



Submitted in Electronic Form

February 28, 2014

Federal Trade Commission  
Office of the Secretary  
Room H-113 (Annex J)  
600 Pennsylvania Ave, NW  
Washington, DC 20580

Re: Public Workshop: Follow-On Biologics: Impact of Recent Legislative and Regulatory Naming Proposals on Competition: Project No. P131208

Momenta Pharmaceuticals, Inc. (“Momenta”) wishes to thank the Federal Trade Commission (“FTC”) and its staff for the opportunity to participate in the February 4, 2014 Roundtable on Follow-On Biologic Drugs (the “Workshop”). There are very important immediate and long term pro-competitive benefits that can and will result from the implementation of the new Section 351(k) abbreviated biosimilar regulatory approval pathway under the Biologics Price Competition and Innovation Act (“BPCIA”). However, several key benefits are now at risk from state law substitution restriction and differential naming proposals. We support the FTC’s initiative to seek public comment and participation, and welcome this opportunity for open dialogue. We appreciate the opportunity to share our perspective in greater detail. As discussed at the Workshop, Momenta believes that:

- Biosimilar and interchangeable biologic policy should be driven and measured by how it:
  - Promotes innovation and attracts investment in delivering safe, effective and affordable biologics
  - Addresses patient needs (including access) and patient safety
  - Avoids using the least innovative and most anti-competitive solutions to achieve these important objectives.
- The opposition to biosimilar and interchangeable biologic competition have much to lose financially when patents and exclusivity expire for a brand product
  - Financial loss and risk is what really motivates the proposals for state substitution restrictions and naming barriers to biosimilar and interchangeable biologic competition
  - State substitution restrictions and differential naming will create barriers to investment in the innovation necessary to provide access to safe, effective and affordable biologics

- The loss of competition will decrease the incentive for brand companies to innovate the next generation of new cures if patent or exclusivity profits continue after expiration or loss of exclusivity
- The FTC should therefore encourage the FDA or HHS to adopt a policy stating that:
  - State substitution restrictions are an unlawful conflict with Section 351(i) of the BPCIA; and
  - The benefits of innovation already underway from ePrescribing, the Sentinel Initiative and other programs, and the confusion that naming differences would cause, mean that biosimilar and interchangeable biologics should share the same non-proprietary name

At the FTC Follow-On Biologics Roundtable in 2008, Momenta provided evidence to demonstrate how the opportunity to develop generic biologics (now referred to as interchangeable biologics) would spur innovation and benefit consumers.<sup>1</sup> The inclusion of an interchangeable biologics designation under Section 351(k)(4) along with explicit authority for the FDA to consider innovative science and exercise discretion to waive clinical and other development requirements has made it possible to reduce development costs and finance development of affordable biosimilars. Interchangeability is competitively critical because under 351(i):

...the [Interchangeable Biologic] may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.

The BPCIA also explicitly recognizes that an interchangeable biologic is not a “new active ingredient” as a result of this additional approval requirement, while a non-interchangeable biosimilar is considered a “new active ingredient.”<sup>2</sup> This is why an interchangeable biologic is substitutable and switchable. Accordingly, interchangeable biologics should not be subject to additional requirements that would trigger physician intervention (requirements that were contemplated for non-interchangeable biosimilars such as physician notice and pre-authorization).

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<sup>1</sup> See Comments of Momenta Pharmaceutical, Inc., FTC Roundtable on Follow-On Biologics, December 22, 2008. <http://www.ftc.gov/news-events/events-calendar/2008/11/emerging-health-care-competition-and-consumer-issues> .

<sup>2</sup> Section 351(n) of the BPCIA, for example, only applies the “new active ingredient” special studies requirement under Section 505B to non-interchangeable biosimilar biologic products, as follows:

- (1) Non-Interchangeable Biosimilar Biologic Product. -- A biological product that is biosimilar to a reference product under section 351...that the Secretary *has not* determined to meet the standards described in subsection (k)(4) of such section for interchangeability with the reference product, *shall be considered to have a new active ingredient* under this section.
- (2) Interchangeable Biosimilar Biologic Product.—A biologic product that is interchangeable with a reference product under section 351...*shall not be considered to have new active ingredient* under this section.

Thoroughly characterizing and understanding biologics and engineering the process controls to assure biosimilarity and interchangeability is no longer “impossible,” but involves difficult and costly innovation. Companies like Momenta have relied on the opportunity created by the Section 351(k) pathway in making the decision to invest. This kind of innovation enhances the level of understanding of all biologics, and it makes affordable biologics possible through a reduction in clinical trial requirements and related development, commercialization and marketing costs. Consumers will benefit from the potential for improved access to both higher quality and more affordable products. If the opportunity for substitution at the pharmacy is impaired by state law restrictions, or by naming requirements, these barriers would then have to be overcome by the use of branding and marketing. This, in turn, would necessitate scientifically unwarranted, expensive clinical trials to generate marketing data to arm and employ a sales force. Collectively, the incentive to invest and innovate interchangeable biologics as envisioned by the BPCIA would be seriously eroded by these barriers to entry.

Our comments focus on three key areas:

- **Historical Context:** There is a substantial history of opposition to biosimilars, and in particular to interchangeable biologics. These efforts are to be expected given the serious competitive alternative created by these products to high priced biologics -- products that are at the peak of their annual revenues when patent rights expire and, when first developed, did not envision the innovative science that would make biosimilar and interchangeable biologic competition a reality.
- **State Substitution Restrictions:** The battle to prevent substitution of generic biologics was lost at the federal level with the enactment of the interchangeability designation under Section 351(k). Historical opposition has shifted to the States to implement restrictions on substitution. Recently, this effort to restrict interchangeable biologic competition has also been supported by some biosimilar companies seeking to protect their future “marketed” biosimilar sales from interchangeable competition. Notably, many of these same companies also develop and market “innovator” biologics that they are also trying to protect from competition. In addition, a key secondary objective of these state substitution laws is to label interchangeable biologics as “different” much in the same way that biosimilars are “claimed” to be different to deter substitution, in order to influence prescribers and make marketing and sales activities a barrier to interchangeable biologic market entry. If this secondary objective succeeds, the costs of unnecessary clinical trials would render interchangeable biologics significantly less competitive or non-competitive due to their innovation costs.
- **Naming Impediments:** Biosimilar naming is an additional tactic being employed by opponents to biosimilars in their advocacy at the FDA and global naming authorities. Their objective is to make biosimilars and interchangeable biologics look different to physicians than reference products and erect barriers to market entry. Differences are used to raise fears and disparage biosimilars and interchangeable biologics. Different names are used to suggest they may not have been demonstrated to be as safe and effective as the reference brand product, when in fact the FDA must determine they have no meaningful clinical differences to the reference product, and for interchangeable biologics, are substitutable and switchable without the need for physician intervention.

A different name also means that every time a physician is asked to write a prescription for a biosimilar, a message of difference is delivered through its name – a message that would be unsupported by data and could not be made in promotional material after an FDA finding of biosimilarity or interchangeability. The argument that post-marketing pharmacovigilance requires biosimilars to have different names is misplaced. The pharmacovigilance concerns that have been raised exist for all products and are best solved by the use of innovative tools, and by a pro-competitive approach for all products. Every product needs to be tracked by lot number and manufacturer to capture quality defects, not just biosimilars. This information is already stored by pharmacists and is available to physicians nationwide electronically or by phone for pharmacovigilance needs. At the same time, differential naming also creates a risk of balkanization of rare safety events by suggesting reference product and biosimilar adverse events may not be related and could interfere with detection of rare events, rather than enhance it.

As the facts and motives are sifted, it becomes increasingly clear that the state substitution restrictions and naming proposals are the current wave of tactics being employed to deter or prevent effective competition from more affordable biosimilar and interchangeable biologic products.

1. Historical lobbying and regulatory advocacy demonstrates that the real motive for state substitution restrictions and differential naming is to entrench barriers to competition into the legal and regulatory pathway and to protect branded product market share from innovation of safe and affordable biosimilars and interchangeable biologics.

There is a well-documented history of lobbying efforts to enact laws and regulations to restrict competition.<sup>3</sup> In 2003, the anti-competitive message was most direct. E.g., There must not be biosimilars because generic biologics are impossible, biologics can only be defined by a manufacturing process, not by the product, and biologics are impossible to characterize and replicate. These arguments continue to exist and underlie the current anti-competitive proposals. For example, based on these arguments, the

A Long Established Campaign Against Biosimilar Innovation and Competition		
Tactic	Message	Barriers to Competition
BIO CP - 2003	<ul style="list-style-type: none"> <li>• Generic Biologics are Impossible</li> </ul>	<ul style="list-style-type: none"> <li>• Prevent Regulatory Approval</li> <li>• Prevent/Deter Legislative pathway</li> </ul>
Oppose Biosimilar Pathway – 2007-2010	<ul style="list-style-type: none"> <li>• Biosimilars are unsafe even if possible</li> <li>• Interchangeable biologics are impossible/different</li> </ul>	<ul style="list-style-type: none"> <li>• Prevent/Deter pathway</li> <li>• Incorporate legislative features that prevent/deter use of the pathway               <ul style="list-style-type: none"> <li>• Mandatory Clinical Trials</li> <li>• Complex IP exchange</li> </ul> </li> </ul>
Influence FDA Guidance - 2011	<ul style="list-style-type: none"> <li>• Same messages</li> </ul>	<ul style="list-style-type: none"> <li>• Emphasize differences (Eg. Naming)</li> <li>• Mandate Unnecessary Clinical trials</li> <li>• Freeze scientific standards for similarity and interchangeability</li> </ul>
Abbvie CP	<ul style="list-style-type: none"> <li>• Same messages</li> </ul>	<ul style="list-style-type: none"> <li>• Delay Biosimilars for 10 years</li> </ul>
Naming Campaign JnJ Citizen Petition	<ul style="list-style-type: none"> <li>• Biosimilars are different and raise safety concerns</li> </ul>	<ul style="list-style-type: none"> <li>• Amplifies anti-biosimilar commercial campaign with providers, payors, patients and regulators</li> </ul>
Restricted Access to Reference Products	<ul style="list-style-type: none"> <li>• Biosimilar companies are irresponsible</li> </ul>	<ul style="list-style-type: none"> <li>• Prevents/Delays initiation of development</li> </ul>

<sup>3</sup> W. Nicholson Price II, Academic Fellow, Petrie-Flom Center for Health Law Policy, Biotechnology and Bioethics, Harvard Law School, recently did a study of pharmaceutical CMC innovation and found that regulatory barriers and calcification may be the principal cause of the absence of innovation in quality by design in pharmaceutical manufacturing; the area where biosimilar and interchangeable biologics companies are most innovative. Price, Making Do in Making Drugs: Innovation Policy and Pharmaceutical Manufacturing (2013); <http://ssrn.com/abstract=2311682>. It is not surprising that industry seeks to enact into law and regulation limits on innovation to impede competition, particularly in the biosimilars field.

Biotechnology Industry Organization (BIO) filed a Citizen Petition with the FDA seeking to ensure that the FDA not approve any generic biologics or biosimilars.<sup>4</sup> In the 2003 CP, BIO cited a 1999 FDA Guidance for Industry: Applications Covered by Section 505(b)(2) and challenged its “suggestion” of the “possibility of follow-on approvals” under an abbreviated regulatory pathway.<sup>5</sup> As a basis for 2003 CP, it stated:

Current science demonstrates that there can be no abbreviated approach to the approval of therapeutic proteins, whether licensed as biological products or approved as new drugs. There are significant differences between therapeutic protein products and “chemical drugs” – in size, complexity, and heterogeneity – and each manufacturer must provide its own full complement of original data....

Patient Safety is the primary concern when discussing proposals to reduce product testing. BIO is, in particular, concerned that significant risks to patient safety would arise if biologically derived products were to be approved based on less than a full complement of original data concerning each manufacturer’s product. In addition, BIO is concerned that any safety problems that could develop as a result of such approvals could undermine the confidence of physicians and patients in biologically derived products.

These two key advocacy messages have not changed in over 10 years, but rather have been re-packaged and reissued in different forms as innovative science demonstrates their obsolescence. Scientific innovation, in our view, no longer prevents biosimilar and interchangeable biologic competition. We must not tolerate the enactment of state laws and advocating rules and policies whose purpose is to achieve the same anti-competitive objective. These messages assume that (A) innovation in characterizing proteins is impossible, and (B) the product will always be defined solely by the process. They are designed solely to raise fears and concerns. Ultimately, the 2003 CP failed in that the FDA approved an application for Omnitrope (somatotropin [rDNA origin] for injection) under Section 505(b)(2) based on an abbreviated application.<sup>6</sup>

In the years following approval of Omnitrope, the legislative campaign to authorize the FDA to approve follow-on biologics began in earnest, leading to a number of proposed bills in the House and the Senate. The various bills ranged in diversity from bills authorizing approval of generic biologics, to bills authorizing only the approval of biosimilars based on mandatory clinical trials providing originator-like data, to the final Senate HELP draft enacted as the BPCIA which contemplates approval of biosimilars as well as interchangeable biologics. Throughout the legislative debate, these same messages were asserted by opponents to biosimilar competition while in parallel innovation continued by potential new entrants in this market.

Despite the assertion that biologics could not be thoroughly characterized, understood and replicated, Congress had the wisdom not to legislate a ceiling on innovation and provided the FDA with the scientific discretion to vary the development requirements for applicants based on

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<sup>4</sup> BIO Citizen Petition: Follow-On Therapeutic Proteins (April 23, 2003) , Docket No. 03P-0176 (the” 2003 CP”).

<sup>5</sup> 2003 CP at 2.

<sup>6</sup> Letter from the Director, Center for Drug Evaluation and Research to Petitioners (May 30, 2006); Docket Nos. 2004P-0231/CP1 and SUP1, 2003P-0176/CP1 and EMC1; and 2004N-0355.

an applicant's ability to demonstrate its understanding and replication of the reference product.<sup>7</sup> This created a powerful market incentive for companies like Momenta to invest in innovative technology to develop biosimilars and created a reward (i.e., abbreviated development) for this innovation. In addition, Congress enacted a separate designation for interchangeable products, to create an incentive to invest in development if interchangeable biologics that could be substituted and switched at the pharmacy without the need for physician intervention.<sup>8</sup>

The enactment of the BPCIA was a breakthrough moment, and one that is leading to pro-competitive, disruptive innovation. Yet undeterred, the opponents of biosimilars and interchangeable biologics continued to make the same arguments to the FDA during its development of guidance documents. In comments filed in 2010 before the FDA, for example, BIO's major message appeared designed to make the pathway too difficult and expensive to use by erecting barriers to innovation and competition. The messages included:

- Patients do not have to accept greater risks or uncertainties in using a biosimilar than an innovator's product. Accordingly, approval of biosimilars must be based on the same rigorous standards of safety, purity, and potency applied by FDA for the approval of innovator biotechnology products.
- Clinical trial evidence and data are fundamental for evaluating and demonstrating the safety and effectiveness of a biosimilar, and must be conducted on a product- by-product basis. In particular, immunogenicity testing is necessary to avoid putting patients at risk of adverse effects from immune reactions.
- Biosimilars must be properly evaluated through post-marketing surveillance and post-marketing clinical studies as needed.
- Biosimilars should be assigned a non-proprietary name readily distinguishable from that of the innovator's version of the product. Assigning the same name to a product that are not the same would be confusing and misleading to patients, physicians, and pharmacists, could result in inadvertent substitution of the products, and would make it difficult to quickly trace and address adverse events that may be attributable to either the innovator or biosimilar product.<sup>9</sup>

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<sup>7</sup> Section 351(k) (2)(A)(ii) provides in relevant part, "The Secretary may determine, in the Secretary's discretion, that an element described in clause (i)(I) [analytical, animal, and clinical studies] is unnecessary in an application submitted under this subsection."

<sup>8</sup> Sections 351 (i)(3) and 351(k)(2)(B) and 351(k)(4).

<sup>9</sup> The opposition understands the effect labelling of biosimilars with a different name would achieve. For when engaging to oppose state legislation that would require labelling or notice regarding genetically modified food, Jim Greenwood, President and CEO of the Biotechnology Industry Organization (BIO), issued the following statement to the press on November 23, 2013:

Just like 27 million voters in California and Oregon, Washington voters saw how this burdensome and deceptive labeling scheme would have created more state bureaucracy, imposed new costs and burdens on local farmers and businesses, and increased food prices for Washington families.

Food labels should convey valuable and accurate information to consumers. Mandatory initiatives to label all foods containing genetically modified ingredients would only serve to confuse consumers and raise food prices without any additional benefits.

- Prescribers are involved in decisions to switch among biological products.<sup>10</sup>

Again, these are messages that assumed by implication that the FDA would not reliably perform its obligations (code words for biosimilars are not really similar or safe and effective), and that clinical trials and originator data were essential for biosimilar approval. Note that interchangeable biologics are not even in the message points because they were still viewed as inconceivable. Thus, opponents argue that a physician must always be involved in the decision to switch among products, and all biosimilars must receive a different name. Immunogenicity is highlighted to amplify the purported patient safety risks, and by implication, an abbreviated approval raises “concerns” as well. In the detailed comments, a whole section is devoted to documenting patient safety and pharmacovigilance “concerns.”<sup>11</sup> Guilt by association with reference product safety concerns seems to be a consistently used argument of choice.

The most frequently cited concerns, however, involve adverse events associated with manufacturing changes to reference products. The comments are silent though about the fact that innovation in the science of understanding the characteristics of biologics may be the more appropriate and innovative solution for addressing these concerns for all biologics and that the type of innovation that would be promoted by the new biosimilar pathway may be the best means to solve the historic problem with biologic quality control associated with product drift, process changes and manufacturing variability. The ability to thoroughly characterize biologics and screen them for defects before delivery to patients would significantly reduce the risk of harm at its source by enabling control of manufacturing more effectively, rather than relying on post-marketing monitoring to catch problems after patients are injured. Because historically reference products relied on “the product is the process”, the incentives to invest in the science that could thoroughly characterize each biologic did not exist and was not believed feasible or possible. Much has been changed by the incentive of the 351(k) pathway to invest and innovate in this capability. Our view then, and today, is that the emphasis of the opposition on these types of arguments is messaging-based. If repeated often enough, it would become dogma and help ensure that if biosimilars, or perhaps even interchangeable biologics were ever approved, that the prevailing view would be they really are different, that they are too difficult to control, and that the risk of their use was not worth the savings. Moreover, the objective was also to

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We should ask why physicians, consumers and pharmacists are not also negatively impacted by the stigmatization of substitution restrictions and special naming requirements in the same way that GMO labelling creates disinformation about GMO foods.

<sup>10</sup> Letter from BIO to FDA (December 23, 2010); Docket FDA-2010-N-0477 at page 2.

<sup>11</sup> Id. at pages 17-19

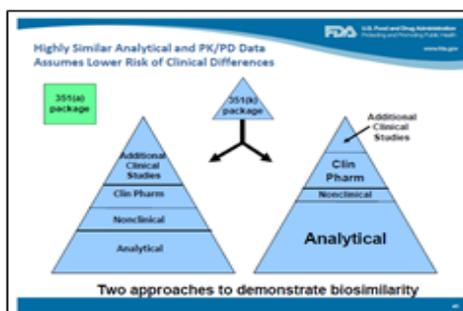
require large and extensive clinical requirements that would make their development financially unattractive. These unjustified burdensome requirements would deter or prevent the use of abbreviated approvals that could lead to more affordable products that are just as safe and effective as the reference products. The irony is that the very innovation that would be stifled is directed to preventing the risk opponents are seeking to detect but not necessarily avoid in the first instance.<sup>12</sup> The FDA considered these comments, and considered the prevailing science, and adopted draft biosimilar guidance documents in 2011.<sup>13</sup> In its guidance documents the FDA reaffirmed the innovation objectives of the BPCIA and adopted a flexible scientific approach. The approach was discussed by Emily Shacter at the Workshop<sup>14</sup> and is summarized in this slide included in Momenta's presentation.

## The FDA Spurs Investment by Promoting Innovation

### 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



<sup>12</sup> Perhaps the best example of this type of innovation is Momenta's experience with generic enoxaparin. Enoxaparin is made from heparin that in turn is made in cells like a biologic. It was believed by the brand manufacturer that like a biologic, enoxaparin could only be defined by a manufacturing process and that it was impossible to thoroughly characterize enoxaparin and reverse engineer its manufacturing process to prove sameness. FDA Response to Citizen Petition of Aventis (sanofi), July 23, 2010. <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM220083.pdf> In the response, the FDA determined it was possible to prove sameness based on thorough characterization. Id. In the course of thoroughly characterizing enoxaparin as a generic, Momenta needed to determine what the active ingredients were as well as the inactive ingredients and develop a thorough understanding of what should and should not be present. A clear benefit of the innovation involved in conducting this research and development was the ability to also use this technology to test blinded samples of heparin for contaminants and this aided the FDA in resolving the safety problem associated with contaminated heparin imported from China. The brand companies that relied on the "product is the process" were not able through ordinary means to detect the contaminant putting patients at risk. See Sasisekharan et. al., Contaminated Heparin Associated with Adverse Clinical Events and Activation of the Contact System, 358 N. Engl. J. Med. 2457-67 (June 5, 2008). The EPREX adverse events that presented themselves with biologics from manufacturing changes might have been detected following a manufacturing change if this kind of technological innovation in analytical science had been conducted to develop a biosimilar to that product. If the opportunity to pursue of abbreviated clinical trials and interchangeability has barriers, it is less likely that this kind of innovation will occur.

<sup>13</sup> 77 FR 8883-8886 (February 15, 2011).

<sup>14</sup> Statement of Emily Shacter at the Workshop.

## The Experience with Generic Lovenox is Relevant to the Development of Biosimilars



The NEW ENGLAND JOURNAL of MEDICINE  
Perspective  
AUGUST 4, 2013  
Developing the Nation's Biosimilars Program  
Steven Kozlowski, M.D., Janet Woodcock, M.D., Karen Midhun, M.D., and Rachel Behman Sherman, M.D., M.P.H.

### PERSPECTIVE

Scientific considerations in the review and approval of generic enoxaparin in the United States

Sun Lee<sup>1</sup>, Andre Raw<sup>1</sup>, Lawrence Yu<sup>1</sup>, Robert Lionberger<sup>1</sup>, Nalini Yu<sup>1</sup>, Daniela Vertheby<sup>1</sup>, Amy Rosenberg<sup>1</sup>, Steve Kozlowski<sup>1</sup>, Keith Webber<sup>2</sup> & Janet Woodcock<sup>2</sup>

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"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



Friday, February 10, 2012

Biosimilars: Similarities to Enoxaparin and the Elephant in the Room

MOMENTA

targeted and reduced. The use of analytical science may be the most discriminating means for identifying structural and functional differences. In November 2013, at the Drug Industry Association Meeting, Leah Christl, Ph.D., Associate Director for Therapeutic Biologics on the OND Therapeutic Biologic and Biosimilars Team, provided a key update on the FDA's activities and on recent biosimilar applicant activity. She shared the following slides to make the point that applicants need to focus on demonstrating biosimilarity, and that clinical trials cannot demonstrate similarity in the first instance but should be targeted to resolving any residual uncertainty that remains after a thorough characterization of the reference brand biologic and the biosimilar development candidate and not to re-proving safety and efficacy:

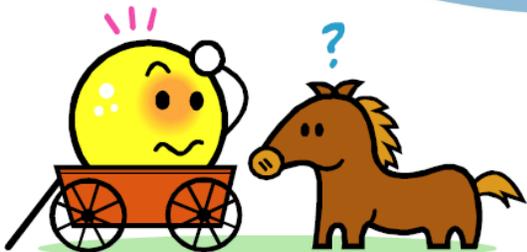
Dr. Christl emphasized in her November 2013 presentation that one could not use clinical trials to test biosimilarity into a product, because clinical trials are not the most effective means for determining product differences. This was a clear rejection of the anti-innovative policy advocated in comments by opponents to the pathway. More importantly, she made the point that applicants that were taking a clinical trial approach to demonstrating biosimilarity without first proving sufficient biosimilarity through non-clinical means were

The FDA also recognized in developing biosimilar guidance that its experience with generic enoxaparin demonstrated that this type of innovation is possible and should be encouraged. The clear import of the FDA's scientific findings as expressed in its policy was and remains that the science is evolving, and that it is now possible to thoroughly characterize biologics. As a result of the innovation in this developing field, it is increasingly likely that clinical trials, which may be the costliest part of biologic development, can now be

## Key Concept #7: Comparative Clinical Study

- The nature and scope of the comparative clinical studies will depend on the extent of residual uncertainty about the biosimilarity of the two products **after** conducting structural and functional characterization and, where relevant, animal studies.
- As a scientific matter, a comparative clinical study will be necessary to support a demonstration of biosimilarity if there are **residual uncertainties** about whether there are clinically meaningful differences between the proposed and reference products based on structural and functional characterization, animal testing, human PK and PD data, and clinical immunogenicity assessment.

putting the “Cart Before the Horse” and were advised to do the appropriate non-clinical characterization testing so that biosimilarity was demonstrated and clinical testing could be targeted to resolving uncertainty.



The illustration shows a yellow character with a lightbulb-like head sitting in a wooden cart, being pulled by a brown horse. The character has a question mark above its head, and the horse has a question mark above its head. The text below reads: "Lessons learned: Put your horse first..."

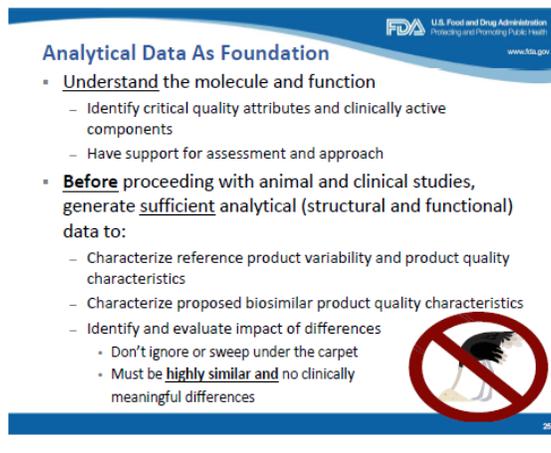
FDA U.S. Food and Drug Administration  
Protecting and Promoting Public Health  
www.fda.gov

Lessons learned: Put  
your horse first...

She specifically pointed out that applicants should not propose traditional “phase 3” trials, but rather trials designed to demonstrate biosimilarity. This was a clear change in direction from prior approaches in Europe where products had demonstrated biosimilarity using large Phase 3 type trials, and signaled that innovation in the science of characterization was and would guide FDA scientific policy.

The take away point, as Dr. Shacter discussed at the Workshop, is that there has been a substantial advance in the opportunity to thoroughly characterize biologics. The reason opponents to the pathway advocated historically for mandatory large scale safety and efficacy trials is now being exposed. The opposition may have retained credibility in the early years of the debate because there were open questions about where innovation would lead. Now, it is increasingly clear that unless clinical trials are targeted to resolving uncertainty, their primary impact would be to erect a barrier to competition by increasing biosimilar and interchangeable biologic development costs. It would also create a marketplace where clinical data would need to be used to sell a biosimilar or interchangeable biologic further increasing the cost and undermining the value and return on investment in an interchangeability designation.

The history of anti-biosimilar advocacy teaches that each tactic was designed to drive the point of competition away from substitution and into a branded-product, marketing-driven marketplace. While the initial campaign asserted that biosimilars and interchangeable biologics were impossible, and then evolved into arguments regarding mandating guidance and the need



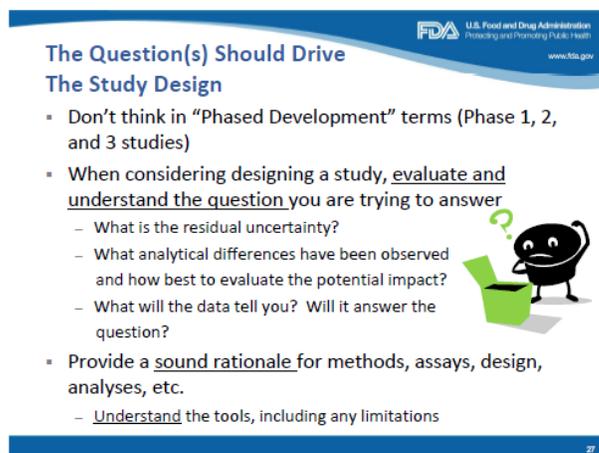
The slide is titled "Analytical Data As Foundation" and contains a bulleted list of points. A red prohibition sign is placed over a small cartoon character.

FDA U.S. Food and Drug Administration  
Protecting and Promoting Public Health  
www.fda.gov

**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

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The slide is titled "The Question(s) Should Drive The Study Design" and contains a bulleted list of points. A cartoon character is shown looking into a green box with a question mark above its head.

FDA U.S. Food and Drug Administration  
Protecting and Promoting Public Health  
www.fda.gov

**The Question(s) Should Drive  
The Study Design**

- Don't think in “Phased Development” terms (Phase 1, 2, and 3 studies)
- When considering designing a study, **evaluate and understand the question** you are trying to answer
  - What is the residual uncertainty?
  - What analytical differences have been observed and how best to evaluate the potential impact?
  - What will the data tell you? Will it answer the question?
- Provide a **sound rationale** for methods, assays, design, analyses, etc.
  - **Understand** the tools, including any limitations

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for originator data from large safety and efficacy trials, we believe that the opponents have always understood that innovation was possible. Their major goal, however, was to engage with physicians, patients and the political and regulatory communities to raise “concerns” that would facilitate the creation of a legal and regulatory scheme that favored marketed products and prevented or made difficult generic-like substitution.<sup>15</sup> In our 2008 comments to the FTC following the November 21, 2008 Roundtable, we made the comment that the law should not be used to put a limit on innovation,<sup>16</sup> and we believe that a fair examination of the history and the on-going opposition tactics makes plain that they are just another example from this playbook.

2. State substitution restriction proposals are designed to interfere or prevent investment in the innovation needed to make the interchangeable biologic part of the biosimilar pathway a success.
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When the previous efforts failed to (A) keep the interchangeability provisions out of the BPCIA and (B) cause the FDA to implement regulatory policy that would have stifled the opportunity to develop and launch interchangeable biologics, anti-substitution advocacy shifted to the States. We believe that opponents are now focused on substitution restrictions because substitution enables sales without the need for marketing and maximizes the affordability of a medicine after exclusive rights expire. The BPCIA authorized the FDA to make determinations of interchangeability for precisely this purpose. The law expressly provides that a physician is not needed to intervene in a dispensing decision, and contemplates that there may be no need to market a product. In fact, it is likely that any marketing claims that assert there are any meaningful differences or advantages in a brand product versus an interchangeable biologic products would be unlawful promotion of a false superiority claim that is not in any approved FDA labelling. Similarly, a claim by a biosimilar manufacturer that its clinical data somehow

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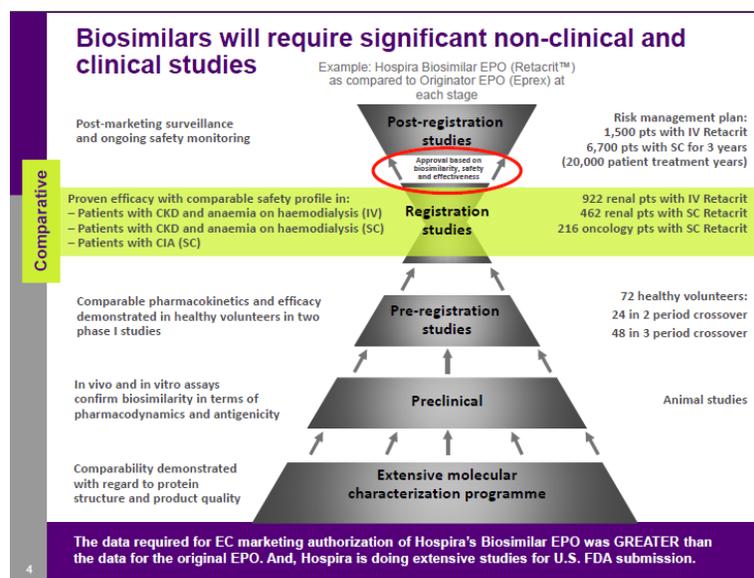
<sup>15</sup> In Europe, the EMA regulatory staff have authored articles recently for the purpose of responding to brand industry claims that biosimilars were different and that the differences raised concerns. These articles made the point that the differences between the approved biosimilars in Europe were no different from the brand than the brand was to itself from lot to lot. Martina Weise, Marie-Christine Bielsky, Karen De Smet, Falk Ehmann, Niklas Ekman, Gopalan Narayanan, Hans-Karl Heiml, Esa Heinonen, Kowid Ho, Robin Thorpe, Camille Vleminckx, Meenu Wadhwa, Christian K Schneider, (members of the Biosimilars Working Party of the European Medicines Agency), Biosimilars – Why Terminology Matters, 29 Nature Biotech 690 (August 2011); Christian K Schneider, Camille Vleminckx, Iordanis Gravanis, Falk Ehmann, Jean-Hugues Trouvin, Martina Weise & Steffen Thirstrup, Setting the stage for biosimilar monoclonal antibodies, 30 Nature Biotech 1179 (December 2012).

<sup>16</sup> Comments of Momenta Pharmaceuticals, Emerging Health Care and and Competition and Consumer Issues; FTC Project No. P083901 (December 22, 2008).

made its biosimilar product safer or better would violate the same promotion prohibitions.<sup>17</sup> But this is precisely the effect of state substitution restrictions. It prompts physician intervention, and puts the state in the position of “counter-detailing” to physicians that differences exist between an interchangeable biologic and the reference product. It would most likely make it necessary to engage in marketing to sell interchangeable products, and may even cause companies to conduct additional or larger clinical trials to address these “fears” and “concerns” when the FDA has concluded the product is interchangeable and additional clinical trials are not necessary.

Thus, restrictions on substitution are designed to force interchangeable biologic companies to market their products to physicians, when the express purpose of the law was to approve the product for substitution at the pharmacy without the need for intervention of a physician. No one is debating that a prior authorization would interfere with pharmacy substitution and would require physician intervention. Yet, discriminatory record keeping, notice and other requirements, would similarly interfere with substitution by putting dispensing barriers in place that would cause a pharmacist not to substitute without prior authorization. Krystalyn Weaver, Pharm.D., made this point crystal clear when, in response to a question about the effect of 10-day post-notification “compromise,” she stated that post-notification (even 10-day post notification) would be no different in effect than pre-substitution notification of the physician. She confirmed that a 10-day post-dispensing notification *would cause a pharmacist to seek pre-substitution authorization* and the reason was clear and demonstrable: Biologics are

<sup>17</sup> At the same time, some companies may choose to use clinical data to explain why residual uncertainty associated with structural differences does not create any meaningful clinical differences. For example, extensive clinical data may be required to demonstrate biosimilarity where significant uncertainty about structural differences. Hospira provided an example of this approach in its presentation at the Workshop:



If, however, the clinical data were used to claim that another biosimilar or interchangeable product did not have a degree of structural difference necessitating such trials, and was somehow suspect for not having extensive clinical data, when in fact the reason targeted clinical data for the second product is due to a lower level of residual uncertainty, then we believe such claims would also be a violative promotional marketing claim.

extraordinarily expensive<sup>18</sup> and are not returnable. As a result, a pharmacist would not take the risk of the financial exposure for dispensing an interchangeable biologic without obtaining pre-authorization.

In addition to the notification requirements in these bills, the proposed language pertaining to “interoperable medical records” appears to be carefully chosen to further disrupt the opportunity for substitution at the pharmacy. The Washington State bill S-3095, for example, contained language requiring that:

...the pharmacist or the pharmacist’s designee shall ... (a) Record the name and manufacturer of the product dispensed in an interoperable health records system shared with the prescribing practitioner, to the extent such as system is available; or in the case that an interoperable health records system is unavailable; (b) [provide special notice to the prescriber].

On its face it sounds simple and the language has been “marketed” to legislators by suggesting that notices will be rare because interoperable medical records are widely available. In fact, interoperable medical records are not well-defined and generally refer to a patient’s complete medical record as opposed to a record of dispensed medicines. As noted by pharmacy representatives at the Workshop, it will not be clear to a pharmacist (and may not be possible for a pharmacist to know) if an interoperable medical record system is available to a physician, and may not be in place at many pharmacies. What is in place and available nationwide for free to physicians today, are interoperable ePrescribing systems which contain prescription dispensing records (not complete health records), which is the precise information needed to conduct effective pharmacovigilance. This is a far more innovative and reliable method for informing physicians than “communication by any means” to the physician.

<sup>18</sup> AARP, among others, testified at the Workshop regarding the increasing proportion of medicines that are biologics and in particular the high product costs:

**Treatment costs are extraordinarily high**

- On average, biologic drugs are 22 times more expensive than traditional drugs<sup>4</sup>
- The average annual cost of a branded biologic is estimated to be \$34,550<sup>5</sup>
- Annual costs can range from \$25,000 to \$200,000 or more<sup>6</sup>



AARP | 5

The burdensome effect of these provisions would likely force an interchangeable biologics manufacturer to engage in otherwise unnecessary marketing and sales activity to overcome the barrier and allow for the substitution. It would in effect reverse the competitive advantage of an interchangeable designation. It would re-elevate physician intervention in direct conflict with the BPCIA interchangeability standard and achieve the opposition's goal of rendering the interchangeability designation non-competitive.

As noted at the Workshop, the advocacy of the so-called "compromise" position by several biosimilar companies is best explained by these effects on competition. The biosimilar companies that are advocating the so-called compromise, are generally companies that have developed products first in Europe, where interchangeability is not an approval standard, and which does not authorize pharmacy substitution. They are likely seeking to introduce those products in the United States as well – a pro-competitive activity – and have limited incentive to restart development to meet an interchangeability standard. What is anti-competitive, however, is the effort to impose a sales and marketing based barrier to entry of interchangeable biologic competition. While non-interchangeable biosimilar products, which are considered "new active ingredients," will have to be marketed because they are not substitutable, as is the case in Europe, there is the possibility for cost savings and a greater level of competition in the United States due to the availability of the interchangeable biologic designation. We believe that a careful examination of the facts and circumstances will show that many of the biosimilar companies that have aligned with the reference brand manufacturers to support substitution restrictions have likely done so because they intend to sell and market branded products --- even if interchangeable --- and also see a competitive advantage in preventing substitutable interchangeable biologic competition or deterring such competition by forcing interchangeable biologics firms seeking to rely on substitution to market their products too.

We also believe that the restrictions on interchangeable biologics, and the attempt to enact discriminatory provisions into state law, are part of the historic disinformation campaign to disparage interchangeable biologic competition generally. Notice provisions deliver a message that interchangeable biologics really are not substitutable like generics; that they are somehow different and risky. This is a message that as noted earlier would be an unlawful comparative claim in the marketing setting, but when adopted as a restrictive state substitution law would enlist the State in this anti-substitution marketing campaign. It also provides a forum for publicizing a

**Legislation Against Biosimilars: Brand Company-supported Bills Were Appropriately Questioned**

**The New York Times**  
Tuesday, January 29, 2013 | Last Update: 6:44 AM ET  
**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.

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

**The New York Times**  
Editorial: Improper Efforts to Limit Competitive Drugs  
February 9, 2013

**Drug Industry Daily**  
Feb. 25, 2013 | Vol. 12 No. 39  
**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."

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message to physicians that cannot be made in the sales and marketing context. As noted at the Workshop, the FDA and the press have recognized the troublesome nature of the campaign to undermine trust in FDA approvals and assert that interchangeable biologics are not really substitutable but are just “biosimilars” and are “different”. This writes the “not a new active ingredient” distinction in Section 351(n) out of the BPCIA.<sup>19</sup>

Finally, the advocates of special notice provisions respond by asserting that it is a bona fide effort to ensure there is “transparency” regarding pharmacy dispensing, and that physicians have a right to know and want to know what is dispensed to ensure that adverse events are properly attributable to the right manufacturer. This argument fails in multiple respects.

First and foremost, all companies support transparency of, and access by physicians to, pharmacist dispensing records. The pharmacist community has established and has in place nationwide recordkeeping of dispensed medications, and includes this information in nationwide ePrescribing systems. These systems offer physicians real time access to patient dispensing records, without charge, and provide a complete picture of the prescription record including the

NDC number that specifies manufacturer, lot as well as product information. This makes it possible to determine which lot of any product was dispensed so that adverse events related to a manufacturing change of any manufacturer can be investigated. Special notice and different names for biosimilars do not achieve this objective. ePrescribing systems also provide a physician (should it be desired) information on all other products dispensed

previously to a patient so that medication conflicts and errors and can be avoided and identified. Importantly, a physician can access the data at no cost through the National ePrescribing Patient Safety Initiative. Thus, all a special notice or different name would do is confuse physicians when it is already possible for a doctor to know what was dispensed on a real time basis. Moreover, the special notice provisions do not provide information on manufacturer lot number for a brand product or for a biosimilar, nor for the interchangeable biologic. If the real objective of these proposals was to make pharmacovigilance more effective, then the special notice does little to achieve that end. Instead, it allows the advocates of state law restrictions *to speak about safety and raise “concerns,”* and to do so in the context of biosimilars and interchangeable biologic substitution. Transparency is not a valid argument for these restrictions.

<sup>19</sup> See note 2, above.

Similarly, safety is not a valid basis for these special notice or other restrictions. First, the better means for tracking and investigating all products would be through the use of the NDC number which identifies the manufacturing lot for every product and, when coupled with manufacturer name, provides proper identification. The EPREX investigation referred to by Amgen at the Workshop is an excellent example. Had the company contacted the physician and the physician been able to look at an ePrescribing system (which was not in place in Europe), it would have known it was another manufacturer's product that caused the adverse event, and, more importantly, would have known the lot number. The lot number could then have been immediately associated with a manufacturing change and the cause more easily identified as a stopper change. What is ironic is that companies developing biosimilars, and even more so interchangeable biologics, have an incentive to thoroughly characterize their products to assure quality through state of the art technology, and do not rely to the same extent on the product is the process. The more one knows what is in the vial, the more likely one is able to prevent the adverse event from occurring in the first place. By enacting state substitution law restrictions, the incentive to develop the safety enhancing technology is diminished as the benefit from doing so, interchangeability, is diminished.

Finally, advocacy based on a need for "transparency" can be easily misused in the legislative context through leading questions. If a physician is asked, do you want to know what your patient was dispensed, it is no surprise that the physician responds yes. Human nature encourages us to respond that we want to be informed, when asked. What was telling, however, is the real world experience of Express Scripts cited at the Workshop. As noted by Dr. Miller in his presentation, when the dispensing information was offered to physicians from Surescripts automatically (like a special notice), it was rejected as undesirable or unnecessary information.<sup>20</sup> This suggests that the special notice provisions will have multiple negative commercial effects on competition from interchangeable biologics. First, if the notice is not received on request at the time of dispensing, it will be viewed as an annoyance and waste of office staff time. Second, it will deliver a message of caution and concern because they do not arrive when biosimilars or brands are prescribed or undergo manufacturing changes. Finally, the so-called compromise form of special notice permits any form of communication (phone call, email, voicemail, text, etc.), so it is not clear that one could know whether the message is even received, or if received, stored in a record that would be accessible should there be a need to use the information. Why? The proponents of special notice have a different objective: to erect barriers to interchangeable biologic competition.

We believe the evidence is clear. The FTC should adopt a policy opposing anti-competitive state substitution laws. State substitution laws conflict with the BPCIA when they require:

- Prior authorization or intervention by a physician for substitution of interchangeable biologics at the pharmacy; or
- Notice to a physician of substitution (pre- or post –dispensing) because in practice it will cause a pharmacist to seek prior authorization to avoid the risk of financial loss on dispensed interchangeable biologics.

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<sup>20</sup> Testimony of Steve Miller, M.D. at Workshop.

The unmistakable effect of these restrictions will be to erect barriers to competition from substitution and require marketing and sales to promote interchangeable biologics based on clinical data. The investment in interchangeability innovation will not be warranted if the competitive advantage of avoiding sales, marketing and clinical costs is lost or significantly diminished. Congress intended to spur innovation in this area by enacting an interchangeable designation, not deter it.

The need for transparency and for pharmacovigilance is best assured by addressing all medicines not spotlighting the concern and applying it to single category of products. By using existing innovation in ePrescribing systems that record more comprehensive information than a “communication” that could be misplaced or not recorded, it avoids the anti-competitive impact and addresses the problem more appropriately.

In short, the FTC should:

- Find that state substitution restrictions are anti-competitive and are not the least restrictive alternative for ensuring transparency and promoting innovation.
  - Encourage the FDA or HHS to issue guidance that state substitution restrictions violate the express provisions of the BPCIA because they would cause, without demonstrable benefit, the intervention of a health care provider in an approved pharmacy substitution decision in conflict with Section 351(i).
3. The campaign to assign different non-proprietary names to biosimilars and interchangeable biologics is also part of a commercial campaign to claim biosimilars are different.

No one disputes that under Section 351(k), a biosimilar will receive rigorous FDA review

and must be shown to be highly similar to the reference product and not to have any clinically meaningful differences. This means that a non-interchangeable biosimilar is safe and effective for use in its approved indications. As with generic drugs in the early years following Hatch-Waxman, there is an effort to assert that we need to be “careful,” that we should have “concerns about patient safety,” and that biosimilars are not really “biosimilar” but are

**“Biosimilar” or “Biodifferent”? The Real Purpose of the Naming Proposal...**

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

Amgen Biosimilars

“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.”

Genentech

**Biosimilars**

**Views On Public Policy**

**Patient Safety**

We believe that because of the differences between biologics, challenging issues exist relating to the development, approval and marketing of biosimilar products. We further believe that patient safety must be of paramount consideration when evaluating these issues.

Bio Industry Organization

**Why is Patient Safety A Concern in the Biosimilars Debate?**

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.”

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different. Websites of the proponents of differential naming are replete with this type of messaging.

Similar anti-biosimilar campaigns have been employed in Europe and, as reported by Hospira and Sandoz at the Workshop, the EMEA has rejected requests for differential naming

### EMA Initiated Education to Address Unfounded Concerns about Biosimilars

## Biosimilars in rheumatology: the wind of change

Christian K Schneider

Correspondence to Dr C K Schneider, Danish Health and Medicines Authority, Medicines Assessment and Clinical Trials, Copenhagen Z300, Denmark, and Twincore Centre for Experimental and Clinical Infection Research, Hanover, Germany; cks@dkma.dk

**...no batch of any reference product is 'identical' to the previous one—'non-identity' 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.**

*Ann Rheum Dis March 2013 Vol 72 No 3*

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proprietary name. This argument fails for all of the reasons cited in section 2 with regard to state substitution restrictions<sup>22</sup> and for additional reasons as well.

The data relied on by Emily Alexander at the Workshop to support differential naming cites the use of brand names by physicians reporting adverse events associated with a generic drug. As discussed at the Workshop, doctors frequently prescribe drugs by the brand name (knowing substitution will occur). Thus, when they report an adverse event associated with a patient, it should not be surprising that the adverse event is reported as a brand product adverse event. The fact that this occurs is well-known and from signal detection purposes is good because the reference brand product company holds the most comprehensive safety database having conducted the original clinical trials, and is in the best position to investigate trends or rare events across all substitutable drugs. The brand company also has primary labelling responsibility. As part of the investigation, the reporting company would report this to the FDA, which maintains a central database, and would/should call the physician (who can call the pharmacist or look in an ePrescribing database like Surescripts) to see what was dispensed to determine if substitution occurred and which product was dispensed to rule out or identify a product quality as opposed to a mechanism of action defect. It is misleading to cite this phenomena as a basis for requiring different names.

By having different non-proprietary names, physicians wrongly assume that related mechanism of action adverse events across multiple biosimilar or interchangeable biologic products are not related, making it more difficult to catch rare but important safety signals.

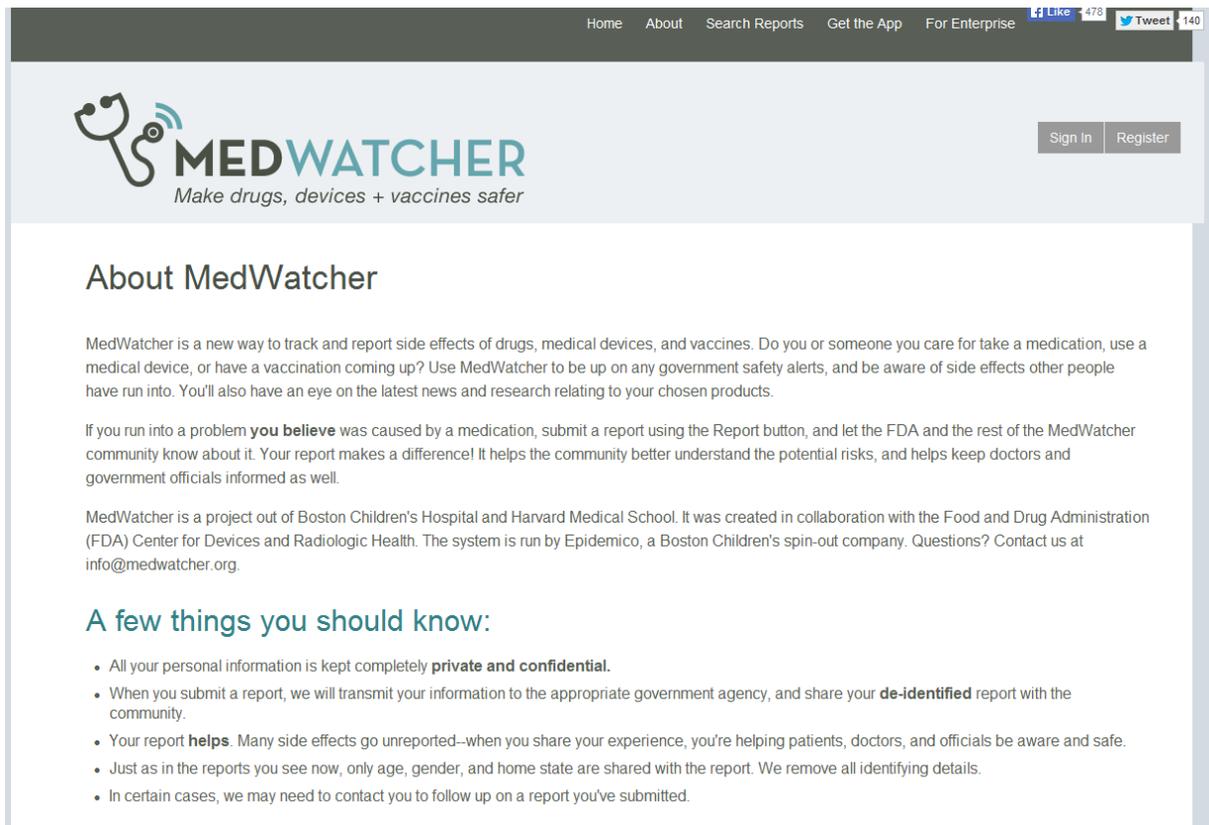
<sup>21</sup> See note 15, above.

<sup>22</sup> See pages 16-17, above.

for biosimilar products. Christian Schneider, the head of the Biosimilar Working Party Group at the EMEA, published an article last year clearly stating that the differences cited in biosimilars is inherent in all biologics and should not be a basis for asserting a reference product versus biosimilar distinction.<sup>21</sup>

Pharmacovigilance is also raised as a “concern” – i.e., that somehow pharmacovigilance is impaired by having a shared non-

Perhaps more importantly, for biologics (each of which is inherently variable), it ignores the most relevant challenge (i.e., that biologics are variable and undergo manufacturing changes). It would provide a false sense of assurance to rely on non-proprietary name rather than properly investigate and identify with the pharmacist a biologic's lot number to see if it was a manufacturing change that triggered the adverse event. By assigning different names, a lack of efficacy in a patient that is continuously on the same product might be ignored and assumed to be a normal progression of the disease, and a signal missed, but if the name was different and the lot number not checked, it might be presumed, incorrectly, that a change to a biosimilar or interchangeable biologic was the assignable case, again causing a signal to be missed. By using the NDC number in all cases, the investigation would identify the relevant information to best assure patient safety and that is what is stored nationwide in pharmacy systems and is now available without charge to physicians.



The screenshot shows the MedWatcher website. At the top, there is a navigation bar with links for Home, About, Search Reports, Get the App, and For Enterprise. On the right side of the navigation bar, there are social media icons for Facebook (478 likes) and Twitter (140 tweets). Below the navigation bar is the MedWatcher logo, which features a stylized stethoscope and the text "MEDWATCHER" in a bold, sans-serif font. Underneath the logo is the tagline "Make drugs, devices + vaccines safer". To the right of the logo, there are two buttons: "Sign In" and "Register". The main content area has a heading "About MedWatcher" followed by a paragraph describing the service. Below this is another paragraph explaining how to use the service to report side effects. A third paragraph provides information about the project's origin at Boston Children's Hospital and Harvard Medical School, and its collaboration with the FDA. Finally, there is a section titled "A few things you should know:" followed by a bulleted list of five key points regarding privacy, reporting, and data sharing.

Home About Search Reports Get the App For Enterprise Like 478 Tweet 140

 **MEDWATCHER**  
Make drugs, devices + vaccines safer

Sign In Register

## About MedWatcher

MedWatcher is a new way to track and report side effects of drugs, medical devices, and vaccines. Do you or someone you care for take a medication, use a medical device, or have a vaccination coming up? Use MedWatcher to be up on any government safety alerts, and be aware of side effects other people have run into. You'll also have an eye on the latest news and research relating to your chosen products.

If you run into a problem **you believe** was caused by a medication, submit a report using the Report button, and let the FDA and the rest of the MedWatcher community know about it. Your report makes a difference! It helps the community better understand the potential risks, and helps keep doctors and government officials informed as well.

MedWatcher is a project out of Boston Children's Hospital and Harvard Medical School. It was created in collaboration with the Food and Drug Administration (FDA) Center for Devices and Radiologic Health. The system is run by Epidemico, a Boston Children's spin-out company. Questions? Contact us at [info@medwatcher.org](mailto:info@medwatcher.org).

### A few things you should know:

- All your personal information is kept completely **private and confidential**.
- When you submit a report, we will transmit your information to the appropriate government agency, and share your **de-identified** report with the community.
- Your report **helps**. Many side effects go unreported—when you share your experience, you're helping patients, doctors, and officials be aware and safe.
- Just as in the reports you see now, only age, gender, and home state are shared with the report. We remove all identifying details.
- In certain cases, we may need to contact you to follow up on a report you've submitted.

There are also important data capture innovations underway that are increasingly available to physicians such as a Medwatcher smartphone APP. The Medwatch APP allows for a physician to use a mobile phone to take a picture and report adverse event information in realtime, facilitating identification of the product, the manufacturer, the NDC number and other critical information. We believe innovation is a far better means to address the concerns being raised that are in our view designed to negatively impact biosimilar and interchangeable biologic competition.

Lastly, the proponents of different names have failed to mention what may prove to be the most useful innovation for addressing pharmacovigilance: the FDA Sentinel Initiative. While ad hoc post-marketing information is vital to patient safety, and will continue to play an



**FDA's Sentinel Initiative**

Sign up for e-mail updates

**Sentinel Initiative**

*Transforming how we monitor the safety of FDA-regulated products*

A national electronic system that will transform FDA's ability to track the safety of drugs, biologics, and medical devices once they reach the market is now on the horizon. Launched in May 2008 by FDA, the Sentinel Initiative aims to develop and implement a proactive system that will complement existing systems that the Agency has in place to track reports of adverse events linked to the use of its regulated products.

Monitoring the safety of its regulated products is a major part of FDA's mission to protect public health. The Sentinel System enables FDA to actively query diverse automated healthcare data holders—like electronic health record systems, administrative and insurance claims databases, and registries—to evaluate possible medical product safety issues quickly and securely.

Sentinel will be developed and implemented in stages. As the system is being developed, data will continue to be managed by its owners and questions would be sent to the participating data holders. Within pre-established privacy and security safeguards, these data holders would evaluate their information and send summary results to FDA.

important role in patient safety, the Sentinel Initiative is aggregating comparative, controlled data on products from patient claims and outcome data from the nation's major hospitals, health care plans, insurance companies and PBMs. It enables rigorous review of the data and a proactive system for signal detection.<sup>23</sup> The Academy of Managed Care Pharmacies is also conducting a similar effort in collaboration with the Sentinel Initiative. According to the AMCP, the system

now captures data from approximately 75% of the patients in the United States and should provide the most reliable kind of information for safety signal detection through this innovative approach and could render the differential naming proponent's pharmacovigilance arguments moot.<sup>24</sup> For this reason, AMCP policy on biosimilar naming provides:

<sup>23</sup> From the FDA Sentinel Program Home Page <http://www.fda.gov/safety/fdassentinelinitiative/default.htm>

<sup>24</sup> Statement of Bernadette Eichelberger, PharmD. On February 18, 2014 at the Biosimilars Committee Meeting, Annual Meeting of GPhA. The Academy of Managed Care Pharmacy (AMCP) is a national professional association of pharmacists, health care practitioners and others who develop and provide clinical, educational and business management services on behalf of more than 200 million Americans covered by a managed pharmacy benefit. AMCP members are committed to a simple goal: *providing the best available pharmaceutical care for all patients*. Some of the tasks AMCP's more than 6,000 members perform include:

- Monitoring the safety and clinical effectiveness of new medications on the market;
- Alerting patients to potentially dangerous drug interactions when a patient is taking two or more medications prescribed by different providers;
- Designing and carrying out medication therapy management programs to ensure patients are taking medications that give them the best benefit to keep them healthy; and
- Creating incentives to control patients' out-of-pocket costs, including through lower copayments on generic drugs and certain preferred brands.

These practices, and more, aim to ensure that *all* patients can receive the medications they need to improve their health while at the same time keeping health care costs under control.

Manufacturers of approved biosimilars should be allowed to use the same government-approved name/international nonproprietary name as the reference product (e.g. epoetin alpha for Procrit®). This will hopefully ease confusion among prescribers and patients and help to encourage substitution of biosimilar products in appropriate instances. However, it is also important to continue to use current mechanisms such as manufacturer name, national drug code (NDC) numbers and lot numbers to effectively differentiate batches for safety monitoring purposes.<sup>25</sup>

What is particularly troubling about the differential naming proposal is the confusion it would cause for interchangeable biologics, biosimilars that are determined by the FDA to be safe to substitute and switch. If a biologic is demonstrated to be substitutable, how could it not have the same name? Reference products undergo manufacturing changes and do not have to demonstrate interchangeability. If a different name is used, it will suggest that an interchangeable biologic is not substitutable. Similarly, there will be confusion when a physician writes a prescription with the non-proprietary name. Will it mean that a product must be “dispensed as written”?

It is also worth noting that many reference brand biologics today are approved under separate BLAs, are known and expected to be different, and share the same non-proprietary name. Examples include Kogenate (antihemophilic factor (recombinant) and Recombinate (antihemophilic factor (recombinant))). No one is asserting a safety concern as a result and we believe the opposite is the case because it has facilitated the capture of important product class safety information.

When the evidence is reviewed, and the arguments parsed, we believe it becomes clear that the primary rationale that motivates differential naming is to erect barriers to biosimilar and interchangeable biologic use. Sales representatives will then promote use of the unique name with brand names to reduce substitution. Pharmacy systems would have to be reprogrammed to accommodate different names. Marketing would be elevated in importance to capture prescription volume. At each step in the reimbursement and distribution and/or sales process, attention would have to be devoted to explaining why the name was different and why biosimilar or interchangeable was an acceptable alternative. Having this hurdle at the time the pathway is implemented is not pro-competitive.

We urge the FTC to review the data and appropriately report that differential naming proposals are anti-competitive and not in the interest of America’s health care consumers.

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<sup>25</sup> Where We Stand on Biosimilar Drug Therapies, Academy of Managed Care Pharmacies, <http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=16640> .

### Summary and Conclusion

We appreciate the opportunity to provide written comments that supplement our participation at the Workshop conclude with our belief that:

- Biosimilar and interchangeable biologic policy should be driven and measured by how it:
  - Promotes innovation and attracts investment in delivering safe, effective and affordable biologics
  - Addresses patient needs (including access) and patient safety
  - Avoids using the least innovative and most anti-competitive solutions to achieve these important objectives.
- The opposition to biosimilar and interchangeable biologic competition have much to lose financially when patents and exclusivity expire for a brand product
  - Financial loss and risk is what really motivates the proposals for state substitution restrictions and naming barriers to biosimilar and interchangeable biologic competition
  - State substitution restrictions and differential naming will create barriers to investment in the innovation necessary to provide access to safe, effective and affordable biologics
  - The loss of competition will decrease the incentive for brand companies to innovate the next generation of new cures if patent or exclusivity profits continue after expiration or loss of exclusivity
- The FTC should therefore encourage the FDA or HHS to adopt a policy stating that:
  - State substitution restrictions are an unlawful conflict with Section 351(i) of the BPCIA; and
  - The benefits of innovation already underway from ePrescribing, the Sentinel Initiative and other programs, and the confusion that naming differences would cause, mean that biosimilar and interchangeable biologics should share the same non-proprietary name

Thank you for the consideration of our views.

Sincerely,

Bruce A. Leicher  
Senior Vice President and General Counsel