Ensuring Patient Safety and Avoiding Anti-Competitive Deterrents to Investment and Innovation in Biosimilars and Interchangeable Biologics

Bruce A. Leicher
Sr. Vice President and General Counsel
Momenta Pharmaceuticals Inc.
September 18, 2014
The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to the Drug Information Association, Inc. (“DIA”), its directors, officers, employees, volunteers, members, chapters, councils, Special Interest Area Communities or affiliates, Momenta Pharmaceuticals, Inc. or any organization with which the presenter is employed or affiliated.

These PowerPoint slides are the intellectual property of the individual presenter and are protected under the copyright laws of the United States of America and other countries. Used by permission. All rights reserved. Drug Information Association, DIA and DIA logo are registered trademarks or trademarks of Drug Information Association Inc. All other trademarks are the property of their respective owners.
Momenta Pharmaceuticals

• Biopharmaceutical company specializing in developing complex mixture therapeutic products
• Founded in 2001
• Expertise in high-resolution analytics, biological characterization and process engineering
• 275+ employees
• Broad pipeline of complex generics, follow-on-biologics, and novel drugs
• There is a history of political action to deter biosimilar innovation
• Substantial agreement exists on ensuring patient safety and physician awareness of biologic safety
• Differences have emerged on the tactics for achieving common goals
• The differences appear to be motivated by commercial competitive concerns
• State substitution legislation and naming policy should:
  – Promote the safe use of all biologics; and
  – Not focus on impeding affordable access to interchangeable biologics and biosimilar use
# A History of Opposition to Biosimilar Innovation and Competition

<table>
<thead>
<tr>
<th>Tactic</th>
<th>Message</th>
<th>Barriers to Competition</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIO CP - 2003</td>
<td>• Generic biologics are impossible</td>
<td>• Prevent regulatory approval</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Prevent/deter legislative pathway</td>
</tr>
<tr>
<td>Oppose Biosimilar Pathway – 2007-2010</td>
<td>• Biosimilars are unsafe even if possible</td>
<td>• Prevent/deter pathway</td>
</tr>
<tr>
<td></td>
<td>• Interchangeable biologics are impossible/different</td>
<td>• Incorporate legislative features that prevent/deter use of the pathway</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Mandatory clinical trials</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Complex IP exchange</td>
</tr>
<tr>
<td>Influence FDA Guidance - 2011</td>
<td>• Same messages</td>
<td>• Emphasize differences (e.g., naming)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Mandate unnecessary clinical trials</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Freeze scientific standards for similarity and interchangeability</td>
</tr>
<tr>
<td>AbbVie CP</td>
<td>• Same messages</td>
<td>• Delay biosimilars for 10 years</td>
</tr>
<tr>
<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>
</tr>
<tr>
<td>Restricted Access to Reference Products</td>
<td>• Biosimilar companies are irresponsible</td>
<td>• Prevents/delays initiation of development</td>
</tr>
</tbody>
</table>
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.”

In order to maximize benefits of the pathway, as policies and laws are developed and implemented, should we be emphasizing similarities or differences?
The State Substitution Campaign is the Next Tactic to Prevent and Restrict Competition from Interchangeable Biologics

• Interchangeable biologics were adopted and embraced in the BPCIA
• The opposition failed at the Federal level and now seeks to use the same anti-competitive messages to enact laws that will deter or prevent investment in interchangeable biologics
• The BPCIA is clear, and is even clearer than Hatch-Waxman, in that it expressly provides:

   “the [interchangeable] biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product” (emphasis added).

• Yet, the States are being asked, in effect, to join in a commercial marketing campaign to
  – Disparage interchangeable biologics
  – Impede substitution; and
  – Use notice restrictions to intervene and raise concern about FDA approved biologics
Legislation Against Biosimilars: Brand Company-supported Bills Were Appropriately Questioned

**Billions at Risk, Firms Lobby States to Limit Generics**
By ANDREW POLLACK

The biotechnology industry’s lobbying effort could blunt new competition to its products and reduce the savings anticipated in the federal health care overhaul.

**Battle over 'biosimilars'**
States shouldn't stand in the way of cheaper versions of biologic drugs the FDA deems safe.

**Editorial: Improper Efforts to Limit Competitive Drugs**
February 9, 2013

**Hamburg Defends Biosimilar Substitution, Says Efforts to Undermine Trust Are ‘Worrisome’**
ORLANDO — FDA Commissioner Margaret Hamburg defended the substitutability of interchangeable biosimilars, saying that attempts to undermine trust in the products are ‘’worrisome and represent a disservice to patients who could benefit from these lower-cost treatments.’’
Why is Substitution so Important?

• Substitution eliminates the need for sales and marketing to physicians and payers
• Impeding substitution would protect pricing and profits in a branded biosimilar market
• Substitution provides for the highest level of access and affordability to medicines after patents and exclusivity expire
• Substitution enables a return on investment for the substantial innovation needed to develop interchangeable biologics that match the reference product
Innovative Biosimilar and Interchangeable Biologics Matter For Patient Access to Lifesaving Medicines

- **Brand Biologics are Expensive**
  - The average daily cost of a brand name biologic product is approximately 22 times greater than a traditional drug.
  - Biologics can cost as much as $10,000 to several hundred thousand dollars per year.

- **Biologics are the Future of Medicine**
  - By 2016 it is predicted that eight of the top 10 products on the market will be biologics.

- **The Price of Brand Biologics Continues to Increase**
  - U.S. average annual spending growth from 2002 to 2007 was 16% for biologics, compared with 3.7% for drugs.

http://www.gphaonline.org/media/cms/General_Fact_Sheet_for_Biosimilars_FINAL.80913.pdf
Perhaps State Substitution Restrictions are Designed to Restrict Competition and Access, Not Improve Safety or Knowledge

- Restrictive notice provisions deliver a message that Interchangeable Biologics are “different” or “suspect” and give marketed products a competitive advantage
  - E.g., BIO appropriately opposes GMO labeling for just this reason
- Restrictive notice and recordkeeping burden pharmacists, deter substitution and promote branded biologics and branded biosimilars
  - Post-dispensing notice will trigger pre-authorization behavior by pharmacists
- Most physicians already have ready access to ePrescribing databases containing pharmacy dispensing records for their patients
  - Access is available for free from the National ePrescribing Safety Initiative
- Pharmacies have always maintained written or electronic records available upon request by a physician for comprehensive pharmacovigilance information
### Both Sides Put Patient Safety First

<table>
<thead>
<tr>
<th>Patient Safety Principles</th>
<th>Areas of Disagreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only interchangeable biologics can be substituted</td>
<td>Both sides agree</td>
</tr>
<tr>
<td>The physician should have the right to prescribe a particular brand</td>
<td>Both sides agree</td>
</tr>
<tr>
<td>The physician should have access to dispensing information to facilitate pharmacovigilance</td>
<td>Agree But</td>
</tr>
<tr>
<td>The patient should be notified by the pharmacist</td>
<td>Both sides Agree</td>
</tr>
<tr>
<td>The pharmacist should keep records of the substitution</td>
<td>Agree But</td>
</tr>
</tbody>
</table>
Do Substitution Restrictions and Special Notice Provisions Solve the Articulated Concerns?

• Articulated “Concerns”:
  – Interchangeable biologics are biosimilars and are not the “same” as the brand
    • But brand biologics are not the “same” either
  – Pharmacovigilance and safety events are not always contemporaneous with administration
    • Eprex case study

• Alternative Solutions Proposed
  – Affirmatively notify by phone, call, facsimile, interoperable health record, electronic record at the time of or near time of substitution
  – Maintain Electronic, interoperable, and/or written records of all dispensed products regardless of substitution

• Notification of Substitution Does not Solve the Concern
  – Incomplete solution
  – Does not address the stated problem of biologic variability
  – Creates barriers to effective pharmacovigilance and affordable competition
Patient Safety is Enhanced by Centralized Dispensing Records; Notice Does Not Work

A Dispensing Record Contains NDC Number, Manufacturer Name, and Dosage Form

Has notification permitted accurate AE attribution?
- Is the AE due to the interchangeable biologic… or the stopper change?
- Are other medicines also involved?
- Notice focuses attention on the wrong medicine
Patient Safety is Enhanced by Centralized Dispensing Records; Notice Impedes Pharmacovigilance

Has notification permitted accurate AE attribution?
- Is the AE due to the interchangeable biologic… or the stopper change?
- Are other medicines also involved?
- Notice goes to the wrong physician
Restrictive Legislation

A pharmacist may substitute a **biosimilar product** for a prescribed **biological product** only if... the pharmacist either verbally, in writing, or by facsimile, email or other electronic transmission and as soon as practicable but no later than **72 hours** after dispensing, except that such notification shall not be required for a prescription refill when the refilled biological product is the same as the product last dispensed by the pharmacist and the pharmacist retains a written record of the biosimilar substitution for a period of no less than **two years**.

Non-Restrictive Legislation

Within a reasonable time following the dispensing of a **biological product**, the dispensing pharmacist or the pharmacist’s designee shall communicate, or be available to communicate, to the prescriber the specific product provided to the patient, including the name of the product and the manufacturer. The communication shall be conveyed by making an entry in an interoperable electronic medical records system or in an electronic prescribing or records system or in a written pharmacy record that is accessible electronically, by telephone call, or by other means upon the request of the prescriber.
## How Do the Laws Measure Up?

<table>
<thead>
<tr>
<th>Patient Safety Principles</th>
<th>IN, PA and DE v. MA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only interchangeable biologics can be substituted</td>
<td>Both sides agree</td>
</tr>
<tr>
<td>The physician should have the right to prescribe a particular brand</td>
<td>Both sides agree</td>
</tr>
<tr>
<td>The physician should have access to dispensing information to facilitate pharmacovigilance</td>
<td>Agree But • In IN, PA and DE – Notification does not capture stated safety concerns about manufacturing changes or other issues for all biologics • In MA, pharmacy recordkeeping will track all dispensed biologics and ensure proper pharmacovigilance of AEs</td>
</tr>
<tr>
<td>The patient should be notified</td>
<td>Both sides Agree</td>
</tr>
<tr>
<td>The pharmacist should keep records of the substitution</td>
<td>Agree But • In IN, PA and DE – Notice is not required when there is no substitution facilitating pharmacovigilance errors • In MA (and nationwide), records are always kept and available on request avoiding misattribution and incomplete evaluation of AEs</td>
</tr>
</tbody>
</table>
Why Then the Push for Suboptimal Notification?

• Do telephone calls or facsimiles to a physician’s office provide a reliable method for informing physicians of all the biologics received by a patient?

• Is it because special notification
  – Impedes substitution?
  – Connects substitution with “safety concerns” – real or imagined?
  – Avoids a focus on brand or non-interchangeable biosimilars?
  – Provides a competitive advantage?
  – Is another tactic in the history of disparaging/preventing biosimilar competition?

• Would it not be better to rely on existing and new electronic records to capture all the dispensing data so that AEs can be fully investigated when necessary?
Can a Compromise Solution Be Found? – YES

• A uniform, non-restrictive record based approach will:
  – Facilitate patient safety
  – Provide physicians with a complete set of medical information
  – Avoid disparagement of biosimilars; and
  – Be consistent with federal law allowing for the substitution of interchangeable biologics without the intervention of a physician
Biosimilar and Interchangeable Biologic Non-Proprietary Naming is Part of the Same Commercial Campaign

- 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
- There is no defensible basis for different non-proprietary names other than to restrict competition
- Will there be different names for each manufacturing facility?
- Like state substitution restrictions, the effort to seek distinct non-proprietary names is primarily a commercial effort to make biosimilars and interchangeable products appear different to physicians and patients
- If successful, it will impair investment, innovation, and the competitive savings expected from biosimilars and interchangeable biologics
Pharmacovigilance Does not Justify Unique Names

• Brand products are sold interchangeably and have the same name despite:
  – Product drift
  – Manufacturing changes
  – Is the quality issue really with products that are not thoroughly tested to assure they are biosimilar or interchangeable?
    • Eprex
    • Heparin

• Competing brand products also share the same non-proprietary name, e.g.:
  – Kogenate antihemophilic factor (Recombinant) vs. Recombinate antihemophilic factor (recombinant)
  – Xyntha antihemophilic factor (Recombinant) plasma/albumin-free) vs. Advate antihemophilic factor (Recombinant) plasma/albumin-free)
  – Avonex Interferon Beta-1A vs. Rebif Interferon Beta-1A
Pharmacovigilance Does not Justify Unique Names

- Safety reporting could be impaired by balkanization of non-proprietary names.
- Rare signals across biosimilar products could be missed if brand and biosimilar product data are treated as unrelated and are used to differentiate products.
- Safety reporting is not dependent on non-proprietary names:
  - NDC number and its bar code is used to track and record products at the pharmacy and is unique to the product and manufacturing batch.
  - Manufacturer name is on the product.
- Alleged pharmacovigilance concerns relate to all medicines and pharmacovigilance generally, not biosimilars:
  - If there is a problem, fix it for all medicines, not just biosimilars.
  - The innovative MedWatcher smartphone app is available and should be re-launched.
  - ePrescribing also records NDC number which is the most useful identifier.
Conclusions

- State legislation should use pharmacy records, not substitution notice to protect patient safety
- Biosimilars and interchangeable biologics should use the same non-proprietary name to focus identification through unique NDC numbers and to avoid misattribution and balkanization of rare safety signals
- HHS, FDA, CMS, and the FTC should issue guidance that:
  - Restrictive notification statutes are inconsistent with the substitution provisions of the BPCIA; and
  - Biosimilars and interchangeable biologics should share the same name to focus pharmacovigilance on all relevant products
Thank you
Back Up Materials
Innovation is the Best way to Create Access to Safe, Affordable Interchangeable Biologics

Standard Biosimilar

<table>
<thead>
<tr>
<th>Brand</th>
<th>BioSimilar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same</td>
<td>Different</td>
</tr>
</tbody>
</table>

Momenta Follow-on-Biologic

<table>
<thead>
<tr>
<th>Brand</th>
<th>BioSimilar</th>
<th>Interchangeable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same</td>
<td>Different</td>
<td>Same</td>
</tr>
</tbody>
</table>

Remove uncertainty. Qualify differences. Demonstrate equivalence.

- Thorough Product Characterization
- Manufacturing Process Design
- Product Control and Quality

No Need for Reliance on Brand Trade Secrets

- Increased POS for approval
- Targeted clinical requirements
- Opportunity for interchangeability
- Improved commercial differentiation
Approval Standards are Rigorous

• Biosimilars must:
  – Be Highly Similar to the Reference Product
  – Not have clinically meaningful differences
• Interchangeable Biologics must also:
  – Be expected to perform the same in any given patient
  – Have the same risk associated with switching as the reference product
  – And Most Importantly:
  – Are By Statutory Definition, Substitutable at the Pharmacy without the Intervention of a Physician

Approach Drives Understanding of what Biologics Are: The Product is not Merely the Process
“Although it [Momenta’s generic Lovenox] is … regulated under [the Food, Drug and Cosmetic Act], it was perhaps one of the most complex reviews imaginable, and it’s a superb example of how physiochemical studies could let us approve a generic drug,” Sherman maintained. “We still needed [non-clinical] immunogenicity studies, so we still needed some information, but that’s about as complex probably as we expect that our average biosimilar application is going to be, and I think it’s a great illustration of the current state of the science and what we hope to be able to do with these applications.”

– Rachel Sherman MD, Director of the Office of Medical Policy, CDER
Biosimilars in rheumatology: the wind of change

Christian K Schneider

...no batch of any reference product is ‘identical’ to the previous one—‘non-identicality’ is a normal feature of biotechnology that has to be controlled by tight specifications of critical product attributes, within current technical and scientific limitations (inherent variability). The ‘art’ for a biosimilar is to demonstrate that the biosimilar is as close as possible to its reference product in all relevant functional and structural aspects.

...What is often not mentioned is that originator mAbs/cepts have undergone changes after their approval—this is what regulators call the ‘life cycle’ of a medicine.
A Biologic has Several Names and Identifiers

- Brand Name
- INN
- Manufacturer
- National Drug Code (NDC)
- Lot number

Identifies

Product
Active substance
Company
Company, product, package
Lot

All trademarks are the property of their respective owners.