Novartis Services, Inc.

May 7, 2019

SUBMITTED ELECTRONICALLY VIA www.regulations.gov

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2013-D-1543 Nonproprietary Naming of Biological Products; Update; Draft Guidance for Industry

Dear Madam/Sir,

Novartis Services, Inc. is submitting this letter on behalf of Novartis Pharmaceuticals Corporation (NPC) and Sandoz Inc. (Sandoz). NPC researches, develops, manufactures, and markets innovative medicines aimed at improving patients' lives. We offer a broad range of medicines, including small molecule drugs and biological products (including cell & gene therapies) for cancer, cardiovascular disease, inflammatory disease, infectious disease, neurological disease, eye disease, organ transplantation, respiratory disease, and skin conditions.

Sandoz is a leader in generic pharmaceuticals and biosimilars, providing access to a broad portfolio of high-quality, cost-effective prescription medicines. Sandoz launched the first biosimilar approved under the Biologics Price Competition and Innovation Act (BPCIA) pathway in the United States (U.S.) and now has three biosimilar products approved in the U.S.

We refer to NPC and Sandoz collectively herein as "Novartis" and therefore offer a balanced view from the perspective of a company that develops and markets both originator biologic and biosimilar drugs.

We appreciate the opportunity to provide comments in response to the U.S. Food and Drug Administration's (FDA's or "the agency's") updated Draft Guidance on Nonproprietary Naming of Biological Products referenced above). We note that the draft guidance offers the following ***new*** interpretation of the agency's previous biologics naming policy (articulated in the 2015 Designation of Official Names and Proper Names for Certain Biological Products Proposed Rule[1] and 2017 Nonproprietary Naming of Biological Products Final Guidance[2]) whereby the nonproprietary name (NPN) of certain biological products will include a *–xxxx* random letter suffix as follows:

- The four-letter suffix **will only apply** to: 1) newly approved originator biological products and 2) all biosimilars and interchangeable biological products.

[1] Designation of Official Names and Proper Names for Certain Biological Products Proposed Rule, Docket No. FDA-2015-N-0648, November 12, 2015
[2] Nonproprietary Naming of Biological Products; Guidance for Industry, Docket No. FDA-2013-D-1543, January 13, 2017

- The four-letter suffix **will not apply** to: 1) previously approved originator biologicals products and 2) products that will be "deemed" biologics by March 2020 according to BPCIA[3] and recent FDA guidance.[4]

As such, FDA's new guidance sets forth a bifurcated and inconsistent policy approach to the naming of biologics that leads to complexity and confusion, creates new pharmacovigilance challenges for current and forthcoming biosimilars, will increase burden and costs to the industry and other stakeholders, and result in a diminished commercial opportunity for biosimilars, all of which we discuss further herein. We encourage the FDA to engage and consider the view of other federal agencies involved in the success of biosimilar in the U.S., and in particular the Federal Trade Commission (FTC).

We are greatly concerned that the draft guidance's proposed naming approach - which will not apply the four-letter suffix to previously approved biological products or "deemed biologics" - may create new pharmacovigilance risks that undermine FDA's pursued objective of enhanced safety. Importantly, these risks will apply to all currently approved biosimilars (and those to come) for at least the next 10 years and will persist for the lifetime of these products.

As stated in prior submissions to the FDA, we continue to believe that a naming suffix is unnecessary to conduct biological product pharmacovigilance and strongly encourage FDA to adopt a consistent and internationally harmonized approach to biologics naming that relies on other product identifiers, such as brand name, NDC numbers, and manufacturer names (among others). While we partially agree with the approach included in FDA's draft guidance whereby the random four-letter suffix will not apply to previously approved biological products (including "deemed biologics"), we encourage FDA to apply this approach to any biological products i.e., **that FDA should not apply the suffix to any biological products**.

We have described herein our rationale that we encourage FDA to consider before it finalizes its inconsistent approach to biologics naming. Our comments seek to address various aspects of FDA's draft guidance on biologics naming – as follows:

1) FDA's approach is unnecessary and the inconsistent implementation of biologics naming will cause new pharmacovigilance issues (see Sections 1-2);
2) FDA's draft guidance will cause sponsors and other stakeholder to incur unnecessary additional burdens and costs while limiting the commercial viability of biosimilar products (see Section 3); and
3) Lastly, if FDA decides to continue with the implementation of the suffix, we put forth two alternative approaches for FDA to consider before it finalizes its proposed naming approach: a) retrospective implementation to only biologics that are reference products of biosimilars/interchangeable products; and b) use of a memorable suffix (see Section 4).

[3] Biologics Price Competition and Innovation Act of 2009 (Adopted: March 22, 2010)
[4] Nonproprietary Naming of Biological Products; Update; Draft Guidance for Industry, Docket No. FDA-2013-D-1543 (March 8, 2019)

1. ACCURATE PHARMACOVIGILANCE IS CRITICAL AND DOES NOT REQUIRE A SUFFIX

The updated draft guidance mentions in several areas the importance of safety and pharmacovigilance for biological products (including biosimilars). Medicinal product safety and pharmacovigilance are key issues of paramount concern to Novartis. We therefore apply the highest standards across our entire portfolio, which includes small molecule originator and generic drugs, originator biologics (including cell & gene therapies) and biosimilars. To ensure a robust and consistent process to oversee pharmacovigilance across the entire Novartis product portfolio, we have created a single, integrated safety department. All pharmacovigilance cases received at Novartis are entered into our single safety database and are then processed, reviewed and reported according to one set of processes regardless of their origin or the product they refer to (e.g., biologics or drugs, originator or generic/biosimilar). Novartis safety department has cumulatively processed over 4,000,000 safety cases globally.

With that as a background for our comments, we offer that the conversation about biologic naming and safety confuses two key yet different notions of pharmacovigilance: accurate product identification for case reporting (i.e., product identification and attribution) and the medical review of cases (e.g., immunogenicity, hypersensitivity, etc.). When done accurately, accurate case reporting facilitates the medical review of cases.

We agree that it is important to have accurate case reporting for all products, including biologics. Adequate pharmacovigilance case processing - i.e., allocating a safety event to a unique medicinal product - has been commonly undertaken for decades across a wide range of products without the use of or need for a random suffix tied to a product's NPN. Accurate case reporting has been done, typically, through the use of a product's brand name but also multiple other product identifiers, including NDC numbers, manufacturer name and lot numbers.

a. Case 1: Somatropins

Novartis has manufactured and marketed biological drugs such as our human growth hormone Omnitrope® (somatropin) that shares the same NPN ("somatropin") with 15 other approved human growth hormones in the U.S. These medicinal products will be deemed to be licensed as a biological product in 2020 according to the BPCIA. Since approval of the first recombinant human growth hormone in 1977 and with >32,000 adverse event reports as of Dec 31, 2018, 84.4% of all reports have been submitted with the brand name (see Table 1).

Table 1. FDA Adverse Events Reporting System (FAERS) Public Dashboard: Somatropin adverse event reporting across multiple products. As of Dec. 31, 2018 (accessed April 15, 2019)

Reported product names	Number of cases (%)
Genotropin®	7,727 (23.97)
Humatrope®	5,932 (18.40)
Nutropin® Aq	3,223 (10.00)
Nutropin®	2,971 (9.22)
Omnitrope®	2,678 (8.31)
Norditropin®	2,004 (6.22)

Saizen®	1,876 (5.82)
Serostim®	547 (1.70)
Nutropin® Aq Nuspin 10	133 (0.41)
Zomacton®	125 (0.39)
Nutropin® Aq Nuspin 20	87 (0.27)
Tev-Tropin®	54 (0.17)
Asellacrin®	36 (0.11)
Crescormon®	15 (0.05)
Zorbitive®	13 (0.04)
Saizenprep®	9 (0.03)
Nutropin® Aq Nuspin 5	5 (0.02)
Bio-Tropin®	3 (0.01)
Nutropin® Aq Pen 10	2 (0.01)
Reported as Generic	5,040 (15.64)
Total	**32,231 (100.00)**

b. Case 2: Interferon Beta-1B

In addition to somatropins, there are two interferon Beta-1B products approved by FDA, Betaseron® (Bayer) and Extavia® (Novartis). Interferon Beta-1B is also marketed by Bayer in Europe under the brand name Betaferon®. Data from all three products are included in the FAERS public dashboard. We are unaware of any safety concerns related to the fact that multiple interferon Beta-1B products share the same nonproprietary names. In fact, for these products, 97.8% of all adverse event reports in FAERS (>35,000 reports as of Dec. 31, 2018) have been reported using the brand name (see Table 2 below).

Table 2. FAERS Public Dashboard: Interferon Beta-1B adverse event reporting across multiple products as of Dec. 31, 2018 (accessed April 15, 2019)

Reported product names	**Number of cases (%)**
Betaseron®	27,206 (76.91)
Betaferon®	4,537 (12.83)
Extavia®	2,936 (8.30)
Reported as Generic	790 (2.23)
Total	**35,372 (100.00)**

There are multiple other examples of biological products approved by CDER and CBER that have shared a common non-proprietary name (some for decades), and for which no pharmacovigilance reporting issues have ever been raised e.g., albumins, antihemophilic factors, immunoglobulins, etc.

c. Other Identifiers Are Adequate for Product Identification

As mentioned above, we firmly believe the tools already in use enable comprehensive pharmacovigilance for biological products, such as manufacturer name, NDC numbers, batch numbers and brand names, among others. This is also implemented in our pharmacovigilance processes, where every report that Novartis receives concerning a biologic product is thoroughly followed up in order to obtain brand names and batch numbers.

The most prominently used identifier is the product's brand name. Indeed, the use of brand name as primary identifier for pharmacovigilance reporting is a more common, globally harmonized approach to adverse event (AE) reporting than the FDA's four-letter suffix – which is supported by data from the FAERS database. The below data from the FAERS database displays safety events for marketed U.S. biosimilars, which are very clearly not being reported using NPN+suffixes but are instead being reported by brand names (See Table 3).

Table 3. FAERS Database Public Dashboard: Safety Events Reporting for Marketed U.S. Biosimilars as of Dec. 31, 2018 (accessed April 15, 2019)

Product identifier entered into FAERS dashboard (NPN+suffix)	Brand name	Safety reports via NPN+suffix	Safety reports via brand name
filgrastim-sndz	Zarxio®	1	311
infliximab-dyyb	Inflectra®	28	3033
infliximab-abda	Renflexis®	3	14
pegfilgrastim-jmdb	Fulphila™	0	10
pegfilgrastim-cbqv	Udenyca™	0	0
filgrastim-aafi	Nivestym™	0	0
epoetin alfa-ebpx	Retacrit™	0	7
		32 (0.9%)	**3375 (99.1%)**

Further, a 2013 publication (prior to implementation of suffixes for any product) revealed that there were more than 75 products that shared 25 NPNs with no reports of significant pharmacovigilance issues related to product nomenclature.[5] At the time of the 2013 publication, there was never a stated concern about pharmacovigilance for these products nor has a concern been voiced for these products since that time. Many of these products are "deemed biologics" which FDA will transition to licensed biologics as of 2020. Under the 2019 draft guidance on naming, FDA has decided that there is not a safety issue posed by these "deemed biologics" and so there is no need to add a four-letter suffix to their NPN. Instead, these products will be distinguishable via their brand names and other product identifiers. Therefore, we encourage FDA to adopt the decision it has made for "deemed biologics" to all biological products.

It is also important to consider data from the most advanced biosimilar market, the European Union (EU), which approved the first biosimilar (Sandoz' Omnitrope (somatropin)) in 2006. Since then, EMA has approved over 50 biosimilar products. Uptake has varied by product and

[5] McCamish M, Gallagher AM and Orloff J. Biosimilar by name and biosimilar by nature. RPM Report. July/Aug 2013.

country, but as a whole, biosimilars have become an accepted part of the EU healthcare system, with over 700 million patient days of treatment through 2016.[6] Importantly, data from the EU experience as reported by the EMA has revealed that safety tracking of biosimilars over the past decade in Europe is successfully accomplished by use of proprietary brand names (96+% proper attribution), *without* a 4-letter random suffix.[7,8] The EMA has concluded that safety tracking of biosimilars over the past decade in Europe is successfully accomplished by use of proprietary brand names, without a 4-letter random suffix.[9,10] However, we are aware that other stakeholders have made their own calculations and have quoted different percentages for correct product attribution of a biosimilar in the EudraVigilance system. Given FDA's strong working relationship with the EMA we urge the FDA to work directly with the EMA to obtain the most accurate information related to product attribution rates in Europe.

Based on this significant and expanding global experience, we do not believe that the addition of a four-letter suffix to the NPN offers tangible benefits in terms of product attribution. We do not believe that a different approach or standard is necessary to adequately allocate a post marketing safety report to a biosimilar product (that is, different from any other product type) and we continue to believe that the globally established standard using the NPN plus other product identifiers (e.g., brand name) are effective and adequate. Further, despite all claims to the contrary, the entire "safety" concern around the naming of biological products remains to date hypothetical. Based on these facts, a number of major health authorities worldwide (EMA, TGA and Health Canada) have comprehensively reviewed the issue of biological naming and concordantly concluded that a specific biological naming convention is not warranted.

Unfortunately, FDA's approach to biological naming has therefore caused a lack of international regulatory harmonization, which we believe is contributing to downstream issues for biosimilar commercialization in the US (discussed further in Section 3). The impact of FDA's naming approach is further minimized by the agency's partial implementation of the biologics naming convention to only a subset of biological products in the US. We believe this should give FDA pause as it finalizes its naming policy for biological products.

We appreciate and support FDA's decision not to retrospectively implement the random four-letter suffix to all previously approved originator biological products (including "deemed biologics") which would have had a prohibitive cost to the healthcare system (see section 4a for more information). We encourage the agency to go one step further and entirely eliminate the use of the four-letter suffix from all biological products.

As stated by FDA's Dr. Janet Woodcock, the brand name is how physicians primarily know a product: "*Even though newer originator biologics will continue to be approved with suffixes,*

[6] Comment from Biosimilar Medicines Group to the US Oncology Drugs Advisory Committee, July 13, 2017. https://www.regulations.gov/document?D=FDA-2017-N-2732-0006 (accessed April 16, 2019)
[7] Vermeer NS, Giezen TJ, Zastavnik S, Wolff-Holz and Hidalgo-Simon A. Identifiability of Biologicals in Adverse Drug Reaction Reports Received from European Clinical Practice. Clinical Pharmacology & Therapeutics (2018) doi: 10.1002/cpt.1310
[8] European Medicines Agency and the European Commission. Biosimilars in the EU-Information guide for healthcare professionals. (2017) https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf (accessed April 8, 2019)
[9] Vermeer et al. (2018) doi: 10.1002/cpt.1310
[10] European Medicines Agency and the European Commission. (2017)

such products ***are generally known by their trade name***."[11] (emphasis added) As she further noted in the same article, she believes that the focus of doctors "*…is not whether the drug has a suffix or not*."[12] Indeed, we fully agree with Dr. Woodcock's assessment and believe the FDA should incorporate this notion into a revised naming convention that altogether eliminates the four-letter suffix for all biological products and instead focuses on other product identifiers, such as the product's brand name.

2. PARTIAL INTRODUCTION OF SUFFIXES IMPACTS ABILITY TO CONDUCT ADEQUATE PHARMACOVIGILANCE

The FDA is proposing a partial implementation of a random four-letter suffix to new originator and biosimilar products' NPNs. We believe this approach raises more challenges and causes more confusion in the short-, mid-and the long-term due to the inconsistent application of the naming policy to some but not all biological products.

The FDA's decision to implement its four-letter suffix only for newly approved biologic originator products and biosimilars makes pharmacovigilance for biologics more challenging. In contrast to the statements of former FDA Commissioner Dr. Scott Gottlieb that "the naming policy will provide consistency among biologics," in fact the updated proposed naming approach being implemented by FDA is doing the exact opposite where, for at least the next 10 years, some NPNs for marketed biologics will have a random four-letter suffix while others will not.

As background, we note that the primary intent of the 2015 biologic naming rule[13] was to improve the ability to accurately identify safety reports between the reference biologic product and the related biosimilar product. The concern behind the intent appeared to be that, if a report is submitted with the NPN only, it may not be attributable to a specific biologic product (a reference product or biosimilar). As such, the Agency shifted away from sharing non-proprietary names by different manufacturers (as done with drugs and with "deemed biologics") to an approach where different products containing a common active substance would be distinguished via their NPN+suffix (a purpose that the NPN was not designed to accomplish). As the FDA stated at that time, if this was consistently implemented across all biological products, the agency's approach should allow more accurate allocation of cases reported by active substance name (i.e., NPN + suffix).

In the updated 2019 draft guidance, the FDA is now proposing to only apply the four-letter random suffix to newly approved originator biologics and biosimilars, but not to any previously approved biological products, including those that are reference products for biosimilars. As noted, while we support FDA's decision not to retrospectively implement the random four-letter suffix to all previously approved originator biological products, we would like to highlight that this approach in itself creates a new significant concern. As we have shown in the previous

[11] Cipriano, M (2019, March 20) *Woodcock: Concerns About US FDA's Biosimilars Suffix Policy Detached From Reality.* Retrieved from https://pink.pharmaintelligence.informa.com/PS124962/Woodcock-Concerns-About-US-FDAs-Biosimilars-Suffix-Policy-Detached-From-Reality

[12] Cipriano, M (2019, March 20) *Woodcock: Concerns About US FDA's Biosimilars Suffix Policy Detached From Reality.* Retrieved from https://pink.pharmaintelligence.informa.com/PS124962/Woodcock-Concerns-About-US-FDAs-Biosimilars-Suffix-Policy-Detached-From-Reality

[13] Designation of Official Names and Proper Names for Certain Biological Products Proposed Rule, Docket No. FDA-2015-N-0648, November 12, 2015

section, suffixes are currently not being used by healthcare professionals for AE reporting. It is therefore possible that AE reports using only the NPN for a biosimilar may be submitted without the suffix. When this occurs, this safety event reported with partial information (NPN only *without a suffix*) will automatically be included under "reported as generic" category for the reference product NPN and it is not possible to distinguish it from safety reports from the reference product submitted using the NPN correctly without a suffix. This new concern leads us to firmly believe that the best approach to naming is to rely on the brand name and other product identifiers.

To help illustrate the impact of the partial implementation of FDA's four-letter suffix, Table 4 describes the three different scenarios of the implementation of the naming rule depicting this major pitfall unique to the partial implementation considered by the agency.

Table 4. Scenarios Related to FDA's Partial Implementation of Biologics Naming Suffix

Scenario	Reporting approach	Consequence	Comment
SCENARIO 1 – No suffix (NPN only with brand name for all biologics)	*Report with **brand name***	Correct attribution	This represents the majority of cases. No change from current practice
	Report with NPN only	Attributed as "possibly related" to all products that share the NPN	This is a minority of cases, and is consistent with current practice. All biologics (originator and biosimilar) are treated equally
SCENARIO 2 – Implementation of suffix for reference products and related biosimilars	*Report with **brand name***	Correct attribution	This represents the majority of cases. No change from current practice
	Report only with NPN+suffix	Correct attribution to the biosimilar or reference product	This is a minority of cases - benefit of naming rule if/as reporters get used to reporting with the suffix
	*Report only with NPN **without** suffix*	Considered as a separate entity that cannot be attributed unambiguously to either product	This is a minority of cases. Prevents misattribution to a specific product
SCENARIO 3 – Partial	*Report with **brand name***	Correct attribution	This represents the majority of cases – no

implementation of suffix to biosimilars but not to already approved reference products			change from current practice
	Report only with NPN+suffix	Correct attribution to the biosimilar	This is a minority of cases - benefit of naming rule if/as reporters get used to reporting with the suffix
	*Report only with NPN **without** suffix*	**Report cannot differentiate between cases correctly reported to RP via NPN only and incomplete reporting of biosimilar via NPN omitting the suffix**	This is a minority of cases but is the **opposite effect of the intent** of the naming rule • May incorrectly ascribe a safety signal to the reference product • Will diminish ability to detect safety signals in the biosimilar

The potential concern with misattribution in Scenario 3 may be already starting to happen with filgrastim. We note that the market share of the reference product (Neupogen® (filgrastim) declined from ~50% in 2017 to ~35% by end 2018 (a decline of approximately one third), likely due to the increase in the market share of Zarxio® (filgrastim-sndz) to ~45% in 2018. At the same time, the FAERS Public Dashboard shows that the safety reports reported using the product name "Neupogen®" increased from 515 reports in 2017 to 600 reports in 2018 (Figure 1) and the number of reports report using the generic name "filgrastim" increased from 986 in 2017 to 1,431 in 2018 (Figure 2). There is often an increase in reporting for a reference product when a generic product is launched due to increased scrutiny of the product class as a whole, so the increase in reports overall may not be completely unexpected. However, while there appears to be some consistency in the reporting frequency between reports using the product name or the NPN over the years 2006 - 2016, there is a more pronounced increase in reports using the generic name in 2018 in particular (Figure 2). The exact reason for the relatively steep increase in report using the generic name is not clear, but it is possible that some of the reports were derived from patients that used Zarxio® but that were incompletely reported as "filgrastim." Any such incomplete reported cases with the biosimilar as reported by the NPN only (without a suffix) would not be differentiated in the FAERS database from cases derived from the reference product that were reported with the INN.

Beyond pharmacovigilance purposes, the FDA also previously argued on the grounds of dispensing risk in that, absent of suffix there may be an unintentional switch from a reference product to a biosimilar. With the partial implementation of FDA's naming policy and given the lack of use of the suffix to date, there is a similar risk that patients on a biosimilar may be "switched back" if the physician uses the NPN without the suffix. We believe that such instances would also represent an unintentional switch.

Figure 1. Safety reports from FAERS where the product identifier was the product name "Neupogen®" as of Dec. 31, 2018 (accessed April 15, 2019)

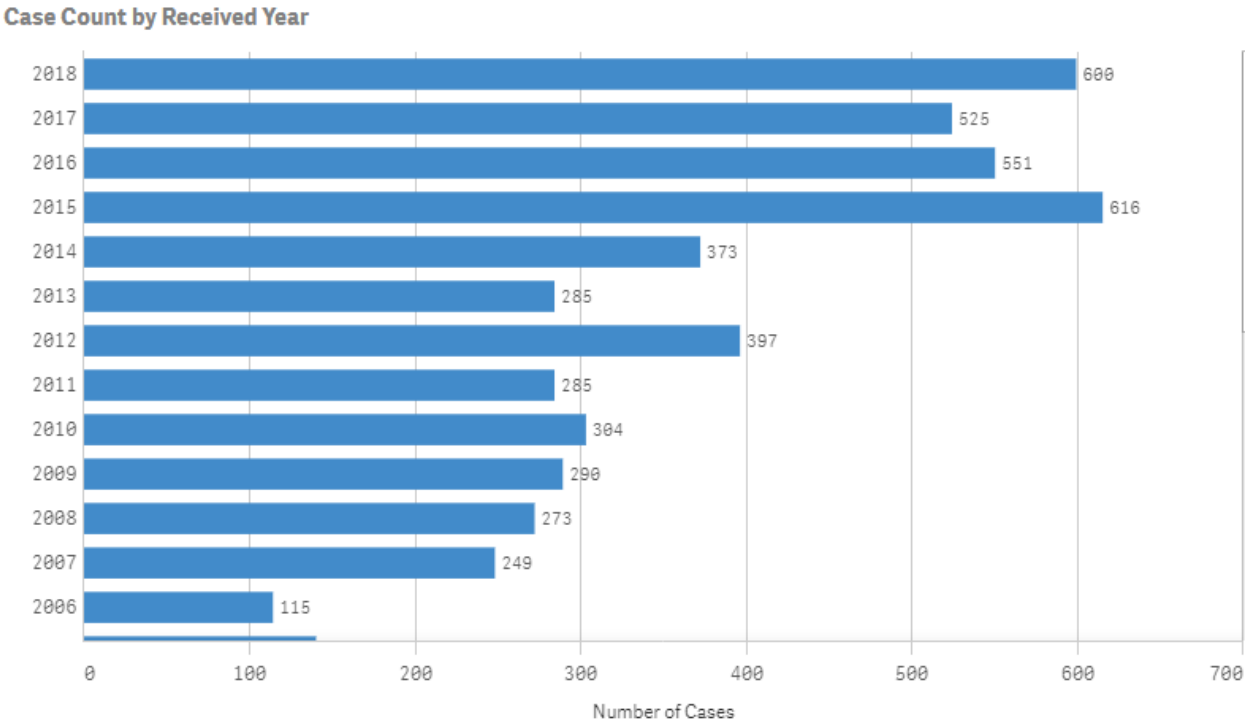
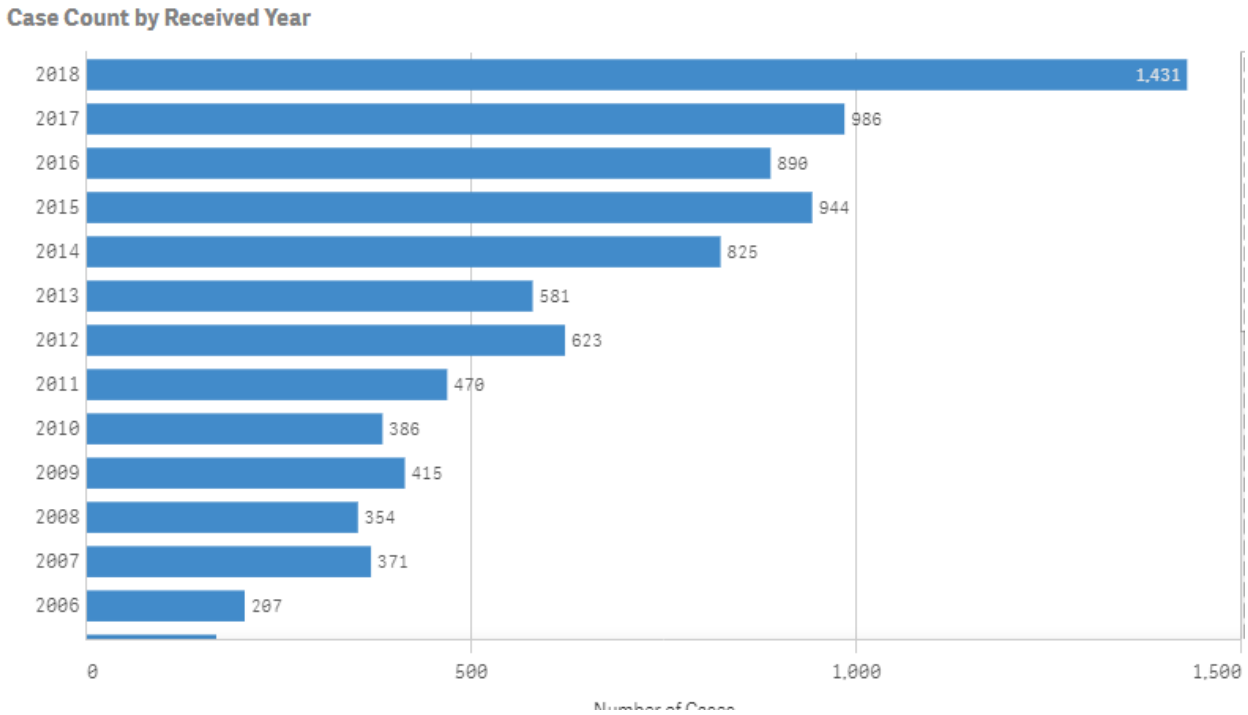


Figure 2. Safety reports from FAERS where the product identifier was the generic name "filgrastim" as of Dec. 31, 2018 (accessed April 15, 2019)



Lastly, the inequitable treatment of biosimilars under the updated draft guidance will enhance the existing misconceptions of some that there are possibly concerns of clinically relevant differences, even when the product is approved by FDA. The importance of consistent implementation was acknowledged in the initial finalized FDA naming guidance, which stated that:

> *"Applying this naming convention only for products licensed under section 351(k) of the PHS Act—but not for the reference product licensed under 351(a) of the PHS Act—could adversely affect health care provider and patient perceptions of these new products. Specifically, such an approach could be misinterpreted as indicating that biosimilar products differ from their reference products in a clinically meaningful way or are inferior to their reference products for their approved conditions of use.*"[14]

It is important to note that, if the FDA chooses to go forward with its intended approach for partial implementation of the biologics naming policy discussed in the updated guidance, the pitfalls identified above will continue over a significant period of time. The agency recently stated, "*As the FDA continues to apply this policy, we expect that a steadily increasing proportion of licensed biological products, including originator products, will have nonproprietary names that include four-letter suffixes*." In addition, FDA leaders stated that "*We expect **that as time goes on**, and more biological products are introduced to the market with distinguishable suffixes, patients and providers increasingly will understand that the suffixes reflect a consistent naming convention and are not an indicator of product quality*".[15]

We believe the Agency is underestimating or minimizing the time impact and how some of the limitations we mentioned above will be long lasting under the proposed implementation. For example:

- It will be at least a decade before the regulatory data protection on the first originator product approved with a suffix will expire. According to the information in the Purple Book, the first originator product approved with a suffix has a regulatory exclusivity until 2029 (vestronidase alfa-vjbk). This does not account for any potential regulatory exclusivity extension or longer patent protection. This means that the different limitations mentioned above will not only apply to the 18 biosimilars currently approved but also any biosimilar product the FDA will approve in the next 10 years.
- The limitations for biosimilars of those reference products with no suffix will carry on perpetually. In at least 10 years from today, there will eventually be consistency in the naming between a recently approved reference products and their future biosimilar products (because they both will have the *–xxxx* random suffix). For already approved biosimilar products, the inconsistency (and related issues) will remain for their lifetime. Even if by then healthcare professionals are accustomed to using suffixes, an accidental omission of the suffix (on a prescription or adverse event report) will remain a bias for pharmacovigilance or dispensing towards the reference product. This can only be

[14] Nonproprietary Naming of Biological Products; Guidance for Industry, Docket No. FDA-2013-D-1543, January 13, 2017
[15] Office of the Commissioner. (2019, March 7). Statement from FDA Commissioner Scott Gottlieb, M.D., on FDA's steps on naming of biological medicines to balance competition and safety for patients receiving these products. Retrieved from https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm632870.htm

addressed if FDA removes all use of the *–xxxx* code or by retrospective implementation of the suffix to reference products.

Therefore, Novartis believes that the partial implementation proposed by the agency represents the worst option because of the significant impact it has on the U.S. pharmacovigilance system:

1) Adds complexity and burden to sponsors and other stakeholders to conduct pharmacovigilance for biologics;
2) Puts the AER system in the U.S. at risk for increased misattribution of products; and
3) Diminishes the ability to detect post-approval safety signals in reference products, biosimilars and interchangeable biologics.

Therefore, FDA's partial implementation of the biologics naming convention could put patients at risk for unintended switching from biosimilars to a reference product. Additionally, FDA's policy decision will have long-lasting impacts to currently marketed and soon-to-be-approved biosimilars at least for the next decade and, for some, well beyond for the lifetime of the products.

3. BIOSIMILAR COMMERCIALIZATION IN THE U.S.

With the exception of Zarxio® (filgrastim-sndz), biosimilar uptake has been slow for biosimilars launched in the U.S. compared to other markets. These products are facing significant head winds in the U.S. from both the commercial and policy perspectives.

As of March 2019, only seven biosimilars are commercially available in the U.S. (Zarxio® (filgrastim-sndz), Inflectra® (infliximab-dyyb), Renflexis® (infliximab-abda), Fulphila™ (pegfilgrastim-jmbd), Retacrit™ (epoetin alfa-epbx), Nivestym™ (filgrastim-aafi), Udenyca™ (pegfilgrastim-cbqv)) and 11 have been approved by the FDA but are not yet commercially available in the U.S. for 9 different reference biologics. Meanwhile, since 2006, Europe has approved 58 biosimilars to 15 reference medicines as of December 2018, of which 54 are commercially available.[16]

The slow growth of biosimilars has already had an impact on biosimilar investment in the U.S. A number of companies have announced that they terminated working on biosimilars and others have announced that they would discontinue working on specific programs or not open new programs, which is a long-term concern for patient access to biologics in the US. Five companies have dropped out of developing biosimilars in the US completely (Allergan, Epirus, Hanwha, Oncobiologics, Shire). Further, some companies, including Coherus, Momenta, Pfenex and Pfizer, have announced that they have reduced or suspended some of their US biosimilar programs, Boehringer Ingelheim and Fresenius-Kabi announced that they will proceed with current programs but have suspended initiating new biosimilar programs.

We believe that challenges in commercialization are in part caused by the new U.S. biologics naming convention, which has unintentionally fueled misinformation campaigns. These campaigns leverage the difference in product naming as a basis for concerns on biosimilar safety

[16] Biosimilars Approved in Europe, Generics and Biosimilars Initiative (GaBi Online). (Originally posted 2011; last updated Dec. 14, 2018) http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe (accessed May 7, 2019)

and efficacy. For example, Pfizer's recent Citizen Petition stated: "A recent tweet by Amgen Biosimilars also contravenes the statutory standard that a biosimilar is highly similar to and has no clinically meaningful differences from the reference product: "Biologics or biosimilars? It's not just apples to apples. While #biosimilars may be highly similar to their #biologic reference products, there's still a chance that patients may react differently. See what you're missing without the suffix: http://bit.ly/2G2zGTa."[17]

In all, FDA has put in place what we consider to be an unnecessary challenge to biosimilar prescribing in the form of its inconsistent biological naming convention which diminishes FDA's ability to succeed at one of its stated goals: to help support the adoption of biosimilars. While the issue of the biologic naming convention, by itself, may not be the reason or even the main reason of the slow uptake of biosimilars in the U.S., we believe it contributes to the overall challenges biosimilars are facing. Taken together, this lessens the ability of the U.S. healthcare system to realize the potential for biosimilars to help balance value, access and cost associated with biological products.

4. AN ALTERNATIVE APPROACH IF FDA DOES NOT ABOLISH THE NPN+SUFFIX NAMING CONVENTION

We agree that retroactive assignment of suffixes to all biologics is not a good approach and the costs to the US healthcare system would be enormous.[18] However, if the agency continues down this path where its biologics naming policy will only be applied to some biologics, then we believe the following alternative approaches should be considered.

a. Retrospective application of suffixes to the nonproprietary name of a reference product of biosimilar

In the event that the FDA elects to retain the bifurcated implementation of its biologics naming policy (where suffixes will only apply to biosimilars and newly approved originator biologics), then Novartis urges the FDA to also assign suffixes to the reference products of biosimilars and interchangeable biologics. While we believe the best way to avoid the pharmacovigilance issues related to FDA's four letter suffix (e.g., misattribution) is to abolish the use of the NPN+suffix naming convention for all biologics, the second best option is that the NPN+suffix should apply to all newly licensed biologics as well as previously approved reference products (which are currently excluded from the NPN+suffix in FDA's 2019 guidance).

In the initial FDA guidance issued in 2017, the FDA indicated the importance of consistent implementation to originator products and related biosimilars for at least four reasons:

> *"FDA's current thinking is that a proper name that includes a distinguishing suffix is warranted for both newly licensed* ***and previously licensed originator biological*** *products, related biological products, and biosimilar products. As with prospective application of the naming convention, retrospective application will help (1) prevent a patient from receiving a product different from what was intended to be prescribed; (2)*

[17] Pfizer Inc. Citizen Petition 21 C.F.R. § 10.30, FDA-2018-P-3281, August 22, 2018 Retrieved from: https://www.regulations.gov/document?D=FDA-2018-P-3281-0001

[18] Nonproprietary Naming of Biological Products; Guidance for Industry, FDA-2013-D-1543, January 13, 2017 (Novartis Comment Letter). https://www.regulations.gov/document?D=FDA-2013-D-1543-0192 (Accessed April 15, 2019)

> *facilitate manufacturer-specific pharmacovigilance by providing a means of determining which biological product is dispensed to patients; (3) encourage routine use of FDA-designated suffixes in ordering, prescribing, dispensing, and recordkeeping practices for these products; and (4) advance accurate perceptions of these biological products."*[19]

As mentioned previously, the partial implementation may create a new pharmacovigilance risk related to misattribution of incomplete adverse event reports to, and only to, the reference product if the report contains only the NPN without a suffix. Our key concern is that with the current inconsistent application of the suffix to the biosimilar only, it is not possible to distinguish in FAERS database between complete safety reports from the reference product submitted using the generic name (NPN without suffix) and incomplete safety report from a biosimilar product submitted with the NPN and omitting the suffix. Both cases are combined in FAERS under "reported as generic" with the NPN of the reference product and it is not possible to distinguish one from another. Given the extremely limited use of the suffix to date, we believe this is a likely possibility and this is a major pitfall that contradicts the pursued objective of the biologic naming.

It is acknowledged that incomplete cases will remain incomplete and provide limited value from the pharmacovigilance perspective overall. However, if a suffix is retrospectively assigned to reference products, at least complete cases from the reference product reported with the proper name (NPN + to be assigned suffix) will be tracked separately from incomplete cases where reporter omitted the suffix from a biosimilar (NPN only). This would allow for:

1. more accurate attribution of cases reported with the proper name only (NPN+suffix, but without brand name) to the correct products (avoid attribution of incomplete cases by default to the reference product);
2. would allow for sensitivity analyses for signal detection with incomplete cases as they would be tracked separately from the complete ones (with suffix) for the reference product and corresponding biosimilars;
3. allow better tracking of actual use of the suffix across the entire group of product for reports based on the proper generic name (NPN+suffix) compared to able to the number of cases reported with the NPN only and/or the brand name; and
4. may promote use of the suffix as reporters are educated to the issues mentioned above.

A retrospective implementation of the naming convention to the reference product would allow better attribution of case reports submitted using the "generic name" only and in particular better differentiate complete cases with identified source product from incomplete reports with only the NPN.

Retrospective implementation to reference products would also align with FDA's initial intent as articulated in the first "final" naming guidance where the FDA stated that equitable treatment was an important point to avoid misperception about biosimilars:

> "*The inclusion of an FDA-designated suffix in the nonproprietary name of biological products licensed under section 351(a) or 351(k) of the PHS Act should have the added*

[19] Nonproprietary Naming of Biological Products; Guidance for Industry, FDA-2013-D-1543, January 13, 2017

benefit of helping to avoid inaccurate perceptions of the safety and effectiveness of biological products based on their licensure pathway."[20]

The stated reason for the FDA's revised decision not to assign suffixes in a retroactive manner to all biologics is that the cost to the U.S. healthcare system would be onerous. Novartis first raised this concern in our October 26, 2015 comments to FDA-2013-D-1543, and quantified the cost in our Feb 10, 2017 submission to the same FDA docket.[21]

The high cost of implementation the U.S. healthcare system would have been driven by two major needs:

1) The need to modify existing systems to incorporate a suffix, and
2) The need to retroactively revise existing licensed biological drug databases. (There are several hundred biologics listed in the Purple Book that would have been impacted.)

The need to modify existing systems to incorporate a suffix is still required as long as suffixes are used for newly approved biological products. We believe that modifications are still ongoing to various databases, distribution networks, hospitals and pharmacy systems etc. This cost impact on the healthcare system could still be substantially minimized if the suffix concept is dropped soon.

The decision in the updated guidance to not retroactively rename already licensed biologics will save the U.S. healthcare system the significant costs of applying the suffix naming convention to the many hundreds of previously approved biologics. The cost of retroactively assigning suffixes only to biologic reference products would apply to a very small number of products (nine, as of April 15, 2019). As a result, the additional cost to the U.S. healthcare system to implement this option would be modest.

Although there are only nine reference products to the 19 biosimilars that are currently approved in the U.S., if one liberally assumes that there will be 20 reference products in the near to mid-term, using the same algorithm we used in our previous comment letter we calculate that the cost to the overall U.S. healthcare system for retrospective implementation to these 20 products would be relatively modest, at less than $25,000,000 (see Table 5 on following page). In this scenario, the costs for retroactive implementation of naming suffixes for reference products only will be further mitigated by the fact that elements of the healthcare systems will still need to be modified to accommodate the naming convention of newly approved biologics that would contain suffixes as a part of their nonproprietary names.

b. <u>Suffixes should be memorable and meaningful</u>

A random suffix only adds complexity and confusion and actually increases the risk of accidentally using the wrong NPN. This complexity may contribute to the current reality, which is that the suffix is essentially not used. It is self-evident that more errors will likely be made when trying to recall a non-meaningful suffix as compared to a meaningful suffix.

[20] Docket No. FDA-2013-D-1543 (January 13, 2017)
[21] Nonproprietary Naming of Biological Products; Guidance for Industry, FDA-2013-D-1543, January 13, 2017, (Novartis Comment Letter) https://www.regulations.gov/document?D=FDA-2013-D-1543-0192 (Accessed April 15, 2019)

Table 5. Estimated Total Resource Burden on U.S. Healthcare system (One Time Effort) for 20 reference products

Impacted system	Conservative Estimate of the Number of Organizations in the U.S. that will Need to Modify their Systems	Time Burden per Organization Category (in Hours)	Cost of implementation (assuming $150/hr)
Distributors/Wholesalers	10	2,000	$300,000
Group Purchasing Organizations	50	10,000	$1,500,000
Health plans (commercial & CMS)	140	28,000	$4,200,000
Providers - Hospital networks	424	84,800	$12,720,000
Providers - healthcare professional networks	125	25,000	$3,750,000
Pharmacy chains	25	5,000	$750,000
Data banks and Compendia	4	800	$120,000
Pharmacovigilance systems	10	2,000	$300,000
Total Projected Hours and Cost		**157,600**	**$23,640,000**

We understand that the primary reason that FDA elected to use non-meaningful suffixes was a stated concern that meaningful suffixes could contribute to a commercial advantage for biosimilars whose manufacturer was better known as compared to a biosimilar from a lesser-known manufacturer. However, in the past several years it has become very clear that the identity of a biosimilar manufacturer does not by itself convey a commercial advantage. Several marketed biosimilars that have struggled to attain significant U.S. market share are marketed by some of the most well-known pharmaceutical companies.

If the intent for the suffix is to "facilitate" accurate product identification by the healthcare professionals for prescribing, dispensing or reporting purposes, a recognizable, memorable and/or meaningful suffix is more adequate than a non-meaningful, random sequence of letters.

NOVARTIS

CONCLUSION

With the proposed implementation of the biologic naming rule as laid out in the updated guidance (partial implementation and based on 4 random letters suffix to NPN), the FDA is adding complexity and confusion around the naming of biologics and creates a new pharmacovigilance risk that is opposite to the pursued objective. In today's reality, FDA's biologics naming policy is one of many key issues that actively contribute to significant patient access challenges that minimize the broad adoption of biosimilars in the U.S. Further, the stated rationale for use of suffixes for biologics is based on a purely hypothetical concern that is not corroborated by any currently available data. Novartis respectfully considers that based on the globally derived data and aligned with the conclusions from other major health authorities, the use of a suffix attached to the NPN is not warranted nor desirable.

We believe FDA should reconsider its approach to align with other regional and country health authorities to rely on the use of brand names and other product identifiers to facilitate pharmacovigilance for biological products.

If the FDA decides to continue with the implementation of a 4-letter suffix for biologic, we urge the Agency to consider selective retroactive implementation to reference products of approved biosimilars and interchangeable biologics to ensure consistency. This approach will at least help mitigate the risks of misattribution introduced by the partial implementation. We also recommend to move away from random letters and to instead adopt meaningful suffixes.

We appreciate the opportunity to provide comments as FDA continues to implement a key policy issue related to use of biological drugs. If there are questions about our comments please do not hesitate to contact us.

Sincerely,

Sala Gautier
Digitally signed by Sala Gautier
DN: dc=com, dc=novartis, ou=people, ou=GX, serialNumber=811693, cn=Sala Gautier
Reason: I am approving this document
Date: 2019.05.07 11:39:41 -04'00'

Mayhew Brian
Digitally signed by Mayhew Brian
DN: dc=com, dc=novartis, ou=people, ou=GD, serialNumber=1747434, cn=Mayhew Brian
Date: 2019.05.07 11:44:41 -04'00'

Gautier Sala
U.S. Head, Biopharma Regulatory Affairs
Sandoz

and

Brian Mayhew
Executive Director, Regulatory Policy
Novartis Pharmaceuticals Corporation