BIOSIMILARS REGULATORY AND POLICY ROUNDUP
LIFE SCIENCES ACCOUNTING AND REPORTING CONGRESS
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Momenta Background

• Founded in 2001; IPO 2004
• Located in Cambridge, MA
• ~300 employees; >75% in scientific development
• Expertise in high-resolution analytics, biological characterization, and process engineering
• Current business areas:
  • Complex drug generics
  • Biosimilars and interchangeable biologics
  • Novel medicines
Momenta Portfolio

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

Technology for the characterization of complex biologic mixtures

Glatopa™
(glartiramer acetate injection)

Physicochemical Analytics

Control of Manufacturing

Biological Characterization
Advances in Science Have Made the Characterization of Biologics a Reality

High-resolution TEM image of IgG antibody; *Procedia Engineering* 36 (2012) 150 – 153

The oldest published image known to have been made with a microscope: bees by Francesco Stelluti, 1630.
Definition: Biosimilarity

Biosimilar or Biosimilarity means:

- that the biological product is **highly similar** to the reference product notwithstanding minor differences in clinically inactive components; and

- 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.
Definition: Interchangeability

Interchangeable or Interchangeability means:

- the biological product is biosimilar to the reference product;
- it can be expected to produce the same clinical result as the reference product in any given patient; and
- for a 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 product and its reference product is not greater than the risk of using the reference product without such alternation or switch.

Note: The interchangeable product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.
Development Framework: Comparative Analytical Characterization Continuum

- Cannot be biosimilar

- Similar
  - Needs additional information to determine if highly similar (e.g., additional analytical data, or other studies to determine if minor differences are “clinically inactive components”)

- Highly similar
  - Permits a selective and targeted approach to determine if biosimilar

- Highly similar with fingerprint-like similarity
  - Permits a more selective and targeted approach to determine if biosimilar
Biosimilar Development – Goal

- The goal is to demonstrate biosimilarity between the proposed product and a reference product.

- The goal is *not* to independently establish safety and effectiveness of the proposed product.
Highly Similar Analytical and PK/PD Data Assumes Lower Risk of Clinical Differences

Two approaches to demonstrate biosimilarity
Elimination of Residual Uncertainty via Thorough Characterization

- Thorough characterization, with additional trials if needed to address residual uncertainty
- Consistent with FDA pathway
Similarity is Shown Primarily Through Characterization

- **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.
Biosimilarity and Interchangeability

Conventional Biosimilar

- A conventionally produced biosimilar will not reproduce the entire complexity of the Brand product
- Clinical trials will demonstrate the differences have no clinical meaningful differences

Interchangeable Biologic

- New technology allows for fuller product characterization, identification of key product quality attributes and technologies to control for PQAs during process development.
- The higher degree of PQA similarity to the Brand reduces the likelihood of failure in development or commercialization and allows for targeted clinical studies
- The potential for substitutability exists with thorough characterization and reproduction
FDA Guidance Recognizes that Science Can Demonstrate Biosimilarity and Interchangeability

“We are using a weight of the evidence method that places much emphasis on the physicochemical comparisons that are done and the functional comparisons, with clinical evidence being seen as more confirmatory...”

– Janet Woodcock, Ph.D.
From DIA Biosimilars 2012 Keynote Address

“Analytical data as foundation ... before proceeding with animal and clinical studies, generate sufficient structural and functional data....”

– Leah Christl, Ph.D.
From DIA Biosimilars 2013 Keynote Address

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Analytical Data As Foundation

- Understand the molecule and function
  - Identify critical quality attributes and clinically active components
  - Have support for assessment and approach
- **Before** proceeding with animal and clinical studies, generate **sufficient** analytical (structural and functional) data to:
  - Characterize reference product variability and product quality characteristics
  - Characterize proposed biosimilar product quality characteristics
  - Identify and evaluate impact of differences
    - Don’t ignore or sweep under the carpet
    - Must be **highly similar and** no clinically meaningful differences
Originator Biologics are not Exact Copies of Themselves

Acceptable changes in quality attributes of glycosylated biopharmaceuticals

Relative content of individual isoforms in Aranesp pre-change (18 batches) and post-change (4 batches).

Antibody-dependent cell-mediated cytotoxicity (ADCC) potency in Rituxan/Mabthera pre-change (11 batches) and post-change (8 batches).
Originator Biologics are not Exact Copies of Themselves

Acceptable changes in quality attributes of glycosylated biopharmaceuticals

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Martin Schiesl, Thomas Stangler, Claudia Torella, Tadej Čepeljnik, Hansjörg Toll & Roger Grau
Sandoz Biopharmaceuticals, Kundl, Austria.

a) Relative amounts of basic variants of pre-change (n=6) and post-change (n=6) batches of Enbrel.
b) Relative amounts of the G2F glycan of the pre-change (n=25) and post-change (n=9) batches of Enbrel.
“Biosimilar” or “Biodifferent”? 

In order to maximize benefits of the pathway, as policies and laws are developed and implemented, should we be emphasizing similarities or differences?

Safety is a priority for the development of all medicines, but biologics raise safety considerations above and beyond those of chemical drugs. This is because biologics are more structurally complex medicines than chemical drugs, and even slight changes in their manufacture can cause undetected changes in the biological composition of the product. These changes can in turn affect the safety and effectiveness of the product in patients. The EPREX example provides a further rationale for not considering a follow-on product to be interchangeable with an innovative product.

“Unlike generic medicines where the active ingredients are identical, biosimilars are not likely to be identical to the originator biologic. Biosimilar development requires significant expertise, infrastructure and investment to demonstrate safety and equivalent efficacy and to ensure safe, reliable supply of therapies for patients.”
Why Innovative Biosimilar and Interchangeable Biologics Matter For Patient Access

- Biologics Treat a Variety of Diseases
- Brand Biologics are Expensive
  - 22 times greater than traditional drugs; $10,000 to >$100K /yr.
- Biologics are the Future of Medicine
  - 8 of top 10 drugs by 2016
- Price of Brand Biologics Keeps Growing
  - Spending growth from 2002 to 2007 was 16% for biologics, compared with 3.7% for drugs
- Interchangeability = Substitutability = Savings

"Interchangeability or substitution is the engine that drives generic competition. It is the reason why generic medicines have generated savings of $1.46 trillion over the past decade and $226 Billion in 2015."

http://www.gphaonline.org/media/generic-drug-savings-2016/index.html
Patient Need Already Drives the Demand for Biosimilar and Interchangeable Biologic Access

- In the US, cancer patients are twice as likely as the general population to go bankrupt a year after their diagnosis\(^1\)
- High deductible plans make many biologics unaffordable
- In Europe, almost \(\frac{1}{4}\) of 46 countries do not provide access to biologics for arthritis\(^2\)
- In Canada, children with juvenile idiopathic arthritis may not receive “standard” care because pediatric coverage for biologics is limited and inconsistent\(^3\)
- Only 50% of severe RA patients receive biologics across EU5, US and Japan\(^4\)

\(^1\)Cancer Diagnosis as a risk factor for personal bankruptcy. ASCO 2011.
\(^2\)EULAR 2012: Annual Congress of the European League Against Rheumatism
\(^3\)Access to biologic therapies in Canada for children with juvenile idiopathic arthritis. J.Rheum. September 2012
\(^4\)Stakeholder Insight: Rheumatoid Arthritis DMHC2592/ Published 09/2010
Economics are Driving Biosimilar Investment and Demand

“$114.7B on specialty medications — mostly biologics — in 2014. At that point, $4 out of every $10 the country spends on prescription drugs will be spent on these complex medications that are only used by 2% of the population.”

“The U.S. would save $250B between 2014 and 2024 ... based on the 11 existing biologic drugs that are the most likely candidates for biosimilars in the next 10 years.”

Source: Steve Miller, M.D., April 23, 2013, HEALTHCARE INSIGHTS, Express Scripts Lab

A recent European study determined eight EU countries could save approximately $40 billion by 2020 by utilizing biosimilars.
## A History of Debate on Policy – Barriers to 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&lt;br&gt;• Prevent/deter legislative pathway</td>
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<tr>
<td>Oppose Biosimilar Pathway – 2007-2010</td>
<td>• Biosimilars are unsafe even if possible&lt;br&gt;• Interchangeable biologics are impossible/different</td>
<td>• Prevent/deter pathway&lt;br&gt;• Incorporate legislative features that prevent/deter use of the pathway&lt;br&gt;• Mandatory clinical trials&lt;br&gt;• Complex IP exchange</td>
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<td>Influence FDA Guidance - 2011</td>
<td>• Same messages</td>
<td>• Emphasize differences (e.g., naming)&lt;br&gt;• Mandate unnecessary clinical trials&lt;br&gt;• Freeze scientific standards for similarity and interchangeability</td>
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<tr>
<td>AbbVie CP</td>
<td>• Same messages</td>
<td>• Delay biosimilars for 10 years</td>
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<td>Naming Campaign JnJ Citizen Petition</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>Restricted Access to Reference Products</td>
<td>• Biosimilar companies are irresponsible</td>
<td>• Prevents/delays initiation of development</td>
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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 brand and biosimilars 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?

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.”

Example from Guidance
replicamab-cznm
replicamab-hixf
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 \textit{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 are they not unique?
  • Unique non-proprietary names can
    • Suggest “meaningful differences” and confuse physicians and patients
    • Result in misattribution of adverse events to a biosimilar
    • 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
Which Pathway is Best? BLA, Biosimilar, Interchangeable or Biobetter

Breadth of Brand Patent Rights over Time (Years after Launch)

(Breadth of Brand Patent Rights over Time) (Years after Launch)
(Note: Patent Protection may vary for each product)
Financial Reporting Implications

- Update your 10K to disclose biosimilar business and competition
- Regulatory policies and litigation process is undergoing rapid change and evolution
- Review your FDA and global regulatory disclosure to capture the differences in regulatory review of biosimilars
- Review your reimbursement disclosure to capture the different reimbursement approaches and risks for your portfolio
- Review your intellectual property disclosure and legal disclosure to capture the potential for IP challenges, litigation and uncertainty regarding the these proceedings and litigation
- Consider whether your disclosure anticipates or estimates market entry and and appropriately considers the regulatory review timing, the litigation timing and the risk of a market launch given potential IP litigation risk
  - Can a brand post a bond to support an injunction?
  - Can a biosimilar company justify a launch at risk?
- Review your risk factors for changes due to biosimilar regulatory and litigation risks
Questions
Thank You