “use the drug safely and for the purposes for which it is intended…” 21 CFR 201.100
    - Approved prescribing information summarizes the essential scientific information needed by health care practitioners for the safe and effective use of a drug. 21 CFR 201.56(a)(1)
    - Must meet content and format requirements of the Physician labeling rule (PLR) 21 CFR 201.56(c)(1)
Labeling Background

• Basic Principles and Questions
  • Labeling must contain adequate directions for use
  • Labeling must specify approved conditions or indications for use
  • Labeling may not be false or misleading
  • Comparative and superiority claims in labeling and promotional materials must be supported by substantial evidence adequate and well controlled clinical trials
Unsupported, Off-Label Comparative Claims are False and Misleading

What is False or Misleading?

- Better or more effective than has been demonstrated by substantial evidence
- Safer (fewer side effects, lower severity) than has been demonstrated by substantial evidence
- Comparative claims (better or safer than other products) without substantial evidence
- Misleading presentation of data
Application of Labeling Principles to Biosimilars

• The labeling reflects and relies on FDA’s finding of safety and effectiveness of the biosimilar

• Biosimilar label starts with the reference product label because it is “highly similar” and has “no clinically meaningful differences”
  • Reference product clinical data is the foundation for use and labeling of the biosimilar
  • Use of the biosimilar is informed by the safety/efficacy/dosing of the reference product
  • Information and data from development of a biosimilar should be described in labeling only when appropriate to inform safe and effective use by a health care practitioner
FDA Rationale for a “Highly Similar” label

• Similarity data designed to prove biosimilarity is not “comparable” to safety and efficacy studies
  • Endpoints are purposefully different
  • Subjects may be healthy volunteers
  • Studies may be small

• Analytical and Functional data is the foundation for approval and for the ability to rely on the reference product clinical data

• Interchangeable Biologics Excluded from the Draft Guidance
Specific Recommendations in the Guidance

• Use of Product Name
  • Use the biosimilar name when referring solely to the biosimilar product
    • If the biosimilar has a proprietary name, FDA recommends using the proprietary name when making a specific reference to the biosimilar product, E.g.,
      • Indications and Usage, Dosage and Administration, Dosage Forms and Strengths, and How Supplied and Handling
      • For specific directions and recommendations for preventing, monitoring, managing or mitigating risks in warnings and precautions
  • Use the reference products proper name for
    • Adverse Reactions (Clinical Trial Experience) and Clinical Studies
    • For warnings and precautions in the reference product labeling that are not specific to the biosimilar directions for use
      • E.g., “treatment with replicamab products increases the risk of ...” when the reference product says “treatment with Junexant increases the risk of...”
Biosimilarity Statement

- Include the following statement following the approval date:
  
  - [BIOSIMILAR PRODUCT’S PROPRIETARY NAME (biosimilar product’s proper name)] is biosimilar* to [REFERENCE PRODUCT’S PROPRIETARY NAME (reference product’s proper name)] for the indications listed.

- Include the following footnote:

  *Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar and the reference product.
Other Recommendations

• “Indications and Usage” and “Limitations of Use” should be specific to the approval for the biosimilar
  • Allows for the equivalent of carve outs for IP reasons
• Statement on the risk of immunogenicity for all therapeutic proteins
• Duty to update labeling for post marketing safety events
Areas of Industry Debate/Concern

- AbbVie Citizen Petition
  - Labeling *Must* State Biosimilar is not licensed for all indications (if applicable) and state that extrapolation was used when used
  - Labeling *Must* State Biosimilar is Not Interchangeable
  - A description of the data developed to support licensure of the biosimilar

- FDA denied the Citizen Petition and placed it in the Draft Labeling Guidance Docket
  - Will the adoption of an interchangeability identifier suffix for the proper name require both the reference product and the brand to change their proper name suffix to identify each of the as interchangeable?
Problems with the AbbVie Citizen Petition

- Labeling Requires Adequate Instructions for Use
- The BPCIA does not require the *same* or mandate *different* labeling for biosimilars
  - Silence means that Congress left it to the scientific expertise and discretion of FDA to ensure labeling provides adequate directions for use...
FDA Draft Guidance Finds that Mandatory Differential Labeling Would be Confusing

• Comparative Claims in a label require Substantial Evidence
• If there are “no clinically meaningful differences,” then any differences in labeling would, by definition, be misleading and confusing to physicians
• Differences in labeling that can be shown by a biosimilar applicant to be necessary to inform healthcare prescribers can be considered
• Differences that are not meaningful or necessary would be confusing and considered “misbranding” in the advertising context
Implications for Advertising and Promotion

- Use of Biosimilar Data that is not in the label?
  - Truthful?
  - Misleading?
  - Is it in the summary basis for approval?
  - Publications?

- Claims that biosimilars are not “identical” to the reference product?
  - Comparative claim?
  - Contrary to the substantial evidence in the approval
Interchangeable Biologics

- Should the label be identical?
- Should evidence of interchangeability be in the label?
- If not, can evidence of interchangeability be shared with physicians?
- Will interchangeability be a quality that can be promoted?
Unique Naming Creates a Tension with FDA Policy on Comparative Claims

- A unique biosimilar name could make a label misleading or confusing in several ways:
  - Does a unique name suggest a “clinically meaningful difference” when there is none?
    - Does the answer differ for non-interchangeable biosimilars vs interchangeable biologics?
  - If additional information has to be in the label for an interchangeable biologic, to what end?
    - Does a physician have to be involved in the substitution at the pharmacy?
    - Is it misleading or confusing to suggest such involvement is necessary?
  - If a non-meaningful structural or functional difference in a biosimilar requires a naming difference, will biologic manufacturing changes (brand or biosimilar) require similar labeling changes?
  - Is it false and misleading to suggest that a biosimilar poses safety concerns when a manufacturing change with similar differences may not have been tested to the same standard as the biosimilar?
Can Current Messaging Survive a Biosimilar or Interchangeable Biologic Approval?

• Will existing commercial messaging survive approval of a biosimilar or interchangeable biologic?

• Are they false and misleading?