NOVARTIS

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

No. FDA-2015-P-2000

19 August 2015

Dear Sir/Madam:

Sandoz, a Novartis company, respectfully submits this response[1] to the AbbVie Citizen petition ("CP") to recommend the Food and Drug Administration ("FDA" or "Agency") reject the CP in its entirety.[2] As the sponsor of the first, and currently only, US licensed biosimilar, Zarxio™ (filgrastim-sndz[3]), Sandoz supports FDA's choice of a label that fully informs the physician about the appropriate use of the biosimilar. The CP refers to "generic-labeling", and while we prefer the term "same-labeling", we believe that, as shown in its application to Zarxio™ by FDA, it is the appropriate approach for labeling biosimilars.

The CP misinterprets the concept of biosimilarity, missing entirely its sound regulatory basis – i.e., that the approval of a biosimilar through appropriate "highly-similar" or "sameness" criteria (just as is the case for a generic as a regulatory matter) is based on the well-established safety and efficacy data of the reference product,

> FDA Guidance "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009", April 2015.[4]
>
> > ***BACKGROUND***
> > *The BPCI Act was enacted as part of the Affordable Care Act on March 23, 2010. The BPCI Act creates an abbreviated licensure pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product.* ***The objectives of the BPCI Act are conceptually similar to those of the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) (commonly referred to as the "Hatch-Waxman Act"),*** *which established abbreviated pathways for the approval of drug products under the Federal Food, Drug, and Cosmetic Act (FD&C Act).*[3] [emphasis added]
>
> > [3] *See section 505(b)(2) and 505(j) of the FD&C Act (21 U.S.C. 355(b)(2) and 355(j)).*

For biosimilars this regulatory concept became the totality of the evidence approach, where robust analytical evaluation demonstrates that the biosimilar is "highly similar" to the reference product, and subsequent clinical trials are confirmatory. Just as the European Medicines Agency (EMA), FDA considers when a biosimilar is approved, that "the active substance of a biosimilar and its reference medicine is essentially the same biological substance"[5], therefore, the label should be focused on providing information regarding the safe and appropriate use of that biologic. Consequently, the arguments made

in the CP rely on inaccurate assumptions that conflict with the regulatory concepts represented by the new PHS Act[6] 351(k) pathway[7] and the legal authority given to FDA by that statute.

We realize that the CP was authored without experience in biosimilar development. Hence, the petitioners have not had the opportunity to discuss with FDA the rationale and role for each of the data elements that comprise the totality of the evidence for a biosimilar in providing evidence of its "high similarity", and that together support its licensure. In contrast, Sandoz has had extensive discussions with the Agency on each of these items throughout development of Zarxio™, as well as for each of our other ongoing development programs.

In addition, from insight gained from our experience with products across the broad portfolio of the Novartis group of companies, comprising originator drugs and biologics, generic drugs, biologics regulated as drugs (e.g., our growth hormone, Omnitrope® as well as our generic biologics and complex generics enoxaparin and glatiramer acetate), and biosimilars, we agree with FDA's labeling decision made for Zarxio™. Namely, that ***the clinical data incorporated into the label of a product should be the data that forms the basis of the safety and efficacy determination for that product and provides necessary information to guide the physician in appropriate clinical use***. This applies to biosimilars, just as it applies to all other biologics and drugs, both originator and generic, and FDA's labeling decision for Zarxio™ reflects the Agency's continued, consistent application of existing labeling practices.[8]

The label developed with FDA and published along with our approval is accurate and appropriate for guiding the clinical use of Zarxio™. Nonetheless, we appreciate the opportunity that the CP has created to offer further clarification more broadly for biosimilars, as well as to rectify some of the misunderstandings about biosimilarity among health care providers, patients, as well as other interested stakeholders (as illustrated in the survey cited in the CP and elsewhere).

Our response addresses the following topics in more detail:

1. The Role of the Label in Prescribing any Medicine
2. The Regulatory Concept of Biosimilarity Put into Context
3. The Regulatory Basis for the Label Format for Generic and Biosimilars is the Same
4. Application of FDA's Extensive Prior Experience with Medicinal Products
5. Transparency is Equally Important for All Medicines
6. The Purple Book is the Orange Book for Biologics when it comes to Substitutability

1. The Role of the Label in Prescribing any Medicine

FDA reviews product applications, determines their safety and efficacy[9], and, with sponsors, ensures that the label fulfils its purpose to inform the physician about appropriate use (as defined under US law and current regulations[10]). Namely:

> "The FDA approved label is the official description of a drug product which includes indication (what the drug is used for); who should take it; adverse events (side effects); instructions for uses in pregnancy, children, and other populations; and safety information for the patient. Labels are often found inside drug product packaging."[11]

FDA works with sponsors to finalize the label for all medicines, and extensive guidance is available to help standardize the approach used.[12] Nothing in the label can be false or misleading, and the label is reviewed annually, with FDA approving any changes.

Further, the Agency only allows essential information within (and excludes extraneous information from) the label. FDA regulation 21 CFR § 201.56 (a)(1) requires that "the labeling must contain a summary of the ***essential scientific information*** needed for the safe and effective use of the drug" [emphasis added]. As a consequence, FDA has always been very careful when including in product labels results based on secondary endpoints, exploratory endpoints or post-hoc analyses as well as supportive studies. The clinical data in product labels is usually obtained from the pivotal studies that first establish the efficacy and safety profile of the drug. Subsequent clinical studies with efficacy or safety endpoints are not incorporated in the product label unless the subsequent study provides additional new information (for example, expanding the clinical indications of use, new safety findings, etc.). FDA has consistently followed this approach for all products approved to date, whether they be drugs or biologics, and irrespective of their regulatory pathway (505(b)(1), 351(a), 505(b)(2), 505(j) or 351(k)).

For drugs, including those biologics regulated as drugs,[13] the label of a corresponding generic matches that of its reference product, because the basis of the approval of that generic is the original clinical data on the reference drug approved by FDA as a new drug application and such data provides appropriate information for clinical use of the product (i.e., an NDA, 505(b)(1) under the FD&C Act pathway). For a generic drug, FDA does not ask for any clinical data beyond limited confirmatory bioequivalence studies, nor are such studies statutorily required as they do not provide additional information modifying the appropriate clinical use of the drug. ***Thus, the original clinical data on the reference drug comprises the information necessary to prescribe the generic, just as it comprises the information necessary to prescribe the reference drug to which that generic refers.***

FDA appropriately applied this "same labeling" approach to the first US biosimilar approved under the 351(k) pathway. Filgrastim-sndz (Zarxio™) was approved as biosimilar to filgrastim (Neupogen®) in all indications of the reference product at the time of approval based on the totality of evidence demonstrating that filgrastim-sndz was "highly similar" to filgrastim. The safety and efficacy of the biosimilar, as well as the mode of use, is established by the reference biologic in a manner analogous to the relationship of a reference drug to its generic approved through the ANDA pathway. Therefore, Zarxio's label ***comprises the information necessary to prescribe the biosimilar because it comprises the information necessary to prescribe the reference biologic to which that biosimilar refers, in this case Neupogen®.*** As such, it is the only appropriate labeling approach for our biosimilar Zarxio™, as well as for future US biosimilars.

Furthermore, the Zarxio™ label follows the principle of including only "essential scientific information." The clinical studies conducted with Zarxio™ do not reveal any clinically relevant differences when compared to the reference product with respect to efficacy or safety. Therefore, since the Zarxio™ clinical studies do not provide new or essential scientific information that modifies the use of the product, FDA correctly applied 21 CFR § 201.56 (a)(1) by excluding those studies from the Zarxio™ label.

The CP claims that "labeling a biosimilar the same as its reference product distorts the safety and efficacy profile of the biosimilar" is misguided.[14] In fact, the sponsor of the biosimilar must provide unambiguous evidence that the biosimilar is highly similar to or "essentially the same" as the reference product with no clinically meaningful differences. As discussed more below, the evidence of high similarity includes a head-to-head comparison of all critical quality attributes of the molecule with special attention to those known to be clinically significant. Once high similarity is established with analytical and functional assays, subsequent clinical studies are designed solely to confirm the high similarity. The safety profile from the targeted biosimilar studies also serve to confirm similarity or "sameness" and must be consistent with the reference product's safety profile established in the

reference product's pre-approval clinical program and extensive post-approval pharmacovigilance. Clinical studies with a biosimilar provide the final confirmation of "sameness" to the reference product and are not designed to establish the *de novo* efficacy or safety profile of the biosimilar, as the very concept of biosimilarity requires that that information be derived from the reference product.

The very fact that Zarxio™ and its reference product were determined by the regulators to have no clinically meaningful differences clearly and unambiguously communicates to healthcare providers and the public that ***the efficacy results and the safety profile expected after administration of the biosimilar are the same as would be expected after administration of the reference product.*** If there were to be any expectation of differences that were clinically meaningful, the biosimilar could not be approved as a biosimilar.

2. The Regulatory Concept of Biosimilarity Put into Context

Congress enacted the Biologics Price Competition and Innovation Act of 2009 ("BPCIA") as Title VII of the Patient Protection and Affordable Care Act on March 23, 2010[15], creating the opportunity for FDA to license biosimilars and interchangeable biologics in the US using the new 351(k) regulatory pathway.

Specifically, BPCIA gave FDA authority to license biologics that refer to the Agency's prior approval of another biologic already established as safe, pure and potent (i.e., biological products licensed under 351(a) of the PHS Act – also called "standalone" biologics by FDA and others).[16] It is critical to understand that the Agency is not using any of the original data submitted by the reference product manufacturer for any comparison of the biosimilar product. The biosimilar sponsor must purchase or acquire the reference product to generate the direct comparative data proving the similarity of the biosimilar to the reference product.

Fundamental to the BPCIA authority is the concept, also recognized for drugs by the Hatch-Waxman generic pathways[17], that the "sameness" of the active ingredient of a medicine will cause it to behave in the same way in patients as its reference product, and that a full clinical development program for the biosimilar is unnecessary.[18] This analytical match (as shown by a head-to-head comparison of the biosimilar with the reference product) is therefore inherent in the approval of a biosimilar as a biosimilar, and any clinical studies are conducted to *confirm* expected clinical outcomes of safety and efficacy and not to establish safety and efficacy *a priori*.[19] Indeed, the better the analytical match the fewer clinical studies are likely to be required, and ultimately none may be required at all, as suggested by some senior FDA personnel.[20] However counterintuitive, it is very plausible that a biosimilar that more closely matches its reference product will be supported by *less* clinical data than a less-closely matching biosimilar to the same reference product. This concept in and of itself suggests that clinical data from biosimilarity trials inserted in a product label would be confusing to the physician who may not understand the biosimilar paradigm.

Just as in the US, the basis for the regulatory finding of safety and efficacy of biosimilars in Europe is established by the clinical studies on the originator reference product. The terminology is also similar across an increasing number of jurisdictions, with the EMA calling biosimilars "essentially the same biological substance."[21] Extensive, global experience exists developing biosimilars in highly regulated markets, including with our filgrastim (known as Zarzio® in the EU). While the legal constructs and precise terminology may differ across jurisdictions, the science of biosimilarity is remarkably similar and, for example, our biosimilar filgrastim is the same product in all of the jurisdictions in which it is available.

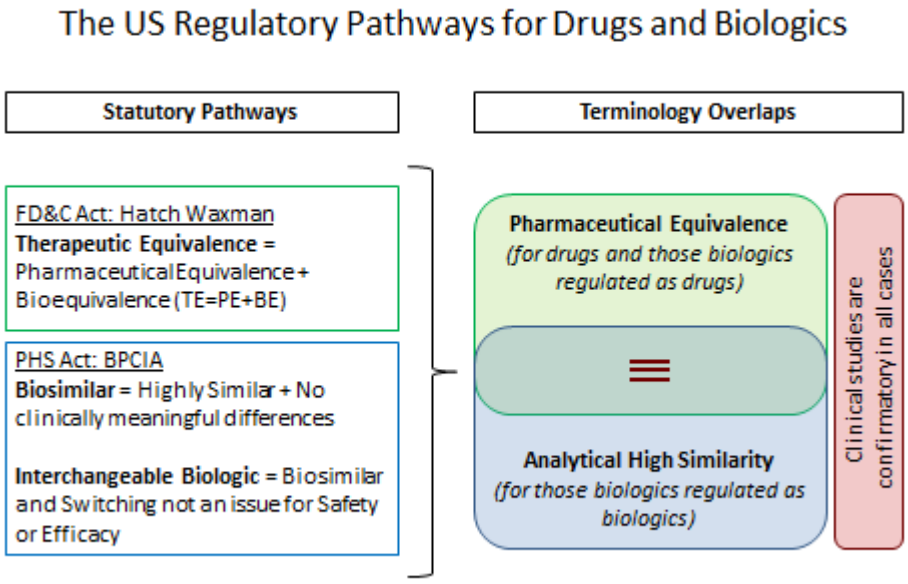
Just as with the regulation of generics, biosimilarity is grounded in analytical data (albeit in this case an analysis of head-to-head data on the biosimilar and its reference, rather than the more routine chemical identity analyses for most small molecule drugs). However, comparative analytical data does not appear in the label for any drug or biologic, irrespective of the regulatory pathway it was approved under. The table below provides a previously published summary[22] of those aspects of biosimilarity that are more like small molecule generics and those that resemble novel molecular entities. Of critical importance here, a biosimilar relies on demonstrating "high similarity" to its reference product and the prior finding of safety and efficacy for that reference product. This is the same regulatory concept as for generic when "sameness" to its reference drug is demonstrated and the generic can then rely on the prior finding of safety and effectiveness for that reference product.

<table>
<tr><th>Novel Molecular Entity</th><th>Biosimilar/
Interchangeable Biologic</th><th>Small Molecule Generic</th></tr>
<tr><td>Unmet Need: Lack of therapeutic options</td><td colspan="2">Already therapeutic options, but may be lack of access through affordability challenges</td></tr>
<tr><td>Often novel mechanism of action (MOA)</td><td colspan="2">Established MOA</td></tr>
<tr><td>Routine analytics</td><td>Exceptional Analytics</td><td>Routine analytics</td></tr>
<tr><td>Broad clinical development program</td><td>Tailored clinical studies to confirm biosimilarity</td><td>Limited confirmatory clinicals (BE)</td></tr>
<tr><td>Demonstration de novo efficacy & safety</td><td colspan="2">Relies on prior finding of safety and efficacy of reference</td></tr>
<tr><td colspan="2">Expertise in therapeutic area fundamental</td><td>Clinical expertise unnecessary</td></tr>
<tr><td colspan="3">Quality Manufacturing Essential (cGMP)</td></tr>
</table>

Derived from: McCamish et al. (2015), Toward interchangeable biologics. CPT. doi: 10.1002/cpt.39, available at: http://onlinelibrary.wiley.com/doi/10.1002/cpt.39/full

As such, conceptually, the requirement for high similarity of a biosimilar to the reference biologic combines two key elements:

- The FD&C Act[23]/ Hatch-Waxman[24] expectations for pharmaceutical equivalence of generics with the fundamental premise that because of its "sameness" to the reference product there is an expectation for the same outcomes clinically (differing for biosimilars in that minor differences are expressly permissible as long as they are demonstrated not to be clinically meaningful[25]), as acknowledged by FDA,[26] and
- The scientific and medical expectations gained by the study and use of originator biologics, which create the efficacy and safety profile of the reference products, are relevant to the biosimilar. This includes both the understanding at its initial approval and the subsequent clinical experience during the evolution of that biologic's use over its life time.



In the context of the second point, it is important to recognize that biologic reference products are not identical molecules from batch to batch, and they can have substantial modifications induced by manufacturing changes over the life time of the product. There is a regulatory process of "comparability" assessments[27] mandated by regulatory authorities using established regulatory science and a determination of "sameness" as is used in the process of evaluating a biosimilar. Similarly, the analytic test data supporting manufacturing changes using comparability (in this case head-to-head data comparing the pre- and post-manufacturing change product) do not appear in the label and are not publicly recorded in the US at all (as they are in Europe).[28] Nonetheless, these manufacturing changes, as overseen by the regulators, are appropriate and necessary and while they can result in variations in the products over time, they are all with the expectation of no clinically meaningful differences in outcomes for patients.[29]

3. The Regulatory Basis for the Label Format for Generics and Biosimilars is the Same

The BPCIA does not contain provisions for labeling biosimilars. Further, while the broader PHS Act regulates biologics, no provision in the PHS Act directly addresses the labeling of biologics. However, all biologics are also drugs and are subject to the FD&C Act as specifically stated in the PHS Act.[30] Therefore, one must infer that the regulatory requirements for labeling of biosimilars must be based on those already in place for other pharmaceutical agents. Accordingly, all branded drugs, generic drugs, drugs approved under the 505(b)(2) pathway, biologics and biosimilars are labeled in accordance with the FD&C Act.

Therefore, it is wholly appropriate for FDA to extend the regulatory policies it has followed in the labeling of other therapeutic agents, including generics, when deciding on a label format for biosimilars. In addition, the overlap in regulatory terminology to describe the "sameness" of the active ingredient of a medicine between a generic and a biosimilar (see Figure 2) provides further support for the appropriateness of a "same-label" format for biosimilars. All drugs (including generics) and all biologics (including biosimilars) must subscribe to the same principles when it comes to labeling, as well as to what is mislabeled and misbranded.[31]

4. Application of FDA's Extensive Prior Experience with Medicinal Products

FDA has a strong history as a science-based agency, approving medicinal products through numerous different statutory pathways and applying consistent labeling requirements and guidance for both biologics and drugs.[32] As described in greater detail below, there is no reason for biosimilars to deviate from this well-established system.

FDA's experience with small molecule drug generics, biologics regulated as drugs and approved as generics, and the Agency's extensive experience with biologics (initial approvals and over their lifetimes) are all relevant to and reflected in the conclusion that FDA has reached with the labeling of this first biosimilar.

FDA's experience in the review of biologics extends from those that are naturally sourced to more recently those manufactured using recombinant technology. Biosimilars, by definition, reference an FDA-licensed biological product with which all stakeholders have had experience with (including familiarity with the label) for at least 12 years (the exclusivity period defined for biologics in BPCIA before which FDA cannot license a subsequent product as a biosimilar or interchangeable biologic). In the case of Zarxio™, the reference product Neupogen® (filgrastim) was licensed February 20, 1991, giving stakeholders a full 24 years of experience with the reference biologic before the biosimilar was approved on March 6, 2015.

Furthermore, FDA has extensive experience monitoring the safety and quality of all biologics licensed in the US - both at initial licensure as well as through all manufacturing changes to those biologics after approval. In the latter case, the Agency has had to consider potentially clinically meaningful differences, including immunogenicity, each and every time a manufacturing change was submitted by a manufacturer for approval. FDA led the world in applying an analytical approach to biologics subject to manufacturing changes – implemented as the Comparability Protocol[33] -- as a way to minimize unnecessary clinical studies. Head-to-head comparability, developed by the Agency in 1996 alongside the originator industry, is soundly science-based and relies on the same regulatory concepts as biosimilarity. Further, it was achieved entirely through guidance, no statutory changes being considered necessary at the time (and this was ultimately affirmed by the Courts[34]). Comparability to support manufacturing changes was formalized across the highly regulated markets as ICH Q5E, and adopted in the US in 2005 with full transparency through FDA notice and comment rulemaking.[35] BPCIA uses the same terminology as ICH Q5E, with highly similar quality attributes being integral to FDA decisions in both cases.[36]

We recognize that "highly similar" first appears as a term of art in US law in BPCIA. However, biosimilarity and comparability to support manufacturing changes share the same science, relevant here in that head-to-head comparability studies have allowed FDA to accumulate extensive pertinent experience about biologics that the Agency can now apply to biosimilarity.[37] This includes experience with cutting edge methodology as it is developed and refined, evaluating the ability to detect differences with these methods and experience in understanding the limitations of each of the assays.[38]

Critical to the labeling discussion, ***in both cases a modified development program (when compared to a standalone 351(a) development program) is able to define the biologic as a regulatory matter. Instead, a targeted development program based on application of head-to-head analytical and functional assays in place of less sensitive clinical studies is used.*** And notably, both comparability[39] and biosimilarity recognize the unique concerns that immunogenicity can present.[40]

Comparable [as defined in ICH Q5E[41]]:

"A conclusion that products have highly similar quality attributes before and after manufacturing process changes and that no adverse impact on the safety or efficacy, including immunogenicity, of the drug product occurred. This conclusion can be based on an analysis of product quality attributes. In some cases, nonclinical or clinical data might contribute to the conclusion."

Notably, when FDA approves manufacturing changes the product is highly similar to, and interchangeable with, the pre-manufacturing change product, and there is complete extrapolation of indications.[42] As mentioned above, the use of comparability is not transparent in the US - the label does not change as the physician and patient are expected to use the product in the same manner as before the manufacturing change occurred (in Europe the use of comparability in support of manufacturing changes is public and available as part of the regulatory correspondence posted by EMA[43]). Notably, patients are switched from the pre-change to the post-change product appropriately and we are aware of no evidence either in terms of safety or efficacy that such switching is a problem.[44] In fact, both pre- and post- change product can be available in the market concurrently.

FDA also has experience with a number of products that are biologics in science, but which for historical reasons were regulated as drugs,[45] and as such are products for which the generic pathways have been available since 1984[46]. This includes our own product Omnitrope® (somatropin), approved as the first biosimilar in Europe in 2006, and in the US that same year as a 505(b)(2) drug – in both jurisdictions referencing Genotropin® (somatropin), approved in the US on August 24, 1995. Similarly, FDA has approved generics to Lovenox® (enoxaparin), a naturally-sourced complex sugar mixture originally approved on March 29, 1993, with our own enoxaparin ANDA in 2010[47], and two more in 2012[48] and 2014[49], respectively; and our generic to Copaxone® (glatiramer acetate), a synthetic mixture of peptides of up to 200 amino acids (larger than the single active ingredient in either filgrastim or somatropin) on April 16th, 2015[50].

Collectively, from these biologics, plus multiple other biologics approved under the FD&C Act regulatory pathways, as well as all the PHS Act reference products that are candidates for biosimilars, FDA has become one of the most experienced regulatory agencies in the world regarding biologics. FDA's extensive and pertinent experience has informed the Agency how to regulate biosimilars, even as we recognize that Zarxio™ (filgrastim-sndz) is the first biosimilar approved under the PHS Act 351(k) pathway.

5. Transparency is Equally Important for All Medicines

We support the need for transparency in regulatory decision-making for all medicines, including for biosimilar products. However, the CP fails to recognize the distinction between the purpose of the information provided on the label (to inform the prescriber for the specific purpose of their health-care decisions for their specific patient), and the vast array of data that are available more broadly to all stakeholders interested in the product itself and how FDA reached its decision to license the product for the uses indicated. A "same-label" model for biosimilars is designed to provide a clear and complete set of information needed to make a fully informed healthcare decision. Other information used for making the regulatory judgement of similarity is included in the summary basis of approval available to all.

Again, unless information is meaningful and adds value for prescribers in their prescribing decisions it should not be added to the label. Such information distracts from and fails to inform the patient-centered decisions that need to be made. The data generated for the licensure of the biosimilar (analytical/functional, nonclinical and clinical) is far too extensive for all of it to be included in the label.[51] Inclusion of non-essential data in the product label places an additional burden on the prescriber to review and assimilate information that does not support the selection of an appropriate prescribing option for patients. The CP obliquely acknowledges this fact by asking only for a "concise description of the pertinent data"[52] which in the case of biosimilars is the analytical data.

The information available on an FDA-approved product is not limited to that contained in the label, and many other available sources contain vastly more information. These include, for example:

- Data from clinical trials on biosimilars published on clinicaltrials.gov.
- The Summary Basis of Approval and other FDA review documents and in-depth discussions posted at FDA.gov.
- The Purple Book[53] (FDA's biosimilar equivalent to the Orange Book[54] for small molecule drugs), which comprises a list of biosimilars, interchangeable biologics and their reference products.[55]
- Published, peer-reviewed, scientific and medical literature on studies as well as the use of biosimilars available in the same manner as for all other biologics, indeed all other medicines.
- For a clinical study conducted at least in part in Europe, study details and results are published on the website of the European Medicines Agency.

Meanwhile, over a product´s lifetime, the information in the label evolves when, upon scientific evaluation, FDA judges further information on the product pertinent for the use of the product (e.g., new signals in clinical studies or post-marketing surveillance). Labels on all medicines should be kept current and updated in a timely manner.

There is already considerable publically available information about all FDA-approved and licensed products and much is available pre-licensure as well as post-licensure (the label being only post-licensure). This will be the case for biosimilars too, and already is for our own product Zarxio™ (filgrastim-sndz). The information is transparent and available to everyone, much of it on FDA's website.

We note that published reports from European regulators have revealed that some products have undergone close to 40 manufacturing changes after initial product approval.[56] It is entirely reasonable to assume that similar manufacturing changes were implemented in the US as well. Published data has shown that some of these changes have introduced changes in critical quality attributes that can be readily detected by analytical methods.[57] Presumably, the manufacturers provided convincing evidence to health authorities that these changes do not impact safety or efficacy. Nonetheless, these changes are not publicly reported in the US and they certainly are not provided in the product label as such information does not provide further guidance to the physician for the safe use of the product. As noted previously, both pre- and post- change product can be available in the market concurrently. We note that when the authors of the CP call for "full transparency," they appear to miss the fact that "full transparency" consistently applied would have to apply to their own products as well.

6. The Purple Book is the Orange Book for Biologics when it comes to Substitutability

Significantly, the CP misses one additional key source of information on both biosimilarity and interchangeability -- the Purple Book -- which was created by FDA subsequent to the Agency issuing its draft guidance on "Scientific Considerations in Demonstrating Biosimilarity to a Reference product" in

2012.[58] The publishing and multiple updates to the Purple Book supersede the CP's concern with the changes between the February 2012 draft guidance and its finalization by FDA this year.

The Purple Book has already been updated *after* the final guidance was issued, and updates will continue to be made as needed and much more rapidly than changes to any product label could ever allow. Updating labels for products is routine, but not feasible in real time to nearly the same extent as those updates that will be provided in the Orange and Purple Books. FDA routinely permits manufacturers to phase in the use of new labels that are supplied in the field with product so as to not disrupt product supply. The Purple Book will likely be more current given that it is maintained by FDA as an on-line resource, just like the Orange Book.

Furthermore, what the prescriber needs to know – and what the label needs to show -- is that FDA has determined a biologic to be safe and effective for use as indicated. It is not relevant from the perspectives of safety and efficacy that a product is or is not approved as a biologic, biosimilar or interchangeable biologic.[59] FDA maintains this data in the Purple Book and it is not needed on a biosimilar product's label – not because it is being hidden but because it is not pertinent to the prescribing decision by a physician and for whom the label is written[60]. That the interchangeable biologic will be a biosimilar on which additional switching studies have been conducted, and the product itself will not change, further makes the point.[61]

With regards to interchangeability, if, as the CP maintains, it is important to note in the product label that a biosimilar and its reference are interchangeable, it unavoidably follows that the reference product's label must be amended as well to make it clear to prescribers that the reference product is also interchangeable, or not, with the biosimilar(s). There is no reasonable basis for selective application of clarity only to the labels of interchangeable biologics and not their reference products.

Importantly, BPCIA defines interchangeability as a designation created for FDA to use when the Agency concurs with the sponsor that substitution of the interchangeable biologic for its reference product can be safely performed by the pharmacist without the involvement of the original prescriber. As defined in BPCIA:

> ''The term 'interchangeable' or 'interchangeability' [ ] means that the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product."[62]

The CP (as well as other submissions to this docket) misconstrues this fundamental concept.[63] An interchangeability designation by FDA is not directly relevant to the prescriber, who can already prescribe a product as they believe appropriate for their patient, including for indications not on the label at all.

In contrast, a FDA designation of interchangeability is directly relevant to pharmacists. For them, it is intended to convey that they can substitute interchangeable biologics for their reference products during the course of treatment for a given patient, as recognized under state laws of pharmacy in the manner of therapeutic equivalence of a generic drug (known as an A-rating in the Orange Book). In the generic drug context, pharmacists routinely use the Orange Book to identify therapeutic equivalents, enabling substitution (as governed by state law). Similarly, the Purple Book fills this role for biologics and biosimilars, and will allow pharmacists to identify interchangeable biologics and their reference products when such products are so designated by FDA. FDA has yet to list a designated interchangeable biologic

in the Purple Book, but the Agency has indicated that it anticipates receiving applications for such products in 2015 and 2016.[64]

FDA established the Purple Book to identify important information about originator, biosimilar and interchangeable biologic products. This builds on the Agency's historic approach to generic drugs with the Orange Book. It makes sense for FDA to apply very similar versions of current systems with which pharmacists and other stakeholders are familiar, especially as this is a successful system that has safely handled originator and generic drugs for decades. There is no reason to believe that this model will not work for biologics, biosimilars and interchangeable biologics too.

The Orange Book also functions as the primary data source for the various computer systems that work behind the scenes to support the safe provision of medicines in various healthcare settings from retail pharmacies to hospitals.[65] FDA is now building upon and extrapolating to biosimilars and interchangeable biologics this transparent and proven system. Again, the Orange Book is maintained in real time by FDA and is available online. The Purple Book will have the equivalent role for biologics – both biosimilars and interchangeable biologics will be listed, and updates can also be as timely.

Finally, FDA has never indicated on the label of any product the regulatory pathway through which the Agency approved the product. For example, for drugs where multiple regulatory pathways have been available since 1984, whether they are approved as a 505(b)(1), 505(b)(2) or 505(j) is not considered relevant to their labeling. Interchangeability or lack thereof is not listed on the label for 505(b)(2) or 505(j) products (including those biologics regulated as drugs). Nonetheless, FDA does list therapeutic equivalence at drugs@FDA, as well as in the Orange Book[66], and does the same for biosimilars in the Purple Book[67]. Thus, whether a biologic is approved via the 351(k) or 351(a) pathway is already transparent and available, just not indicated on the label as this information is not needed by the physician to appropriately prescribe the drug.

Conclusion

Our experience as the product's sponsor gives us particularly pertinent understanding as to the reasoning behind the label for Zarxio™. We agree with FDA that the label format applied to Zarxio™ is appropriate and accurate for advising health care providers on how to use this product. And we believe this should be the basis for US labels for future biosimilars. All biologics, including biosimilars, approved by FDA are safe, pure and potent for their conditions of use and must be so labelled, and consequently the label for Zarxio™ must match that of its reference product Neupogen®. The labeling of Zarxio™ is entirely consistent with the authority given to FDA in BPCIA.

We applaud the process by which the Agency is implementing the regulatory framework to allow safe and effective biosimilars to become available for US patients. We believe that the Agency's approach for biosimilar review provides reassurance to prescribers, patients and other stakeholders as to the quality of these products. The label format chosen by the Agency focuses, as it should, on what the physician needs to know in order to make the appropriate prescribing decision for his or her patient.

We want to thank FDA for the time and interest the Agency took in reviewing our application for Zarxio™, and we look forward to working with the Agency on many more applications in the future so that Americans can enjoy the benefits of the biosimilar pathway. This will enable patients in the US to achieve greater access to these often life-saving biological medicines, knowing that they will be of the same quality, and as safe, pure and potent as their reference products. Consistency in the development, regulatory

review and approval of biosimilars can instill confidence regarding biosimilars in US patients and physicians just as has occurred in Europe and elsewhere. Only then will the public health benefit offered by biosimilars be more broadly and fully realized.

Yours sincerely

Mark McCamish, MD, PhD

Acronyms:
ANDA = Abbreviated New Drug Application (505(j) pathway)
BPCIA = Biologics Price Competition and Innovation Act of 2009
CP = AbbVie' Citizen Petition docket FDA-2015-P-2000
EMA = European Medicines Agency
FDA = Food and Drug Administration
FD&C Act = Federal Food Drug and Cosmetic Act
cGMP = Current Good Manufacturing Practices
Hatch Waxman Act = Drug Price Competition and Patent Term Restoration Act of 1984
ICH = International Committee on Harmonization
NDA = New Drug Application
PHS Act = Public Health Service Act
PPACA or ACA = Patient Protection and Affordable Care Act of 2010

Endnotes:

[1] We incorporate by reference all cited materials in these endnotes.

[2] AbbVie Citizen Petition dated June 2, 2015, and Supplement to Citizen Petition dated August 10, 2015, docket number: FDA-2015-P-2000, available at: http://www.regulations.gov/#!documentDetail;D=FDA-2015-P-2000-0001 (accessed August 19, 2015).

[3] We have chosen not to discuss the nonproprietary name in this correspondence, but would note that the Novartis Group of companies has the position that the same nonproprietary name should be given to a biosimilar as for its reference, just as occurs for our biosimilars in Europe, and indeed for the product discussed here where it is known as Zarzio™ (filgrastim).

[4] FDA Guidance "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009", April 2015. Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm444661.pdf (accessed August 19, 2015).

[5] EMA, Questions and answers on biosimilar medicines (similar biological medicinal products), EMA/837805/2011, September 27, 2012, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf (accessed August 19, 2015).

[6] 42 U.S.C. §262. Regulation of biological products, available at: http://www.gpo.gov/fdsys/pkg/USCODE-2010-title42/pdf/USCODE-2010-title42-chap6A-subchapII-partF-subpart1-sec262.pdf (accessed August 19, 2015).

[7] TITLE VII: IMPROVING ACCESS TO INNOVATIVE MEDICAL THERAPIES. Subtitle A: Biologic Price Competition and Innovation (BPCI Act) provisions of the Patient Protection and Affordable Care Act (PPACA), available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf (accessed August 19, 2015).

[8] 21 CFR § 201.56 (a)(1)-(2). Requirements on content and format of labeling for human prescription drug and biological products, available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.56 (accessed August 19, 2015).

> *Sec. 201.56 Requirements on content and format of labeling for human prescription drug and biological products.*
>
> *(a) General requirements . Prescription drug labeling described in 201.100(d) must meet the following general requirements:*
>
> *(1) The labeling must contain a summary of the* ***essential scientific information needed for the safe and effective use of the drug.***
>
> *(2) The labeling must be informative and accurate and neither promotional in tone nor false or misleading in any particular. In accordance with 314.70 and 601.12 of this chapter, the labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading.*
>
> *(3) The labeling must be based whenever possible on data derived from human experience. No implied claims or suggestions of drug use may be made if there is inadequate evidence of safety or a lack of substantial evidence of effectiveness. Conclusions based on animal data but necessary for safe and effective use of the drug in humans must be identified as such and included with human data in the appropriate section of the labeling.*
>
> [emphasis added]

[9] For biologics, the regulatory standard under 42 U.S.C. §262 (PHS Act) is "safety, purity and potency," but we use the term "safety and efficacy" throughout this correspondence to cover both drugs and biologics. See FDA Draft Guidance for Industry: "Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act," August 2014, FN15, available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm407844.pdf (accessed August 19, 2015):

> *The standard for licensure of a biological product as "potent" under section 351(a) of the PHS Act has long been interpreted to include effectiveness (see 21 CFR 600.3(s) and the guidance for industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products). In that guidance,* ***we use the terms "safety and effectiveness" and "safety, purity, and potency" interchangeably in the discussions pertaining to biosimilar products.*** [emphasis added]

[10] 21 CFR § 201.56 (a)(1)-(2). Requirements on content and format of labeling for human prescription drug and biological products, available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.56 (accessed August 19, 2015), and
FDA website: PLR Requirements for Prescribing Information, updated July 1, 2015, available at: http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/lawsactsandrules/ucm084159.htm (accessed August 19, 2015)

[11] FDA website: Drugs@FDA Glossary of Terms, "Label," updated Feb. 2, 2012, available at: http://www.fda.gov/drugs/informationondrugs/ucm079436.htm (accessed August 19, 2015).

[12] FDA Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements, February 2013, available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075082.pdf (accessed August 17, 2015).

[13] Biologics regulated as drugs are those that are regulated under the Federal Food, Drug & Cosmetic Act (FD&C Act) rather than the Public Health Service Act (PHS Act).

[14] AbbVie Citizen Petition dated June 2, 2015, subsection 4 on page 15, docket number: FDA-2015-P-2000, available at: http://www.regulations.gov/#!documentDetail;D=FDA-2015-P-2000-0001 (accessed August 19, 2015).

[15] TITLE VII: IMPROVING ACCESS TO INNOVATIVE MEDICAL THERAPIES. Subtitle A: Biologic Price Competition and Innovation (BPCI Act) provisions of the Patient Protection and Affordable Care Act (PPACA), available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf (accessed August 19, 2015).

[16] FDA Draft Guidance for Industry: "Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act," August 2014, FN15, available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm407844.pdf (accessed August 17, 2015):

> *The standard for licensure of a biological product as "potent" under section 351(a) of the PHS Act has long been interpreted to include effectiveness (see 21 CFR 600.3(s) and the guidance for industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products). In that guidance,* ***we use the terms "safety and effectiveness" and "safety, purity, and potency" interchangeably in the discussions pertaining to biosimilar products.*** [emphasis added]

[17] Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) (commonly referred to as the Hatch-Waxman Act) outlining abbreviated regulatory pathways 505(j) and 505(b)(2), available at: http://www.gpo.gov/fdsys/pkg/STATUTE-98/pdf/STATUTE-98-Pg1585.pdf (accessed August 19, 2015).

[18] Woodcock J. et al, "The FDA's Assessment of follow-on protein products: a historical perspective," *Nature Reviews Drug Discovery*, 6, 437-442 (June 2007), at page 438:

> *This approach also reflects the FDA's longstanding policy of permitting appropriate reliance on what is already known about a drug, thereby saving time and resources in drug development and approval processes and* ***avoiding ethical concerns associated with unnecessary duplication of human or animal testing.*** [emphasis added]

[19] FDA Briefing Document for the Oncologic Drugs Advisory Committee, January 7, 2015,BLA 125553, EP2006, a proposed biosimilar to Neupogen® (filgrastim), Sandoz Inc., a Novartis company, available at: http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/oncologicdrugsadvisorycommittee/ucm428780.pdf (accessed August 19, 2015).

[20] Public statement of Dr. John Jenkins during discussion of biosimilars at RPM Summit, Washington DC, 2013.

[21] EMA, Questions and answers on biosimilar medicines (similar biological medicinal products), EMA/837805/2011, September 27, 2012, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf (accessed August 17, 2015), see page 1: What is a biosimilar medicine?:

*The active substance of a biosimilar and its reference medicine is **essentially the same biological substance**, though there may be minor differences due to their complex nature and production methods. Like the reference medicine, the biosimilar has a degree of natural variability. When approved, its variability and any differences between it and its reference medicine will have been shown not to affect safety or effectiveness.*[emphasis added]

[22] McCamish M, Pakulski J, Sattler C, and G Woollett, "Toward interchangeable biologics," *Clinical Pharmacology & Therapeutics*, 97(3):215-17 (March 2015), available at: http://onlinelibrary.wiley.com/doi/10.1002/cpt.39/pdf(accessed August 19, 2015).

[23] FD&C Act Chapter V: Drugs and Devices, updated July 13, 2015, available at: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/FDCActChapterVDrugsandDevices/default.htm (accessed August 19, 2015).

[24] Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) (commonly referred to as the Hatch-Waxman Act), available at: http://www.gpo.gov/fdsys/pkg/STATUTE-98/pdf/STATUTE-98-Pg1585.pdf (accessed August 19, 2015).

[25] FDA Guidance for Industry: "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009," April 2015, available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm444661.pdf (accessed August 19, 2015), pages 3-4:

*Section 351(k) of the PHS Act (42 U.S.C. 262(k)), added by the BPCI Act, sets forth the requirements for an application for a proposed biosimilar product and an application or a supplement for a proposed interchangeable product. Section 351(i) defines biosimilarity to mean "that the biological product is highly similar to the reference product **notwithstanding minor differences in clinically inactive components**" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product" (see section 351(i)(2) of the PHS Act).*[emphasis added]

[26] FDA Guidance for Industry: "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009," April 2015, available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm444661.pdf (accessed August 17, 2015), page 3:

BACKGROUND

*The BPCI Act was enacted as part of the Affordable Care Act on March 23, 2010. The BPCI Act creates an abbreviated licensure pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product. **The objectives of the BPCI Act are conceptually similar to those of the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) (commonly referred to as the "Hatch-Waxman Act"),** which established abbreviated pathways for the approval of drug products under the Federal Food, Drug, and Cosmetic Act (FD&C Act).[3]* [emphasis added]

[3]*See section 505(b)(2) and 505(j) of the FD&C Act (21 U.S.C. 355(b)(2) and 355(j)).*

[27] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline: "Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process **Q5E,**" November 18, 2004, at page 11, available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf (accessed August 17, 2015).

[28] Schneider C. "Biosimilars in Rheumatology: the Wind of Change," *Am Rheum Dis* 72(3):315-318 (March 2013), available at: http://ard.bmj.com/content/72/3/315.full.pdf (accessed August 19, 2015).

While the author provides data on the number of manufacturing changes for Europe, similar changes will have been undertaken for the US, where the use of comparability is not public.

[29] Schiestl M., Stangler T., Torella C., Cepeljnik T., Toll H., Grau R. Acceptable Changes in Quality Attributes of Gylcosylated Biopharmaceuticals, Nature Biotechnology, Volume 29, Number 4, Pages 310-312 (April 2011).

[30] 42 U.S.C. §262. Regulation of biological products, available at: http://www.gpo.gov/fdsys/pkg/USCODE-2010-title42/pdf/USCODE-2010-title42-chap6A-subchapII-partF-subpart1-sec262.pdf (accessed August 19, 2015).

[31] Labeling and misbranding provisions of the FD&C Act (sections 501, 502 and 508)–these represent a single set of requirements for all medicines; no such provisions are found in the PHS Act (42 U.S.C. §262). See FD&C Act Chapter V: Drugs and Devices, updated July 13, 2015, available at: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/FDCActChapterVDrugsandDevices/default.htm (accessed August 19, 2015).

[32] FDA Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements, February 2013, available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075082.pdf (accessed August 19, 2015).

[33] FDA, Guidance: Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products (Apr. 1996), available from: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122879.htm (accessed August 19, 2015).

[34] See *Berlex Laboratories, Inc. v. FDA*, 942 F. Supp. 19 (D.D.C. 1996).

[35] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline: "Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process **Q5E,**" November 18, 2004, at page 11, available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf (accessed August 19, 2015).

[36] ICH Q5E defines "Comparable" as: "A conclusion that products have highly similar product quality attributes…," and BPCIA's required information to demonstrate biosimilarity includes (unless waived) "analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components…" See International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline: "Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process **Q5E,**" November 18, 2004, at page 11, available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf (accessed August 19, 2015); and
TITLE VII: IMPROVING ACCESS TO INNOVATIVE MEDICAL THERAPIES. Subtitle A: Biologic Price Competition and Innovation (BPCI Act) provisions of the Patient Protection and Affordable Care Act (PPACA), available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf (accessed August 19, 2015).

[37] Schneider C. "Biosimilars in Rheumatology: the Wind of Change," *Am Rheum Dis* 72(3):315-318 (March 2013), available at: http://ard.bmj.com/content/72/3/315.full.pdf (accessed August 19, 2015).

While the author provides data on the number of manufacturing changes for Europe, similar changes will have been undertaken for the US, where the use of comparability is not public.

[38] By definition, the use of analytical studies over the lifetime of an originator reference biologic using comparability will predate the analytics used to approve a biosimilar, given that a biosimilar cannot be approved less than 12 years from the initial date of licensure of the reference product. Clearly some reference products will have been subject to more manufacturing changes than others.

[39] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline: "Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process **Q5E,**" November 18, 2004, definition of comparability at page 11, available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf (accessed August 19, 2015).

[40] In the Eprex® and PRCA example, immunogenicity problems occurred with the post-change product and not with switching between pre- and post- change product. The safety problem was identified through a metadata analysis, not through routine surveillance, and then the relationship was traced back to particular batches of a single product, but only after the connection of PRCA was identified. See Casadevall, N. "Immune-response and adverse reactions: PRCA case example," presentation available at: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2009/11/WC500011064.pdf (accessed August 19, 2015).

[41] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline: "Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process **Q5E,**" November 18, 2004, definition of comparability at page 11, available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf (accessed August 19, 2015).

[42] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline: "Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process **Q5E,**" November 18, 2004, definition of comparability at page 11, available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf (accessed August 19, 2015).

[43] Schneider C. "Biosimilars in Rheumatology: the Wind of Change," *Am Rheum Dis* 72(3):315-318 (March 2013), available at: http://ard.bmj.com/content/72/3/315.full.pdf (accessed August 19, 2015). While the author provides data on the number of manufacturing changes for Europe, similar changes will have been undertaken for the US, where the use of comparability is not public.

[44] In the Eprex® and PRCA example, immunogenicity problems occurred with the post-change product and not with switching between pre- and post- change product. The safety problem was identified through a metadata analysis, not through routine surveillance, and then the relationship was traced back to particular batches of a single product, but only after the connection of PRCA was identified. See Casadevall, N. "Immune-response and adverse reactions: PRCA case example," presentation available at: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2009/11/WC500011064.pdf (accessed August 19, 2015).

[45] The biologics regulated as drugs essentially comprise the hormones and this assignment was based on where the expertise lay at the Agency at the time of their initial approval. This assignment of products

was well prior to the reorganization in 2003 when recombinant products were assigned to CDER but the latter stayed as PHS Act licensed BLAs (i.e., licensed under 42 U.S.C. §262). See FDA website, "Transfer of Therapeutic Products to the Center for Drug Evaluation and Research (CDER)," updated April 15, 2015, available at: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133463.htm (accessed August 19, 2015).

[46] Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) (commonly referred to as the Hatch-Waxman Act), available at: http://www.gpo.gov/fdsys/pkg/STATUTE-98/pdf/STATUTE-98-Pg1585.pdf (accessed August 19, 2015).

[47] FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (The Orange Book), 35th Edition (2015), available at: http://www.fda.gov/downloads/drugs/developmentapprovalprocess/ucm071436.pdf (accessed August 19, 2015). See page 3-130, listing Sandoz's enoxaparin (ANDA July 23, 2010) as A rated.

[48] FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (The Orange Book), 35th Edition (2015), available at: http://www.fda.gov/downloads/drugs/developmentapprovalprocess/ucm071436.pdf (accessed August 19, 2015). See page 3-129, listing Amphastar's enoxaparin (ANDA September 19, 2011) as A rated.

[49] FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (The Orange Book), 35th Edition (2015), available at: http://www.fda.gov/downloads/drugs/developmentapprovalprocess/ucm071436.pdf (accessed August 19, 2015). See page 3-130, listing Teva's enoxaparin (ANDA June 23, 2014) as A rated.

[50] Sandoz's Glatopa® (glatiramer acetate) ANDA approval letter, April 16, 2015, available at: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/090218Orig1s000ltr.pdf (accessed August 19, 2015).

[51] 21 CFR § 201.56 (a)(1)-(2). Requirements on content and format of labeling for human prescription drug and biological products, available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.56 (accessed August 19, 2015).

> *Sec. 201.56 Requirements on content and format of labeling for human prescription drug and biological products.*
>
> *(a) General requirements . Prescription drug labeling described in 201.100(d) must meet the following general requirements:*
>
> *(1) The labeling must contain a summary of the* ***essential scientific information needed for the safe and effective use of the drug.***
>
> *(2) The labeling must be informative and accurate and neither promotional in tone nor false or misleading in any particular. In accordance with 314.70 and 601.12 of this chapter, the labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading.*
>
> *(3) The labeling must be based whenever possible on data derived from human experience. No implied claims or suggestions of drug use may be made if there is inadequate evidence of safety or a lack of substantial evidence of effectiveness. Conclusions based on animal data but necessary for safe and effective use of the drug in humans must be identified as such and included with human data in the appropriate section of the labeling.*
>
> [emphasis added]

[52] AbbVie Citizen Petition dated June 2, 2015, docket number: FDA-2015-P-2000, available at: http://www.regulations.gov/#!documentDetail;D=FDA-2015-P-2000-0001 (accessed August 19, 2015). See ask (c) on page 1.

[53] FDA website: "Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations," updated July 27, 2015, available at: http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm411418.htm (accessed August 19, 2015).

[54] FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (The Orange Book), 35th Edition (2015), available at: http://www.fda.gov/downloads/drugs/developmentapprovalprocess/ucm071436.pdf (accessed August 19, 2015). Also available at FDA's website: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm (accessed August 19, 2015) (current through July 2015).

[55] The Purple Book was created by FDA subsequent to the issuance in 2012 of the Agency's draft guidance on "Scientific Considerations in Demonstrating Biosimilarity to a Reference product."

[56] Schneider C. "Biosimilars in Rheumatology: the Wind of Change," *Am Rheum Dis* 72(3):315-318 (March 2013), available at: http://ard.bmj.com/content/72/3/315.full.pdf (accessed August 19, 2015).

[57] Schiestl M., Stangler T., Torella C., Cepeljnik T., Toll H., Grau R. Acceptable Changes in Quality Attributes of Gylcosylated Biopharmaceuticals, Nature Biotechnology, Volume 29, Number 4, Pages 310-312 (April 2011).

[58] AbbVie Citizen Petition dated June 2, 2015, docket number: FDA-2015-P-2000, available at: http://www.regulations.gov/#!documentDetail;D=FDA-2015-P-2000-0001 (accessed August 19, 2015). See asks (a) and (b) on page 1.

[59] Biologic (351(a)), biosimilar (351(k)) and interchangeable biologic (351(k)) are the three options for biologics created in the PHS Act, as amended by BPCIA in 2010

[60] 42 U.S.C. § 262 (i)(3). TITLE VII: IMPROVING ACCESS TO INNOVATIVE MEDICAL THERAPIES. Subtitle A: Biologic Price Competition and Innovation (BPCI Act) provisions of the Patient Protection and Affordable Care Act (PPACA), available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf (accessed August 19, 2015):

> *(3) The term "interchangeable" or "interchangeability", in reference to a biological product that is shown to meet the standards described in subsection (k)(4), means that the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.*

[61] McCamish M, Pakulski J, Sattler C, and G Woollett, "Toward interchangeable biologics," *Clinical Pharmacology & Therapeutics*, 97(3):215-17 (March 2015), available at: http://onlinelibrary.wiley.com/doi/10.1002/cpt.39/pdf (accessed August 19, 2015).

[62] 42 U.S.C. § 262 (i)(3). TITLE VII: IMPROVING ACCESS TO INNOVATIVE MEDICAL THERAPIES. Subtitle A: Biologic Price Competition and Innovation (BPCI Act) provisions of the Patient Protection and Affordable Care Act (PPACA), available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf (accessed August 19, 2015).

[63] Amgen submission to AbbVie Citizen Petition, docket number: FDA-2015-P-2000 would appear to imply that the physician needs to know whether the product is designated as interchangeable by FDA or not, and that such a designation represents a higher approval standard, whereas the

interchangeability designation is to advise the dispenser (subject to state law), not the prescriber (see endnote 60, above). Comment from Amgen available at: http://www.regulations.gov/#!documentDetail;D=FDA-2015-P-2000-0005 (accessed August 19, 2015).

[64] FDA Federal Register Notice: "Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; General Licensing Provisions; Section 351(k) Biosimilar Applications, 80 FR 37635, July 1, 2015, docket No. FDA-2012-N-0129, available at: http://www.gpo.gov/fdsys/pkg/FR-2015-07-01/pdf/2015-16128.pdf (accessed August 19, 2015) (anticipating 5 biosimilar and 2 interchangeable biologics applications)

[65] National Council for Prescription Drug Programs, letter to FDA dated June 6, 2014 and attached presentation from May 1, 2014, available at: http://www.gphaonline.org/media/cms/NCPDP_Follow-Up_Letter_to_FDA_Re_Biosimilar_Naming_Jun6_14.pdf (accessed August 19, 2015).

[66] FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (The Orange Book), 35th Edition (2015), available at: http://www.fda.gov/downloads/drugs/developmentapprovalprocess/ucm071436.pdf (accessed August 19, 2015). Also available at FDA's website: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm (accessed August 19, 2015) (current through July 2015).

[67] FDA website: "Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations," updated July 27, 2015, available at: http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm411418.htm (accessed August 19, 2015).