



October 26, 2015

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

RE: Nos. FDA-2013-D-1543-0001 and FDA-2013-D-1543-0002

Dear Sir/Madam:

Sandoz, a Novartis company, respectfully submits this response<sup>1</sup> to the FDA's Federal Register Notice entitled "Nonproprietary Naming of Biological Products; Draft Guidance for Industry"<sup>2</sup> and the associated FDA draft guidance "Nonproprietary Naming of Biological Products"<sup>3</sup>. The Agency proposal to apply new conventions in the US with respect to nonproprietary names for all biologics has significant ramifications for all biologics sponsors, as well as those who will be expected to routinely use these new names – namely those involved in "ordering, prescribing, dispensing, recordkeeping and pharmacovigilance practices for biological products"<sup>4</sup>. As we explain in more detail below, we do not believe a need exists to depart from the currently established nonproprietary naming system. Indeed, changing the system as FDA suggests will instead create confusion and require sponsors and other stakeholders to make significant and costly (and possibly continual) changes to their systems, without substantiated expected benefits or lessened risks to patients. We instead support increased adherence to the existing adverse event reporting system and ensuring that all records are complete and accurate.

The policy being proposed in this draft guidance, as well as the name changes proposed by FDA's concurrently-issued proposed rule "Designation of Official Names and Proper Names for Certain Biological Products"<sup>5</sup> immediately impact Sandoz as the sponsor of the first, and currently only, US licensed biosimilar, Zarxio<sup>TM</sup> (filgrastim-sndz<sup>6</sup>) as well as all stakeholders touched by Zarxio<sup>TM</sup>. However, we note that the new nonproprietary naming proposals will also impact originator biologics. The concurrently issued proposed rule "Designation of Official Names and Proper Names for Certain Biological Products"<sup>7</sup> highlights that five out of the six names for which changes are proposed are products that were approved as originator biologics and not biosimilars.

Very importantly, the draft guidance acknowledges that there are no special issues created by biosimilars or by interchangeable biologics that are not also applicable to originator biologics. Importantly, the BPCIA<sup>8</sup> does not include the word "name" at all, nor does the statute mention or otherwise contemplate the need to establish unique naming conventions for biosimilars. Furthermore, given the consistent positioning by FDA and all US stakeholders, including

physician and patient groups, that biosimilars must not be viewed as generic biologics, it is anticipated that US biosimilars will have brand names<sup>9</sup> (which is not the case for most 505(j) ANDA generic drugs). We appreciate that FDA has made the proposed rule fair by applying the Agency's reasoning for the change to all biologics<sup>10</sup>.

### **Executive Summary**

It is not necessary to modify the existing naming system that has worked well for over 60 years. Biosimilars and interchangeable biologics should share the same non-proprietary name as their respective reference products. Introduction of suffixes to the non-proprietary names of biologics is not necessary and may even be problematic.

If FDA does impose the addition of suffixes to the non-proprietary names of biologics, it is important that the suffix be memorable, preferably derived from the name of the company that licensed the biologic. If FDA imposes suffixes to the non-proprietary names of biologics, then all biologics, biosimilars and interchangeable biologics licensed by a given company should share the same suffix. Evidence reveals that random letter suffixes will not be well remembered, defeating the stated FDA purposes of safety and enhanced pharmacovigilance.

Changing non-proprietary names will be onerous for companies, payers (commercial and CMS), providers (hospitals, clinics, HCPs, pharmacies), pharmacovigilance systems, GPOs, distributors, wholesalers, databases and compendia. The FDA should consult all the stakeholders that will need to enact these changes to learn of their estimates as to the resources needed to make these changes, and, equally essential, how much time it will take them to build a robust system and validate each step as well as re-establish interoperability throughout the system. If a new naming system is to be imposed, FDA should evaluate now and then undertake a reevaluation of the new system 2-3 years after it is initiated to assess whether it has increased patient safety or if it has created new problems, including poorer pharmacovigilance.

The process for naming interchangeable biologics should be the same as that applied to all biologics, including biosimilars. Interchangeable biosimilars must be allowed to keep the original suffix granted when first approved as a biosimilar. Given that the Purple Book will be the definitive source of status as a biosimilar or an interchangeable biologic, the suffix of an interchangeable biologic does not need to match that of the respective reference product.

The WHO Biologics Qualifier proposal should not be implemented in the US.

## Introduction and Background

The recent debate on nonproprietary naming emerged concurrently with efforts to create and implement a pathway for biosimilars and interchangeable biologics in the US. However, we note that FDA's proposals in both the draft guidance and proposed rule apply to all biologics. While we do not see the need to make any changes to the current systems used for nonproprietary names (discussed further below), we appreciate the Agency recognizing that any changes to the current nonproprietary naming conventions need to be applied equally and concurrently to all biologics. Implementation of any changes will not be trivial, and consequently any such undertaking needs to be achieved consistently and fairly for all sponsors, and the costs and timelines managed appropriately. Timely coordination will present challenges, especially if the nonproprietary name change of a reference product must be synchronized with market introduction of a corresponding biosimilar.

It is important to recognize that BPCIA is silent about naming. The nonproprietary name has always been intended to reflect the active ingredient as established by the conventions of USAN<sup>11</sup> and WHO<sup>12</sup> (and, therefore, shared among products containing that active ingredient) – indeed, FDA's policy paper to WHO stated as much<sup>13</sup>. In contrast, the brand or proprietary name is the name of the single product and designed to be recognizable, clear and easy to use in the local language. The brand name is always unique, and proprietary. This naming system was in place at the time of enactment of BPCIA. However, FDA is now changing a basic component of this paradigm with the issuance of these naming policies.

Nevertheless, the question of whether biosimilars should share an international non-proprietary name (INN) with their reference products has become the subject of much public debate<sup>14, 15</sup>. Unfortunately, that debate has confused the concept and current utilization of the nonproprietary name by departing from the nonproprietary name's intended purpose of facilitating the identification of pharmaceutical substances, not least as the consequences of FDA breaking with global conventions will be significant well beyond the US (see Section 5 below - Global consequences). Further, it is critical to clarify up front that what is currently being proposed for the US is NOT the same as the WHO's Biologics Qualifier (BQ) proposal. While superficially the format appears similar (i.e. four letters as a suffix to the nonproprietary name), the BQ is entirely separate from the INN (i.e., un-hyphenated) whereas the US proposal incorporates the suffix as an integral part of the nonproprietary name (i.e., hyphenated and considered part of the same data field). Notably, Janet Woodcock, CDER, unambiguously emphasized on the record that it is important to FDA that the suffix be tied with the current nonproprietary name<sup>16</sup>:

“It doesn't help us if there's a suffix and it isn't attached in the prescribing systems and all the other systems that we use to track and so forth,” she said.

“And I don't think it helps the prescribers either if they want to make sure their patients get a specific drug if they simply get the core name ... It's very easy for [the nonproprietary name] to get separated.”

Unfortunately, the recent dialogue, as well as this FDA draft guidance (and associated proposed rule) suggests that the nonproprietary name is intended to facilitate the identification of a specific product. This has resulted in confusion in the use of an otherwise straightforward data element, and a worldwide system effectively in use for over six decades, to inform healthcare providers as to the active ingredients in the pharmaceutical products that they use<sup>17</sup>. Many products, including biologics, currently marketed in the United States have shared nonproprietary names for decades<sup>18</sup> and we are not aware of any issues with their safe and effective use. It has not escaped notice that changes to these naming conventions have only been sought after biosimilars began to be developed in the US, and that the groups calling for these changes did not vocalize any concerns prior to that time.

Certainly, we are not arguing that brand names are, or can be, the only tools used for tracking and tracing, but we do not support nonproprietary names being amended in the belief that they can assume that ambitious purpose either. We are simply concurring with FDA's own 2006 position<sup>19</sup>, and the use and value of nonproprietary names within the US health care system where, despite their being shared among products, they have been in "routine usage [ ] in ordering, prescribing, dispensing, record keeping and pharmacovigilance practices<sup>20</sup>", and as part of an integrated<sup>21</sup> and validated<sup>22</sup> system, not as the sole data field for any product, drug or biologic, innovator or generic/biosimilar/interchangeable biologic.

The broad and far ranging public discussion about nonproprietary names for biologics and biosimilars now includes the use of the term "unique nonproprietary names" – a term of art that is inherently problematic as any name that is unique to a product, and cannot be shared with other products, is by definition no longer "nonproprietary"<sup>23</sup>. This conflation of the role of the brand name (proprietary) with the nonproprietary name (also called generic name for drugs, and proper or official name for biologics) of products is an aspect of the debate designed to confuse many stakeholders – including those that will be impacted by the Agency's proposed rule and draft guidance. The Novartis amendment to our Citizen Petition (CP)<sup>24</sup> discusses the possibility of situations where a biologics product may lack a brand name, but such cases would be the exception and not the rule<sup>25</sup>.

To revise a key component of the U.S. naming conventions<sup>26</sup> will create a new and more complicated system of unknown risks. This will not necessarily create a safer system but it will increase uncertainty, create confusion and entail a significant financial burden on many stakeholders well beyond product sponsors. If the issue with the current system is the completeness and accuracy of the records, FDA risks compounding these problems by introducing a new naming system for biologics. We believe the concerns with the current system can be addressed by targeting education and training on the use of existing naming convention and adverse event (AE) reporting systems where those deficiencies have been identified<sup>27</sup>. The creation of a new system and its implementation will necessarily require a significant and much more substantial educational undertaking, and until the new and untested system is completely functional the completeness and accuracy of the record keeping will inevitably be worse.

We have structured our response in order to address each of the following topics in greater detail:

1. **Analysis of the FDA Proposal for Newly Designated Nonproprietary Names for All Biologics**
2. **Novartis/Sandoz Preferences for Biologic Nonproprietary Names**
3. **Process of Assigning Newly Designated Nonproprietary Names for All Biologics**
4. **Novartis/Sandoz Position on Interchangeability and the Ramifications of Multiple Nonproprietary Name Changes**
5. **Need for Global Harmonization to maintain the Original Objectives of an International Nonproprietary Name**

### **1. Analysis of the FDA Proposal for Newly Designated Nonproprietary Names for All Biologics**

The stated goal for FDA's suggestion to incorporate a suffix into the nonproprietary name (also called a proper or official name) of biologics, including originator biologics, biosimilars and interchangeable biologics, is to improve pharmacovigilance and clearly differentiate among biological products that have not been determined to be interchangeable. Further, the Agency has concurrently published a proposed rule for six approved products (five originator products licensed under 351(a) and one biosimilar licensed under 351(k))<sup>28</sup> with the following reasoning:

"FDA is proposing to take action with respect to these six products because of the need to **encourage routine usage of designated suffixes in ordering, prescribing, dispensing, recordkeeping, and pharmacovigilance practices** for the biological products subject to this rulemaking, and to avoid inaccurate perceptions of the safety and effectiveness of biological products based on their licensure pathway." [emphasis added]

#### **Proposed Change Would Be Complex and Difficult to Implement:**

While these are laudable goals, we are aware of no quantitative evidence that the addition of a suffix will lead to the desired goals. Absent data to the contrary, the benefits of the proposed suffix remain hypothetical while the risks of changing the current system to one that is more complex, in many ways yet to be defined, and inevitably less well understood, are considerable. For the proposed naming system to be successful, multiple stakeholders will all have to comply with the revised system, including sponsors, distributors, data banks and software companies, benefit managers, insurance companies that will manage reimbursement and patients involved in the use of any biologics in any setting for any condition of use. All of these various stakeholders will have to cooperate and modify their systems to ensure 100% accurate and complete record keeping. The ambitious nature of the proposed rule (see bolded text in quote above), combined with the extremely short time over which this is to be achieved, despite the precedent-setting nature of changing nonproprietary names (which represents their "identity") for currently licensed and marketed products, results in considerable uncertainty.

Given that the Agency's pharmacovigilance concern with the current system appears to be rooted in incomplete or inaccurate records and not a problem with the system itself, it is unclear how creating a more complicated system will ensure better outcomes. Indeed, the converse would appear to be much more likely.

#### **Lack of Evidence that a Change is Needed:**

In contrast, ample and indisputable evidence exists that there are no safety concerns in the US when biologics share a nonproprietary name. At present, there are 25 nonproprietary names shared among approximately 77 biologic products<sup>29</sup>. These products have been FDA approved or licensed, and available to patients and their providers for many years with no evidence of any confusion in their use or inadvertent substitution between them in a manner that is contrary to the practices of medicine and pharmacy. It is telling that no concerns were voiced about the fact that many biologics already share nonproprietary names until the advent of the development of biosimilars for the US market. Ironically, those that voice concern for biosimilars sharing nonproprietary names with their reference products have not voiced concern for the biologics currently sharing nonproprietary names. The latter were each developed independently without any studies to establish comparable safety and efficacy to the products with which they share non-proprietary names<sup>30</sup>. Nonetheless, if legitimate risks to patient safety exist, then FDA should rename these products first, given that their absence of similarity would presumably make any risk of inadvertent switch between them a greater concern than would be the case for a biosimilar and its reference product.

FDA's initial list of products to be renamed includes those that are approved in the E.U. another highly regulated markets. Importantly, no evidence of any confusion based on their shared nonproprietary names exists there. This is not surprising in Europe, as these products have brand names which are designed for recognizability and ease/clarity of use<sup>31</sup> – and usually very short in length when compared to the nonproprietary name (which describes the active ingredients chemical makeup in more or less detail as the case may be). In the U.S., all brand names are vetted by FDA to ensure that they will not be confused with other brand names<sup>32</sup>. Healthcare providers in the U.S. could manage biologics through the required use of the brand name, a simple naming approach that FDA has elected not to consider<sup>33</sup>.

Hence, it is essential to acknowledge that the most common identifier of any biologic (or drug) is the brand name, and that is the one that will also be most commonly tracked in the US. Given that it is designed to be unique to a specific product using a process closely overseen by FDA<sup>34</sup>, yet readily recognized and written, it is also the most useful for tracking a product to a specific manufacturer. It is notable that what the FDA is proposing for biologics is not a system that they have traditionally supported for brand names – where prefixes and suffixes are discouraged as inherently confusing most especially if they lack meaning<sup>35</sup>. The Novartis amendment to our CP addresses the situation where a biologic does not have a brand name, but this is the rare exception for biologics<sup>36</sup>.

Currently, a biologic's brand name is used throughout the track and trace system and is captured in the vast majority of adverse event reports. And in the case of biosimilars this is no different. Below are examples of the tracking that we are able to provide for our biosimilars in

Europe, which all have the same nonproprietary name as their reference products, and from which it is clear that when biologics are prescribed by use of a brand name we are both able to track with a high level of confidence, and that the reports are only very rarely made using the nonproprietary name.

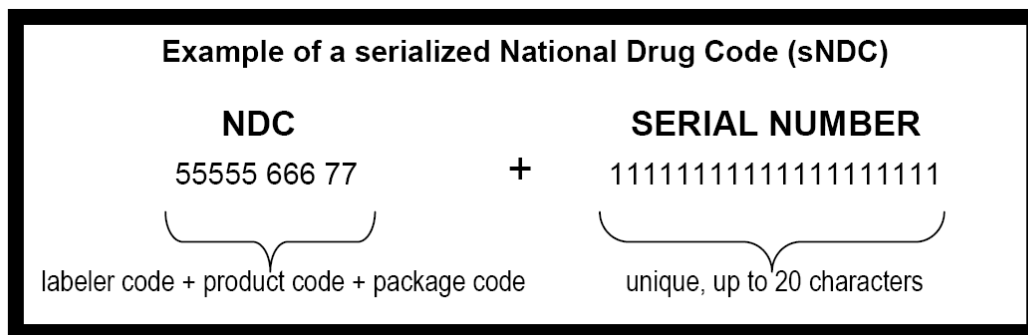
## Product names, not NPNs, are used in reports on Sandoz' biosimilar products

<p><b>Epoetin alfa: Binocrit®/ Epoetin alfa Hexal®/ Abseamed®/ Novicrit®</b> <b>Total Spontaneous (HCP, Non-HCP) AEs/ ADRs reported through 31Aug15: <u>310</u></b></p> <p>Reported as: Abseamed: 93 Binocrit: 194 Epoetin alfa Hexal: 16 Epoetin alpha Sandoz: 1 Erythropoietin Sandoz: 1 Novicrit: 1 Unknown Erythropoietin alfa/ Epoetin alfa/ Erythropoietin: 4</p> <p>133,289,219 patient days, through 28Feb15 (Date of PSUR: 16Apr15).</p>	<p><b>Somatropin: Omnitrope®/ Scitropin®</b> <b>Total Spontaneous (HCP, Non-HCP) AEs/ ADRs reported through 31Aug15: <u>1498</u></b></p> <p>Reported as: Omnitrope®: 1439 Scitropin®: 6 Somatropin BS S.C. Injection (Sandoz Japan) : 12 Unknown somatropin: 41 (None from US)</p> <p>Somatropin: 80,097,829 patient-days through 31Mar15 (Date of PSUR: 13May15)</p>	<p><b>Filgrastim: Zarzio®/ Filgrastim Hexal®</b> <b>Total Spontaneous (HCP, Non-HCP) AEs/ ADRs reported through 31Aug15: <u>389</u></b></p> <p>Reported as: Zarzio®: 342 Filgrastim Hexal®: 14 Filgrastim Sandoz: 3 Unknown Filgrastim: 27 Unknown GCSF: 3</p> <p>9,444,754 patient days through 31Jan15 (Date of PSUR: 13Mar15)</p>
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**Table 1:** This data is intended to illustrate that Adverse Events are reported by brand name and not the nonproprietary name. This data is not intended to provide regulatory, legal or medical advice with regard to reporting adverse events nor is it intended to report any adverse event. ©2015 Sandoz Inc. All Rights Reserved.<sup>37</sup>

### Multiple Tracking Elements Already Exist:

The US has additional data fields already available and in routine use for additional tracking, most notable the NDC number used for reimbursement purposes. The NDC contains additional information over and above that represented by the brand name and the nonproprietary name<sup>38</sup>. Thus additional data is routinely collected that identifies how specific biologics have been used over and above that available outside of the US. The US also has the Standardized Numerical Identifier (SNI)<sup>39</sup> that includes the NDC number and can include even more specific information on the batch/lot of product, as long as Global Trade Item Numbers (GTIN) standards are applied<sup>40</sup> - see figure below<sup>41</sup>. There are very few products (a number of blood, blood component, human cell and tissue) to which these systems are not currently applied but they are physician administered usually in a hospital setting.



**Table 2:** FDA Final Guidance “Standards for Securing the Drug Supply Chain - Standardized Numerical Identification for Prescription Drug Packages”<sup>37</sup>.

The nonproprietary name, even as revised, will never contain the level of detail of these systems, and increasingly these systems are part of the more broadly implemented Electronic Medical Record (EMR), in and of itself ever more automated and not dependent on handwritten records. While none are yet comprehensive, there is no question that the US has one of the more advanced pharmacovigilance systems in the world<sup>42</sup>. As such, in the US, we would appear to have fewer risks of inadequate records than in other jurisdictions, not more, and the data so far from these other jurisdictions already indicates minimal problems through shared nonproprietary names with current pharmacovigilance systems. The data from these other markets shows a very good ability for these other systems to track an adverse event to a specific product.

For reasons outlined in our CP of October 28, 2013, as supplemented in 2015, and as reiterated here, Novartis remains convinced that a suffix is unnecessary to properly monitor the safety of a biologic and to ensure that it is used properly. Further, to change the current system, and to add complexity by creating longer nonstandard nonproprietary naming formats, is in and of itself a hazard to the effective use of the very systems it presumes to improve.

Nonetheless, if the Agency imposes use of suffixes to the nonproprietary names of biologics, Novartis believes that the best option to meet the stated goals of the FDA is to retain its placeholder policy where upon a suffix is derived from the name of the manufacturer. For Sandoz biologics, the suffix would be “-sndz”, as was issued by the FDA upon approval of Zarxio<sup>TM</sup> (filgrastim-sndz). Under this scenario, the policy would apply to all biologics.

We do not support random suffixes of four consonants for any biologics as the likelihood for errors in the prescribing, dispensing and tracking chain would inevitably be very high. The ability to easily recall the suffix is absolutely critical on many levels, including safety through preventing medication errors, pharmacovigilance, and market access, and would be more likely when the suffix is based on the manufacturer’s name. We contend that a suffix that is meaningful and related to the company name would be more readily remembered than a totally random four consonants. Literature on human psychology and computer passwords clearly reveals that letter sequences that are memorable are more readily recalled than letter sequences that are random.



As noted by Yan et. al (and references cited therein) with respect to human memory of letter and symbol sequences<sup>43</sup>:

“When humans do remember a sequence of items, those items must be familiar chunks such as words or familiar symbols.”

For this same reason we do not support the WHO proposal of a suffix of four random consonants either (albeit the fact that WHO is not changing the nonproprietary name itself is an advantage of their proposal<sup>44</sup>). If a suffix is ultimately deemed necessary, we urge that the same, ideally company-related suffix, be appended to all biologics manufactured by any given sponsor to ensure consistent and fair application of the naming policy across all biologics, including originator products, reference products, biosimilars, and interchangeable biologics.

FDA needs to be consistent in its application of any naming policy and inevitably that requires the retroactive application of any new nonproprietary name policy to biologics previously approved. As the firm marketing the only biosimilar currently approved in the US, we are already encountering general perceptions that products with nonproprietary names that have suffixes somehow differ in quality compared to products that have nonproprietary names that lack a suffix. To ensure fair market acceptance, it is critical that the US public and their health care providers understand that biosimilars are manufactured to the same quality standards as any other biologic. To do so, it is important that the naming conventions be the same, applied fairly, consistently and concurrently.

## 2. **Novartis/Sandoz Preferences for Biologic Nonproprietary Names**

For reasons outlined in our 2013 CP, as supplemented in 2015, Novartis remains convinced that a suffix is unnecessary to properly monitor the safety of biologics and to ensure that it is used appropriately by healthcare providers and their patients. To suggest otherwise is to imply that many of the biologics on the US market today are being unsafely used.

### **A Company-Derived Suffix is the Preferred Option for all Biosimilars from a Given Company:**

Nonetheless, if the Agency decides to impose the use of suffixes for the nonproprietary names of biologics, Novartis prefers use of a suffix that has meaning, and is derived from the name of the manufacturer. For Sandoz biologics, we would propose that the suffix used in the “placeholder nonproprietary name”<sup>45</sup> given to our first biosimilar, Zarxio™, namely “-sndz” is appropriate. While still not a brand name, and still just representing the active ingredient as is appropriate to the nonproprietary name, we propose that this same company-related suffix be appended to all biologics manufactured by Sandoz irrespective of the regulatory pathway by which they are approved. This would avoid any of the confusion with nonproprietary name changes that we discuss below,

Given the importance of easy recall, we believe that if a suffix is imposed, the use of letters derived from the company name would make it easier for healthcare practitioners (HCPs) to

identify the product used. Recognizing that the Agency has specified that the suffixes are not be promotional in nature, Sandoz believes that use of a suffix linked to the company name by itself is not promotional because it does not infer any particular use or any advantage. A company name is less likely than a random code to infer a difference (as in a clinically meaningful difference) as it will simply be interpreted to represent the company who makes the product whereas a random code can connote differences in the product itself<sup>46</sup>. Indeed, the company name in full is already on all the FDA-approved packaging associated with any given product.

### **Dangers of a Suffix Comprised of a Random Sequence of Letters:**

Use of random letter and symbol sequences has been studied with respect to human psychology and computer passwords. As noted above, “When humans do remember a sequence of items, those items must be familiar chunks such as words or familiar symbols.”

While we have not conducted a specific study of the memorability of random sequences when applied to biologics, we would suggest FDA conduct such a study to avoid any question of bias. We do not see any reason that the results would differ from those found with the research already conducted. As such it is plausible and highly likely that healthcare practitioners will struggle to accurately remember a random sequence of consonants. The same will apply to the public at large under many circumstances, including situations when they must submit an adverse event report. As such, we remain concerned that the use of random consonants will endanger public safety. They will inevitably lead to adverse event reports that cannot be attributed to a specific manufacturer, or are attributed to the wrong manufacturer, if such reports depend on the nonproprietary name alone. The use of vowels, such that suffixes are pronounceable, may help, and we note that FDA has included a proposal with a vowel for a company abbreviation in the proposed rule<sup>47</sup>.

### **Company-Derived Suffixes Will Not Have a Commercial Impact**

We appreciate that some may claim that use of a name associated with the manufacturer will confer an unfair advantage to companies that have expended significant resources to create corporate name recognition. We do not believe that this confers a market advantage. In the case of biosimilars all sponsors will face a new therapeutic paradigm and commercial situation – yet to be defined or tested thereby making it a level playing field for all companies in this nascent field. We hope that the US public will come to accept biosimilar companies as new suppliers in a broader and more expanded supply of biologics. As historically a manufacturer of primarily generic drugs, we are aware that the Sandoz name does not have the same level of recognition as that associated with long-established branded pharmaceutical companies. Nonetheless, we firmly believe that healthcare practitioners and pharmacists that select our biosimilar products will quickly learn to associate the “-sndz” suffix with Sandoz as a company but will not associate it with any other product feature. Indeed, most integral of all will be FDA approving all biologic products to the same standards of safety, purity and potency, even if the route to that approval is different for those using the 351(k) rather than the 351(a) regulatory pathway<sup>48</sup>. We expect that brand names will continue to play a significant role for all biologics in the future, just as they do today, and that brand names will eclipse the non-proprietary name as

the primary product recognition factor making the inclusion of a company-derived suffix at most a minor issue from a corporate recognition standpoint.

It is important to note that if all sponsors have a single suffix appended to the non-proprietary name for their products that is derived from their company name and is applied to all of their biosimilar products, any advantage or disadvantage will be applied equally to all. Indeed, newer and perhaps smaller companies may obtain a level of recognition beyond what they had previously had. In sum, if one believes that company-derived suffixes to non-proprietary names in fact may have a commercial impact, there are reasons to believe that it could confer a limited advantage to smaller, newer companies and at the same time and in a different manner to more established companies. The end result would be that neither type of company would be advantaged.

### **There Should be Limited Opportunities to Change a Suffix**

As with any naming element, if there are public safety concerns detected after a suffix is implemented the FDA would have the mandate to change the assigned suffix. We strongly believe that the circumstances for which a suffix change would be permissible should be defined in advance by the FDA to ensure that that the need is compelling. A change in a suffix derived from the company name should also be permissible if there are business circumstances that make it necessary, such as a change in ownership. A company would need to petition the FDA for any such change and would need to provide detailed rationale for the change. As a practical matter, companies will be highly incentivized to retain a name or naming element whenever possible because the very act of changing an approved name or naming element is costly and is highly disruptive in the market. The current system avoids these challenges because since there is no unique suffix included as part of the nonproprietary name, sponsorship changes do not precipitate changes in the nonproprietary name.

### **Need to Assess Impact of the Use of Suffixes:**

It is absolutely essential that any model created for renaming biologics be appropriately validated prior to implementation.

Given that the addition of suffixes will unquestionably increase complexity, it is an open and very valid question as to whether the increase in name specificity will lead to an increase in accurate attribution, or if the increase in complexity will lead to a concomitant increase in identification errors that in turn will lead to misattribution of adverse events at a level that ultimately obviates the goal of the new system. It is unacceptable to dismiss the need to evaluate the FDA proposal by claiming that the reporting rates will increase with education – that is too loose a metric, not least if the flaws with the current system are in and of themselves associated with incomplete or inaccurate records that could be improved by education<sup>49</sup>. Educational efforts may or may not be successful for any given system but given that the US public has been using the same naming convention for many decades it is not credible to automatically assume that those involved would be as successful with a new and more complicated system. Further appropriate checks and balances must be built into any system, new or old, with appropriate redundancy to provide additional consistency cross-checks. These

exist today and help optimize the functioning of the system as a whole. They need careful design and planning for concurrent implementation.

A recent study by the Tuft University Center for the Study of Drug Development analyzed FAERS data from MedWatch from 4Q4 2005 through Q3 2013 and found that 92% of adverse event reports for human growth hormone and 84% of adverse event reports for insulins were associated with a brand name. This is a definitive and unbiased metric, and we suggest that it be used as the baseline to determine if addition of a suffix will increase adverse event reporting above these thresholds<sup>50</sup>. If after 24-36 months the data reveals that use of a suffix has not improved pharmacovigilance but is harmful in some manner, FDA should stop using a suffix.

We appreciate the added complexity that will be created when the rollover on March 23, 2020 of the FDC Act Section 505 biologic drugs to become available as reference products for Section 351(k) biosimilars and interchangeable biologics regulated under the Public Health Service Act (PHS Act). Indeed, our preferred approach -- to maintain the existing system -- would obviate the FDC Act Section 505 to PHS Act Section 351 conversion as a source of confusion or regulatory inconsistency with regard to nonproprietary naming. The 505 biologic drugs include our own Omnitrope<sup>®</sup> (somatotropin) that shares the same nonproprietary name as its reference product Genotropin<sup>®</sup> (somatotropin) and was approved in 2006, as well as the considerably more complex generic biologics to Lovenox<sup>®</sup> (enoxaparin) and Copaxone<sup>®</sup> (glatiramer acetate) that were approved by the FDA in 2010<sup>51</sup>, 2012<sup>52</sup>, 2014<sup>53</sup> and 2015<sup>54</sup>. The generic versions of enoxaparin and glatiramer acetate are fully interchangeable with their reference products, but only the former and not the latter, will become available as a reference product for biosimilars and interchangeable biologics in 2020. We urge that the nonproprietary names as well as the interchangeability status for these products remain unchanged when the 505 rollover occurs.

### **Renaming Priorities:**

Assuming that a new naming paradigm for naming of biologics is imposed, we recommend the following as the listing of priorities for retroactive application of a new naming format:

- a) Currently market biologics with shared nonproprietary names should be given suffixes as expeditiously as possible as these are the products in use by patients and their providers today.
- b) New biologics should be approved with nonproprietary names that contain suffixes.
- c) Revised names must be assigned to biologics that are being used as reference products for biosimilars that are under Agency review. This seems to be aligned with current Agency thinking<sup>55</sup>.
- d) The Agency should also prioritize products that are available as reference products for biosimilars. This would include those 16 reference products to which 57 biosimilar candidates are being discussed in FDA's Biosimilar Product Development Program<sup>56</sup>, as well as biologics approved 12 years or more ago and on which BPCIA exclusivity has expired.

- e) Once the above products are renamed all remaining biologics should also be renamed to ensure consistency of naming policy, and no implied disparities between those with suffixes and those without.

We also suggest that the FDA waive the renaming policy for products that are manufactured as a public service for which demand is extremely low but when there is a need that medical need is great. Such examples could include black widow spider anti-venin and rattlesnake anti-venin.

### 3. **Process of Assigning Newly Designated Nonproprietary Names for All Biologics**

For reasons outlined in our 2013 Citizen Petition on biosimilar naming, as supplemented in 2015, as well as for the additional reasons listed above, Novartis remains convinced that a suffix is unnecessary to properly monitor the safety of biologics and to ensure that it is used appropriately by healthcare providers and their patients. Indeed to suggest otherwise is to imply that many of the biologics on the US market today are being unsafely used.

#### **Imposition of a New Naming Paradigm for Biologics will have a Wide-Ranging Operational Impact on Existing Systems:**

Provided below is a high level outline of the steps that we would anticipate having to take if FDA imposes a new nonproprietary name convention on existing biologics. This includes Zarxio™ and the other marketed biologics identified by FDA, as well as all existing biologics that share the same nonproprietary name<sup>57</sup>.

- a) Impact on Internal Sandoz Systems & Processes if Name is Changed Once Biosimilar is Marketed
- Generate new NDC numbers for each SKU with the new name
  - Update internal material master, and material/inventory/production enterprise management systems
  - Update internal quality systems
  - Update internal customer service, order entry, pricing and contract management, chargeback systems and invoicing systems
  - Update internal financial systems for reporting including government pricing
  - Produce new materials for production and packaging – new product labels, cartons, package inserts
  - Update all promotional materials (hard copy and digital), and Sandoz materials that mention the non-proprietary name
  - Modify internal safety monitoring systems to automatically aggregate reports from products with different names
- b) Impact on External Systems & Processes if Name is Changed Once Biosimilar is Marketed
- Distributors/Wholesalers: update their distribution and financial management enterprise systems – inventory management, order entry, pricing and contract management, invoicing, etc.

- GPOs: update contract and contract management systems
- Payers (Commercial and CMS): update their formulary and adjudication systems, ensure new NDC/names have appropriate reimbursement codes, CMS would need to map new NDCs to relevant HCPCS codes
- Providers (Hospitals, Clinics, HCPs, Pharmacies): update their inventory management systems, ensure new NDC/names properly included in billing and reimbursement software, incorporate into Electronic Medical Record systems
- Update software packages in dispensing systems to allow product with either of 2 names to be dispensed during time that a biosimilar will have both names on market
- Data Banks need to be modified to identify products with different names as identical
- Compendia: update information in various external compendia
- Address in external pharmacovigilance systems (e.g. FAERS, Sentinel)

It is important for FDA to consult with all the stakeholders that will need to enact these changes to learn of their estimates as to the processes and resources needed to make these changes, and, equally essential, how much time it will take them to build a robust system and validate each step, as well as establish their interoperability. With this information, the Agency can then help coordinate these stakeholder needs into an overall action plan for each product. We would suggest the Agency consult with NCPDP, APhA, NACDS, NCPDP, PCMA and other such professional organizations that will be able to facilitate FDA understanding of the ramifications of any changes to current systems.

Indeed, changing the nonproprietary name of any marketed product should not be considered lightly. Given that historically this has never occurred and the product itself does not change, we anticipate considerable risks of confusion, compounded by the likely situation where two different nonproprietary names are in use concurrently for the same product as inventories are exhausted of the older product packaged prior to the labeling change. How long these two products (same product, different names) will exist together in the market will be based on the shelf life of the material -- which for biologics is commonly 24 to 36 months (2-3 years). Some lyophilized biologics may have shelf lives that are as long as 60 months (5 years).

Given that changing suffixes for products already in the market will be a significant operational challenge, and impose significant burdens on multiple stakeholders to obviate the inevitable confusion that will result, we recommend that FDA consult all stakeholders who will have to implement such changes, even if they are not traditionally seen as FDA-regulated entities. The database system issues alone are not trivial, but the education and detailing necessary to explain that two products with different names for their active ingredients are indeed the same is considerable. Furthermore, the situation outlined above, the concurrent marketing and use of potentially multiple differently named product at the same time, interjects more complexity. The complexity builds when we take into account that in the case of biosimilars and their reference product this may actually be at least two products (recognizing in addition that one or more biosimilars may share the same reference product<sup>58</sup>) with at least four names, and one or more of the products may or may not have the same conditions of use, and may or may not be interchangeable.

### **Imposition of a New Naming Paradigm for Biologics will be Time and Resource Intensive:**

The estimate of the costs to implement the changes as proposed by FDA clearly fails to take into account the full range of stakeholders that will be impacted, only including a very limited subset of the activities. The Federal Register Notice announcing the proposed rule on the Designation of Official Names and Proper Names for Certain Biological Products<sup>59</sup> cites the Paperwork Reduction Act<sup>60</sup> and provides Calculations on the estimated cost of implementation of the proposed rule on the six biologics identified. This calculation has to be applied more generally to all biologics if indeed FDA decides to proceed with the new naming conventions as described in the draft guidance. We question the FDA calculations and the very low estimates provided in the Notice. These costs significantly underestimate the time and resources that we believe to be necessary for the implementation of the rule even to these six products, let alone as applied to all biologics currently licensed in the US, as well as the cost of the downstream stakeholders responsible for fulfilling FDA's aspirations for the use of these new naming conventions – namely:

“FDA is proposing to take action with respect to these six products because of the need to encourage routine usage of designated suffixes **in ordering, prescribing, dispensing, recordkeeping, and pharmacovigilance practices** for the biological products subject to this rulemaking, and to avoid inaccurate perceptions of the safety and effectiveness of biological products based on their licensure pathway.”<sup>61</sup>[emphasis added]

We are unable to assess the costs of the change for “all ordering, prescribing, dispensing, recordkeeping, and pharmacovigilance practices for the biological products”, however we can assess and report on the costs incurred for the sponsors of the biologic products themselves. FDA will need to consider the other stakeholders obligations separately, and we are concerned that because these other stakeholders are not routinely directly regulated by FDA the estimates provided by the Agency either do not include their costs or that the cost estimates may be extremely inaccurate.

FDA estimates that each respondent will spend only 40 hours compiling and submitting a naming request. This is an extremely severe underestimation of the actual costs that will be incurred. It would appear that the estimate of six hours is based only on the last step, which is the time to prepare the FDA submission itself – covering only the period of time that a sponsor may spend compiling the regulatory submission once the three selected suffixes are already decided. This is a critically important distinction. The cost and time of the final step is trivial in comparison of all other steps involved.

FDA suggests that each respondent submit three suggested suffixes for Agency consideration. Each four letter suffix needs to be individually investigated to ascertain whether or not it is suggestive of a specific meaning, including sound-alike, look-alike analysis, incorporating both printed and cursive letters. Our own company experience is that an analysis of an individual name for this purpose is in excess of 720 hours when one factors in the need to

have multiple people involved for multiple days. If three names are investigated, 2160 hours will be expended to be needed.

Using the FDA metrics provided in the Federal Register Notice – “Designation of Official Names and Proper names for Certain Biological Products” that a submission that takes 40 hours will incur a cost of \$780,000 to \$3,040,000, the cost of a submission that requires in excess of 2000 hours will be at least an order of magnitude higher.

Given the cost estimates provided by the Federal Trade Commission in 2009<sup>62</sup> that a biosimilar will cost between \$100- \$200 million dollars to develop, addition of a new naming convention such as proposed for the nonproprietary name will by itself add up to 3% to the overall development costs of a biosimilar, and perhaps higher.

#### 4. **Novartis/Sandoz Position on Interchangeability and the Ramifications of Multiple Name Changes**

There are additional implications for naming of biologic products that the FDA has designated as interchangeable beyond those approved as originator or biosimilar products<sup>63</sup>. By definition an interchangeability designation by FDA applies to a biosimilar product for which it is demonstrated that switching between it and the reference product has no safety or efficacy implications. While most of the naming implications apply to the biosimilar there is also an impact on the reference product and if/how it is indicated to be interchangeable with the biosimilar.

Interchangeability is an authority given to FDA in BPCIA that allows for two biologic products to be substituted without the need for the original prescriber to be consulted – analogous to the manner in which generic small molecule drugs are interchanged as therapeutically equivalent products under 505(j)<sup>64</sup>. We recognize that, just like with generic drugs there may be other issues that apply beyond the medicine containing the same active ingredient (the basis of which is the nonproprietary name or identity of the product), such as the variety of dosage forms available and other aspects of the presentation. Indeed, given that biologics are usually injected or infused, most will likely not be self-administered and very few go through a retail pharmacy. However, for those self-administered the device component can also be important. As such patient support programs are expected for biologics based on their indication, the type of patient for whom they are developed as well as the setting of care in which they are to be used. They are to all intents and purposes branded products in terms of the practices of medicine and pharmacy.

The Agency proposes two options for naming of interchangeable biologics<sup>65</sup>. These are:

- A. a suffix that is distinct from that of the reference product, or
- B. a suffix that is shared with the reference product.



## **Retaining the Same Suffix Granted with Initial Approval is By Far the Preferred Option for Naming of Interchangeable Biologics:**

As outlined above, Novartis disagrees with the initial underlying premise that a suffix is necessary because the concerns voiced by the FDA are purely hypothetical, and not substantiated by those biologics on the US market today that share nonproprietary names. Further we think the addition of more naming elements will reduce rather than enhance the likelihood of complete and accurate records being maintained for all biologics. However, of the two options offered by the Agency in the draft Guidance, there is no doubt that the safest and most reliable approach is that interchangeable biologics should retain the suffix assigned at their initial approval as a biosimilar. The changing of suffixes of approved products will be complicated, will be confusing in the market, and will be difficult to implement for reasons articulated in Section 3 above.

Given that, if FDA proceeds with the proposal to use suffixes, the Agency will have also imposed a suffix on the reference product, so it becomes inevitable that the suffix of the two different biologics (i.e. biosimilar and its reference product) subsequently designated as interchangeable by the FDA will initially be different, assuming as many do that all biosimilars for the foreseeable future will use the 2-step process of first seeking a biosimilar approval and then a subsequent interchangeability designation (noting that two steps are not required by BPCIA and may not be pursued by all sponsors in the future<sup>66</sup>). If the decision is made to change the name of the suffix of the interchangeable biologic to be that of the reference product, the sponsor of the interchangeable biologic would incur all the difficulties and costs outlined in Section 3, with the attendant increase in risk from safety and commercial perspectives. In contrast, the originator would not have any of these difficulties. This violates the principle of treating interchangeable biologics and their reference products in an equitable manner.

Another option could be to impose yet a third new suffix on the interchangeable biologic and reference product. Use of a third new suffix in order to burden both equally would be particularly unfortunate for all stakeholders. In addition, it would lead to the need to continuously change suffixes a third, fourth or perhaps even more often if multiple interchangeable biologics are approved to a single reference product. This possibility alone makes the “third new suffix” concept impractical.

The only other option would be to drop the suffixes for both and return to the unencumbered nonproprietary name. However, our concerns about the confusion and cost with any nonproprietary name changes, means that we see serious risks with the latter and so we continue to strongly advocate for our primary choice of maintaining the current system of INN/USAN's with no suffixes as the global system for nonproprietary names for all biologics. If our primary choice of not imposing a suffix system were to have been selected as the naming process for biologics, there will be no need for a change to any nonproprietary name of either the reference or the biosimilar should the products be determined by FDA to be interchangeable – and clearly at that point their having the same nonproprietary name is appropriate as they will be treated for the purposes of substitution by a pharmacist (subject to state law) in the identical manner to generic small molecule drugs.

## **The Purple Book will be the Authoritative Reference Source for Identifying Interchangeable Biologics<sup>67</sup>:**

The Agency has established the Purple Book to clearly identify biologics that are biosimilar to a reference product, as well as those biologics that are interchangeable with their respective reference product. The Purple Book will be used as a reference for pharmacists and other healthcare professional in a manner analogous to the manner in which the Orange Book<sup>68</sup> is used for chemically synthesized drugs. There is a wealth of experience in the US that indicates that the Orange Book is already well accepted and frequently used by pharmacists and payers, and is built into the data bases and software in routine use in the practice of medicine and pharmacy. The definition of interchangeability is important to consider here – it is an authority given to FDA to make a designation that a dispensing pharmacist (subject to state law) can recognize. Namely:

“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”<sup>69</sup>

Interchangeability is not a designation relevant to the prescriber as they will always prescribe the most appropriate product for their patient, and can switch that patient between medicines according to their own clinical judgment. To be clear, interchangeability is a designation that is relevant to the dispensing pharmacist only. The lack of understanding of this point by some stakeholders may be part of the reason that a suggestion that a change in nonproprietary names is needed – not least as the interchangeable biologic will be a biosimilar on which additional studies have been done. It is not a new and different product<sup>70</sup>. Namely, while not strictly necessary as a matter of law, current Agency practice is to encourage sponsors to first seek approval as a biosimilar, and then in a separate review of distinct additional data that shows that for products administered more than once switching is not a problem.

## **If Pharmacovigilance Truly is of Concern then Interchangeable Biologics and Reference Products Must Have Unique Names Just as is the Case for All Other Biologics:**

While generally but only loosely associated with biosimilars, and never well defined, concerns have been raised about pharmacovigilance for biologics in the US, and this is an area noted in the proposed regulation by the Agency. Much of the FDA’s reasoning for the proposal to require distinguishable suffixes is based on the need to clearly differentiate between the biologics that are administered to a patient, and the ability to know rapidly who got what in the event of a safety concern with a particular product. However, if one accepts this premise as valid and that the nonproprietary name has anything to do with such identification of products<sup>71</sup> then interchangeable biologics and their corresponding reference products would also need to be able to be differentiated by nonproprietary name. In fact, because it is more likely that patients would be switched between these products, given that that is the point of an interchangeability designation, this would increase rather than decrease the need to differentiate between them by unique nonproprietary names.

However, we do note that, of the six product proposed for new nonproprietary names in the proposed rule, one Epoetin alfa, already has two brand names assigned to a single nonproprietary name and FDA is proposing a single amended nonproprietary name to apply to both – hence we still end up with a shared nonproprietary name for two products. If the nonproprietary name has to be as unique as the product then two suffixes - one for Epogen® and one for Procrit® - become necessary.

#### **Impact of Changing Names for Interchangeable Biologics:**

In Section 4, a), above, we list some of the activities that would need to be taken within Sandoz to address a change in the suffix portion of the nonproprietary name. We readily acknowledge that there may be steps that have yet to be identified, and have supplied the list for illustrative purposes only. The timing for roll-out of all of these steps will need to be carefully coordinated. It is critical to note that there will be Zarxio™ product in the US market at the same time with different nonproprietary names. While we are in the process of calculating the cost to Sandoz, it is anticipated to be in the millions of dollars.

In Section 4, b), above, we list some of the activities that would need to be undertaken by organizations and companies other than Sandoz in order to introduce, track and otherwise accommodate the change of the nonproprietary name for Zarxio™. We acknowledge that there may be steps not yet identified, and have supplied the list for illustrative purposes only, because these are by definition areas beyond our routine responsibility and control, and indeed are the obligation of stakeholders that are not traditionally FDA-regulated. The number of organizations, companies and systems that are impacted and that would incur a significant cost is very large, and most of these organizations and companies gain no benefit from the change in nonproprietary name – the change becomes a cost of operation and involves cooperation between the data banks who assemble the data, the software purveyors who organize the data for a purpose and the users of the information, such as pharmacists.

Since these are costs that are external to Sandoz, it is more difficult for us to provide an accurate estimate, but it is easy to see how these costs can be in the tens of millions of dollars, especially when the need to validate the systems is taken into account – especially to the accredited standards of NCPDP<sup>72</sup>/GS-1<sup>73</sup> etc., that we would anticipate being necessary. These are costs that would need to be borne by external organizations and companies and we cannot attest to the scalability of these systems. Similarly, we do not know how comparable the projections for a change only of filgrastim-sndz to filgrastim-bflm would be for the other six products listed in the proposed rule, let alone the many hundreds of biologics currently licensed by the FDA. These same costs may need to be incurred every time that a biosimilar from any company is subsequently approved as an interchangeable biologic, although we are not supportive of any nonproprietary name changes for any biologic let alone multiples changes for the same biologic over time. Depending on the number of interchangeable biologics that are approved in the US, the costs to the US healthcare system would be considerable, possibly in the hundreds of millions of dollars. Nonetheless, we would ask that at every level for every product, irrespective of the regulatory pathway by which FDA issued the license, that the Agency be consistent in their nonproprietary name requirements. Ideally that will be the application of the same non-proprietary name to biosimilars, interchangeable biologics and

reference products that is so well-articulated in the FDA document entitled “FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars the FDA to WHO” in 2006.<sup>74</sup> While this document was sent by the FDA to the WHO prior to the enactment of BPCIA, the issues addressed and FDA confidence in the current systems in the US will not have changed.

As must now be apparent, just the costs of converting the nonproprietary name after an interchangeability designation is granted could significantly diminish any potential savings recognized by the US healthcare system through use of biosimilars. These additional costs would be pass-through costs and ultimately would need to be paid by consumers. Given the complexity of all the changes that would need to be made in series and concurrently, there is a high likelihood of error without thorough testing and validation of the systems by those stakeholders that will have to implement them. This will include, for example, those responsible for adverse event reporting as well as those responsible for managing inventory and obtaining payment to ensure continuity in supply. Difficulties in obtaining appropriate reimbursement could limit the availability of these critical products in both the short and long terms – the ramifications for patients from these changes could easily be more immediate and more considerable than any hypothetical risk of inadvertent substitution by a pharmacist – not least as most of these products are physician administered anyway.

To Sandoz, the need to potentially change the name of a biosimilar a second and possibly even a third time is a very real possibility if we seek and obtain approval of Zarxio™ as interchangeable with the reference product. Furthermore, if the final Agency decision is to assign a random letter suffix to a biosimilar so that the non-proprietary name of Zarxio™ is switched from filgrastim-sndz to filgrastim-bflm, Sandoz could be forced to change the nonproprietary name a second time if the final decision is that interchangeable biologics and the reference product are to share non-proprietary names. This change will need to be implemented throughout our distribution pipeline as well in order to ensure that all systems used in the US by other companies and organizations also change the nonproprietary name accordingly. The changes required for the second name change are exactly the same as would be required with an initial name change as outlined in Section 3. The need for a name change would impose an additional cost on the sponsor of the interchangeable biologic. By virtue of this cost, some sponsors may decide that the additional cost does not warrant further development of a biosimilar to become designated as an interchangeable biologic. If a sponsor then elects not to develop a biosimilar as an interchangeable biologic because of the quantifiable costs associated with renaming that are in the millions of dollars, the true loser will be the US public for whom market access to interchangeable biologics will be restricted.

Priorities for retroactive application of a new naming format are discussed in section 2 above, but clearly consistent use of any naming convention for all biologics is essential to its credibility and potential value in assuring patient safety.

## **5. Need for Global Harmonization to maintain the Original Objectives of an International Nonproprietary Name**

### **Value of a Common Global Name:**

Novartis and Sandoz manufacture pharmaceutical products that are available to patients around the world, and we see immense value in having a single non-proprietary name for each of our products in all markets. The brand names can vary because of the needs of different communities that operate in different languages (although we do note that Europe is now able to accommodate a single brand name despite working across the community of 28 countries with 24 official languages<sup>75</sup>), but generally we use the same or similar brand names whenever possible. The nonproprietary name has however been largely consistent, and the exceptions rare<sup>76</sup>.

Novartis supports the principles of the shared nonproprietary name based on the active ingredient, and as such the administrative responsibilities given to WHO to run the INN system on behalf of the world. We also recognize that some countries do not have the wherewithal to manage the complexity of brand names and have allowed prescribing by INN. It is on this basis that we submitted our supplement to our CP earlier this year<sup>77</sup> and proposed that in those cases where there is no brand name available, and the conventions of the highly regulated markets for all biologics, including but not limited to biosimilars, cannot be applied a suffix not linked to the INN may be appropriate. However, the corollary is equally true, where there is a brand name such a suffix is not appropriate, and indeed we consider for the reasons given above it is counterproductive. It is with these caveats that we offer very limited support to the WHO in the development of their proposed Biosimilars Qualifier (BQ) program. Such a system is neither necessary nor appropriate in the US, nor in other highly regulated markets, such as the EU. The system ONLY has value in countries in which use of brand names are not available or permitted. It is our understanding that the EMA does not plan to apply the BQ, and as the regulator with the greatest experience, we would suggest that their experience is particularly pertinent.

### **The FDA Proposal and the WHO BQ Proposal Are Very Different:**

We see important value in the FDA coordinating with WHO on the proposals that may change the drug and biologics naming conventions that have been in place since 1952. In the US this also involves coordination with the USAN Council<sup>78</sup> (the official committee of which FDA is a member along with AMA, APhA and USP). But it is critical to note that as currently described, while superficially looking the same, the WHO BQ proposal is fundamentally different from the FDA's proposal.

As acknowledged in the Federal Register Notice, even if not in the text of the draft guidance, the naming scheme being proposed by the Agency has some similarities to the current proposal of the World Health Organization (WHO). Also driven by the advent of biosimilars worldwide, the WHO has undertaken a reassessment of their long-standing INN naming process to evaluate how it may apply to biologics including biosimilars, most particularly in those countries appealing for advice because they allow prescribing by INN. The WHO proposal has substantially evolved and has not yet been finalized, let alone implemented, but they are proposing a "Biologics

Qualifier” (BQ) that would also consist of four random letters (consonants only, no vowels) that would follow the INN, but not be directly connected to it, nor part of the INN itself. As shown below (Table 4), there are many significant differences between the Draft FDA Guidance and the most recent WHO proposal. Most importantly, while the FDA has taken care to ensure that biosimilars and their corresponding reference products are treated equally, the current WHO proposal does not contain similar provisions. We consider that omission to be a fatal flaw with the WHO proposal – naming of biosimilars and their corresponding reference products must be treated in the same manner.

	<b>FDA</b>	<b>WHO</b>
Suffix	<p>Four random letters that have no meaning</p> <p>Random examples are consonants only, but company-specific examples include vowels</p> <p>Will consider alternatives, including suffixes that are linked to the manufacturer or are otherwise meaningful</p>	<p>Four random letters that have no meaning</p> <p>Consonants only, no vowels</p> <p>May include a number – TBD</p> <p>Issued for each product randomly – not shared by all products of a given sponsor</p>
Who assigns suffix?	Sponsors have opportunity to suggest the suffix	WHO assigns the suffix
Linkage to nonproprietary name	Suffix linked via a hyphen to the core name. The suffix is an integral part of the nonproprietary name	Suffix not linked to core name and not a part of the INN
Must it be used?	Mandatory	Voluntary – a decision to be made separately by each regulatory authority
Applies to the reference product?	Yes	Not part of most recent proposal but should be applied consistently where possible
Applies retroactively?	Yes	Not part of most recent proposal but should be applied consistently where possible
Biosimilar and Corresponding Reference Product Treated Equally?	YES	NO

**Table 3.** Comparison of FDA and WHO proposals for naming of biologics

### **The WHO BQ Proposal Should Not Be Adopted:**

Novartis prefers that the US follow the naming convention adopted and successfully used in the European Union since 2006, which is that the biosimilar and reference product share the same nonproprietary name. If a suffix is to be implemented in the US, Sandoz urges that the US retain the naming convention that is under discussion, and not implement the WHO proposal for several reasons. (1) Most critical, a biosimilar or interchangeable biologic must be treated equally to the corresponding reference product, and (2) Sandoz firmly believes that a suffix, if required, must be memorable, or the stated FDA goals of having a suffix (safety and pharmacovigilance) will not be met.

### **6. Conclusions**

The current worldwide naming system, which consists of a nonproprietary name that identifies the active ingredient in the product (whether a drug or biologic in science) and the brand name that applies to the product itself and can accommodate the local language, has compelling advantages. We do not believe that two unique names (one brand and one “unique nonproprietary name”) are needed for each biologic, nor that the availability of biosimilars and interchangeable biologics in the US market will create any new issues that require substantial changes to the current naming conventions.

To the extent that FDA has concerns with inadequate or inaccurate record keeping, and these impact patient safety, we share the concern to identify and resolve those issues as a priority, but our solution is not to upend the current naming system that is working well for the majority of patients and providers<sup>79</sup>. To conflate occasionally poor record keeping with the capabilities of the system, and to suggest new policies without the involvement of those who know and understand data systems and their limitations<sup>80</sup>, is to propose a solution that may be vastly more dangerous and onerous than the problem it purports to solve. The Novartis companies support the current system of shared nonproprietary names for biosimilars and their reference products based on our experience with biosimilars in multiple markets, many with less sophisticated health care record systems than the US.

Nonetheless, if despite the above stated concerns the FDA elects to impose a suffix that will be part of the non-proprietary name, we believe that memorability of the suffix is critical to avoid medication errors. In our opinion, the best solution would be to select a suffix that is derived from the current sponsor name as long as the suffix does not have a promotional connotation. This policy must apply equally to all biologics, and as such must be enforced retroactively, and priority given to those biologics currently on the US market. A new and more complicated system can only be done with sound and identifiable reasons for change, the solution must match the identified problem, and the new system must be fully validated and tested so that all the stakeholders can be confident that the change will solve the identified problem(s).

If a given biosimilar is also approved as an interchangeable biologic, the name should not be changed because the interchangeability status is clearly denoted in the Purple Book. Any

further name changes would not provide additional benefit but would most certainly be costly and introduce confusion for health care providers and patients alike.

We appreciate the care provided in the FDA review of 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 and interchangeable biologics pathway.

We want to thank FDA for the time and interest that is being taken to address key policy issues to ensure the success of the biosimilar pathway in the US. These activities 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

A handwritten signature in black ink, appearing to read "Mark McCamish". The signature is fluid and cursive, written in a professional style.

Mark McCamish, MD, PhD

**Acronyms:**

AE = Adverse Event

ANDA = Abbreviated New Drug Application (505(j) pathway)

APhA = American Pharmacist's Association

BPCIA = Biologics Price Competition and Innovation Act of 2009

BQ = Biologics Qualifier (part of the WHO proposal)

CDER = FDA's Center of Drug Evaluation and Research

CMS = Centers for Medicare and Medicaid Services

CP = Citizen Petition

EMA = European Medicines Agency

EMR = Electronic Medical Record

FAERS = FDA Adverse Event Reporting System

FDA = Food and Drug Administration

FD&C Act = Federal Food Drug and Cosmetic Act

GPO = Group Purchase Organization

GTIN = Global Trade Item Number

HCPCS = Healthcare Common Procedure Coding System



NACDS = National Association of Chain Drug Stores  
HCP = Health Care Providers/Practitioners  
NCPDP = National Council for Prescription Drug Programs  
NDA = New Drug Application  
NDC# = National Drug Code Number  
NPN = Nonproprietary Name  
PCMA = Pharmaceutical Care Management Association  
PHS Act = Public Health Service Act  
PPACA or ACA = Patient Protection and Affordable Care Act of 2010- BPCIA comprises Title VII of ACA  
SKU = Stock Keeping Unit  
SNI = Standardizer Numerical Identifier (includes the NDC#)  
USAN = United States Adopted Name  
WHO = World Health Organization  
WHO BQ Proposal = WHO's Biologics Qualifier Proposal

Endnotes:

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- <sup>1</sup> We incorporate by reference all cited materials in these endnotes; we also incorporate by reference the Novartis Group of Companies' Citizen Petition dated October 28, 2013, docket # FDA-2013-P-1398, and the Novartis Group of Companies' Citizen Petition Supplement, dated May 4, 2015, docket # FDA-2013-P-1398, and all the references included in both.
  - <sup>2</sup> FDA Federal Register Notice "Nonproprietary Naming of Biological Products; Draft Guidance for Industry; Availability", 80 FR 52296, August 28, 2015, Docket No. FDA-2013-D-1543 Available at: <https://www.federalregister.gov/articles/2015/08/28/2015-21383/nonproprietary-naming-of-biological-products-draft-guidance-for-industry-availability> (Accessed October 14, 2015)
  - <sup>3</sup> FDA Draft Guidance "Nonproprietary Naming of Biological Products", August 2015. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf> (Accessed October 14, 2015).
  - <sup>4</sup> See FDA Federal Register Notice, Proposed Rule "Designation of Official Names and Proper Names for Certain Biological Products," 80 FR 52224, August 28, 2015, Docket No. FDA-2015-N-0648. Available at: <http://www.gpo.gov/fdsys/pkg/FR-2015-08-28/pdf/2015-21382.pdf> (last accessed October 6, 2015). According to the proposed rule, the nonproprietary names for six products will be changed Neupogen® (filgrastim), Zarxio™ (filgrastim-sndz), Granix® (tbo-filgrastim), Neulasta® (pegfilgrastim), Epogen®/Procrit® (epoetin alfa) and Remicade® (infliximab).
  - <sup>5</sup> FDA Federal Register Notice, Proposed Rule "Designation of Official Names and Proper Names for Certain Biological Products" 80 FR 52224, August 28, 2015, Docket No. FDA-2015-N-0648. Available at: <https://www.federalregister.gov/articles/2015/08/28/2015-21382/designation-of-official-names-and-proper-names-for-certain-biological-products> (Accessed October 14, 2015).

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- <sup>6</sup> 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 all our biosimilars in Europe, and indeed for the product discussed here, in Europe where it is known as Zarzio™ (filgrastim).
- <sup>7</sup> FDA Federal Register Notice, Proposed Rule “Designation of Official Names and Proper Names for Certain Biological Products” 80 FR 52224, August 28, 2015, Docket No. FDA-2015- N-0648. Available at: <https://www.federalregister.gov/articles/2015/08/28/2015-21382/designation-of-official-names-and-proper-names-for-certain-biological-products> (Accessed October 14, 2015).
- <sup>8</sup> 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 October 14, 2015).
- <sup>9</sup> “GPhA supports biosimilar sponsors selecting unique trade names for their products.” GPhA website, biosimilars. Available at <http://www.gphaonline.org/issues/biosimilars/> (Accessed October 15, 2015).
- <sup>10</sup> We do note that FDA has not proposed to apply the naming rule/draft guidance to those biologics in science that are regulated as drugs and which already share the nonproprietary name of their reference product. Some, but not all, of these biologic drugs will rollover and become subject to BPCIA pathways March 23<sup>rd</sup>, 2020. Dr. Woodcock, on a teleconference about the proposed rule and draft guidance held by FDA on August 27<sup>th</sup> 2015, made it clear that the Agency has not decided how to name these products. It is not clear that biologics regulated under FD&C § 505 should be subject to different naming rules than those regulated under PHS § 351, but whatever approaches are ultimately chosen by FDA they must be consistent and science-based. The regulatory pathway does not change the science.
- <sup>11</sup> The USAN Council was formed January 2, 1964, to succeed the AMA–USP Nomenclature Committee - see preface to the USP Dictionary of USAN and International Drug Names
- <sup>12</sup> INN started formally in 1959, although the “INN proposed” lists go back to 1953. In 1967, negotiations were completed to provide for participation by FDA in the INN Program at WHO. See World Health Organization, INN WHO, “International Nonproprietary Names.” Available at: <http://www.who.int/medicines/services/inn/en/> (Accessed October 14, 2015).
- <sup>13</sup> FDA paper submitted to WHO, “U.S. FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars” (Sept. 2006). Available at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm375086.htm> (Accessed October 15, 2015), noted as “Archived Content. The content on this page is provided for reference purposes only. This content has not been altered or updated since it was archived.”
- <sup>14</sup> See e.g., FDA, Part 15 public hearing on approval pathway for biosimilar and interchangeable biological products November 3, 2010, transcript available at: <http://www.fda.gov/downloads/Drugs/NewsEvents/UCM289124.pdf> (Accessed October 15, 2015); FDA, Center for Drug Evaluation and Research, Office of Medical Policy, Part 15 public hearing on draft guidances relating to the development of biosimilar products May 11, 2012, transcript available at: <http://www.fda.gov/downloads/Drugs/NewsEvents/UCM310764.pdf> (Accessed October 15, 2015); Richard Dolinar, “It’s All About the Name: What Is the Imperative of Adopting Unique Names for Biologic and Biosimilar Therapeutics?,” *FDLI’s Food and Drug Policy Forum*, 2 (22) (Nov. 28, 2012); Steve Miller, “Is it Necessary to Depart from International Naming Conventions for Biosimilars in the US to Ensure the Safety of Biologic and Biosimilar Therapeutics?: A Response to ‘It’s All About the Name: What is the Imperative of Adopting Unique Names for Biologic and Biosimilar Therapeutics?’” *FDLI’s Food and Drug Policy Forum*, 3 (1) (Jan. 9, 2013).

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- <sup>15</sup> McCamish, Gallaher, Orloff “Biosimilar by Name and Biosimilar by Nature”, RPM Report, June 28, 2013. <https://www.pharmamedtechbi.com/publications/rpm-report/9/7/biosimilar-by-name-and-biosimilar-by-nature> (Accessed October 16, 2015)
- <sup>16</sup> Gingery Derrick, “Biosimilar Naming Reg Could Pit FDA Against WHO” *The Pink Sheet*, September 7, 2015.
- <sup>17</sup> National Council for Prescription Drug Programs (NCPDP) letter to Margaret Hamburg, Commissioner FDA, dated June 6, 2014 re: Meeting held 1<sup>st</sup> May 2014 to discuss Nonproprietary Naming of Biologics. [http://www.gphaonline.org/media/cms/NCPDP\\_Follow-Up\\_Letter\\_to\\_FDA\\_Re\\_Biosimilar\\_Naming\\_Jun6\\_14.pdf](http://www.gphaonline.org/media/cms/NCPDP_Follow-Up_Letter_to_FDA_Re_Biosimilar_Naming_Jun6_14.pdf) Accessed October 16, 2015
- <sup>18</sup> McCamish, Gallaher, Orloff “Biosimilar by Name and Biosimilar by Nature”, RPM Report, June 28, 2013. <https://www.pharmamedtechbi.com/publications/rpm-report/9/7/biosimilar-by-name-and-biosimilar-by-nature> (Accessed October 16, 2015)
- <sup>19</sup> FDA paper submitted to WHO, “U.S. FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars” (Sept. 2006). Available at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm375086.htm> (Accessed October 15, 2015) , noted as “Archived Content. The content on this page is provided for reference purposes only. This content has not been altered or updated since it was archived.”
- <sup>20</sup> See FDA Federal Register Notice, Proposed Rule “Designation of Official Names and Proper Names for Certain Biological Products” 80 FR 52224, August 28, 2015, Docket No. FDA-2015- N-0648. Available at: <https://www.federalregister.gov/articles/2015/08/28/2015-21382/designation-of-official-names-and-proper-names-for-certain-biological-products> (Accessed October 14, 2015).
- <sup>21</sup> The commonality of standards and their interoperability internationally is critical to reliable supply chains in multiple industries and countries – see GS1 Standards at: <http://www.gs1us.org/resources/standards> (Accessed October 16, 2015).
- <sup>22</sup> Standards are used throughout the supply chains and NCPDP has played a leading role in their development for pharmacy systems. See Standards Information at <https://www.ncdp.org/Standards/Standards-Info> (Accessed October 16, 2015).
- <sup>23</sup> By becoming product specific and unique to a single product, the new “nonproprietary name with the suffix” can no longer be used by anyone other than that single sponsor for that single product – in this sense it has become a second proprietary name (in addition to the brand name, which is always proprietary). Generic drugs rarely use brand names and share the nonproprietary name as the name of the active ingredient, so there are no unique names for the product and a combination of sponsor and nonproprietary name serves to identify the product.
- <sup>24</sup> The Novartis Group of Companies’ Citizen Petition Supplement, dated May 4, 2015, docket # FDA-2013-P-1398.
- <sup>25</sup> All GPhA members have committed to brand names for their biosimilars, so this is not an argument that it is appropriate to make in the context of the FDA’s implementation of the new 351(k) pathways. The biologics without brand names are largely old blood-derived products. See Endnote 9.
- <sup>26</sup> 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)
- <sup>27</sup> We are not sure what the specific areas of concern are, but note that the proposed changes in the naming systems are predicated on these unspecified concerns and the supposition that the new system will alleviate them. We will be happy to help with appropriate education to fill any gaps.

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- <sup>28</sup> FDA Federal Register Notice, Proposed Rule “Designation of Official Names and Proper Names for Certain Biological Products” 80 FR 52224, August 28, 2015, Docket No. FDA-2015- N-0648. Available at: <https://www.federalregister.gov/articles/2015/08/28/2015-21382/designation-of-official-names-and-proper-names-for-certain-biological-products> (Accessed October 14, 2015). However, we note that in the proposed rule, epoetin alfa is given a suffix, but that name corresponds to two separate products with two different brand names (albeit one BLA) manufactured for different companies. Therefore, it is unclear how naming two products with one nonproprietary name follows the aspirations for FDA’s proposed rule to uniquely identify different products. In addition, there may be other products that are in a similar situation.
- <sup>29</sup> McCamish, Gallaher, Orloff “Biosimilar by Name and Biosimilar by Nature”, RPM Report, June 28, 2013. <https://www.pharmamedtechbi.com/publications/rpm-report/9/7/biosimilar-by-name-and-biosimilar-by-nature> Accessed October 16, 2015
- <sup>30</sup> In the case of Myozyme® (alglucosidase alfa) and Lumizyme® (alglucosidase alfa) the two products represent a comparability failure after a manufacturing scale up, and are two separate BLAs but continue to share the same nonproprietary name.
- <sup>31</sup> FDA Guidance for Industry “Contents of a Complete Submission for the Evaluation of Proprietary Names”, February 2010, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> (accessed October 15, 2015). See page 4.

#### “C. Proprietary Name Confusion and Medication Errors

“In the U.S. medication-use system, **health care providers rely on the proprietary name as the critical identifier of the appropriate therapy in a market of thousands of products**; therefore, accurate interpretation of the product name is essential to ensure that the correct product is procured, prescribed, prepared, dispensed, and administered to the patient. Products “might be prone to error in use due to sound-alike or look-alike names, unclear labeling, or poorly designed packaging.” Product names that look and/or sound alike can lead to medication error and potential harm to patients by increasing the risk that health care providers could misunderstand the product name, prescribe the wrong product, dispense and/or administer the wrong product, or dispense a product incorrectly. Similarly, product names that look and/or sound alike may lead consumers to select or administer their nonprescription medication incorrectly.” [emphasis added]

- <sup>32</sup> FDA Reference page: “Proprietary Name Review for Biologic Products”, <http://www.fda.gov/biologicsbloodvaccines/developmentapprovalprocess/advertisinglabelingpromotionalmaterials/ucm110900.htm>, Accessed 16Oct15; also “Does FDA approve the proprietary names of prescription drugs?”, available at: FDA <http://www.fda.gov/aboutfda/transparency/basics/ucm211441.htm>, accessed 16Oct15
- <sup>33</sup> Novartis Group of Companies’ Citizen Petition dated October 28, 2013, docket # FDA-2013-P-1398, and the Novartis Group of Companies’ Citizen Petition Supplement, dated May 4, 2015, docket # FDA-2013-P-1398
- <sup>34</sup> See FDA Guidance for Industry “Contents of a Complete Submission for the Evaluation of Proprietary Names”, February 2010, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> (Accessed October 15, 2015).
- <sup>35</sup> FDA Guidance for Industry “Contents of a Complete Submission for the Evaluation of Proprietary Names”, February 2010, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> (accessed October 15, 2015). See Page 10:

#### *4. Intended Meaning of Proprietary Name Modifiers (e.g., prefix, suffix)*

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A modifier, such as a prefix or suffix, in the proprietary product name might suggest different meanings to health care professionals and consumers, which could potentially lead to product confusions. When an applicant or sponsor submits a product name with a modifier (for example with the prefix Lo- or suffix XR), the submission should include the intended meaning of the modifier, the rationale for the modifier, and any studies that have been conducted to support the use of the modifier.

- <sup>36</sup> The Novartis Group of Companies' Citizen Petition Supplement, dated May 4, 2015, docket # FDA-2013-P-1398.
- <sup>37</sup> The material contained in this data set may not be printed, copied or reproduced without express written consent from Sandoz Inc. Unauthorized use is prohibited.
- <sup>38</sup> National Drug Code Directory; information available at: <http://www.fda.gov/Drugs/InformationOnDrugs/ucm142438.htm> (accessed October 16, 2015)
- <sup>39</sup> See FDA Guidance for Industry "Standards for Securing the Drug Supply Chain - Standardized Numerical Identification for Prescription Drug Packages", March 2010. Available at: <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM206075.pdf> (Accessed October 14, 2015).
- <sup>40</sup> See [www.gs1.org](http://www.gs1.org) -- Healthcare GTIN Allocation Rules (ratified July 2015). Available at: <http://www.gs1.org/1/gtinrules/index.php/p=static/t=healthcare> (Accessed October 15, 2015)
- <sup>41</sup> See FDA Guidance for Industry "Standards for Securing the Drug Supply Chain - Standardized Numerical Identification for Prescription Drug Packages", March 2010. Figure on page 4. Available at: <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM206075.pdf> (Accessed October 14, 2015).
- <sup>42</sup> As cited by FDA in their FDA 2006 position to WHO as a reason AGAINST changing the nonproprietary name in a world with biosimilars:

#### **"Support of INN's Original Purpose**

"The United States Food and Drug Administration (U.S. FDA) continues to support the original purposes, premises, and uses of the INN and believes the system has provided many positive elements to the world's public health, especially in facilitating the exchange of scientific data and reports on various products with the same active ingredient(s).

"The USA recognizes the INN system as a cataloging system whereby many products worldwide may share the same internationally recognized nonproprietary name based on drug substance. In this manner, the INN system provides a clear mechanism to health care professionals worldwide for identifying medicines and communicating unambiguously about them based on pharmacological class.

"The U.S. FDA's concerns in today's discussion are (a) that the INN not be used in ways that could jeopardize the health of patients, and (b) **that we not unnecessarily institute changes that could jeopardize the public health benefits of the present INN system.** [emphasis added]

"Specifically, INNs should not be used to imply pharmacologic interchangeability of products with the same active ingredient(s) when no credible scientific data exist that demonstrate such. Likewise, INNs should not be used to differentiate products with the same active ingredient(s) when credible scientific data demonstrate that no pharmacologically relevant differences exist."

FDA paper submitted to WHO, "U.S. FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars" (Sept. 2006). Available at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/A>

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[approvalApplications/TherapeuticBiologicApplications/Biosimilars/ucm375086.htm](http://www.fda.gov/oc/foia/2015/20151015_001.pdf) (Accessed October 15, 2015), noted as “Archived Content. The content on this page is provided for reference purposes only. This content has not been altered or updated since it was archived.”

- <sup>43</sup> Yan J, Blackwell A, Anderson R and Rant q. Password memorability and Security: Empirical results. Technical Report No. 500 from the University of Cambridge Computer Laboratory (September 2000). Available at: <https://www.cl.cam.ac.uk/techreports/UCAM-CL-TR-500.pdf> (accessed Oct 11, 2015)
- <sup>44</sup> WHO, “Biological Qualifier, An INN Proposal,” Revised draft June 2015. Available at: [http://www.who.int/medicines/services/inn/bq\\_innproposal201506.pdf.pdf?ua=1](http://www.who.int/medicines/services/inn/bq_innproposal201506.pdf.pdf?ua=1) (Accessed October 15, 2015).
- <sup>45</sup> See FDA Media Briefing “First Biosimilar Approval in the United States” March 6, 2015. Available at: <http://www.fda.gov/downloads/newsevents/newsroom/mediatranscripts/ucm437548.pdf> (Accessed October 15, 2015); FDA press release “FDA approves first biosimilar product Zarxio” March 6, 2015. Available at: <http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm436648.htm> (Accessed October 15, 2015).
- <sup>46</sup> Historically the use of suffixes in brand names has had an expectation of meaning, and hence, has been discouraged by the Agency. See FDA Guidance for Industry “Contents of a Complete Submission for the Evaluation of Proprietary Names”, February 2010, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> (accessed 16Oct15). See Page 10:
- 4. Intended Meaning of Proprietary Name Modifiers (e.g., prefix, suffix)*
- A modifier, such as a prefix or suffix, in the proprietary product name might suggest different meanings to health care professionals and consumers, which could potential lead to product confusions. When an applicant or sponsor submits a product name with a modifier (for example with the prefix Lo- or suffix XR), the submission should include the intended meaning of the modifier, the rationale for the modifier, and any studies that have been conducted to support the use of the modifier.
- <sup>47</sup> FDA suggests the suffix “-amgn”. See FDA Federal Register Notice, Proposed Rule “Designation of Official Names and Proper Names for Certain Biological Products” 80 FR 52224, August 28, 2015, Docket No. FDA-2015- N-0648. Available at: <https://www.federalregister.gov/articles/2015/08/28/2015-21382/designation-of-official-names-and-proper-names-for-certain-biological-products> (Accessed October 14, 2015).
- <sup>48</sup> This is also where the model that FDA has chosen to date for the labeling of biosimilars is appropriate. See the Novartis Group of Companies submission to the AbbVie Citizen Petition docket # FDA-2015-P-2000, dated August 19, 2015. Available at: <http://www.regulations.gov/#!documentDetail;D=FDA-2015-P-2000-0008> (Accessed October 15, 2015)
- <sup>49</sup> See Testimony of Janet Woodcock, M.D., Director, CDER, FDA before the Committee on Health, Education, Labor and Pensions, United States Senate, September 17, 2015. Available at: <http://www.help.senate.gov/imo/media/doc/Woodcock4.pdf> (Accessed October 15, 2015). Hearing video available at: <http://www.help.senate.gov/hearings/biosimilar-implementation-a-progress-report-from-fda> (Accessed October 15, 2015). The hearing emphasized education of all stakeholders and Dr. Woodcock stated FDA needed more resources to accomplish the Agency’s goals.
- <sup>50</sup> Stergiopoulos S, Brown CA, Grampp G, Felix T and Getz KA. “Identifying and Quantifying the Accuracy of Product Name Attribution of US-Sourced Adverse Event Reports in MedWatch of Somatropins and Insulins.” *Therapeutic Innovation and Regulatory Science*, 2015. 49(5): 706-716
- <sup>51</sup> Sandoz’s enoxaparin sodium ANDA No. 077857, referencing Lovenox®, FDA approved July 23, 2010. Approval letter available at:

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- [http://www.accessdata.fda.gov/drugsatfda\\_docs/appletter/2010/077857s000ltr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/077857s000ltr.pdf) (Accessed October 15, 2015).
- <sup>52</sup> Amphastar's enoxaparin sodium ANDA No. 076684, referencing Lovenox®, FDA approved September 19, 2011. Approval chemistry review available at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/anda/2011/076684Orig1s000ChemR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/anda/2011/076684Orig1s000ChemR.pdf) (Accessed October 15, 2015).
- <sup>53</sup> Teva's enoxaparin sodium ANDA No. 076726, referencing Lovenox®, FDA approved June 23, 2014.
- <sup>54</sup> Sandoz's glatiramer acetate ANDA No. 090218, referencing Copaxone®, FDA approved April 16, 2015. Approval letter available at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/appletter/2015/090218Orig1s000ltr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/090218Orig1s000ltr.pdf) (Accessed October 15, 2015).
- <sup>55</sup> See FDA Federal Register Notice, Proposed Rule "Designation of Official Names and Proper Names for Certain Biological Products" 80 FR 52224, August 28, 2015, Docket No. FDA-2015- N-0648. Available at: <https://www.federalregister.gov/articles/2015/08/28/2015-21382/designation-of-official-names-and-proper-names-for-certain-biological-products> (Accessed October 14, 2015), and the discussion and rationale provided by the Agency on the Agency's teleconference held on August 27, 2015.
- <sup>56</sup> Testimony of Janet Woodcock, M.D., Director, CDER, FDA before the Committee on Health, Education, Labor and Pensions, United States Senate, September 17, 2015. Available at: <http://www.help.senate.gov/imo/media/doc/Woodcock4.pdf> (Accessed October 15, 2015). Hearing video available at: <http://www.help.senate.gov/hearings/biosimilar-implementation-a-progress-report-from-fda> (Accessed October 15, 2015).
- <sup>57</sup> McCamish, Gallaher, Orloff "Biosimilar by Name and Biosimilar by Nature", RPM Report, June 28, 2013. <https://www.pharmamedtechbi.com/publications/rpm-report/9/7/biosimilar-by-name-and-biosimilar-by-nature> Accessed October 16, 2015.
- <sup>58</sup> In Europe, the 22 approved biosimilars are made to 7 reference products – these are likely the first candidates for the US market – as shown by Zarxio™, approved in the US in 2015, but on the market in the EU since 2009. There are now 9 filgrastim biosimilars approved in Europe, some with shared data packages, but represented by 9 brand names, plus the reference product Neupogen® (filgrastim). In Europe this is not a safety issue as they can all be collectively captured under the INN "filgrastim" and individually tracked using brand names – two unique names not being considered necessary and each name serving a particular purpose (to bundle or split). It would appear that in the US this will no longer be an option, even though 11 names for the same active ingredient concurrently on the US market might present some problems.
- <sup>59</sup> FDA Federal Register Notice, Proposed Rule "Designation of Official Names and Proper Names for Certain Biological Products" 80 FR 52224, August 28, 2015, Docket No. FDA-2015- N-0648. Available at: <https://www.federalregister.gov/articles/2015/08/28/2015-21382/designation-of-official-names-and-proper-names-for-certain-biological-products> (Accessed October 14, 2015).
- <sup>60</sup> Paperwork Reduction Act of 1995 (Pub. L. 104-13 (May 22, 1995)).
- <sup>61</sup> FDA Federal Register Notice, Proposed Rule "Designation of Official Names and Proper Names for Certain Biological Products" 80 FR 52224, August 28, 2015, Docket No. FDA-2015- N-0648. Available at: <https://www.federalregister.gov/articles/2015/08/28/2015-21382/designation-of-official-names-and-proper-names-for-certain-biological-products> (Accessed October 14, 2015).
- <sup>62</sup> U.S. Federal Trade Commission "Follow-On Biologic Drug Competition: A Federal Trade Commission Report" June 2009. Available at: <https://www.ftc.gov/sites/default/files/documents/reports/emerging->

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[health-care-issues-follow-biologic-drug-competition-federal-trade-commission-report/p083901biologicsreport.pdf](http://www.fda.gov/oc/ohrt/health-care-issues-follow-biologic-drug-competition-federal-trade-commission-report/p083901biologicsreport.pdf) (October 15, 2015).

- <sup>63</sup> 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 October 14, 2015).
- <sup>64</sup> Appropriate consideration needs to be given to the consequences under state law of any changes in the naming conventions, as this may impact the ability of FDA determinations to be immediately recognized by health care providers on behalf of their patients. These laws should not create any variation among patients based on where they live
- <sup>65</sup> See FDA Federal Register Notice, Proposed Rule "Designation of Official Names and Proper Names for Certain Biological Products," 80 FR 52224, August 28, 2015, Docket No. FDA-2015-N-0648. Available at: <http://www.gpo.gov/fdsys/pkg/FR-2015-08-28/pdf/2015-21382.pdf> (last accessed October 6, 2015); FDA Federal Register Notice "Nonproprietary Naming of Biological Products; Draft Guidance for Industry; Availability", 80 FR 52296, August 28, 2015, Docket No. FDA-2013-D-1543. Available at: <https://www.federalregister.gov/articles/2015/08/28/2015-21383/nonproprietary-naming-of-biological-products-draft-guidance-for-industry-availability> (Accessed October 14, 2015).
- <sup>66</sup> See FDA Draft Guidance "Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009" May 2015, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf> (Accessed October 15, 2015).
- Q. I.14 Can an applicant obtain a determination of interchangeability between its proposed product and the reference product in an original 351(k) application?*
- A. I.14. (Proposed Answer): Yes. Under the PBCI Act, FDA can make a determination of interchangeability in a 351(k) application or any supplement to a 351(k) application. An interchangeable product must be shown to be biosimilar to the reference product and meet the other standards described in section 351 (k)(4) of the PHS Act. At this time, it would be difficult as a scientific matter for a prospective biosimilar applicant to establish interchangeability and the sequential nature of that assessment. FDA is continuing to consider the type of information sufficient to enable FDA to determine that a biological product is interchangeable with the reference product.
- <sup>67</sup> FDA website: "Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations," updated September 3, 2015, available at: <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm411418.htm> (accessed October 14, 2015).
- <sup>68</sup> FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (The Orange Book), 35<sup>th</sup> 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).
- <sup>69</sup> PHS Act § 351(i)(3).
- <sup>70</sup> 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 October 14, 2015).
- <sup>71</sup> We do not accept this premise as valid based on the absence of any pharmacovigilance problems identified for the 77 biologics that share 25 NPNs in the U.S



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- <sup>72</sup> Standards are used throughout the supply chains and NCPDP has played a leading role in their development for pharmacy systems. See Standards Information at <https://www.ncdp.org/Standards/Standards-Info> (Accessed October 16, 2015).
- <sup>73</sup> The commonality of standards and their interoperability internationally is critical to reliable supply chains in multiple industries and countries – see GS1 Standards at: <http://www.gs1us.org/resources/standards> (Accessed October 16, 2015).
- <sup>74</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 September 1, 2006. Available at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm375086.htm> (Accessed October 15, 2015) noted as “Archived Content. The content on this page is provided for reference purposes only. This content has not been altered or updated since it was archived.”
- <sup>75</sup> The 24 official languages in Europe are identified here: [http://ec.europa.eu/dgs/translation/translating/officiallanguages/index\\_en.htm](http://ec.europa.eu/dgs/translation/translating/officiallanguages/index_en.htm) (Accessed October 14, 2015).
- <sup>76</sup> In Australia, the Australian Biologics Name (ABN) has varied from the INN for the epoetin biosimilars, but not for somatropin, filgrastim or infliximab. Their guidelines are available at: <https://www.tga.gov.au/book/naming-conventions-biosimilars> (accessed October 16, 2015)
- <sup>77</sup> The Novartis Group of Companies’ Citizen Petition Supplement, dated May 4, 2015, docket # FDA-2013-P-1398.
- <sup>78</sup> USAN Council, a discussion of its role is available at: <http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/about-us.page?> (accessed October 21, 2015)

### **USAN Council**

The United States Adopted Names (USAN) Council serves health professions of the United States by selecting simple, informative and unique nonproprietary names for drugs by establishing logical nomenclature classifications based on pharmacological and/or chemical relationships. The USAN Council is comprised of five members, one from each of the sponsoring organizations- the AMA, APhA and USP- and one from the Food and Drug Administration (FDA), as well as a member-at-large. One member is nominated to the USAN Council annually by each sponsoring organization; the FDA nominates one liaison member annually, and the member-at-large is selected by the sponsoring organizations from a list of candidates proposed by the AMA, APhA, and the USP. The nominees to the Council must be approved annually by the three sponsoring organizations. Individual members may serve up to ten consecutive years.

- <sup>79</sup> United States Adopted Names are administered by the AMA, and they support a position on consistent nonproprietary naming for all biologics. Their position on biosimilars (as issued August 17, 2015) is below

### **Biosimilar Nomenclature**

The USAN Council supports the policy that innovator biological drugs should share the same USAN and INN with the follow-on biological product (biosimilar drugs). We trust that the regulatory authorities in the United States will be able to accurately determine the efficacy and quality of the biosimilar drugs and will be able to provide pharmacovigilance of all biologic and similar biologic drugs prescribed. However, we understand that in some markets, pharmacovigilance activities may not be robust and we would support the INN Biological Qualifier (BQ) proposal, and in particular the principle that the BQ should apply to all biologics and be kept in a database and not published as part of the nonproprietary name.

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The USAN Council pledges to work with its partners, the AMA, USP and APhA and with the FDA and the INN to continue to develop a global approach to the naming of all biologicals not just biosimilars that is built on and consistent with existing, accepted scientific principles critical to supporting a globally relevant approach to the quality assessment of biological drugs.

<sup>80</sup> National Council for Prescription Drug Programs (NCPDP) letter to Margaret Hamburg, Commissioner FDA, dated June 6, 2014 re: Meeting held 1<sup>st</sup> May 2014 to discuss Nonproprietary Naming of Biologics, [http://www.gphaonline.org/media/cms/NCPDP\\_Follow-Up\\_Letter\\_to\\_FDA\\_Re\\_Biosimilar\\_Naming\\_Jun6\\_14.pdf](http://www.gphaonline.org/media/cms/NCPDP_Follow-Up_Letter_to_FDA_Re_Biosimilar_Naming_Jun6_14.pdf); NCPDP Letter to Sylvia Burwell HHS and Margaret Hamburg FDA, dated February 27, 2015 available at: [http://www.ncdp.org/NCPDP/media/pdf/NCPDP\\_Zarxio\\_Ltr\\_FDA\\_HHS.PDF](http://www.ncdp.org/NCPDP/media/pdf/NCPDP_Zarxio_Ltr_FDA_HHS.PDF) ; NCPDP letter to Ronald T. Piervincenzi, CEO, United States Pharmacopeial Convention, dated May 18, 2015 re: Nonproprietary Naming of Biologics, Biosimilars, and Interchangeable Biologics: Zarxio (filgrastim), available at: <http://www.ncdp.org/Resources/Hot-Topics>. All accessed October 16, 2015