



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

RE: Workshop on Follow-On Biologics: Project No. P131208

Via Electronic Submission: <https://ftcpublic.commentworks.com/ftc/biologicsworkshop>

March 1, 2014

Dear Sir/Madam:

The Novartis Group of companies (hereafter “Novartis”) appreciates the opportunity to provide public comments in follow up to our participation at the FTC meeting “Follow-On Biologics Workshop: Impact of Recent Legislative and Regulatory Naming Proposals on Competition” in Washington DC on February 4th, 2014. Novartis’s product portfolio includes both originator biologics and biosimilars and it is with our experience globally developing and marketing these products that we provide the comments contained herein.

While there are no marketed biologics in the US today that use the biosimilar pathway, Novartis/Sandoz is the global leader in developing and bringing off patent biologics to market.<sup>1</sup> In the US, our European biosimilar to somatropin has also been marketed since 2006 as a 505(b)(2) drug, and we also market Enoxaparin in the US as a generic drug. We are the leading sponsor of biosimilars approved to the standards of high similarity required of the highly regulated markets.<sup>2</sup>

As the legal and regulatory framework for biosimilars has been implemented in the US, we have endeavored to make constructive suggestions that support the commitment and experience of FDA’s staff. In particular, we have emphasized the value of consistency and science-based review for all biological products based on data from sponsors submitted to and evaluated by FDA. Additionally, as the leading sponsor of biosimilars in Europe and as the sponsor of the generic biological drug Enoxaparin in the US along with our partner, Momenta (enoxaparin is often cited by the FDA as an example of the more complex potential biosimilars), we are contributing our experience to the peer reviewed scientific literature and to this comment opportunity in the hope that FTC will support the FDA in the implementation of their new authority in a manner that is consistent with their scientific and regulatory history.

The availability of biosimilars in the US, as shown already in EU and elsewhere, will facilitate competition in the biologics market, qualify some of the concerns with specialty trends, while also fostering greater access and affordability to these critical medicines. We believe that equally safe, pure and potent biosimilars can be made available to American patients just as has occurred in the EU and other highly

regulated markets. And just as in those other highly regulated markets there have been no unexpected adverse events in any marketed biosimilars, so we believe the same quality can be assured in the US. It is important to note that we do not regard as biosimilars those products not developed to these standards of high similarity. As such, these other products should not be used to cast aspersions of safety or quality concerns at those biosimilars approved to the standards demonstrated by EMA, as well as authorized by BPCIA for FDA.

In the interests of facilitating your consideration of the topics raised in the November 15th, 2013 Federal Register Notice, namely the impact of recent legislative and regulatory naming proposals on competition in the biologics space, we are referencing a variety of documents that we and others have contributed to the public debate over the last decade – please consider them all as submitted to the record. They include data as well as policy rationales in support of access and affordability that will be pertinent to your own evaluation of the competitive landscape involving biologics, biosimilars and interchangeable biologics in the US. In addition we refer you to my presentation given at the workshop, as well as the comments that I made during the panel discussions and for which you have a transcript.

### **Nonproprietary Names<sup>3</sup> of Biosimilars Must Match Those of Their Reference Product for Effective Competition to Ensue:**

It is critical that any discussion of distinguishable names clearly notes whether the proprietary or non-proprietary name is being discussed. We agree that a distinguishable name is required for every biologic but this is the role of the brand name, not of the non-proprietary name. This is also why the discussion of small molecule drug generics, and adverse event reporting for generics, is not relevant as none of these products have brand names. However, interestingly the discussion at the FTC meeting did not have those speakers who raised generic examples conclude that generics should have amended nonproprietary names or forced to have a brand name.

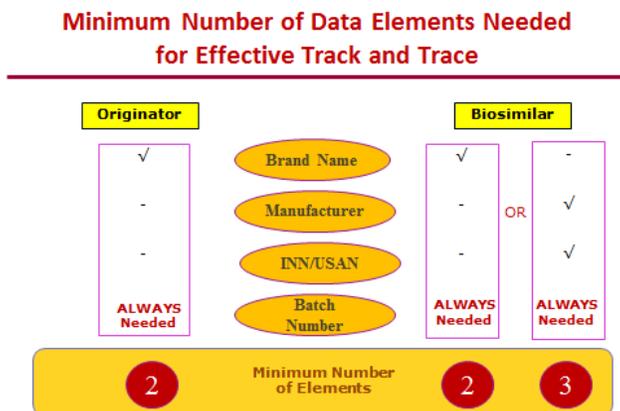
Our marketed products outside of the US include biosimilars to somatropin, epoetin alfa and filgrastim.<sup>2</sup> Each of our biosimilars has a brand name, Omnitrope<sup>®</sup> (somatropin), Binocrit<sup>®</sup> (epoetin alfa) and Zarzio<sup>®</sup> (filgrastim), and each of their nonproprietary names matches that of its reference product - Genotropin<sup>®</sup> (somatropin), Eprex<sup>®</sup> (epoetin alfa) and Neupogen<sup>®</sup> (filgrastim), respectively.

All Novartis/Sandoz biosimilars in the US will have a brand name, and will be labelled first and foremost as biologics, with all the accompanying labeling distinctions appropriate to good pharmacovigilance, as well as post market surveillance commitments just as apply to any other biologic today. Consequently, there is no need to change the premise of the nonproprietary name as the descriptor of the active ingredient.<sup>4</sup> The brand name for a biosimilar, just like any other biologic, is the distinguishable name for the product itself. We note that some biologics currently on the US market with competitors in the same class and with the same active ingredient that have never been compared share nonproprietary names, and there have been no documented cases of safety problems as a result.<sup>5</sup>

Likewise, originator products pre and post manufacturing changes (of which there may be many in series over the life time of a product – one recent example being 37 in series<sup>6</sup>) show differences analytically<sup>7</sup> and yet share the same nonproprietary names. The one frequently cited case of a safety problem with Eprex<sup>®</sup> (epoetin alfa), which is an originator product and not a biosimilar, makes the case for the need to accurately record batch numbers.<sup>8</sup> The product sponsor has not proposed that the nonproprietary name of this product be changed each time there is a manufacturing change requiring comparability of

the post-manufacturing change product to the pre-manufacturing change product. These arguments are described in detail in the Novartis Citizen petition, filed with the FDA October 28<sup>th</sup>, 2013<sup>9</sup>, as well as in our recent publication in the RPM report.<sup>10</sup>

The two part 15 hearings held by FDA in November 2010 and May 2012 both raised the naming issue, even though the BPCIA does not contain any provisions addressing naming.<sup>11</sup> During these public meetings and in our discussions with FDA the basic premises of our naming position, and the minimal number of data elements needed to appropriately track products given to patients was described. In particular we refer you to our submissions to the FDA Part 15 hearing in November 2010<sup>12</sup>. See Figure 9.



As we observed back in 2010 as the legend to this figure:

“The minimum number of data elements for track and trace is two when there is a Brand name, or three if not, however extra elements create redundancy and cross checks, for instance the shared INN/USAN enables data pooling, and reduces the likelihood of double-dosing. The batch number is always necessary.”

This point about the number of elements needed to uniquely identify each biologic, including the value of distinct brand names was reiterated in our response to the FDA’s three draft guidances on biosimilars issued in February 2013 and the Part 15 hearing held by FDA on May 12<sup>th</sup> 2013, where the Agency again raised the naming question. We refer you to our docket submission to the FDA of April 12<sup>th</sup>, 2013<sup>13</sup>.

As mentioned above, the use of a unique Brand name provides a distinct identifier to biologics and biosimilars. To the extent that FDA elects to approve a biosimilar *without* a brand name, then the additional data element of the manufacturer is useful. This is already always on the label of a product approved and marketed in the US. However, this does not necessitate a change to the nonproprietary name, the name of the active ingredient that is issued by WHO, used globally and routinely reflected by a matching USAN for the US marketed product.<sup>14, 15</sup>

The same nonproprietary name is appropriate for biosimilars by virtue of their approval by FDA as biosimilars. Indeed the highly similar standard as applied today for manufacturing changes is already an appropriate precedent, and in both cases no clinically meaningful differences are anticipated in the subsequent product compared to the reference product. If the Agency does not concur that the active

ingredients are sufficiently similar for the same clinical outcomes to be expected, the product does not warrant the FDA's approval as either comparable or biosimilar (both defined in part as highly similar product quality attributes<sup>16, 17</sup>). Should the sponsor choose to pursue an interchangeability designation from FDA, the same biosimilar product will be subject to additional studies. Today any product, biologic or drug retains the same nonproprietary name throughout its life time and the same should apply to biosimilars. It is clearly appropriate that interchangeable biologics have the same nonproprietary name as their reference product, and insofar as a product is approved as biosimilar first and nonproprietary names do not change this would create a conundrum if biosimilars were forced to have a different name.

Hence, the corollary is also true. Namely, to force different nonproprietary names on biosimilars is to label them as having a different active ingredient from their reference product. This will be competitively disadvantageous to the extent that they will have to be marketed and detailed in the manner of a new biologic product. To be unable to compete based on having demonstrated biosimilarity, even when subsequently designated as interchangeable is particularly inappropriate. The additional marketing investment associated with a different name for either biosimilars or interchangeable biologics will reduce the ability of both to compete as effectively for market share based on price.

#### **The Role of State Pharmacy Substitution Laws in Enabling a Competitive Market Place for Biologics and an Increase in Access and Affordability for Patients:**

Interchangeability is unique to the US law, and it is explicitly defined in the statute as meaning that the product can be substituted for its reference without the involvement of the original prescriber.<sup>18</sup> An interchangeable biosimilar should be able to be treated by the market according to the same principles as a generic small molecule drug today. Given that the practices of medicine and pharmacy are state authorities so we need to address the importance of amending current state laws to accommodate biosimilars fairly and appropriately.<sup>19</sup>

To ensure rapid uptake of future interchangeable biologics in the US, it will be critical to streamline automatic substitution for those medicines deemed by FDA as interchangeable with their reference products. For that reason, Sandoz and its parent company Novartis, support an equitable, consistent and pro-competitive approach to implementing the necessary state-level legislation. State pharmacy laws across the US should be updated in a consistent manner to enable pharmacy level substitution of all biologics determined by the FDA to be interchangeable. In cases where interoperable electronic health records (EHR) are not available, pharmacist communication of substitution would be required to the prescriber of all biologic products dispensed. This principle would apply equally to all biologic medicines, in line with the long standing Novartis principle of ensuring a "level playing field" for all biologics, including biosimilars and other interchangeable biologics.

Further, any additional requirements to current records, such as an additional field or a change in the nonproprietary name, will further confuse and undermine the quality of the overall records. Data bases will need to be changed to accept new field codes, and the interoperability of all individual systems assured and users appropriately trained. As FDA concluded in their submission to the WHO on Biosimilar Naming Policies in September 2006:<sup>20</sup>

“Considering the inherent difficulties in additional INN product distinctions (e.g. retroactive and lifecycle changes in naming, additional INN responsibility and liability), if the world community decides to proceed with a change in the policies regarding the assigning of INNs, it should be preceded by (a) appropriate exploration of alternatives (e.g. improvements in education and/or labeling), (b) assuring the such changes fall within the scope, competence, and expertise of the INN program, and (c) the performance and independent validation of a formal risk assessment and/or documentation of events with appropriate statistical treatment.”

We would like to incorporate all references given in this letter into this submission to the FTC public comments, along with all the references made in our Citizen Petition of October 28<sup>th</sup>, 2013, and any other documents referred to in the publications cited.

We want to thank the FTC for its time and interest in ensuring that a competitive market place emerges for biologics in the US, and for its commitment to Americans gaining the benefit of the abbreviated biosimilar pathway. This will enable patients in the US to achieve greater access through meaningful savings on life-saving biological medicines that will be of the same quality, and as safe, pure and potent as their reference products. This public process is part of a dialogue between FTC and stakeholders on these important issues. In the meantime enlightened product specific review and approval of biosimilars must continue in parallel as direct experience will be the real test, and just as we have seen in Europe, only with real products coming to market can patients and their physicians gain confidence and the benefits to the public health be achieved.

Yours sincerely

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**Acronyms:**

EMA (formerly EMEA) = European Medicine Evaluation Agency

EU = European Union

FDA = Food and Drug Administration

FTC = Federal Trade Commission

ICH = International Committee on Harmonization

INN = International Nonproprietary Name

USAN = United States Adopted Name

WHO = World Health Organization

## Endnotes

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- <sup>1</sup> Statement Of Mathias Hukkelhoven, Ph.D., Senior Vice President, Global Head Drug Regulatory Affairs. Novartis Pharmaceuticals Corporation, Before The FDA Public Workshop “Scientific Considerations Related To Developing Follow-On Protein Products, Rockville, Maryland, September 14-15, 2004, and followup submission by the same author 12Nov04, FDA Docket No. 2004N-0355 - Attached
- <sup>2</sup> List of Sandoz approved biosimilars in Europe: Omnitrope<sup>®</sup> (Somatotropin) approved 12Apr06; Binocrit<sup>®</sup> (Epoetin alfa) approved 28Aug07; Epoetin alfa Hexal<sup>®</sup> (Epoetin alfa) approved 28Aug07; Abseamed<sup>®</sup> (Epoetin alfa) approved 28Aug07; Zarzio<sup>®</sup> (Filgrastim) approved 6Feb09; Filgrastim Hexal<sup>®</sup> (Filgrastim) approved 6Feb09
- <sup>3</sup> Variously called established name, International Nonproprietary Name (INN), United States Adopted Name (USAN). In the case of small molecule drugs it is also known as the generic name, but notably small molecule drugs do not have brand names. We also refer you to the USP submission to the FDA Part 15 hearing in Spring 2013 where a clear description of the various names is provided. Comments of USP on “Draft Guidances Relating to the Development of Biosimilar Products; Public Hearing” Docket No. FDA-2011-D-0618, 77 Fed. Reg. 12853 (March 2, 2012). This is available at regulations.gov and submitted as an attachment
- <sup>4</sup> WHO, “International Nonproprietary Names,” available at: <http://www.who.int/medicines/services/inn/en/> (accessed 28Feb14).
- <sup>5</sup> McCamish, Gallaher, Orloff “Biosimilar by Name and Biosimilar by Nature”, RPM Report, June 28, 2013. Available at [http://www.sandoz-biosimilars.com/cs/groups/public/@sbs\\_com/documents/document/n\\_prod\\_844479.pdf](http://www.sandoz-biosimilars.com/cs/groups/public/@sbs_com/documents/document/n_prod_844479.pdf) (accessed 28Feb14) - Attached
- <sup>6</sup> Schneider C. “Biosimilars in Rheumatology The Wind of Change”, Am Rhem Dis March 2013, available at <http://ard.bmj.com/content/72/3/315.full.pdf> (accessed 28Feb14). While the data on the number of manufacturing changes is provided for Europe, similar changes will have been undertaken for the US, but the use of comparability is not made public in the US. Attached
- <sup>7</sup> Martin Schiestl, et al. “Acceptable Changes in Quality Attributes of Glycosylated Biopharmaceuticals”, Nature Biotechnology, Volume 29, Number 4, Pages 310-312 (April 2011). Available at: <http://www.nature.com/nbt/journal/v29/n4/abs/nbt.1839.html> (subscription required)
- <sup>8</sup> Casadevall N. Immune-response and adverse reactions: PRCA case example. [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Presentation/2009/11/WC500011064.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2009/11/WC500011064.pdf) (accessed 28Feb14). Attached
- <sup>9</sup> Novartis Naming CP, filed 28Oct13, Docket# FDA-2013-P-1398. Available at: <http://www.regulations.gov/#!docketDetail;D=FDA-2013-P-1398> (accessed 28Feb14), Attached
- <sup>10</sup> McCamish, Gallaher, Orloff “Biosimilar by Name and Biosimilar by Nature”, RPM Report, June 28, 2013. Available at by subscription [http://www.sandoz-biosimilars.com/cs/groups/public/@sbs\\_com/documents/document/n\\_prod\\_844479.pdf](http://www.sandoz-biosimilars.com/cs/groups/public/@sbs_com/documents/document/n_prod_844479.pdf) (accessed 28Feb14) - Attached

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<sup>11</sup> TITLE VII: IMPROVING ACCESS TO INNOVATIVE MEDICAL THERAPIES. Subtitle A: Biologic Price Competition And Innovation (BPCIA) provisions of the Patient Protection and Affordable Care Act (PPACA) Available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf> (accessed 28Feb14)

<sup>12</sup> Novartis group of companies submissions to the Fall 2010 FDA Part 15 hearing, available at regulations.gov. Docket No. FDA-2010-N-0477. Attached

<sup>13</sup> Novartis Group of companies submissions to the FDA docket 3 draft biosimilar guidances in April 12th, 2013 available at regulations.gov; Dockets No. FDA-2011-D-0605, Draft Guidance Scientific Considerations in Demonstrating Similarity to a Reference product; No. FDA-2011-D-0602 Draft Guidance Quality Considerations in Demonstrating Similarity to a Reference product; No. FDA-2011-D-0611 Draft Guidance for Industry on Biosimilars: Questions and Answers. Attached

<sup>14</sup> We refer the reader to a number of recent presentations at WHO public meetings in 2013, including those attached – EGA Presentation to INN Consultation, Open Session to Stakeholders at WHO headquarters, Geneva, October 16, 2012; EGA presentation to INN Consultation, Open Session to stakeholders WHO headquarters, Geneva, October 22, 2013; GPhA presentation to INN Consultation October 21, 2013; Hospira Whitepaper on Biosimilar Naming 2013. Attached

<sup>15</sup> Martina Weise et al, Biosimilars: what clinicians should know, Blood First Edition Paper, prepublished online October 23, 2012; DOI 10.1182/blood-2012-04-425744. Available at: <http://bloodjournal.hematologylibrary.org/content/120/26/5111.full.pdf> (accessed 28Feb14). Attached

<sup>16</sup> ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process. EU: Adopted by CPM, December 1, 2004, CPMP/ICH/5721/03, date for coming into operation: June 2005; MHLW: Adopted 26 April 2005, PFSB/ELD Notification No. 0426001; FDA: Published in the Federal Register, Vol. 70, No. 125, June 30, 2005, p. 37861-37862. [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Quality/Q5E/Step4/Q5E\\_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf) (accessed 25Feb14). Definition:

“Comparable: 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.”

<sup>17</sup> BPCIA definition of biosimilar/biosimilarity is that:

“there are no clinically meaningful differences between the biological product and the biosimilar in terms of safety purity and potency of the product”.

See definition in Section 7002(b)(3) of the Affordable Care Act, adding section 351(i)(2)(B) of the PHS Act) in TITLE VII: IMPROVING ACCESS TO INNOVATIVE MEDICAL THERAPIES. Subtitle A: Biologic Price Competition And Innovation (BPCIA) provisions of the Patient Protection and Affordable Care Act (PPACA) Available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf> (accessed 28Feb14).

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<sup>18</sup> TITLE VII: IMPROVING ACCESS TO INNOVATIVE MEDICAL THERAPIES. Subtitle A: Biologic Price Competition And Innovation (BPCIA) provisions of the Patient Protection and Affordable Care Act (PPACA) Available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf> (accessed 10 April 2012)

<sup>19</sup> For example see recent Sandoz Testimony and letter, February 2014 in support of SB 262 to enable pharmacy laws that support competition through substitution of interchangeable biosimilars. Attached

<sup>20</sup> U.S. FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm375086.htm> (accessed 25Feb14) Attached