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

**Subject: FDA-2013-D-1543:**

**FDA Draft Guidance and Proposed Rule on biosimilar naming**

Dear Sir/Madam:

Amgen is a global biotechnology and pharmaceuticals products company based in Thousand Oaks, CA. We are pleased to have the opportunity to offer comments on the Draft Guidance for Industry on Nonproprietary Naming of Biological Products. We have included the following comments on relevant sections in an effort to support the FDA in this endeavor.

Sincerely,

Steven Galson
Senior Vice President, Global Regulatory Affairs and Safety
Amgen, Inc

ENCLOSURE: Amgen comments on: **FDA Draft Guidance for Industry on Nonproprietary Naming of Biological Products**

**AMGEN COMMENTS to FDA docket on draft guidance on biosimilar naming**

Thank you for the opportunity to comment on the draft guidance. Amgen is a biotechnology pioneer and developer of one of the largest portfolios of biosimilar medicines designed to facilitate patient access. It is from this vantage point, with more than 35 years of experience in the challenges associated with biotechnology, that we provide comments on the proposed biosimilar naming policy.

**Executive Summary**

Amgen congratulates FDA on promulgating a science-based biologics naming policy for the United States that protects the public health. We believe that all biosimilar policies must be consistent with the science behind complex biotechnology medicines and agree with FDA that protecting patient safety and public health must be the top priority.

As the Agency articulated in the draft guidance, the science of biologics is complicated and creates challenges that must be met by appropriate public policy solutions. The biologics naming convention proposed by the Agency will "help minimize inadvertent substitution" and will "also facilitate pharmacovigilance." (Draft guidance pg. 1) The proposed approach of assigning biologics a nonproprietary name (NPN), also referred to as the proper name, that has a shared core and distinguishable suffix achieves clear product identification while enabling stakeholders to recognize associated products. FDA's proposal is a practical means to help prevent inadvertent switching of products and improve pharmacovigilance, both of which are essential to the long-term safety of biologic medicines and to the success of the biosimilar pathway.

There is a need for a sound, science-based naming convention now, before the proliferation of biosimilar products makes clear identification even more difficult. With this goal in mind, Amgen suggests several modifications to the proposal that we believe will achieve these objectives more fully and efficiently. First, the naming convention should apply to all biologics, including interchangeable products, in order to advance effective pharmacovigilance without compromising adoption of the new naming convention. Second, the suffix should be meaningful (by identifying the sponsor) and consistent across the product sponsor's portfolio. Such a naming convention would help prescribers and patients with product identification, thereby avoiding inadvertent substitution and fostering accurate attribution of adverse events. Third, the suffix should be memorable for the same reasons it should be meaningful. Fourth, retrospective application of the naming protocol to currently marketed products should be implemented by first convening a stakeholder working meeting to identify legal and logistical challenges and define solutions to mitigate the impact on health care practice and attendant risks to patients who rely on these medicines.

**Distinguishable Names for Biologics Are Necessary for Pharmacovigilence and Safe Use**

Amgen shares FDA's commitment to patient safety and agrees with the Agency that, "There is a need to clearly identify biological products to improve pharmacovigilance and, for the purposes of safe use, to clearly differentiate among biological products that have not been determined to be interchangeable." (Draft Guidance pg. 1, Ln 19-21). As FDA notes, and as biosimilar sponsors like Amgen know, biosimilar medicines will be safe and effective for the indications of use, but unlike generic drugs, biosimilar medicines are not exact copies of their respective reference products and will not necessarily or even routinely be deemed interchangeable with the reference product. Indeed, although differences in indications, routes of administration, and delivery systems between reference and biosimilar or related biological products may be permitted, and even expected, such differences create potential risks of medication error.

For the reasons articulated by FDA in the draft guidance, all biologics (originators, biosimilars, and interchangeable products) must be carefully monitored throughout the lifecycle of the product for any unexpected change in patient impact. Distinguishing between multiple manufacturers' versions of a particular biological product will enable all manufacturers to be accountable and will help to ensure the optimal medical care of all patients who rely upon these important biological medicines. As discussed in the scientific literature and referenced in Amgen's submission to FDA in response to the September 19, 2013 Generic Pharmaceutical Association Citizen Petition on biosimilar naming, biologic medicines present an increased risk of unwanted immune reactions due to their size, complexity, and sensitivity to the process of manufacturing, handling, and the environment, among other things.[1] Shared NPNs create an increased and unnecessary risk of ambiguity in product identification and thus an unacceptable risk of delay in time-critical safety research.[2,3,4,5] Distinguishable NPNs close a significant gap in the pharmacovigilance system associated with the current design limitations of many health information technology systems.[6,7,8]

Distinguishable Naming Is Not Material To Market Acceptance

Although the success of the biosimilar industry is arguably outside the scope of FDA's mission, the topic has been raised repeatedly by some stakeholders in conjunction with the question of biosimilar naming conventions, and is therefore relevant to address in this discussion. As a developer of biosimilars, Amgen is acutely sensitive to the potential impact of a naming construct (or any other policy) on the eventual success of biosimilars. We have examined this issue in depth and have found that distinguishable naming does not appear to be a material factor in the market acceptance, or "uptake,"

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[1] See §II of "Comments of Amgen Inc. on GPhA and Novartis's citizen petitions requesting identical non-proprietary names for biological products and their respective reference products (Docket Nos. FDA-2013-P-1153; FDA-2013-P-1398, respectively)". Document FDA-2013-P-1153-000, available at http://www.regulations.gov/#!documentDetail;D=FDA-2013-P-1153-0003.

[2] Ibid. §III

[3] Grampp et al. *Exp. Op. Drug Saf.* 2015; 14(3):349-60

[4] Stergiopoulos et al. *TIRS.* 2015; 49(5) 706-716

[5] Lietzan EF, Sim LE, Alexander EA. *FDLI's Food and Drug Policy Form*—Biosimilar Naming: How do Adverse Event Reporting Data Support the Need for Distinct Nonproprietary Names for Biosimilars? Washington, DC: Food and Drug Law Institute; 2013

[6] Casadevall N et al. *BioDrugs.* 2014;28(5):439-444

[7] Grampp et al. "US Health Care Professional Perspectives on Adverse Drug Event Reporting in the Hospital Setting and the Opportunity for Information Technology". Oral presentation O35 at the 15th annual International Society of Pharmacovigilance meeting (October 28, 2015, Prague Czech Republic). Amgen and the Tufts Center for the Study of Drug Development presented research demonstrating that the majority of surveyed health care providers in hospitals could not reliably retrieve product identifiers for manufacturer, NDC or lot number from their health information technology systems. Program available at: http://isop2015prague.org/final-programme.htm

[8] Amgen recently surveyed ten e-prescribing providers at HIMSS 2015 to assess their system's capabilities to capture and display for products administered or dispensed the product name, national drug code (NDC), manufacturer name, and lot/batch number; to translate the NDC into text; and to implement the National Council for Prescription Drug Programs SCRIPT 10.6 patient medication history standard. We found that all systems displayed the drug name; five displayed the NDC. None of the systems translated the NDC to convey the manufacturer name and product characteristics or displayed the manufacturer name or lot/batch number. Seven systems implemented the SCRIPT 10.6 standard. We concluded that substantial gaps and variations among e-prescribing systems exist; not all have implemented current standards. To support accurate adverse event reporting in the biosimilar era, further steps are needed, such as legislation requiring prescriber notification of biologic substitutions and use of e-prescribing systems that provide access to patient medication history.

of biosimilars. Biosimilar products with distinguishable names have been licensed in several developed economies including Japan, Europe, and Australia. These regions and countries also include classes of biosimilars sharing the same NPN, so it is possible to perform some comparison of market uptake in these settings. Amgen provided an extensive analysis of the dynamic between naming and uptake in these jurisdictions in its comments[9] submitted to the Federal Trade Commission docket February 28, 2014. In sum, we have found no compelling evidence that distinguishable naming policies for biosimilars adapted in certain regions have played a significant role in determining biosimilar uptake.

In Japan, for instance, epoetin alfa biosimilar 1 – a biosimilar epoetin product – has 94% market share despite the requirements that it have a different NPN and that it specifically be identified as a biosimilar.[10] In four of the five largest European markets, Germany, Italy, Spain, and the UK, a biosimilar with a distinguishable NPN has a greater market share than a biosimilar with the same NPN (where both products reference the same originator biologic).[11] In Australia, the NPN of the biosimilar short-acting erythropoiesis-stimulating agent (ESA) is distinguishable from the reference product, but biosimilar G-CSFs do not have distinguishable names; the biosimilar ESA and G-CSFs respectively have 47% and 57% of unit shares of their accessible markets, suggesting no strong correlation between the naming convention and uptake.[12] The factors that will ultimately drive uptake of a biosimilar are myriad and more complicated than the NPN.

In contrast to the impact on market acceptance, an analysis of adverse event reporting in Europe and Australia did reveal that naming conventions had a material impact on the accuracy of product identification In March, 2015 Amgen provided FDA data sets showing significant deficiencies in attribution of products to specific manufacturers for filgrastim products in the European Union and Australia.[13] Filgrastim products all share the same NPN in these markets. A supplemental analysis of adverse event data in Australia shows that 42% of filgrastim-related adverse event reports (AERs) identify the product only by the shared NPN and are therefore unattributable to a specific manufacturer.[14] In contrast, for the recombinant erythropoietin (epoetin) product class wherein each product has a unique NPN in Australia, only 5% of AERs are not assigned to a specific product.[14] In both cases, the AERs attributed to specific manufacturers' products are out of proportion with reported distribution of sales across competitors, suggesting a pattern of incorrect attribution where NPNs are shared.

**FDA's Proposed Naming Framework**

Amgen supports FDA's proposal that the proper name of biologics should have a shared core and a distinguishable suffix that "will provide a consistent, readily available and recognizable mechanism for patients and health care professionals, including providers and pharmacists, to correctly identify these products." (Draft guidance pg. 6, ln 231-233). We agree with the Agency that this naming convention will "help minimize inadvertent substitution" and will "also facilitate pharmacovigilance." (Draft

[10] IMS MIDAS, calculating shares of Counting Units with the most recent quarter available (Q2 2015).
[11] IMS MIDAS, calculating comparative shares by either volume (i.e., Counting Units) or sales (i.e., Local Currency) generates the same result; analyzing the most recent quarter available (Q2 2015)
[12] IMS MIDAS, calculating shares of Counting Units with the most recent quarter available (Q2 2015); notably, there is only one biosimilar ESA in Australia, versus three biosimilar G-CSFs, so it stands to reason that the G-CSF market will experience more biosimilar erosion.
[13] Comment from Amgen, Inc. Posted to regulations.gov March 12, 2015. ID: ID FDA-2013-P-1153-0027. Available at http://www.regulations.gov/#!documentDetail;D=FDA-2013-P-1153-0027
[14] See attachment 1.

guidance pg. 1, ln 33-36). This approach achieves the balance of clear product identification while enabling stakeholders to recognize associated products and is a practical tool for facilitating the safe use of biologics, including accurate attribution of adverse events.

**Recommended Modifications**

Although Amgen supports the general approach proposed by FDA, we suggest several modifications to more fully and efficiently achieve the Agency's stated goals. First, the naming convention should apply to all biologics, including interchangeable products, in order to advance effective pharmacovigilance without compromising adoption of the new naming convention. As noted by FDA, product problems for biologics can develop at any point in the life cycle of the product; therefore it is essential that all biologics can be identified with specificity and associated with a manufacturer, regardless of whether the biologic is a reference product, a biosimilar, or an interchangeable product.

Shared NPNs would hinder pharmacovigilance by making it difficult or impossible to distinguish between the reference product and the interchangeable product or products. Allowing interchangeable products to share the NPN of the reference product would also require a name change for products initially entering the market as biosimilar, which we expect to be significantly disruptive to the health care ecosystem, as discussed below with regard to retrospective application of the naming convention. Although a sponsor could avoid a name change by choosing to delay marketing until a product has been designated as interchangeable, that would delay competition and patient access to an additional treatment option, and is thus not a positive alternative. As discussed more fully in response to Question 2 below, Amgen sees no public health benefit for an interchangeable product sharing the NPN of the reference product. The benefits that accrue from a designation of interchangeability are achieved regardless of the products' NPNs.

A second change Amgen recommends to the FDA naming proposal is the use of a consistent suffix across the license holder's portfolio. This approach was presented by FDA for consideration and discussion in the draft rule implementing a name change for six biologic products, including three Amgen products. On page 16 of the draft rule, FDA presented for consideration EPOGEN®, NEUPOGEN® and Neulasta®, each with the proposed suffix of "-amgn". Assigning a "meaningful" suffix such as the proposed "-amgn" or "-sndz" most realistically accounts for the fact that these suffixes will be used by people (as opposed to just machines) —and people would benefit from an easy-to-use solution. A system of meaningful suffixes would help prescribers, patients, and pharmacists recognize products easily and consistently and thereby avoid inadvertent substitution. Clear recognition will also foster accurate attribution of adverse events. The current proposal of random suffixes that vary across a license holder's products would require identifying a distinct suffix for every biologic and biosimilar, which will create an increased administrative burden for FDA and prescribers and be a challenge for sponsors. If the suffix is random and different for every product, we foresee complications, including a proliferation of meaningless identifiers that may confuse healthcare providers (HCPs) and patients.

Meaningful suffixes that are easily associated with a particular manufacturer as a result of routine use make product identification easier for all stakeholders, even in the event of commercial arrangements or transactions such as the joint marketing of a product, out-licensing the product to other companies, or selling the product rights completely. Although sometimes framed as a complication to the adoption of a policy of meaningful suffixes, these situations are a simple aspect of a commercial arrangement. Most transactions that change the license holder of biological products happen pre-approval. Of the 70 non-vaccine biologics that had over $100M in US sales in 2014, only seven of these products were

subject to such a deal post-FDA approval.[15]As with all other aspects of the commercial arrangement, the parties would be responsible for negotiating whether, under the new biologics naming construct, the NPN remains the same or the suffix is modified. So long as the guiding principle of not permitting shared NPNs remains constant, commercial dynamics do not need to complicate the naming construct.

Closely related to the above suggested change regarding meaningful suffixes, Amgen urges FDA to permit the adoption of suffixes that are memorable for the same reasons they should be meaningful. Physicians have consistently commented on the complexity of proper drug names and the challenge of keeping up with the ever increasing list of drugs available. Patient care should not be further complicated by a biologics "identifier" that is unidentifiable because it is random and unmemorable. FDA and the biosimilar industry have the significant challenge of educating prescribers and other stakeholders about biosimilars, including the ways in which biosimilars differ from generic drugs. Biosimilar naming should be simplified to the extent possible and consistent with advancing safety and avoiding medication errors, in order to encourage adoption.

Amgen's fourth recommendation relates to retrospective application of this naming convention to already marketed products. We will address the implementation of this element in greater detail in our response to the Proposed Rule changing the names of six biologic products already on the market, including three of Amgen's products. However, we offer the following comments for purposes of framing the parameters of the draft guidance.

Retrospective application of the naming convention to already-marketed products has the potential to be disruptive for stakeholders, particularly when implemented in conjunction with the introduction of biosimilars of the already-marketed products. Indeed, we have received recent feedback from stakeholders that both prescribers and pharmacists prefer to keep originator names without the suffix to avoid product confusion and the workload associated with updating electronic systems. We do understand, however, that having a uniform system of suffixes across all biologics has policy benefits. Therefore, Amgen recommends that as a first step, FDA convene a stakeholder working meeting to identify and discuss legal and logistical challenges and define solutions to mitigate the impact on patient access, healthcare practice, the conduct of clinical trials, labelling, distribution, and the healthcare ecosystem more broadly.

In evaluating the steps Amgen will need to take to implement a new name, it is clear the roll-out will take several years. It will be essential for the Agency to allow for adequate time for implementation. In response to Question 5, we provide some additional thoughts on the implementation process and challenges. This topic will be more fully addressed in response to the Proposed Rule. However, some of the logistical and legal hurdles that stakeholders will face include the following:

1. Reference product sponsors must update product labeling, packaging, websites, and promotional material;
2. Biosimilar product sponsors must update clinical trial protocols, pharmacy instructions, investigator's brochures, and other materials that reference the originator and/or biosimilar proper name prior to the name change;
3. Biosimilar sponsors may face challenges with import and export laws that may be implicated when the proper names of products reflected in the initial documentation have been changed;
4. Vendors must generate updates to electronic prescribing and record keeping systems;

[15] EvaluatePharma, data on file.

5. Pharmacists and payers must incorporate updates to electronic systems as provided by the vendors or generate updates to their own proprietary systems;
6. Physicians must secure and implement updates to electronic prescribing, record keeping, and medical records;
7. Payers and stakeholders with whom they interface must update systems to reflect the modified product names;
8. Technical and medical journal articles that reference products by original proper name will have to develop and implement a protocol to reflect new product names;
9. Prescribers, pharmacists, and payers must be introduced to the new naming protocol and trained to use the suffix consistently; and
10. States may need to modify medical and pharmacy practice guidelines to address how prescriptions that lack a valid suffix should be addressed.

A delayed roll-out of the new NPN for previously licensed products could be an important means to avoid, among other consequences, disrupting patient access, interrupting ongoing clinical trials, and causing unnecessary waste of medicines and labels already stocked. Rules and guidance from the Agency prior to implementation will be important to prevent legal and regulatory violations associated with mislabeling/misbranding of products in the US and globally.

**Response to Questions Posed by FDA**

In response to the questions posed in the Federal Register Notice of Opportunity to Comment, Amgen provides the following comments.

1. ***What are the potential benefits and challenges of designating a suffix in the proper name of a biological product that is:***
   - ***Devoid of meaning versus meaningful (e.g., a suffix derived from the name of the license holder)***
   - ***Unique to each biological product versus unique to each license holder and shared by each biological product manufactured by that license holder.***
     ***In your comments, please address how each option would impact the following: Safe use of biological products; pharmacovigilance; and market acceptance and uptake for certain products***

     Amgen strongly supports suffixes that are meaningful (rather than random) and suggests a suffix that is associated with the license holder. This approach will be more memorable and thus more likely to be adopted and less prone to errors, which will advance safe use and pharmacovigilance. A meaningful system for suffix assignment is likely to minimize confusion related to the adoption of the new naming convention and thereby advance acceptance and potentially uptake of these products. Biosimilar experience in Europe, Australia, and Japan demonstrates that distinguishable names do not deter uptake of products.[16]

     Consistency of the suffix across products held by a license holder will advance the success of the naming convention. The easier it is to remember a suffix, the more likely it is to be used, and used correctly. Prescribers and dispensers will be more likely to identify and remember a meaningful suffix and are prone to forget or to make transcription errors with a random series of letters. A meaningful suffix will more likely promote continuity of product utilization, as well

[16] See above and Amgen comments to FTC

as support intentional changes when appropriate. Meaningful suffixes associated with the biologics license holder will also advance transparency and accountability, thereby promoting public health.

***2. What would be the potential benefits and challenges for an interchangeable product to share the same suffix as designated in the proper name of the reference product?***

Amgen recommends that biosimilar and interchangeable products adhere to the same naming convention, that is, a shared core and distinguishable suffix. As noted by FDA, product problems for biologics can develop at any point in the life cycle of a product; therefore it is essential that all biologics can be identified with specificity and associated with a manufacturer, regardless of whether the biologic is a reference product, a biosimilar, or an interchangeable product.

Assigning interchangeable products the same suffix as the reference product would have adverse consequences in several regards. First, pharmacovigilance would be hindered if the reference and interchangeable products, of which there may be multiple, could not be clearly distinguished from one another. Second, applying a policy of shared names for interchangeable products would require a name change for biosimilar products that were designated interchangeable after initially entering the market as a biosimilar. A sponsor may choose to delay marketing until a product has been designated as interchangeable and thereby avoid a name change; however, that would also delay competition and patient access to an additional treatment option.

Amgen sees no public health benefit to an interchangeable product sharing the NPN of the reference product. The benefits that accrue from a designation of interchangeability are achieved regardless of the product's NPN. The opportunity for pharmacy-level substitution of biologics has already been established by 20 states, most recently California, and in every state, that authority is associated with the FDA designation, regardless of the product name. As a result, the framework exists for payers to leverage an interchangeability designation and provide financial incentives for pharmacists to substitute interchangeable products as they do therapeutically equivalent generic drugs. Indeed, FDA has created the *Purple Book* to facilitate pharmacists' awareness of which products have been designated as interchangeable and thus eligible for substitution. As we have commented elsewhere, identifying the status of a product as biosimilar or interchangeable on the product label will further assist HCPs in identifying the status of a product as interchangeable.[17]

It would be counterproductive for FDA to indicate a product's status as interchangeable via a shared NPN. The Agency and the biosimilar industry already have a significant challenge in educating prescribers, patients, pharmacists, and payers on the differences between biosimilar and generic paradigms as well as the differences between approval as a biosimilar versus interchangeable. Accurate traceability via a distinct NPN can co-exist easily with a system for encouraging uptake via pharmacy-level substitution of interchangeable products. However, the reverse is not true. Shared names thwart effective pharmacovigilance, irrespective of whether that pharmacovigilance is directed toward reference products, non-interchangeable biosimilars, and/or interchangeable biosimilars.

[17] See also *Transparent labeling of biosimilars,* Amgen comments to Docket no. FDA-2015-P-2000.

3. ***Would there be additional benefits or challenges if the suffix designated in the proper name of a biosimilar product that is subsequently determined to be interchangeable were changed to that of the reference product upon a determination of interchangeability? Would there be benefits or challenges to allowing the manufacturer of the biosimilar product that is subsequently determined to be interchangeable to have the option of retaining its original suffix or adopting the same suffix as the reference product?***

   As discussed in our response to Question 2, traceability is compromised by shared NPNs; therefore, no license holder should have the option to share the NPN with any other independently licensed biologic.

   Furthermore, retaining the distinguishable NPN would be less disruptive to patients, HCPs, and other stakeholders. The costs associated with a name change are not limited to the manufacturer; electronic prescribing systems, compendia, electronic medical record systems, billing systems, and more will have to be changed to accommodate a new name. It is inappropriate to impose a system-wide burden, particularly when public health will suffer as a result of less robust pharmacovigilance.

   Finally, a memorable and meaningful suffix that is consistent across a manufacturer's biologic products is the best way to encourage informed use of these suffixes. The use of shared NPNs would undermine this effort.

4. ***How could FDA and/or other Federal partners improve active pharmacovigilance systems for purposes of monitoring the safety of biological products?***

As we have described in a recently published article in *Biodrugs*[18], building a robust pharmacovigilance system for biologics must account for both passive and active acquisition of signals [19] and for different settings of use (eg, the pharmacy benefit for self-administered biologics versus the medical benefit for physician-office administered biologics). Each of these situations is currently subject to distinct gaps that impact the fidelity of adverse event data conveyed to FDA or the manufacturer. FDA, the Center for Medicare and Medicaid Services (CMS), and/or the US Department of Health and Human Services (HHS) can influence standards and best practices to improve pharmacovigilance. Below we identify the settings of use and the agency with jurisdiction over the recommended action:

For all settings of use:

- FDA: Assign distinguishable NPNs to mitigate against the common practice of using a generic placeholder name for all members of the product class.

[18] Grampp and Felix, *Biodrugs*. 2015; available on line at http://link.springer.com/article/10.1007/s40259-015-0137-2.

[19] Pharmacoepidemiol Drug Saf. 2009 Aug;18(8):713-21. doi: 10.1002/pds.1772.
*Adverse drug reaction active surveillance: developing a national network in Canada's children's hospitals.*
Carleton B[1], Poole R, Smith M, Leeder J, Ghannadan R, Ross C, Phillips M, Hayden M.

- FDA: Update the MedWatch on-line web interface to issue prompts for specific product names and lot numbers for biologic products.[20]
- HHS: Refine diagnostic codes to better differentiate serious immune related adverse events and thereby improve the specificity of active surveillance for the problems specific to biologics.
- HHS: Encourage use of bar-coded technology to convey drug identifiers, soon to be available on secondary product packaging via the Drug Supply Chain Security Act (DSCSA), into patient electronic health records.
- HHS: Amend standards to promote capture of manufacturer name and lot number in claims databases.

Physician-office or hospital-administered biologics:

- HHS: Update national standards for health information technology (HIT) systems to include specific drug product identifiers such as manufacturer, lot number, and National Drug Code (NDC), in addition to brand and NPN.
- HHS: Improve integration of HIT systems to capture drug product data available in bar codes into the patient-based electronic health record (EHR).
- CMS: Assign distinct J-codes for all biologics, including biosimilars, to facilitate clear identification of products via claims databases.

Biologics dispensed in the pharmacy:

- HHS: Update national standards for the patient medication history report to include specific drug product identifiers such as manufacturer and lot number, in addition to brand, NDC, and NPN.
- HHS: For situations where pharmacy substitution could occur, encourage states to require pharmacists to capture biologic dispensing data in databases accessible to other HCPs, as already occurs for the vast majority of pharmacy-administered vaccines.

FDA works with the National Library of Medicine (NLM) to develop standardized product nomenclature and associated coding systems that are widely referenced in drug compendia. FDA and NLM have historically had several layers of hierarchy in these nomenclature and codes, wherein only the active ingredient is identified at the highest layer, and specific drug product packaging units are identified (by NDC) at the most detailed layer. Although the NDC is the most specific identifier for a particular product and has been adapted as the US-drug product identifier in the "**Id**entification of **M**edicinal **P**roducts" (known as IDMP) standard for pharmacovigilance case reports, the NDC is not always available in spontaneous reporting data. In such cases, reports often default to identification at the level of the active ingredient (ie, the INN or USAN).

It has been reported that FDA and NLM have recently adapted an intermediate layer of identification of the biological drug substance, which tracks to the proposed proper names, including a distinguishable suffix[21]. It will be important for FDA to work with national and

[20] The United Kingdom Yellow Card adverse event reporting interface was updated in 2014 to include a prompt for specific trade name and lot number identifiers for biological products. Available at: https://yellowcard.mhra.gov.uk/

[21] For example, the substance UNII code PVI5M0M1GW is shared by NEUPOGEN® (filgrastim) and a licensed biosimilar, Zarxio™ (filgrastim-sndz), but a new biological drug substance code distinguishes these products via hyphenated suffixes, PVI5M0M1GW-1 and PVI5M0M1GW-SNDZ-1 respectively. See NIH DailyMed SPL Resources at http://dailymed.nlm.nih.gov/dailymed/spl-resources-all-indexing-files.cfm.

international stakeholders to encourage appropriate use of such identifiers in pharmacovigilance systems. For example, US manufacturers could incorporate the biological substance identifier code, rather than the active ingredient code, in reports submitted under ICH E2B standards. Also, the ISO IDMP standard should be updated to include a layer of product coding that aligns with the emergence of biological qualifiers in the US and other jurisdictions, such that reports could link to products containing specific biological substances rather than defaulting to an ambiguous association with the entire class of products sharing the same INN.

***5. What process and reasonable timeframe should FDA use to designate a suffix to include in the nonproprietary name of a previously licensed biological product?***

Amgen acknowledges that retrospective application of distinguishable NPNs with memorable and meaningful suffixes can help avoid unintended and inappropriate substitution that may result from omission of a suffix. However, we recognize that changing the names of products already on the market will have wide-ranging implications for stakeholders far beyond the product sponsor and US borders. Retrospective application can help drive universal adoption of the biologic suffix across all systems and settings. However, if it is executed with inadequate lead time and a failure to mitigate stakeholder concerns, patient care, clinical trials, and confidence in biosimilars may suffer.

The implementation process is complex and will require thoughtful coordination of steps to protect the public health. Additionally, input from stakeholders will be important to help FDA map out the process for updating systems in order to ensure a coordinated change that provides minimal disruption to health care services.

Because we do not yet know how long it will take to make these changes – a preliminary assessment indicates several years[22] – we recommend that FDA adopt a multi-phase approach that allows identification of impacts and affected stakeholders, development of implementation strategies, and time for stakeholders to incorporate changes sequentially and progressively. As a first step, FDA should convene a stakeholder working meeting to identify and discuss legal and logistical challenges and define solutions to mitigate the impact on patient access, healthcare practice, and the healthcare ecosystem more broadly. FDA should also conduct and share with stakeholders a legal analysis of the global and local impact of adopting new NPNs (e.g., clinical trial protocol changes globally and import/export challenges). In order to facilitate efficient adoption of the new names, FDA should work with stakeholders to develop and publish a model implementation map.

Once FDA and partner stakeholders (including manufacturers) have mapped out a process and set expectations for timeliness, FDA should invite and encourage other license holders to prospectively change the NPN of their marketed biologics in anticipation of biosimilar competition.

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[22] Some previous timelines FDA utilized when implementing changes to labeling may be instructive:
The final rule, **Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products** (71 FR 3922), included an implementation table for NDA, BLA, or efficacy supplement to implement the new regulations. Of interest, a 3 year implementation timeline was listed for applications pending for one year or less when the rule was finalized. (http://www.fda.gov/ohrms/dockets/98fr/06-545.pdf)
For the **serialization requirement under DSCSA**, the implementation timeline for manufacturers and others was 4 years to implement a 2-D barcode on their product. Slide 28 (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/UCM445614.pdf)

6. ***What criteria should FDA use to prioritize retrospective application of this naming convention to previously licensed biological products?***

   For purposes of retrospective application of naming conventions to already marketed products, Amgen agrees with FDA's initial prioritization of products for which biosimilar applications are pending and for which "related" products are approved or applications are pending. However, because changes to the NPN of products already marketed will have wide-ranging ramifications for stakeholders throughout the healthcare ecosystem, FDA should adopt an implementation plan that both allows for a transition period and defines a specific date by which all products will have shifted to names with distinguishable suffixes. Sponsor discretion in implementation of name changes will facilitate the smoothest path forward for all stakeholders. The first products to transition to new names will bear the brunt of the learning curve both in terms of their own changes and the changes that other stakeholders must make and the implications this has for patient access, payment systems, clinical trial protocols, and more. Therefore, the first round of changes must occur over several years and allow for contingencies to accommodate unexpected glitches after the changes "go live".

7. ***What are the expected time frames for sponsors of previously licensed biological products to distribute products that conform to this naming convention after approval of a labeling supplement?***

   Amgen is actively investigating this question, both from the perspective of process steps a manufacturer must take and from the perspective of systems and healthcare practitioners to ensure minimal disruption to their work. The analysis of outside systems is being conducted by independent consultants and is not yet complete; Amgen will provide the information to FDA when it is available.

   In looking at our own processes and timelines to implement such a change following an approved labeling supplement, Amgen would need multiple years to implement this change. A thorough analysis of internal processes is ongoing. Although concurrent implementation for multiple products is possible, it does increase the implementation window due to shared personnel and other resources across the product portfolio. Furthermore, an implementation estimate would be highly susceptible to unknown or unforeseen complications that Amgen and other sponsors may face during the changeover process, which may alter the proposed timeframe significantly.

   Amgen recommends against adopting firm deadlines for retrospective implementation of the proposed naming convention until the Agency has conducted a working meeting with stakeholders to map out the points within the healthcare ecosystem that will be affected and timelines for implementation are understood. A stakeholder workshop will help FDA identify and mitigate areas of concern more fully than is likely to result from the comment period without an opportunity for stakeholders to engage in a dialogue. A legal analysis should also be conducted by the Agency to identify areas that may create a risk of misbranding or other legal concerns for which FDA should establish a clear safe harbor during the transition window.

8. ***What strategies could FDA use to enhance stakeholders' understanding of and education about this naming convention?***

The US healthcare community will benefit from FDA's direct engagement and leadership in educating HCPs and patients on the reasons for and practical implications of this naming policy. The list of stakeholders needing education would include: patients, caregivers, pharmacists (retail and hospital), compendia, prescribers, hospital pharmacy and therapeutics committees, specialty pharmacy, pharmacy benefit managers, group purchasing organizations, and Pharmacopeia.

We recommend that the FDA should take material steps as follows:

- Promulgate policy to advance a distinguishable labeling construct that identifies the product as biosimilar versus interchangeable and transparently identifies the product investigated in the clinical studies section. Because labels are the primary source for prescribing decisions, including this transparency in a label will facilitate prescribers' understanding on their terms;
- Develop an easy-to-read Frequently Asked Questions (FAQ) or infographic on the importance of distinguishable names so patients and prescribers can be rapidly oriented to this policy;
- Develop clear written publications by FDA on practical implications, and publish these findings in peer-reviewed scientific journals read by the stakeholders identified above;
- Develop a webinar on practical implications, and house a recorded version on FDA's public website;
- Send FDA experts to speaking engagements at public forums, congresses, etc.;
- Produce a PowerPoint or white paper on the topic that should be made available on FDA's public website;
- After consultation with stakeholders implementing this change, host a series of "best practice" work products (eg, PowerPoint presentations, white papers) to highlight how stakeholders in various parts of the US healthcare system have successfully implemented the change (including, if available, challenges these stakeholders faced and means to overcome those challenges);
- Set up a designated area on website for naming issues, where related information could be housed;
- Issue a press-release for wide distribution to the news media that will alert patients about changes to naming; and
- Include on website a list of products for which the name has been retroactively changed such that patients/ HCPs can easily identify old/new names.

Materials should address following issues:

- Guidance or suggestions for how to ensure physician intent and pharmacovigilance concerns are addressed in the implementation of the policy;
- Guidance for e-prescribing systems, EHRs, and compendia/data providers on implications and recommended actions;
- Suggestions for pharmacists and specialty pharmacies to consider when processing and dispensing prescriptions; and
- General guidance around hospital inventory and pharmacy systems impacts.

9. ***FDA notes that this naming convention (i.e., use of a suffix) has some similarities to the World Health Organization (WHO) proposal, "Biological Qualifier--An INN Proposal." WHO adopts a Biological Qualifier proposal, how should the biological qualifiers generated by WHO be considered in the determination of FDA designated proper names for the biological products within the scope of this guidance?***

The FDA proposal is very consistent with the WHO BQ draft with respect to the morphology of the code and its intended purpose and proposed usage. However, the WHO system is voluntary and will require implementation by national regulatory authorities. FDA's implementation of a suffix system will provide a useful example, supplementing the experience in Australia and Japan, that such a suffix is important and workable (as noted above). We urge FDA to act on its naming convention proposal promptly, which will encourage WHO to move forward and provide regions with less robust pharmacovigilance systems a means of tracing and accountability. The need is clear from experience in Thailand. There, as of 2009, 14 intended copy versions of epoetin alfa were licensed using the same NPN, and the class has been associated with clusters of severe immune-induced anemia since the mid- 2000's[23]; the government is unable to determine which of the products are safe and which are causing this life-threatening adverse immune response.

Differences between FDA and WHO proposals in terms of the administrative vetting of codes could result in disparities between the two systems. WHO proposes to assign a randomly generated code to each unique biological drug substance. The WHO program would be implemented with minimal administration costs and hence, unlike the FDA proposal, may not accommodate a vetting process wherein several options could be reviewed for conflicts with good naming practices. This difference in administrative approach could result in disparate codes between the US and other jurisdictions that would reference WHO's system. While such disparity may be difficult to avoid, the anticipated risk of such proliferation of naming systems was cited by WHO as a key factor motivating the BQ proposal. Therefore, we would encourage FDA to work with WHO to determine if FDA-vetted qualifiers could be adopted by WHO in lieu of randomly generated codes.
Amgen strongly supports a meaningful suffix that is consistent across the biologics license holder's portfolio in order to advance accountability and use of the system. FDA's naming of the Sandoz filgrastim biosimilar, filgrastim-sndz, is an example of best practice.

**Conclusion**

Amgen supports FDA's proposal to adopt distinguishable NPNs for all biologics. However, we recommend several modifications to advance the Agency's state objectives more fully and efficiently. The naming convention should apply to all biologics, including interchangeable products. The suffix should be meaningful, memorable and consistent across the product sponsor's portfolio. Finally, retrospective application of the naming protocol to currently marketed products should be implemented by first convening a stakeholder working meeting.

[23] Praditpornsilpa et al., Biosimilar recombinant human erythropoietin induces the production of neutralizing antibodies. Kidney Intl. 80: 88-92 (2011).

## Attachment 1: Analysis of implications of distinguishable naming on adverse event reports and uptake in Australia for two biological product classes

In March 2015, Amgen provided FDA data sets showing significant deficiencies in attribution of products to specific manufacturers for filgrastim products in the European Union and Australia.[24] We herein provide updated data from the Therapeutic Goods Administration (TGA), Australia's regulatory authority for therapeutic goods including medicines, that indicate lack of brand attribution in 42% of spontaneous reports for filgrastim products, but only 5% of epoetin products since the launch of biosimilars.

The TGA has created an accessible spontaneous report query tool available to the public. This tool may be used to search for all reports associated with specified suspect drugs over a given time frame. The database includes reports received directly by TGA or forwarded by manufacturers.

We examined adverse event reports for two product classes, filgrastims and epoetins, selecting the off-patent first generation versions of these products subject to direct biosimilars competition. In Australia the reference filgrastim (NEUPOGEN®) and the three licensed biosimilar filgrastims all share a common Australian Biologics Name (ABN) "filgrastim" which is identical to the International Nonproprietary Name (INN). In contrast, the two originator first-generation epoetins, EPREX® (epoetin alfa); Neorecormon® (epoetin beta); and the biosimilar Novicrit® (epoetin lambda) each have distinguishable ABNs as indicated in the names in parentheses. Novicrit® (epoetin lambda) was licensed as a biosimilar version of epoetin alfa but received a distinguishable ABN after the TGA identified differences in glycosylation structure.[25]

A query of the TGA public database reveals that 19 spontaneous total reports each for the filgrastim and epoetin classes have been received since biosimilar entry in March 2011, cumulative through March 2015 (Table 1 and Table 2). Of the 19 filgrastim-related reports, 8 (42%) were coded as "filgrastim (not specified)". In contrast, of 19 epoetin-related reports only 1 (5%) was coded as an ambiguous identification ("epoetin NOS" (not specified)".

[24] Comment from Amgen, Inc. Posted to regulations.gov March 12, 2015. ID: ID FDA-2013-P-1153-0027. Available at http://www.regulations.gov/#!documentDetail;D=FDA-2013-P-1153-0027

[25] [Add reference to ABN naming rule for lambda – PBS note 2010]

Table 1. Summary of Spontaneous Reports for Filgrastim in Australia (from March 2011 to March 2015)[26]

| Product name coded in DAEN database | Safety Reports [No. (%)] |
|---|---|
| filgrastim (not specified) | 8 (42%) |
| Nivestim®* | 1 (5%) |
| Tevagrastim®* | 0 (0%) |
| Zarzio®* | 0 (0%) |
| NEUPOGEN® | 10 (53%) |
| Total | 19 |

* Branded biosimilar products marketed in Australia as of 2014

Table 2. Summary of Spontaneous Reports for Epoetin products in Australia (from March 2011 to March 2015)[27]

| Product name coded in DAEN database | Safety Reports [No. (%)] |
|---|---|
| Epoetin NOS (not specified) | 1 (5%) |
| Novicrit® (epoetin lambda)* | 1 (5%) |
| Eprex® (epoetin alfa) | 12 (63%) |
| Neorecormon® (epoetin beta) | 5 (26%) |
| Total | 19 |

* Branded biosimilar products marketed in Australia as of 2014

We also examined filgrastim and epoetin market volume share available by subscription to IMS data (Table 3 and Table 4) to evaluate whether reporting of adverse events tracked market share. The total biosimilar filgrastim market share versus the reference product (NEUPOGEN®) reached 54% as of the first quarter of 2015, with a time-averaged market share of 27% over the interval evaluated. Individual biosimilar uptake ranged from 1% to 21% averaged over the assessment period. The biosimilar epoetin lambda reached 46% volume share versus its reference product in the first quarter of 2015, with time-averaged market share of 19% over the interval evaluated.

[26] Data source: TGA Database of Adverse Event Notifications – medicines, available at: http://apps.tga.gov.au/PROD/DAEN/daen-entry.aspx

[27] Data source: TGA Database of Adverse Event Notifications – medicines, available at: http://apps.tga.gov.au/PROD/DAEN/daen-entry.aspx

Table 3. Summary of Volume Market share for Filgrastim in Australia (from January 2011 to March 2015)[28]

| Product | Time-average volume share | Market share Q1 2015 |
|---|---|---|
| Nivestim®* | 21% | 38% |
| Tevagrastim®* | 5% | 10% |
| Zarzio®* | 1% | 6% |
| Total biosimilar share | 27% | 54% |
| NEUPOGEN® | 63% | 46% |

* Branded biosimilar products marketed in Australia as of 2014

Table 4. Summary of Volume Market share for Biosimilar Epoetin in Australia (from January 2011 to March 2015)[29]

| Product | Basis of comparison | Time-average volume share | Market share Q1 2015 |
|---|---|---|---|
| Novicrit® (epoetin lambda)* | Versus reference product | 19% | 46% |
| | Versus epoetin product class | 16% | 37% |

* Branded biosimilar products marketed in Australia as of 2014

Conclusion:

The finding of 42% unattributed filgrastim (not specified) reports received by TGA since the entry of biosimilars to the Australian market in 2011 indicates that a shared non-proprietary name may be undermining the ability of TGA to track individual filgrastim product safety. In contrast, only 5% of epoetin related reports were not identified to a specific product. This observation does not prove that the distinguishable ABNs for epoetins improved their traceability in AERs, but there is clearly an issue with traceability of filgrastims due to the apparent tendency of adverse event reporters in Australia to use the ABN rather than a figrastim brand name.

For both product classes only 1 safety report each was attributed to a specific biosimilar (5% of total reports), despite these biosimilars achieving approximately 20% volume market share versus their reference products.[30] Assuming that inherent safety risks are well balanced for biosimilar and originator products this finding suggests that safety issues are unreported for biosimilars in Australia. Similar findings have been observed for generic drugs in the United

[28] Data source: TGA Database of Adverse Event Notifications – medicines, available at: http://apps.tga.gov.au/PROD/DAEN/daen-entry.aspx

[29] Data source: TGA Database of Adverse Event Notifications – medicines, available at: http://apps.tga.gov.au/PROD/DAEN/daen-entry.aspx

[30] Data source: IMS data available upon request.

States[31], but it is notable that this has occurred even when each Australian biological product has a unique brand name.

Finally, some advocates have commented that use of distinguishable names may impact the market success of biosimilars in the United States. In Australia the biosimilars of filgrastim and epoetin alfa have been marketed for approximately the same duration under different naming paradigms. It is notable that, as of March 2015, the uptake of biosimilar epoetin lambda versus its reference product has reached levels commensurate with the uptake of biosimilar filgrastims (both individually and as a class). Consistent with the findings of other analysts, we believe that payer reimbursement and additional class-specific factors other than product naming are more relevant to market uptake of biosimilars.

[31] Lietzan EF, Sim LE, Alexander EA. *FDLI's Food and Drug Policy Form*—Biosimilar Naming: How do Adverse Event Reporting Data Support the Need for Distinct Nonproprietary Names for Biosimilars? Washington, DC: Food and Drug Law Institute; 2013