



Submitted Via Regulations.Gov

October 27, 2015

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, MD 20852

**Comments of Momenta Pharmaceuticals, Inc. regarding Docket FDA-2013-D-1543:
Nonproprietary Naming of Biological Products; Draft Guidance for Industry.**

Gentlemen/Mesdames:

Momenta Pharmaceuticals, Inc. ("Momenta" or "we") respectfully submits these comments to the Draft Guidance for Industry: Nonproprietary Naming of Biological Products ("Draft Guidance"). Momenta appreciates the significant efforts undertaken by the FDA in developing the Draft Guidance and, in particular, its focus on fostering a set of principles that will protect patient interests in safety, affordability and access to biologic medicines. As the biosimilar pathway is implemented, there is a danger in adopting policies and practices, however, that could confuse physicians, patients and payers, discourage biosimilar adoption, and interfere with established pharmacovigilance practices. This confusion could stifle the kind of innovation paramount to the development of high quality, biosimilars and interchangeable biologics and undermine the primary goals of the Biologics Price Competition and Innovation Act (the "BPCIA").

Nonpropriety naming policy has traditionally informed, and should continue to inform, physicians, patients and pharmacists of the non-branded active ingredient of a product, and not serve a commercial purpose. If it incorporates a commercial identifier or distinguishing function, it runs the risk of moving into the commercial messaging realm, implying unsubstantiated product differences and undermining the primary FDA marketing approval finding: namely, a regulatory determination of biosimilarity and/or interchangeability.

As recognized in the Draft Guidance, there is a strong need for education about the safety and science supporting biosimilar development, approval and use. There are reasons for this strong need. Biosimilars are new, and there is a long history of negative commercial messaging suggesting that they are "impossible", not the "same" as their reference product, and pose safety concerns as a result. With this backdrop, the adoption of a unique naming policy emphasizes this

historic commercial messaging and could directly and materially validate these negative messages impacting competitive access to safe and more affordable biologics. Momenta submits these comments with a view toward supporting the Agency in formulating a final guidance document (“Final Guidance”) that relies on science, not commercial messaging for future policy. The goal should be to promote innovation and continuous improvement in biologic product knowledge. Impeding biosimilar development and adoption will not foster this goal.

In February 2014, the Federal Trade Commission (the “FTC”) conducted a workshop to examine the competitive impacts of regulation on state substitution and naming. The workshop focused on the competitive restrictions such regulations might have on biosimilar investment, innovation and adoption. Momenta participated in and submitted comments to the FTC setting forth in greater detail how the history of negative commercial messaging about biosimilars and the adoption of a unique naming policy could ratify that messaging and undermine the goals and objectives of the BPCIA (the “Momenta FTC Comments”). These comments supported a pro-innovation policy of having the same nonproprietary (or “proper name,” as used in the Draft Guidance) for biosimilars and interchangeable biologics with their reference product.¹ A key part of these comments focused on and also explained how product quality and patient safety can be enhanced by biosimilar innovation, but that barriers to their commercial success will undermine the incentive to invest in these scientific advances.²

To date, the FDA has strongly supported biosimilar innovation by recognizing:

- the central role of using structural and functional analysis as the primary means for demonstrating biosimilarity and interchangeability;³ and
- the inherent value of using this knowledge to improve all products through quality by design development.

It should be noted that many initial biosimilar pathway participants had at first submitted clinical trial based information rather than sufficient characterization data indicating that innovative biosimilarity testing was not an approach initially adopted by some applicants nor is it accepted by many opponents to the biosimilar pathway.⁴ Rather, as the initial biosimilar pathway guidance encouraged, applicants should submit primary biosimilarity data so that

¹ Comments of Momenta Pharmaceuticals, Inc. at pages 4-5 and 17-21, Public Workshop: Follow-On Biologics: Impact of Recent Legislative and Regulatory Naming Proposals on Competition: Project No. P1312208 (February 14, 2014). On March 4, 2014, Momenta submitted the Momenta FTC Comments to the Janssen, Novartis, and GPhA Citizen Petition Dockets FDA-2014-P-0077, FDA-2013-P-1153, and FDA-2013-P-1398) regarding biosimilar non-proprietary naming. A copy of the Momenta FTC Comments is attached as Exhibit A.

² Momenta FTC Comments at 16.

³ Momenta FTC Comments at 9-10 (citing Leah Christl, Ph.D, Associate Director for Therapeutic Biologics, November 2013 presentation at the Drug Industry Association).

⁴ *Id.* at 10. (Dr. Christl stated: “Lessons learned: put your horse first...”).

clinical trials could be targeted to resolve residual uncertainty that arises from the nature and extent of any differences identified between the biosimilar and/or interchangeable biologic and the reference biologic. This policy creates a significant incentive to invest in technology to advance the understanding of biologic manufacturing and process control, and structural and functional characterization so that in the future clinical trials may become confirmatory or perhaps even unnecessary.

If, however, unique names are adopted for biosimilars and/or interchangeable biologics, the value of these advances would be undermined commercially. Unique names will invite physicians to question whether a biosimilar really has “no clinically meaningful differences” or an interchangeable product really can be “substituted.” A biosimilar sponsor would then be forced to engage in medical communication to counter these concerns, and to hire marketing and sales forces – activities that were anticipated to be significantly reduced or avoided as a means of driving biosimilar affordability and access. Moreover, biosimilar sponsors might also find it necessary to conduct additional clinical research for commercial reasons to support this education, not for regulatory review, in order to counter these messages. This would be particularly detrimental to the viability of the interchangeable biologic part of the biosimilar pathway, where substitution at the pharmacy, not sales and marketing were expected to be the primary means of commercialization and would provide the return on the additional investment and innovation necessary to develop an affordable interchangeable biologic.

Momenta encourages the FDA to take these broader biosimilar pathway objectives into consideration as it formulates a Final Guidance and that it not adopt naming conventions that create unnecessary barriers to investment, development and market entry for biosimilars and interchangeable biologics. The Final Guidance should be science based. It should focus not only on early biosimilar applications that rely more heavily on clinical assessment,⁵ but on the incentive impact the Final Guidance could have on continued scientific innovation to develop structural/functional data. This could enhance the quality of all biologics through greater product knowledge and increased understanding of biologic manufacturing process control. Policy decisions taken today will undoubtedly influence the direction sponsors will take in investing in innovation as they proceed to develop biosimilars and interchangeable biologics in the years to come.

⁵ Most early biosimilar applicants in the United States initiated development in Europe where the biosimilar development regime enacted in 2006 was initially clinically-focused and until more recently, following the enactment of the BPCIA, has only become more structure/function based for determining biosimilarity. In addition, the European regulatory regime does not contemplate the development of interchangeable biologics that would be substitutable at the pharmacy, creating a commercial dynamic that favors the use of clinical data for commercial purposes. As a result, these early biosimilar applicants may favor unique names because they do not contemplate interchangeability, and may view sales and marketing as a competitive advantage for non-interchangeable biosimilars.

1. The Final Guidance should use the same proper name without a suffix for each biosimilar and its reference biologic and FDA should not adopt guidance to apply a suffix to each biologic manufacturer's proper name.

For the reasons set forth in the Momenta FTC Comments,⁶ unique proper names, whether by suffix or not, communicate the message that there are meaningful clinical differences between biological products – just as it would if unique proper names were used for generic drugs. With the significant backdrop of negative commercial messaging against the biosimilar pathway, during the implementation of the pathway and now as naming and labeling policies are developed, it is even more important that FDA formulate science-based policy and not “name” biosimilars based on commercial concerns or in a manner that undermines their potential for success.

Notably, the first statement often used commercially in discussing biosimilars is they are not “identical” to the reference product and thus must have a different name. This is an oversimplification that omits key scientific facts that makes it misleading and thus is a “red herring”. FDA policy in the advertising and promotion context has found statements to be misleading, even if they are technically true, when they are used to deliver a comparative or scientific message that in the absence of complete information is in reality misleading. As the FDA appropriately recognizes in the Draft Guidance, *all* biologics (biosimilar or reference) have inherent variability and no biologics are identical. Focusing this message on biosimilars makes it misleading when no reference biologic is identical to itself. Yet, there is no proposal to create unique proper names for variations of a particular biologic as it undergoes manufacturing changes or when it is manufactured in multiple locations and is determined to be “comparable” taking into consideration such differences. The adoption of unique naming will play directly into the hands of those seeking to mislead physicians by making this incomplete claim. The FDA should not adopt a proper name policy that creates this commercial marketing advantage for reference biologic sponsors.

A second rationale given by persons that are not familiar with biosimilars is that pharmacovigilance is at risk for biologics if proper names are not unique. First, most products are referred to by brand name, and it should not be a surprise that many adverse events for identical drugs, are reported to the reference product manufacturer because the brand name is often noted on the medical record. This is also because the reference drug has primary labeling responsibility for the product. With that said, the pharmacy dispensing record contains the information of the actual product dispensed and is readily accessible to the physician for pharmacovigilance purposes. To change the naming system for biologics, when it is viewed as acceptable for drugs again seems misplaced. This is particularly so because pharmacovigilance is and can be effectively managed by other means. First, each product (drug or biologic) has a unique National Drug Code (“NDC”), and is identified on its packaging by its manufacturer, which allows for tracking and tracing and pharmacovigilance. This is a well understood approach and should be the focus of education of physicians and pharmacists; to use the NDC number and manufacturer name as opposed to the brand name. Separate names would instead create balkanization of reporting and could cause physicians to not attribute adverse events to the all of the biologics sharing the root of a proper name when it occurs with one of the uniquely named products.

⁶ Momenta FTC Comments at 17-21.

To create a different pharmacovigilance regime for biologics and biosimilars than for drugs will also mislead physicians, pharmacists, payers and patients about the meaning of a biosimilar and/or interchangeable biologic application approval by the FDA and suggest there are differences and concerns despite the FDA concluding they have no clinically meaningful differences. It is a well understood quality principal that having a single approach for pharmacovigilance for all products will reinforce compliance and minimize confusion. Everyone should look at the manufacturer and NDC number and brand name as the key information for *all* products.

As more fully discussed below in Section 4, below, the addition of a suffix will also be confusing. The existence of a suffix will suggest there are specific concerns to be tracked for each product and is even more confusing when there is a transition from non-interchangeable biosimilar to interchangeable biologic. Thus, the question was asked in the Draft Guidance about how to implement naming for interchangeable biologics. There is simply no good answer to what to do with the suffix at that point in time. Several choices are possible:

- Have no suffix on a biologic to begin with;
- Leave a differentiating suffix on the interchangeable biologic making it appear non-interchangeable;
- Apply the reference biologic suffix to the interchangeable biologic adding no helpful information; or
- Drop the suffix from both the reference biologic and the interchangeable biologic at the time the first interchangeable product is approved.

Other than having no suffix, each of these alternatives will raise questions from physicians, patients and payers about their medicines, interfere with appropriate substitution, and put sand in the gearbox of biosimilar and interchangeable biologic distribution and competition.

Another argument raised to advance unique naming is that a pharmacist would inappropriately substitute non-interchangeable biosimilars. This should not be a basis for adopting unique proper names. All non-interchangeable biosimilars may only be dispensed on prescription of a physician and there is no evidence to suggest that pharmacists would violate state or federal law and substitute a product that was not interchangeable. Just as with generic drugs which have interchangeability identified in the Orange Book, pharmacists can look at the Purple Book for an interchangeability designation for each biosimilar. We should enhance compliance by not varying the practice for interchangeable products at the pharmacy. For drugs, a different proper name would indicate that it is not substitutable and the same proper name would still require the pharmacist to check the Orange Book for an interchangeability rating of “AP” or “AB” to determine substitutability. A different proper name for an interchangeable biologic would be inconsistent and imply it was not substitutable because drugs with different names are not substitutable. This could create significant confusion about substitution of drugs and biologics. Would the variation in naming convention for drugs and biologics suggest that non-substitutable drugs are substitutable too? Moreover, we believe that many biosimilar manufacturers would support the inclusion of their interchangeability approval in their labeling as a secondary means for ensuring appropriate substitution.

By implementing the same proper name for a biosimilar (interchangeable or not) with its reference product, the educational burden is simplified. Physicians, pharmacists, payers and patients can be educated that proper names function for biosimilars and interchangeable biologics just as they do for drugs. They refer to the active ingredient and do not identify a manufacturer or brand. That would reinforce the traditional use of proper names and allow education to focus on how to include manufacturer name or NDC number when tracking or reporting adverse events or product concerns. This is no different than that for generic drugs. It avoids setting up different approaches for drugs and biologics.

2. If the Final Guidance, nevertheless, adopts the use of a suffix for all biologics, the proper name for an interchangeable biologic should be the same as its reference biologic.

The explicit purpose of creating an interchangeable biologic part of the biosimilar regulatory pathway is to enable substitution and more affordable access to biologics. A key element of these savings comes from removing the need for sales and marketing, and by allowing for competitive contracting and distribution to drive affordability. Unique naming for interchangeable biologics would lead to confusion for patients and potentially mislead physicians causing them to seek to intervene *unnecessarily* in the permitted substitution process. This is in direct contravention of the statutory language of the BPCIA that permits the substitution of an interchangeable biologic at the pharmacy *without the intervention of a physician*. The goal of the BPCIA was to realize cost savings from generic-like commercialization of interchangeable biologics. Unique proper names would likely create a need to use sales and marketing communication to resolve the confusion and eliminate the incentive to seek interchangeability. A significant incentive for companies to pursue the designation of interchangeability, however, is to allow for commercialization without sales and marketing communication. Thus, this kind of confusion could make investment in development for interchangeability uneconomic, and significantly reduce the opportunity for innovation and savings that might otherwise have been achieved.

A unique proper name for interchangeable biologics is unnecessary. As noted earlier, the pharmacist, physician, payer and patient can look at the Orange Book for drugs and now the Purple Book for biologics, and determine interchangeability status. We also anticipate that companies that receive an interchangeable biologic approval could be expected to include that approval designation in their labeling. A unique name or suffix would change the traditional experience of pharmacists by raising doubts about substitutability. They might assume an interchangeable biologic with a unique proper name is *not* substitutable and not take the step of looking in the Purple Book. Thus it would do little or nothing to assure appropriate substitution, however, it would raise questions and confusion and interfere with the goal of substitutability. The result would be that it would create a requirement for sales and marketing and undermine the opportunity to allow for cost savings and affordability.

Unique proper names, as noted in the Momenta FTC Comments, would also treat like products differently and communicate to physicians, payers and patients that they are different. This is contrary to FDA's legal responsibility to treat like products equally under the law. An interchangeable biologic will have been thoroughly characterized, and shown to be interchangeable based on structural and functional data and any necessary targeted clinical data.

It must be expected to perform the same in any given patient. A reference biologic, however, when it undergoes a manufacturing change or is made in a new facility could be expected to have the same or greater variability to its initially approved version than an interchangeable biologic. Reference biologic variations are tested for comparability, not interchangeability. Although comparability testing is applied to manufacturing changes to assure patient safety, the Draft Guidance does not propose unique proper naming for comparable changes in a reference biologic. If there is a need for unique proper names for interchangeable biologics, there is certainly the same need for unique proper names for comparable reference biologics; particularly because interchangeable biologics are demonstrated to be substitutable with the reference biologic and comparable reference biologics do not undergo interchangeability testing. Science should drive the policy here, and as the FDA reviews the batch to batch variability of reference biologics and observes that interchangeable biologic variability is equivalent to the reference biologic, it would be wrong to apply unique names to interchangeable biologics and not to variations of reference biologics. It would also be misleading to physicians, patients, pharmacists and payers in light of such science to allow comparable versions of reference biologics to have the same name from version to version and not allow interchangeable biologics to have the same name from version to version.⁷

It is also important to note that traditional FDA policy is that advertising and promotion is misleading in a comparative context when it is not supported by substantial evidence. The use of unique proper names sets up a comparison between an interchangeable biologic and its reference biologic that creates a distinction when the only comparative data, and the only substantial evidence, is that the interchangeable product meets interchangeability standards and is substitutable at the pharmacy. There is no substantial evidence of a difference or that a unique name would be warranted; yet if the Final Guidance established a unique naming requirement, each interchangeable biologic would have to be promoted and advertised with this unsubstantiated comparison.

3. Assuming a unique suffix is required for all biologics, the suffix should not be a form of promotional branding, and interchangeable biologics should have the same suffix as their reference biologic to reflect their substitutable status.

The Draft Guidance proposed the use of a suffix for *all* biologics by proposing to implement unique suffixes for each reference biologic and for each biosimilar. The Draft Guidance further recognizes that this approach may not work for interchangeable biologics and asks for comments on whether or not and how a single unique reference biologic suffix might also need to apply to an interchangeable biologic. FDA recognized the potential confusion about whether an interchangeable biologic that has a different proper name was substitutable at the pharmacy and that a unique name might thus be confusing and mislead physicians, pharmacists, patients and payers. Assuming a suffix is used for all biologics, then Momenta strongly recommends that a brand-name oriented suffix *not* be utilized for a proper name so that it remains “nonproprietary.”

⁷ The disparate treatment of naming as applied to multiple versions of reference biologics to interchangeable biologics also applies to non-interchangeable biosimilars in that biosimilars have demonstrated they have no clinically meaningful differences from the reference biologic and each version of the reference biologic does not have to meet the biosimilarity standard.

When the first biosimilar of filgrastim was licensed, a brand oriented suffix was selected for the applicant, i.e., filgrastim-sndz. The use of “sndz” appears to be derived from the Sandoz brand and is thus “promotional” in nature. As noted in the Draft Guidance, a proper name should not be “promotional,”⁸ and by referring to a company name, it would be promotional. Moreover, the use of a brand or corporate name based suffix for interchangeable biologics creates even more confusion. Suppose the reference product proper name was filgrastim-amgn following this convention. What would happen should filgrastim-sndz receive an interchangeable biologic approval? Would it become filgrastim-amgn? This would be confusing at best, and misleading at worst because of the branded suffix. It would identify another Company’s brand with the interchangeable biologic rather than identify two active ingredients as being interchangeable through the use of a common, non-branded proper name.

For these additional reasons, we still believe the best remedy would be to not use a suffix for all biologics and to have all biosimilars share the same proper name. If, however, a suffix will be used for all biologics then it should be a random set of characters that is assigned to each biologic manufacturer.

4. Even if random, a suffix creates even more confusion at the time a biosimilar achieves interchangeability than it purports to solve.

Even if a random set of characters is used for a non-interchangeable biosimilar and its reference product, it raises more confusion when a non-interchangeable biosimilar is subsequently approved as an interchangeable biologic. This is because if the interchangeable biologic retains the same random code it had as a non-interchangeable biosimilar, it would always have a different proper name than the reference product – indicating it is different than the reference biologic, even when it is interchangeable. If it adopts the same suffix as the reference biologic, even if random, it would not achieve the original purpose of pointing to the biosimilar manufacturer. Simply put, no alternative solves the purported problem. Another option might be to have the suffix dropped altogether from the reference biologic and the interchangeable biologic at the time the first interchangeable biologic is approved. This third option would remove the “equality” benefit of applying suffixes to all biologics when an interchangeable biologic was approved. However, it would impose costs of conversion and change for both the reference product manufacturer and the interchangeable biologic manufacturer leading to confusion among physicians, pharmacists, patients and payers as well. Dropping the suffix would allow for equal treatment and for interchangeable biologics substitution, however, it would render the remaining non-interchangeable biosimilars less competitive by emphasizing their difference. Again, these downstream complications further support not having a suffix in the first place for biologic proper names.

⁸ Draft Guidance at 10.

5. The FDA and other Federal partners could most effectively promote patient safety and pharmacovigilance by adopting a consistent framework for biologics and drugs, educating medical providers on the importance of including NDC numbers and manufacturer names in product quality and adverse event reports, and promoting innovation that enhances the quality of all biologics.

The evidence submitted by brand manufacturers suggesting a rationale for unique names for biologics is based largely on data gathered from the reporting of product quality and adverse information from drugs. If there are concerns associated with drugs, then the problem is not addressed by adopting a unique proper naming guidance for biologics. Rather, the problem should be addressed for all products, drugs and biologics alike. If medical providers are not providing manufacturer name or NDC number when adverse events are reported, then education is warranted and is the most logical next step to address the issue for both drugs and biologics.

In addition to education, however, there are other means to ensure that information is available for pharmacovigilance. For example, commercial insurers frequently require payers to include NDC numbers when seeking reimbursement and NDC number is a field in the electronic records that are used for recording dispensing of prescriptions by pharmacists. This further ensures that the NDC number is included in the medical and pharmacy records.

CMS, a federal partner, could add a requirement to its Medicare reimbursement rules, as exists under state Medicaid rules, to require the use of the NDC number in reimbursement claims making it more readily accessible in pharmacovigilance activities. This would parallel commercial practice. As noted in the Momenta FTC Comments,⁹ the use of electronic prescribing and medication history is now nationwide, and captures the vast majority of specialty prescriptions. In the specialty pharmacy area, which is largely managed by pharmacy benefit manager firms, pharmacists report that NDC number is the means used for tracking all prescriptions and is in the electronic record. Physician participation is increasing each year due to incentives to promote ePrescribing and electronic medical records. For specialty products, we estimate that most prescriptions are captured because all major pharmacy benefit managers feed NDC numbers in to the system. In addition, every physician has the right to access the electronic prescription database for free through the National ePrescribing Patient Safety Initiative and in any event can always contact the patient's pharmacy that has a record of all prescriptions by NDC number and manufacturer. A move to unique naming could result in disruption of the electronic system which does not provide for suffixes at this time and more importantly, a loss of focus on the NDC number and manufacturer name that should apply and work for all products – drugs and biologics alike.

Finally, Momenta is investing in developing interchangeable biologics through the use of innovative technology that allows for increasingly precise control of biologics manufacture and more thorough characterization of biologics. The incentive to invest in this kind of innovation is closely tied to the opportunity to achieve interchangeability and have the commercial advantage offered from such achievement. Associated with greater process control and product knowledge, is the increased opportunity to avoid, in the first instance, product quality problems and adverse events before they occur in patients. One of the most frequently cited examples of why

⁹ Momenta FTC Comments at 15.

biosimilars should be uniquely named is the challenges faced when EPREX underwent a manufacturing stopper change. The manufacturing change resulted in undetected product quality changes resulting in fatal adverse events.¹⁰ These changes in product quality were not tested in clinical trials, may not have been detected due to their low frequency in clinical trials, and were not detected in comparability testing or the product quality release tests for the EPREX product. The argument made suggests that biosimilars or an interchangeable biologic is somehow like EPREX and poses the same inherent safety risk. A biosimilar, and an interchangeable biologic in particular, however, because it must undergo thorough structural and functional characterization offers a greater opportunity to detect and avoid these types of “oft-cited” risks during their development. This work often leads to greater ability to avoid and detect product quality issues before products are released to patients. Momenta learned this first hand during the heparin crisis. Because Momenta was seeking to prove “sameness” of its generic enoxaparin, a highly complex, glycosolated low molecular weight heparin product, it was necessary to thoroughly characterize and understand the structure of enoxaparin and heparin as part of its development program. A benefit of that innovative science was that Momenta was able to assist in the identification of contaminants in the heparin crisis – contamination that was not detected by heparin commercial suppliers that had no had a reason to thoroughly characterize and understand heparin.

Because of the negative commercial messaging regarding biosimilars and interchangeable biologics by the use of examples such as the EPREX adverse events, there is already significant misunderstanding of how biosimilars and interchangeable biologics offer the opportunity for innovation and enhancement of the quality and safety of all biologics. There is a compelling need, as noted in the Draft Guidance for education by the FDA and the industry to provide fair balance and science to support biosimilar adoption and development.

The need to educate about biosimilars, and the opportunity to educate will also be impacted not only by FDA policy on naming, but on labeling, advertising and promotion. Education needs to be considered in light of FDA’s policies in each of these areas. Educational activities should use science as its core and inform policy positions that support appropriate use of biosimilars and interchangeable biologics. The degree to which FDA educates industry on its views can either advance biosimilar understanding or potentially undermine their development and adoption. For example, when a biosimilar or interchangeable biologic is approved, is it misleading for a reference product sponsor to assert in promotional material that a biosimilar or interchangeable biologic is “not identical” to the reference product when no biologic is identical batch to batch? Does fair balance require a statement that regarding the extent and nature of variability testing of the reference biologic, including a statement that the current version is a variation of what may have been tested in pivotal clinical trials? It could be more difficult to address this issue if FDA issues guidance that biosimilars must have unique names.

¹⁰ Momenta FTC Comments at 16.

Do statements such as those made in the course of the debates regarding the adoption of the BPCIA, that biosimilars or interchangeable biologics are “impossible” or are have “safety concerns” need to be corrected? And does a decision to adopt a unique naming suffix suggest, even without intention, that these historic commercial messages are valid claims?

These questions need to be addressed in education and communication to physicians, patients, pharmacists and payers by both the FDA and industry. The means for addressing these questions, however, will be impacted by FDA policy on labeling and advertising and promotion and should be carefully considered before adopting a requirement for unique proper names for biologics. For example:

- Traditionally, statements by a reference product sponsor that a biosimilar is “not identical to” the reference biologic would be comparative advertising. As such, a biosimilar or interchangeable biologic approval that established no clinically meaningful differences and/or interchangeability should render such statements misleading because they are not supported by “substantial evidence.” The FDA should consider communicating this as part of its educational activities relating to proper names and as it adopts labeling and advertising and promotion guidance for biosimilars. Perhaps this should be considered before adopting unique proper names or suffixes for biosimilars, or certainly for interchangeable biologics, because unique names could undermine well established rules regarding comparative advertising and the importance of preventing misleading claims?
- If a biosimilar sponsor is seeking to educate physicians, pharmacists, patients and payers on the science used to demonstrate biosimilarity and/or interchangeability, will characterization and structure/function data used in medical communication or education have to be limited to the information included by the sponsor in the label or will it be considered on-label communication as long as it was used to demonstrate biosimilarity and/or interchangeability within the approved indications? The need for this type of communication will in turn be impacted by the degree to which proper names support or undermine a finding of biosimilarity and or interchangeability. If a biosimilar sponsor has to overcome the commercial message of a unique name, it will be even more important to educate physicians, patients, pharmacists and payers on the critical role biosimilarity testing plays in the development and approval process.

We raise these questions not to answer them in this submission but to help make it clear that we are at the start of the implementation of the biosimilar pathway and policies on naming could adversely impact policies in other areas. The science is being explored and is advancing rapidly. The ability to thoroughly characterize and develop high quality biosimilars and potentially interchangeable biologics should no longer be a question but commercial interests are still asserting otherwise. The FDA has the opportunity to balance and regulate negative messaging.

The adoption of unique proper names could make this more difficult. For this reason, we encourage the FDA to use its unique role, as reviewer of multiple biosimilar files, to follow the science and then to adopt as flexible approach as possible at this stage in policy development so that guidance adopted today, does not stifle investment and put a ceiling on biosimilar innovation.

Sincerely,

A handwritten signature in blue ink, appearing to read "B. Leicher".

Bruce A. Leicher
Senior Vice President and General Counsel

Attachments:

Exhibit A: March 4, 2014 Comments to the Janssen, GPhA and Novartis Citizen
Petition Dockets and February 4, 2014 Momenta FTC Comments



Submitted Via Regulations.Gov

March 4, 2014

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, MD 20852

COMMENTS OF MOMENTA PHARMACEUTICALS, INC. ON JANSSEN PHARMACEUTICAL COMPANIES OF JOHNSON & JOHNSON (JOHNSON & JOHNSON OR THE COMPANY) CITIZEN PETITION REQUESTING DIFFERENT NON-PROPRIETARY NAMES FOR BIOSIMILAR AND INTERCHANGEABLE PRODUCTS AND THEIR RESPECTIVE BIOLOGIC PRODUCTS (DOCKET NO. FDA-2014-P-0077) AND GPhA AND NOVARTIS'S CITIZEN PETITIONS REQUESTING IDENTICAL NON-PROPRIETARY NAMES FOR BIOLOGICAL PRODUCTS AND THEIR RESPECTIVE REFERENCE PRODUCTS (DOCKET NOS. FDA-2013-P-1153 AND FDA-2013-P-1398, RESPECTIVELY).

Gentlemen/Mesdames:

Momenta Pharmaceuticals, Inc. ("Momenta" or "we") respectfully submits these comments on the citizen petition or petitions by Janssen Pharmaceutical Companies of Johnson & Johnson ("Janssen") (Docket No. FDA-2014-P-0077) posted on January 14, 2014. In its petition Janssen requested that unique non-proprietary names be assigned to biosimilar biologics. We are also filing these comments to the dockets for the citizen petitions by the Generic Pharmaceutical Association ("GPhA") (posted September 19, 2013; Docket No. FDA-2013-P-1153) and the Novartis Group of companies ("Novartis") requested that FDA "require that a biosimilar[] be identified by the same [INN] . . . as the reference product" (posted November 26, 2013; Docket No. FDA-2013-P-1398). For the reasons set forth below, Momenta believes that the Janssen citizen petition should be denied and both the GPhA and Novartis citizen petitions granted.

Momenta participated in the Federal Trade Commission Workshop on the competitive impacts associated with state law substitution restrictions and differential naming proposals on February 4, 2014 and submitted written comments to the FTC on February 28, 2014. Copies of the written comments and the presentation are attached to this letter. Momenta believes that its comments and presentation are highly relevant to the consideration of these citizen petitions and submits them for your consideration.

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March 4, 2014

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For the reasons stated in our attached filing with the FTC, we believe that the motivation for differential naming proposals are derived from commercial interests in deterring investment in innovation, delaying the launch of biosimilar and interchangeable products, and seeking to enlist the FDA and the naming authorities in advocating that biosimilars are somehow “different” than their reference products in ways that are meaningful. We also believe that the use of different names could interfere with pharmacovigilance best practices by masking discovery of lot based manufacturing changes, and causing confusion among physicians conducting pharmacovigilance about whether biosimilar adverse events are related to reference product adverse events. We urge the FDA to adopt guidance that leaves in place current policy that would allow for biosimilars and interchangeable biologics to share the same non-proprietary name.

Sincerely,

A handwritten signature in blue ink, appearing to read 'B. Leicher', with a stylized flourish at the end.

Bruce A. Leicher

Senior Vice President and General Counsel

Attachments:

February 28, 2014 Comments of Momenta Pharmaceuticals to the Federal Trade Commission

February 4, 2014 Presentation at the FTC Workshop on Follow-On Biologics



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.¹ 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.”² 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).

¹ 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> .

² 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.³ 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"> Generic Biologics are Impossible 	<ul style="list-style-type: none"> Prevent Regulatory Approval Prevent/Deter Legislative pathway
Oppose Biosimilar Pathway – 2007-2010	<ul style="list-style-type: none"> Biosimilars are unsafe even if possible Interchangeable biologics are impossible/different 	<ul style="list-style-type: none"> Prevent/Deter pathway Incorporate legislative features that prevent/deter use of the pathway <ul style="list-style-type: none"> Mandatory Clinical Trials Complex IP exchange
Influence FDA Guidance - 2011	<ul style="list-style-type: none"> Same messages 	<ul style="list-style-type: none"> Emphasize differences (Eg. Naming) Mandate Unnecessary Clinical trials Freeze scientific standards for similarity and interchangeability
Abbvie CP	<ul style="list-style-type: none"> Same messages 	<ul style="list-style-type: none"> Delay Biosimilars for 10 years
Naming Campaign JnJ Citizen Petition	<ul style="list-style-type: none"> Biosimilars are different and raise safety concerns 	<ul style="list-style-type: none"> Amplifies anti-biosimilar commercial campaign with providers, payors, patients and regulators
Restricted Access to Reference Products	<ul style="list-style-type: none"> Biosimilar companies are irresponsible 	<ul style="list-style-type: none"> Prevents/Delays initiation of development

³ 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.⁴ 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.⁵ 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.⁶

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

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

⁵ 2003 CP at 2.

⁶ 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.⁷ 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.⁸

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.⁹

⁷ 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."

⁸ Sections 351 (i)(3) and 351(k)(2)(B) and 351(k)(4).

⁹ 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.¹⁰

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.”¹¹ 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

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.

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

¹¹ Id. at pages 17-19

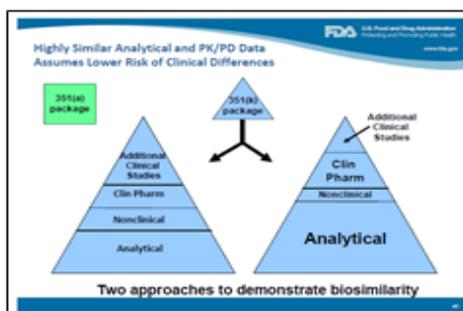
require large and extensive clinical requirements that would make their development financially unattractive. These unjustified burdensome requirements would deter or prevent the use of abbreviated approvals that could lead to more affordable products that are just as safe and effective as the reference 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.¹² The FDA considered these comments, and considered the prevailing science, and adopted draft biosimilar guidance documents in 2011.¹³ 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 Workshop¹⁴ 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



¹² 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.

¹³ 77 FR 8883-8886 (February 15, 2011).

¹⁴ 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 Lee¹, Andre Raw¹, Lawrence Yu¹, Robert Lionberger¹, Nalaji Siv¹, Daniela Vertheby¹, Amy Rosenberg¹, Steve Kozlowski¹, Keith Webber² & Janet Woodcock²

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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:

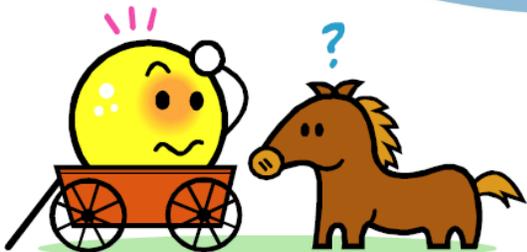
Dr. Christl emphasized in her November 2013 presentation that one could not use clinical trials to test biosimilarity into a product, because clinical trials are not the most effective means for determining product differences. This was a clear rejection of the anti-innovative policy advocated in comments 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..."

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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

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 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.¹⁵ 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,¹⁶ 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.
-

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

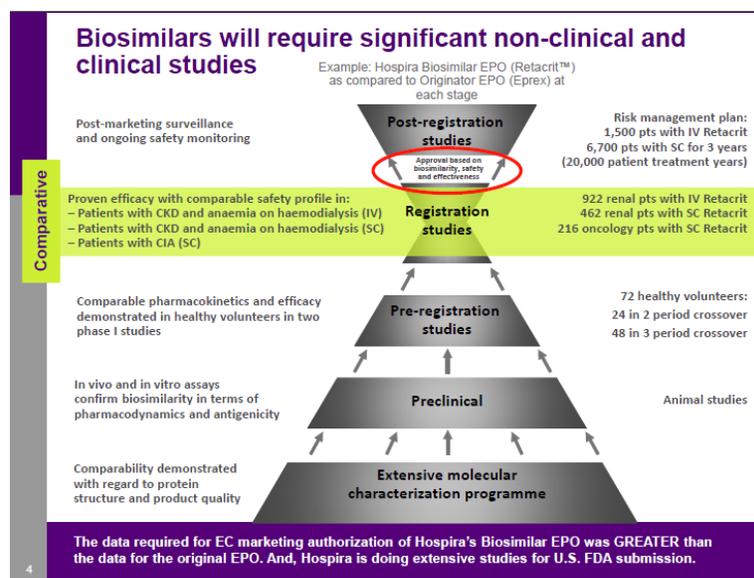
¹⁵ In Europe, the EMA regulatory staff have authored articles recently for the purpose of responding to brand industry claims that biosimilars were different and that the differences raised concerns. These articles made the point that the differences between the approved biosimilars in Europe were no 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).

¹⁶ 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.¹⁷ 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

¹⁷ 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 expensive¹⁸ 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.

¹⁸ 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 drugs⁴
- The average annual cost of a branded biologic is estimated to be \$34,550⁵
- Annual costs can range from \$25,000 to \$200,000 or more⁶



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.¹⁹

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.

¹⁹ 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.²⁰ 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.

²⁰ 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

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 2300, 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 restrictions²² 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.

²¹ See note 15, above.

²² 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.²¹

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.

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 **MEDWATCHER**
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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.

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.²³ 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.²⁴ For this reason, AMCP policy on biosimilar naming provides:

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

²⁴ 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.²⁵

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.

²⁵ 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

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Anti-Competitive Deterrents to Investment and Innovation in Biosimilars and Interchangeable Biologics

*Follow-On Biologics Workshop
Bruce A. Leicher, Sr. Vice President and General Counsel, Momenta Pharmaceuticals Inc.
Federal Trade Commission February 4, 2014*

Corporate Overview

- Biotech company founded 2001 based on technology developed at the MIT for the precise understanding of complex mixture medicines
- 250+ employees located in Cambridge, MA
 - Substantial Growth (100+) in Employment due to new Biosimilar Pathway
- Expertise in high-resolution analytics, biological characterization, and process engineering



Introduction

- Biosimilar and Interchangeable Biologics policy should be driven and measured by how it:
 - Promotes Innovation and Attracts Investment
 - Addresses Patient Needs and Patient Safety
 - Avoids using the least innovative and most anti-competitive solutions to achieve these objectives
- The opposition to Biosimilar and Interchangeable Biologic Competition:
 - Is the central factor that motivates restrictions on substitution of Interchangeable Biologics
 - Undermines the attractiveness of investment in, and access to, safer, more affordable biologics
- The related commercial campaigns to require different non-proprietary names, and to restrict access to brand product for FDA-regulated biosimilarity and interchangeability testing are designed to impede investment in, development of, and competition by, safe and affordable Biosimilars and Interchangeable Biologics.

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A Long Established Campaign Against Biosimilar Innovation and Competition

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

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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
 - Restrict substitution; and
 - Provide notice to doctors to intervene and be concerned about FDA approved biologics

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Why is Substitution so Important?

- Substitution eliminates the need for sales and marketing to physicians and payors
 - Note that some biosimilar companies now support a so-called “compromise”
 - Note also that each of these biosimilar companies
 - May not be seeking to develop interchangeable biologics, and/or
 - May plan to market their biosimilars and interchangeable biologics with a sales force, and
 - Thus benefits from preventing substitution to protect pricing and profits in their branded and “marketed” biosimilar business
- 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

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MOMENTA

Anti-Biosimilar déjà vu: State Substitution Restrictions are Designed to Restrict Competition, Not Improve Safety or Knowledge

- Notice Provisions are designed to deliver a message that Interchangeable Biologics are “different” or “suspect” and give marketed products a competitive advantage
 - E.g., BIO appropriately opposes GMO labelling for just this reason
- Special notice and recordkeeping burden pharmacists to deter substitution and promote branded biologics and branded biosimilars
- This matters
 - To patients, who cannot access or afford life saving biologics
 - To physicians, who want transparent and reliable information from biologics manufacturers about all products
 - To payors, who cannot pay for biologics and other critical care
 - To novel developers, who rely on headroom in payor budgets from generics to pay for novel new medicines
 - To regulators, who want to promote quality by design innovation

7

MOMENTA

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

The New York Times

Tuesday, January 29, 2013 Last Update: 8:41 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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MOMENTA

Why Innovative Biosimilar and Interchangeable Biologics Matter For Patient Access

- **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

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MOMENTA

Anticipated Annual Changes in U.S. Spending on Traditional Drugs

Therapy Class	2013	2014	2015	3-Year Compounded Total
DIABETES	8.9%	6.8%	6.7%	24.1%
HIGH BLOOD CHOLESTEROL	-6.9%	-4.0%	-5.3%	-15.4%
HIGH BLOOD PRESSURE /HEART DISEASE	-7.2%	-5.9%	-6.0%	-17.9%
ASTHMA	-7.3%	0.8%	1.3%	-5.4%
ULCER DISEASE	-5.6%	-6.4%	-13.2%	-23.3%
DEPRESSION	-4.7%	-8.7%	-6.5%	-18.6%
ATTENTION DISORDERS	4.4%	10.0%	8.6%	24.8%
MENTAL/NEUROLOGICAL DISORDERS	-7.4%	-1.8%	-5.7%	-14.2%
PAIN	-3.3%	-4.5%	-4.2%	-11.6%
INFECTIONS	-6.9%	-6.8%	-6.0%	-18.4%
OVERALL TRADITIONAL	-1.0%	-1.7%	-1.4%	-4.1%

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MOMENTA

Anticipated Annual Changes in U.S. Spending on Specialty Drugs (Many are Biologics)

Therapy Class	2013	2014	2015	3-Year Compounded Total
INFLAMMATORY CONDITIONS	25.1%	17.2%	17.4%	72.2%
MULTIPLE SCLEROSIS	19.8%	18.5%	16.8%	65.6%
CANCER	21.3%	20.9%	21.0%	77.4%
HIV	9.2%	9.6%	9.4%	30.9%
HEPATITIS C	33.0%	58.5%	168.4%	465.8%
GROWTH DEFICIENCY	6.2%	5.9%	6.5%	19.9%
ANTICOAGULANT	-0.3%	-0.2%	0.0%	-0.6%
PULMONARY HYPERTENSION	11.0%	11.1%	10.5%	-14.2%
RESPIRATORY CONDITIONS	24.8%	29.5%	27.9%	36.3%
TRANSPLANT	-2.2%	1.0%	-1.2%	-2.4%
OVERALL SPECIALTY	17.8%	19.6%	18.4%	66.8%

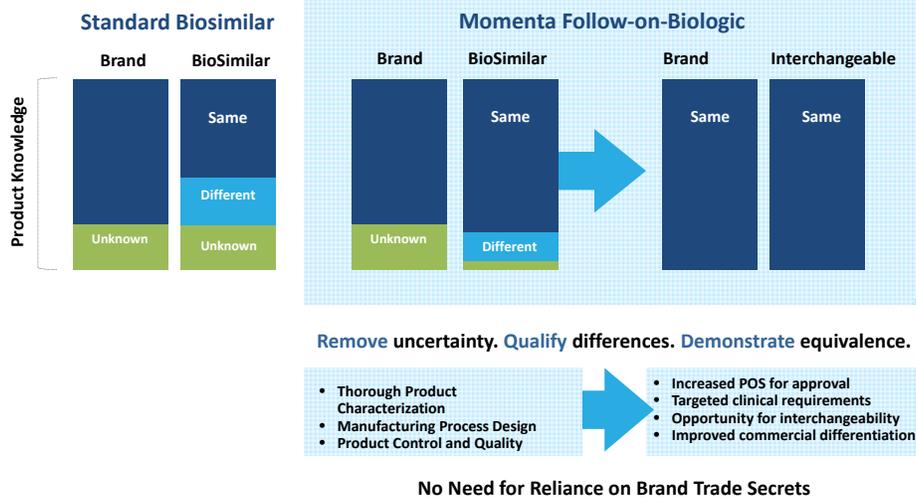
5.21.13 | Glen Stettin, MD
Specialty Drug Spending to Jump 67% by 2015

HEALTHCARE INSIGHTS
FROM THE EXPRESS SCRIPTS LAB

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MOMENTA

Innovation is the Best way to Create Access to Safe, Affordable Interchangeable Biologics



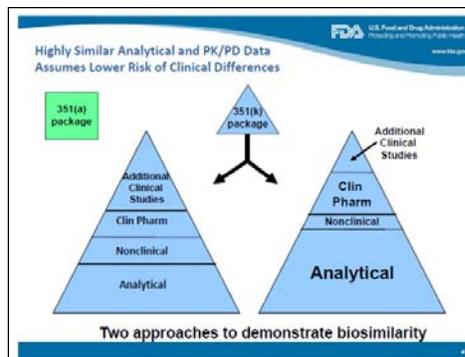
MOMENTA

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



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MOMENTA

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



The NEW ENGLAND JOURNAL of MEDICINE

Perspective

AUGUST 4, 2011

Developing the Nation's Biosimilars Program

Steven Kozlowski, M.D., Janet Woodcock, M.D., Karen Midhun, M.D., and Rachel Sherman Sherman, M.D., M.P.H.

PERSPECTIVE

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

Sau Lee¹, Andre Rava¹, Lawrence Yu¹, Robert Lionberger¹, Naiqi Ya¹, Daniela Verthelyi², Amy Rosenberg², Steve Kozlowski², Keith Webber² & Janet Woodcock²

VOLUME 31 NUMBER 3 MARCH 2013 NATURE BIOTECHNOLOGY

"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

Elsevier
BusinessIntelligence

Friday, February 10, 2012

Biosimilars: Similarities to Enoxaparin and the Elephant in the Room

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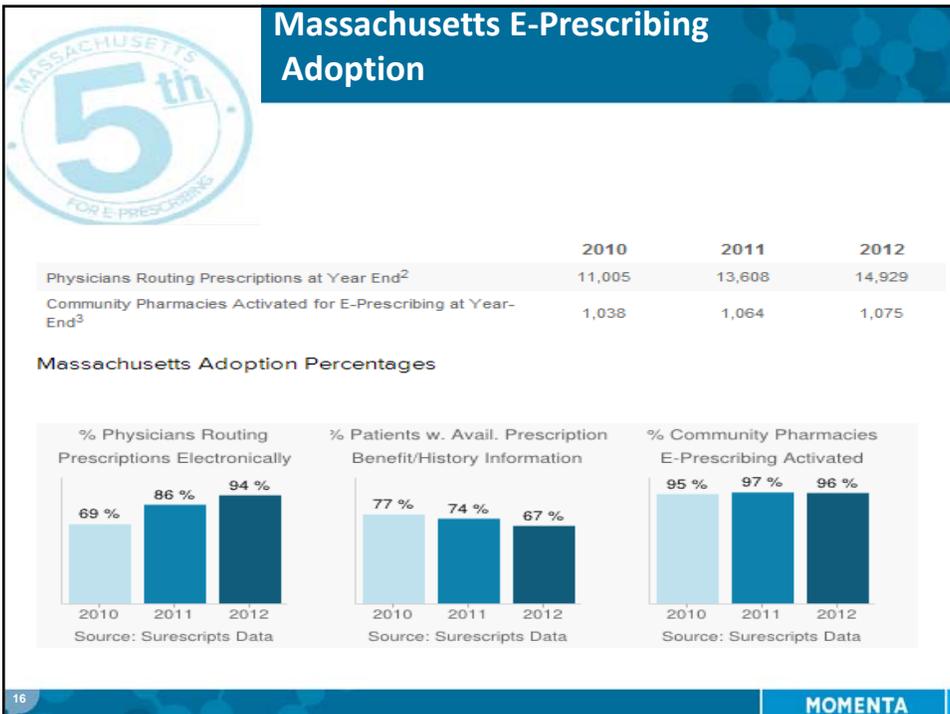
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Innovation is the Pro-Competitive Way to Provide Substitution Transparency

- Special notification proponents argue for special notice under the guise of transparency - Why? Special Notice
 - Favors marketed brand and biosimilar products
 - Restricts and disparages substitutable Interchangeable Biologics
- Nationwide ePrescribing networks provide comprehensive transparency without restricting competition
 - Surescripts provides real time access to all dispensed medications and improves patient safety without discouraging substitution
 - Surescripts access is free to all physicians through the National ePrescribing Patient Safety Initiative
 - Any doctor can access and see what was dispensed
 - It reduces prescription conflicts and errors as well
 - ePrescribing is universally available and can be used even if a physician writes a prescription on paper

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National ePrescribing Patient Safety Initiative

eRx National ePrescribing Patient Safety Initiative™

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The Time for ePrescribing is Now.

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

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

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



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17 **MOMENTA**

State Pharmacy Substitution Bill In Massachusetts

- Encourages Investment and Innovation in Safe and More Affordable Interchangeable Biologics:
 - Authorizes Pharmacist Substitution of Interchangeable Biologics
 - Relies on Electronic Medical Records to ensure Physicians aware of the biologic their patient receives
 - Avoids “disparagement” of biosimilars and interchangeable biologics
 - No physician intervention required
 - No prior notice required
 - No special record keeping is required
 - Substitution is handled in the same manner as generic substitution
 - Promotes Cost Effective Patient Access
 - Uses Innovation to develop Interchangeable Biologics and to Inform Physicians
 - Avoids Anti-Competitive practices
- Today’s science allows for demonstration that biologics are the “same”. (*Professor William S. Hancock, Barnett Institute of Chemical and Biological Analysis, Northeastern University, MassBio Policy Leadership Breakfast (January 23, 2013)*).

18 **MOMENTA**

CA Bill Vetoed



“Senate Bill (SB) 598 would affect two changes to our state’s pharmacy law. First, **it would allow interchangeable “biosimilar” drugs to be substituted for biologic drugs**, once these interchangeable drugs are approved by the FDA. **This is a policy I strongly support.**

....Second, it requires pharmacists to send notifications back to prescribers about which drug was dispensed.**to require physician notification at this point strikes me as premature.**

....I am returning SB 598 without my signature.”

—Edmund G. Brown Jr., Governor of California

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MOMENTA

The FTC Should Adopt a Policy Opposing Anti-Competitive State Substitution Laws

- State Substitution Conflicts with the BPCIA and Restricts Competition when they require:
 - Prior intervention by physician for substitution
 - Prior notice to provoke intervention by physician before substitution
 - Subsequent notice to provoke intervention by physician and discourage substitution
 - Notice would be used by brand sales representatives to say Interchangeable products are different (code for an unproven safety risk)
 - Interchangeable Products would need sales and marketing support to compete (causing increased costs for consumers)
- Restrictions will deter critical investment required to Innovate and Develop Interchangeable Biologics
 - We should not pass laws that put a ceiling on innovation
- Special Notification is unnecessary and will discourage use of ePrescribing that appropriately ensures access to transparent dispensing information by physicians
- The FTC should encourage the FDA or HHS to Adopt a Preemption Policy to Preclude State Substitution Conflicts and Promote Consistency with the Definition of Interchangeability under the BPCIA

“[an 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).

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Biosimilar and Interchangeable Biologic Non-Proprietary Naming

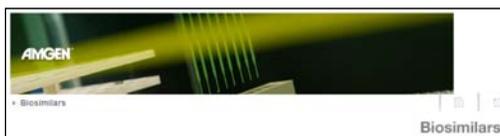
- Biosimilars are carefully reviewed and approved by the FDA
 - Biosimilars must be highly similar and have been shown not to have clinically meaningful differences
 - Interchangeable Biologics must also be demonstrated to be capable of being substitutable at the pharmacy without the need for intervention of a physician.
- There is no defensible basis for different Non-Proprietary Names other than to restrict competition
- 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

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“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?



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



Why 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.”

A screenshot of a Genentech website page. At the top, the Genentech logo is visible, along with navigation tabs for 'SCIENTISTS', 'MEDICAL PROFESSIONALS', 'PATIENTS', 'MEDIA', and 'GOOD'. The main heading is 'Biosimilars'. Below the heading, there is a section titled 'Patient Safety' with a sub-heading 'Views On Public Policy'. The text discusses the complexity of biologics and the importance of patient safety.

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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 2300, Denmark, and Twincore Centre for Experimental and Clinical Infection Research, Hanover, Germany;chsc@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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Pharmacovigilance Does not Justify Unique Names

- 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

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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 is treated as unrelated and are used to differentiate products

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Pharmacovigilance Does not Justify Unique Names

- Brand Products that 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

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Restricted Access Programs

- Biosimilarity and Interchangeability Testing requires access to Brand Comparator Products
- Restrictive Distribution Networks and REMs Programs are increasingly used to track and potentially prevent comparative testing of biosimilar products, Cf., Actelion
 - Restricted Access programs are used to monitor, prevent and delay competitive development
 - Vertical restrictions with distribution chain prevent or restrict the re-sale of product to biosimilar competitors
- FTC should confirm that it is unlawful to restrict or delay access to reference product for FDA regulated biosimilar testing

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Conclusion

- Biosimilar and Interchangeable Biologic policy should be driven and measured by how it:
 - Promotes Innovation and Attracts Investment
 - Addresses Patient Needs and Patient Safety
 - Avoids using the least innovative and most anti-competitive solutions to achieve these objectives
- The opposition to Biosimilar and Interchangeable Biologic Competition:
 - Motivates restrictions on substitution of Interchangeable Biologics; and
 - Undermines the attractiveness of investment in, and access to, safer, more affordable biologics
- The FTC should encourage the FDA or HHS to adopt a Preemption Policy to ensure State Substitution legislation is:
 - Consistent with the BPCI; and
 - Facilitates investment to promote the use of innovation to provide patient access to safe and affordable Interchangeable Biologics
- The FTC should oppose as anti-competitive, efforts to:
 - Require different non-proprietary names; and
 - Restrict access to reference product for biosimilarity and interchangeability testing.

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