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

CITIZEN PETITION

The Novartis Group of companies (Novartis) submits this petition under 21 C.F.R. § 10.30 to request that the Commissioner of the Food and Drug Administration (FDA) take the action requested below.

A. Action Requested

Novartis respectfully requests that, to encourage and protect the safe and rational use of all medicines, FDA require that a biosimilar, be identified by the same international nonproprietary name[1] (INN) as the reference product. A biosimilar, by definition of its approval, has successfully met FDA's demanding standard of high similarity to a reference product and, further, the Agency has concluded that the totality of the evidence demonstrates that there will be no clinically meaningful differences in terms of safety, purity and potency between it and the reference product.

B. Summary

The United States enacted the Biologics Price Competition and Innovation Act (BPCIA) in 2010 to establish a pathway for FDA to approve biologic products as biosimilar to already-approved biologics. Under the statute, a biosimilar must demonstrate to the satisfaction of FDA that it is highly similar to an originator reference product and, further, to demonstrate the safety, purity, and potency of the proposed biosimilar. The biosimilar will be considered interchangeable with its reference product if the applicant provides sufficient information to show that the biosimilar can be expected to produce the same clinical result as the reference product in any given patient.

The BPCIA is appropriately silent about the nomenclature FDA should apply to biosimilars, as such nomenclature should be self-evident from FDA's current practice. Nevertheless, the question of whether biosimilars should share an international non-proprietary name (INN) with their reference product has been the subject of much public debate.[2, 3] Such debate has confused the concept and current utilization of INN by departing from the INN's intended purpose of facilitating the identification of pharmaceutical substances. Instead the current dialogue has implied that the INN is intended to facilitate the identification of a specific product. This implication is untrue and has resulted in confusing an otherwise straightforward issue. Many products, including biologics, currently marketed in the United States share INNs (see Table 1

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below). But INNs are not, and cannot be, the only or even the primary tools used for tracking and tracing. Indeed, despite their shared INNs, these products have been successfully traced for pharmacovigilance purposes.

Moreover, assigning unique INNs to biosimilars that FDA concurs are highly similar to a reference product would imply that INNs are intended to communicate more than just molecular characteristics and a pharmacological class.[4] It would imply that INNs are intended to communicate an aspect of the regulatory status itself, such as interchangeability or lack thereof. FDA has clearly argued against unique INNs for biosimilars when it stated: "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."[5] Indeed, many biologic products on the market today share INNs even though they have never been compared directly to each other, and should a demonstration of "sameness" be required by FDA retrospectively today, many of these products would fail to meet it. Nevertheless, and most importantly, the fact that these products share INNs has not resulted in any safety issues being identified.

Assigning different INNs to products approved as biosimilars would introduce unnecessary confusion into the healthcare system and could unintentionally communicate increased caution, unfounded risk, or other regulatory reservations that are purely hypothetical. Significantly, it would put into question years of FDA's practice of using the well-established analytical standard of high similarity[6] to approve major manufacturing changes of originator biologic products without a parallel change in the originator INN, despite the fact that the manufacturing changes have altered, sometimes substantially, the originator biologics' molecular structures.[7] Using the high similarity standards, FDA has in these cases satisfied itself that the altered originator biologic would produce the same clinical result in terms of safety, purity and potency as its pre-manufacturing change version, and applied this reasoning multiple times for the same product with the same confidence.[8] Similarly, FDA will use these same standards to satisfy itself that the biosimilar would produce the same clinical result as the reference product. Requiring separate INNs for biosimilars but not originator biologics would undermine FDA's own approval decisions, which in both cases require FDA's determination that the compared product (biosimilar or the post-manufacturing change originator biologic) produces the same clinical outcomes as its comparator (respectively, the reference product or the pre-manufacturing change biologic).[9, 10]

Novartis submits that imposing unique INNs on biosimilars would not improve any aspects of patient safety, pharmacovigilance or tracking, and would instead undermine the safe use of all biologics by introducing unfounded confusion into the healthcare system. Novartis therefore respectfully requests that, rather than imposing unique INNs on biosimilars, FDA instead require them to be identified by the same international nonproprietary name as the reference product to encourage and protect the safe and rational use of all medicines.

C. Statement of Grounds

I. INNs are not, and cannot, be the primary tool relied on for tracking and tracing.

The World Health Organization (WHO) administers an international naming convention, known as the International Non-proprietary Naming system. INNs are intended to facilitate the identification of pharmaceutical substances or active pharmaceutical ingredients by health care

professionals worldwide.[11] They are granted based only on molecular characteristics and pharmacological class of active ingredients. In the United States, a sponsor may obtain a United States Adopted Name (USAN), and USANs have been generally consistent with the INN naming convention. INNs are by definition non-proprietary and therefore not designed to identify a specific product; indeed, once an INN is established, it identifies ALL products matching the respective molecular characteristics.

Novartis agrees that for pharmacovigilance purposes all drug products and biologics must be tracked. However, a tracking system does not require, nor would it be helped by, unique INNs for biosimilars. As INNs were designed to be shared among products, they were never intended to function as the basis – and certainly not the sole basis - for tracking and tracing specific products. It is the proprietary, or trade name of a product that is more useful in that regard. And even trade names comprise only a part of the track and trace tool portfolio as products are also traced by national drug codes (NDCs), manufacturer names, and batch and lot numbers.

Despite the suggestions to the contrary, there is no indication that this system will not work for biosimilars. Although no product has been approved as a biosimilar under the BPCIA to date, FDA has set the regulatory precedent by approving numerous biologics which appropriately share INNs even though they were approved under separate approval pathways and are manufactured by different manufacturers. (See Table 1 below). While a few of these products have been discontinued (but unless taken off the market due to safety or efficacy reasons can still be a reference product, hence they are included in the table[12]), the products that have not been discontinued are currently being marketed under separate brand names, and the fact that they share INNs has not resulted in any unique traceability issues.

If there are any weaknesses in the current system with regard to the traceability of a specific product to an adverse event, such weaknesses are not related to the INN and must be addressed for all currently approved products. Indeed, Novartis would support a vigorous enhancement of track and trace methods, and education of physicians and pharmacists.

Furthermore, there are compelling data from other highly regulated jurisdictions confirming that different INNs are not necessary as a mechanism for tracking and tracing. In Europe, where biosimilars have been on the market since 2006, they share the same INNs[13] (see attached Table 2) with their corresponding reference products', and in each case the individual biosimilar product is identified by a brand name[14]. A recent study of the identification of biosimilars in the European Union pharmacovigilance system found that the naming convention for biosimilars has a successful product identification rate of 96.2% across all three marketed biosimilar classes (somatropin, filgrastim and epoetin).[15] There is no reason to expect that the United States' pharmacovigilance system cannot achieve similar or even higher product identification rates given that, unlike the European Union, the United States has the advantage of a singular, nationwide NDC product identification system for tracking.

II. Assigning different INNs to products approved as biosimilars would unnecessarily put into question years of FDA's practice of approving manufacturing changes of originator biologic products without a resulting change in the originator INN.

FDA reviews and approves manufacturing changes in biological products using comparability approaches that use the same highly similar standard that has been written into the biosimilar legislation enacted by U.S. Congress. Both similarity exercises are based on the highly

similar concept as used in the BPCIA and described in FDA's draft guideline on the quality of biosimilars, as well as the International Conference on Harmonization Q5E guideline (ICH Q5E). ICH Q5E focuses on assessing quality of the altered molecule pre- and post-manufacturing change, and when the magnitude of the change so requires, on assessing preclinical and clinical data as well. This approach has been coordinated among regulatory authorities across the highly regulated markets,[16] and also in the form of guidance by WHO for biosimilars in other, emerging markets where patient access is critically important.[17]

FDA has confirmed this approach. When discussing the biosimilar review process, FDA commented that "[its] experience with biologics provides important relevant knowledge. Since the mid-1990s, for example, physicochemical and functional assays have been used to characterize changes in manufacturing processes for some biologics, and then animal or clinical studies are used to resolve any remaining uncertainties about the comparability of the products created before and after such changes and to provide sufficient confidence that safety and efficacy are not diminished."[18] Indeed, data published in peer-reviewed scientific literature demonstrate that, while originator products do change over time, they are well controlled between manufacturing changes, and, even after manufacturing changes, the clinical attributes of the products are acceptable.[19]

Given the fact that the comparability assessment of biological products pre- and post-manufacturing changes not only mirrors, but is in fact the very basis for assessment of biosimilarity, requiring different INNs for biosimilars would unnecessarily put into question years of FDA practice in reviewing and approving such changes without requiring new INNs for post-manufacturing change biologics, whose molecular structure, variant composition or impurity profile has been altered, sometimes substantially, by the manufacturing change. If an identical, consistent naming system is not adopted, patients and physicians may - and should - ask why they were not notified of the change in the originator biologic, which continued to be identified by the same INN and brand name and whose label did not reflect the manufacturing change or the corresponding change in the product itself. The practice of maintaining the same INNs for post-manufacturing change originator biologics is well founded in law, health authority guidelines and science, and should apply equally to naming considerations for biosimilars.

There is no need to introduce confusion and doubt through an unequal application of naming conventions when FDA has such in-depth understanding of all the biologics that they have reviewed and licensed for the United States market, which by definition comprise the entirety of the reference products for biosimilars in the United States.[20] If FDA applies regulatory science consistently, such that the highly similar standard for manufacturing changes is the same as the highly similar standard for biosimilars, then patients can be confident that a biosimilar will generally be as similar to its reference as that reference is to itself over its lifetime, and more importantly, that in both cases any minor differences between them will be in clinically inactive components only.

III. Assigning different INNs to products which conform to an established compendial monograph in the US would be inconsistent with the current regulations governing USP names.

The United States Pharmacopeia (USP) General Notices specify how the compendial standards, including monographs for particular drug substances and drug products, are developed. The current USP and National Formulary (NF) standards are then publically listed and referenced

in the Federal Food, Drug, and Cosmetic Act (FDCA).[21] FDA is therefore responsible for the enforcement of USP standards.

The FDCA states that drugs, including biologics,[22] will be deemed adulterated[23] or misbranded[24] if they do not conform to recognized compendial standards relating to nonproprietary naming and identity, and strength, quality and purity. Therefore, if USP has a monograph for a biologic product, which would be applicable to a biosimilar, such biosimilar will be deemed misbranded unless its label bears the official title recognized in USP-NF.[25] Of course, FDA has the authority to change a USP name[26] in the interest of usefulness and simplicity, but first it must submit its act to public notice and comment and provide the opportunity for judicial review.[27]

IV. Far from advancing it, unique INNs for biosimilars would be detrimental to patient safety.

Assigning unique INNs to biologics, which were proved to be highly similar to their reference products, would send a signal that INNs are intended to communicate more than the molecular characteristics and the pharmaceutical class of the active ingredient. It would send a signal that, instead of simply being used as a global cataloguing mechanism for products with a related active ingredient, INNs are somehow intended to communicate an aspect of the regulatory review and approval itself, such as pharmacologic interchangeability or lack thereof in products with the same active ingredient(s).

A determination of pharmacologic interchangeability of products with the same active ingredient(s) must be made by regulatory agencies based on credible scientific data.[28] For example, in the United States, FDA must make an affirmative determination that two products bearing the same INN are therapeutically equivalent, i.e., that in FDA's judgment they are expected to have equivalent clinical effect.[29] It is this determination by FDA and the subsequent listing of the products as therapeutically equivalent – **and not the products' INN** – that informs physicians, pharmacies, state agencies and other stakeholders that the products can be substituted with the full expectation that they will produce the same clinical effect and safety profile. Similarly, FDA will have to make a separate determination of interchangeability with respect to a biosimilar, and it will be that determination and its reflection on the biosimilar's label that will inform of the biosimilar's interchangeability with its reference product.

FDA previously expressed concern at the potential confusion that could be created by the implication that assigning the same INNs to products was tantamount to a determination of pharmacological interchangeability, as opposed to a high degree of similarity.[30] This concern was echoed in a number of stakeholder letters to the Agency.[31] Representative of these comments are those from a letter authored by the American Pharmacists Association (APhA), the National Association of Chain Drug Stores (NACDS) and the National Community Pharmacists Association (NCPA) submitted to FDA's Draft Guidances Relating to the Development of Biosimilar Products docket:

> "Unique INNs for common active ingredients may generally increase confusion, leading to increased safety concerns and possibly medication errors. Physicians are already pressed for time, and therefore it is imperative that there are no additional and unnecessary obstacles that hinder them from timely decision-making, especially in cases of urgent care. The use of different INNs would increase the burden of being able to distinguish which products are biosimilar and interchangeable with which reference drug and may pose

difficulties in recognizing the best alternative drug for therapeutic use in a timely manner. Such confusion may lead to medication errors such as therapeutic duplication."[32]

The determination of safety, efficacy, and in appropriate cases, interchangeability, is and should remain beyond the scope of any naming convention. If FDA were to assign different INNs to products with the same active substance for the purpose of preventing inappropriate substitution, it would necessarily create an equally inappropriate implication that all products with the same INNs are by definition interchangeable. This implication could have potentially negative effects on patient safety; especially if such an implication were to be applied to products which share INNs but which have never been compared with each other and which may even have been licensed by FDA for different indications. However, it must be remembered in this context that FDA already allows different recombinant and naturally-derived products from different manufacturers to share INNs, even though such products have been approved by FDA under separate Biologics License Applications (BLAs) and have never demonstrated comparability. The fact that they share INNs has not resulted in any safety issues, but an implication that the same INNs indicate that they are all interchangeable would indeed negatively impact the safe and rational use of these and other medicines which share INNs.

The corollary is also true. Requiring different INNs for biosimilars, and presumably other biologics produced by different sponsors that share active ingredients, would suggest that prescribing by INN could be as appropriate in the future as brand name prescribing is today – after all biologics would essentially have two unique names going forward. Anticipating that such an argument could be made, we tested a recent FDA decision to require that one of the biosimilars approved in Europe with the INN filgrastim to be licensed in the US with the interim established name[33] of TBO-filgrastim. See the MedERRs report summarized in Figure 1 below. Historically, in the context of Brand names, FDA has recommended against the use of pre-fixes and suffixes because of their ability to lead to confusion[34] and this policy is confirmed in the analysis conducted for TBO-filgrastim. Whether or not such confusion will result in practice has yet to be determined as the product in question has not yet been launched in the US.

Figure 1: Med-ERRS® Report for TBO-filgrastim found a "high vulnerability" for medication errors

Proposed name	Score	Vulnerability	Issues
tbo-filgrastim	2	high	Look-alike name(s) Sound-alike name(s) misinterpretation of prefix

Strong look-alike and strong sound-alike similarity was noted with filgrastim (NEUPOGEN, others: used in the treatment of chemotherapy-induced neutropenia), especially if the "tbo" prefix is separated from the rest of the name, missed or misinterpreted. Filgrastim is an injectable product that is used for the same indication as tbo-filgrastim. The dose, dosage strengths, clinical setting for use and patient population all are the same. Both drugs would be ordered by the same type of practitioner (eg., oncologist). Both filgrastim and tbo-filgrastim are stored in the refrigerator. If confusion occurred, the risk of harm generally is moderate due to the bone pain and fever associated with the use of filgrastim. However, due to the clinical similarities between the two drugs, the harm is likely to be negligible.
Slight sound-alike similarity was noted with pegfilgrastim (NEULASTA; used in the treatment of chemotherapy-induced neutropenia). Pegfilgrastim is an injectable product that is used for the same

indication as tbo-filgrastim. The clinical setting for use and patient population are the same. Both drugs would be ordered by the same type of practitioner (e.g., oncologist). Both pegfilgrastim and tbo-filgrastim are stored in the refrigerator. Pegfilgrastim is given at a different dose than tbo-filgrastim. If confusion occurred, the risk of harm generally is moderate due to the bone pain associated with the use of pegfilgrastim. However, due to the clinical similarities between the two drugs, the harm is likely to be negligible, unless pegfilgrastim is administered on a daily basis as if it were tbo-filgrastim, in which case the harm would be increased.

A number of misinterpretations were noted for the "tbo" prefix. These include "to be ordered," "TVO" for "telephone verbal order," "the," "Hb" for the abbreviation for hemoglobin, "TB" for the abbreviation for tuberculosis and "TKO" for the abbreviation "to keep [vein] open." If any of these misinterpretations occurred, the practitioner would likely dispense and/or administer a filgrastim product rather than a tbo-filgrastim product.

INNs are assigned based on the molecular structure and pharmacological class of products and have been utilized successfully as one component of pharmacovigilance monitoring. INNs are used in national and regional pharmacovigilance systems, along with other key identifiers such as brand name, to facilitate the detection of new safety information related to pharmaceutical substances on a global level. They allow the aggregation of safety data, detection of class effects, and appropriate and timely response to safety alerts. These significant safety benefits would be undermined if products with the same active ingredients were assigned different INNs, especially when such products have been shown to produce the same clinical result in terms of safety, purity and potency by credible scientific data. Different INNs (USANs) will necessarily decouple biosimilars approved in the United States from safety data of the same products elsewhere in the world, where consistent INNs are currently used, and vice versa. This could contribute to the breakdown of the current international system with ramifications for public health more broadly than just in the US.

V. Conclusion

The BPCIA was enacted to provide a pathway for approval of products that reference already-approved biological molecules. It is for FDA to determine whether an applicant under the BPCIA meets the demanding standards of high similarity to the reference biological molecule. If it does not demonstrate high similarity, it is for FDA to simply not approve it as a biosimilar. Approving it under a separate INN would run counter to the very purpose of the BPCIA, a major goal of which is to create competition in the marketplace for biologics and expand access to, and increase the affordability of, these critical medicines. This goal of providing patients and providers with access to high quality, lower cost alternative products and incentivizing innovation in the field of medicine should never compromise patient safety. It is the FDA review process, however, and not separate INNs, that will ensure patient safety is never compromised. Indeed, assigning separate INNs to biosimilars will undoubtedly undermine this objective by creating confusion in the healthcare system and unnecessarily casting doubt on FDA's robust and well-established practice of reviewing the relevance of differences in originator products after manufacturing changes. As unfortunate as such a result would be, it will only be compounded unnecessarily and equally tragically by thwarting the congressional intent of increasing patient access to affordable biologics. Therefore, Novartis submits that imposing unique INNs on biosimilars would not improve any aspect of patient safety, pharmacovigilance or tracking, and would instead undermine the safe use of all biologics by introducing unfounded confusion into the healthcare system. Novartis therefore respectfully requests that, rather than imposing unique INNs on biosimilars, FDA instead require

them to be identified by the same international nonproprietary name as the reference product to encourage and protect the safe and rational use of all medicines.

D. Environmental Impact

The actions requested herein are subject to categorical exclusion under 21 C.F.R § 25.30.

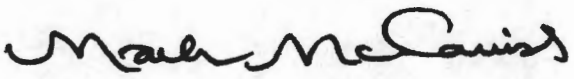
E. Economic Impact

Pursuant to 21 C.F.R. § 10.30(b), an economic impact statement will be submitted only at the request of the Commissioner.

F. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted on behalf of the Novartis Group of Companies



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Acronyms:

APhA = American Pharmacists Association
BLA = Biologics License Application
BPCIA = Biologics Price Competition and Innovation Act
FDA = Food and Drug Administration
FDCA = Federal Food Drug and Cosmetic Act
ICH = International Committee on Harmonization
INN = International Nonproprietary Name
NACDS = National Association of Chain Drug Stores
NCPA = National Community Pharmacists Association
NF= National Formulary
Novartis = Novartis Group of companies
USAN = United States Adopted Name
USP = United States Pharmacopeia
USP-NF= United States Pharmacopeia – National Formulary
WHO = World Health Organization