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Submitted electronically on www.regulations.gov

Re: Docket No. FDA-2013-D-1543-0001 (Nonproprietary Naming of Biological Products; Draft Guidance for Industry; Availability)

Dear Drs. Ostroff and Woodcock:

Public Citizen, a consumer advocacy organization with more than 400,000 members and supporters nationwide, submits these comments on the Food and Drug Administration's (FDA's) draft guidance concerning nonproprietary naming of biological products, also known as biologics.[1] We agree with the agency that the nonproprietary names assigned to biologics warrant close consideration given the need to balance patient safety and access to safe and effective biologic medicines.

[1] Food and Drug Administration. Draft Guidance: Nonproprietary Naming of Biological Products. August 2015. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm459987.pdf. Accessed October 13, 2015. [Hereafter referred to as "FDA Draft Guidance"]

In summary, we agree with the FDA's proposal to include random, nonmeaningful four-letter suffixes to all biosimilar, reference, and related biologics in the near term, and to eventually append such four-letter suffixes to all originator and related biologics with no biosimilar counterparts. We also believe that all biosimilars deemed interchangeable with a reference biologic should share an identical suffix with that biologic so as to facilitate and encourage the use of interchangeable products.

We agree with the FDA that unique suffixes for non-interchangeable biosimilars will facilitate both active and passive pharmacovigilance efforts by allowing the FDA and others to trace adverse events associated with such biologics to particular manufacturers. However, this advantage would not apply to interchangeable products with identical suffixes. Furthermore, as noted by the FDA, the structure of biologics varies in subtle, but potentially clinically relevant ways, not only by manufacturer but also by the facility, lot or batch from which the product originates. Therefore, it is critical that the FDA work with other federal agencies to both encourage and, where feasible, require the inclusion of other identifying information for all biologics in both the medical records assessed by active pharmacovigilance systems and in adverse event reports submitted voluntarily to the FDA.

We further encourage the FDA to lead efforts to educate physicians, pharmacists, and patients of the new naming system and to promptly notify these end-users of every name change on an ongoing basis. The FDA should periodically monitor the success of such efforts and work to improve their reach.

A final point before addressing the FDA's questions. To our knowledge, the concern over the potential risks of decreased efficacy or increased harm resulting from the substitution of non-interchangeable biosimilars for reference biologics is currently based on theoretical considerations that have not yet been validated with sufficient empirical data. Our comments accept the premise that interchangeability and biosimilarity are distinct categories. However, should sufficient data eventually emerge that indicate that all biosimilars, like small-molecule generics, are interchangeable with reference biologics and with one another, we would reassess our position on biologic naming.

We enclose below specific responses to each of the nine questions to which the FDA solicited feedback concerning the draft guidance.

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.

The FDA draft guidance proposes that the four-letter suffix be devoid of meaning and unique (with the possible exception of interchangeable biosimilars) to each biologic. We agree with both approaches, for three reasons. First, a random suffix devoid of meaning would enable interchangeable biosimilars to share the same suffix as the reference biologics with which they have been deemed interchangeable (see response to Question 2). Second, a meaningful suffix specific to the product's manufacturer may prompt some physicians and patients to inappropriately prefer certain manufacturers' products over others, based on marketing, reputation, brand loyalty, or other nonmedical reasons, interfering with competition and unnecessarily increasing health care costs. Third, such a naming convention accords with the biologics international nonproprietary names (INN) naming convention currently proposed by the World Health Organization (WHO), facilitating improved global monitoring of adverse events.[2]

We acknowledge the potential advantages of memorable suffixes, and specifically those based on company names. A memorable suffix may reduce inadvertent substitution and possibly facilitate some types of adverse event reporting by making it easier to identify the product's manufacturer. However, we believe that the benefits of a random suffix outweigh these considerations, and we urge the FDA to implement other strategies to address the potential problems of inadvertent substitution and insufficient pharmacovigilance.

2. What would be the potential benefits and challenges for an interchangeable product[3] to share the same suffix as designated in the proper name of the reference product? Your response should consider that FDA's publicly available electronic resource, the Purple Book,[4] will identify biological products determined by FDA to be biosimilar to or interchangeable with a reference product. If an interchangeable product does share the same suffix as the reference product, how would this impact your responses to question 1, including pharmacovigilance?

We agree with the FDA that one of the primary purposes of the novel naming system for biologics is the "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."[5] It follows from this that any naming system must clearly distinguish interchangeable products from their non-interchangeable counterparts.

Because of this, we believe that interchangeable biologics should share the same suffix as the reference biologics with which they have been deemed interchangeable. This would: 1) distinguish non-interchangeable biosimilars from their interchangeable counterparts; and 2)

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[2] World Health Organization. Biological Qualifier: An INN Proposal. INN Working Doc. 14.342. Draft 2.2 – June 2015. http://www.who.int/medicines/services/inn/bq_innproposal201506.pdf.pdf. Accessed October 14, 2015.

[3] Interchangeable product means a biological product that has been shown to meet the standards described in section 351(k)(4) of the PHS Act and may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product (see section 351(i)(3) of the PHS Act).

[4] The Purple Book: Lists of Licensed Biological Products With Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluation is available on FDA's Web site at http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm411418.htm.

[5] FDA Draft Guidance, at 1.

facilitate and encourage the use of interchangeable biosimilars, while eliminating the need to refer to the Purple Book to verify interchangeability status. This latter point is important not only because it would increase prescribing of interchangeable biosimilars but also because it might eliminate potential medication errors by physicians misreading or misinterpreting the entries in the Purple Book.

A disadvantage to identical suffixes for interchangeable products is the inability to trace interchangeable biologics to specific manufacturers based solely on the product's nonproprietary name, which is attached to its licensing application. However, we note that even products manufactured under a single licensing application may be subject to variability (e.g., by facility, lot, or batch), and these differences also are not traceable through a suffix naming system specific to each application. Providing unique suffixes to interchangeable products therefore would fail to provide all of the information necessary to ensure adequate active pharmacovigilance of biologics. This is addressed further in the response to Question 4.

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 explained in the response to the previous question, we believe that any product deemed interchangeable by the FDA should share the same four-letter suffix as the relevant reference biologic. This should be the case regardless of whether the determination of interchangeability is made at the time of initial approval or subsequent to a product's change in status from a non-interchangeable to an interchangeable biosimilar. The same benefits, namely facilitating and maximizing the use of interchangeable biologics where appropriate, would apply to both cases equally.

We acknowledge that changing the suffix of a previously approved biosimilar to match that of a relevant reference biologic has the potential to introduce some confusion at the point of end-use of the product. However, we think that the same educational and procedural measures that hopefully would be instituted to notify end-users of the addition of suffixes to reference biologics (see response to Question 8) could be deployed to notify the same authorities of a suffix change to a biosimilar product upon a determination of interchangeability.

It is important that the Purple Book be updated in real time with every new determination of interchangeability, perhaps with each newly deemed interchangeable biosimilar denoted in some way to alert end-users of the change in status. Another necessary measure would be to immediately merge the previously collected adverse event reports cataloged under the non-interchangeable biosimilar name with those newly submitted under the interchangeable suffix.

4. How could FDA and/or other Federal partners improve active pharmacovigilance systems for purposes of monitoring the safety of biological products? For example, because NDC numbers are not routinely recorded in billing and patient records in many clinical

settings in which biological products are dispensed and administered, are there other identifiers besides distinguishable nonproprietary names that are routinely accessible by active pharmacovigilance systems and could enable as good as or better pharmacovigilance? How can FDA and/or other Federal partners help ensure that a distinguishable identifier for each biological product would be captured at the point of dispensing or administration to the patient and be routinely accessible in systems used for pharmacovigilance?

Biologics present unique challenges to pharmacovigilance efforts,[6] and providing distinguishable identifiers only partially addresses these challenges. Just as biologics manufactured by different companies under separate licenses may differ in slight but clinically important ways, so, too, can a particular biologic product produced by the same manufacturer under a single license vary slightly from facility to facility, lot to lot or batch to batch.[7] This makes it important to be able to trace a biologic to a) the manufacturer, b) the facility producing the product, and c) the lot or batch in which it was produced.

The proposed four-letter suffix will enable active pharmacovigilance systems to determine the manufacturer of a biologic, so long as the suffix is unique to a single manufacturer. However, such naming will not allow pharmacovigilance systems to identify a) different facilities operating under the same marketing license, or b) the lot or batch for the product. Furthermore, it would not allow such systems to identify the manufacturers of interchangeable biologics that share the same suffix and the FDA notes that national drug codes (NDCs), which could identify a product's manufacturer, are not routinely recorded in the clinical settings in which many biologics are usually administered.[8]

Therefore, providing distinguishable identifiers to biosimilars is only a partial solution, and there must be other methods employed to aid in active pharmacovigilance of biologic medications. The meeting minutes for a 2013 workshop at the Brookings Institution noted a suggestion that Medicare begin requiring providers to record NDCs in claims forms for drugs administered in an inpatient health care setting (as is already required by Medicaid), which may, in turn, spur private insurers towards a similar requirement.[9]

While beyond the scope of this question, the potential pharmacovigilance challenge posed by biologics should serve as a catalyst to improve the FDA's passive pharmacovigilance system of voluntarily submitted adverse event reports. The agency should undertake outreach and educational efforts encouraging physicians, pharmacists, and patients to include more useful

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[6] Brookings Institution, Engelberg Center for Health Care Reform. Developing Systems to Support Pharmacovigilance of Biologic Products. November 15, 2013. http://www.brookings.edu/~/media/events/2013/11/15-fda-biosimilars/2013114-biosimilars-summery. Accessed October 14, 2015.

[7] *Ibid.*

[8] FDA Draft Guidance, at 6.

[9] Brookings Institution, Engelberg Center for Health Care Reform. Developing Systems to Support Pharmacovigilance of Biologic Products. November 15, 2013. http://www.brookings.edu/~/media/events/2013/11/15-fda-biosimilars/2013114-biosimilars-summery. Accessed October 14, 2015.

information (e.g., manufacturer and, if known, lot/batch number) in adverse event reports submitted directly to the agency, for biologics as well as other FDA-regulated products.

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?

This is addressed in our response to Question 6.

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

We agree with the FDA's proposal to focus its efforts on adding suffixes to previously licensed biologics initially to those referenced in new biosimilar approvals and to any related biologics.[10] We believe that the FDA should do so at the time of the biosimilar approval, in order to ensure that physicians and patients do not mistakenly view biosimilars with suffixes as distinct from or inferior to reference biologics without such suffixes. For the same reason, the FDA should move quickly to retrospectively add suffixes to originator and related biologic products without biosimilar counterparts, to minimize the possibility that reference biologics with suffixes are viewed as inferior to other, nonsuffixed biologics approved for the same use.

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?

As stated above, we urge the FDA to ensure that reference biologics (and related products) have suffixes appended to their names at the time of the approval of a biosimilar. To this end, the FDA should require that the makers of reference and related biologics begin distributing labels with the appendix suffix as soon as a decision is made to approve a biosimilar. Given that already-distributed batches of the reference (and related) biologics will continue in circulation for a time after the new labels go into effect, the sponsor should be required to immediately alert all end-users of the name change and to implement monitoring mechanisms to ensure adequate understanding of the change.

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

The FDA must undertake, in conjunction with biologics makers, an educational and outreach campaign, explaining the new naming system to all potentially affected stakeholders. Given that the FDA observed in its proposed rule on biosimilar naming that biologics are typically administered in hospitals, clinics, and physician offices,[11] this includes all officials (both administrators and pharmacists) responsible for managing inpatient and outpatient formularies, in addition to the end-users (physicians and patients) of the products. The campaign must entail

[10] FDA Draft Guidance, at 9. For a definition of related biologics, see FDA Draft Guidance, at 2.
[11] 80 FR 52224-52231. Food and Drug Administration. Docket No. FDA-2015-N-0648. RIN 0910-AH25. Designation of Official Names and Proper Names for Certain Biological Products. August 28, 2015. http://www.gpo.gov/fdsys/pkg/FR-2015-08-28/pdf/2015-21382.pdf. Accessed October 14, 2015.

some mechanism whereby both the FDA and drugmakers can monitor the extent to which the policy change is understood by the relevant stakeholders.

Parallel to this general educational campaign, and on an ongoing basis, the FDA should require all biologics makers to notify administrators and pharmacists responsible for managing formularies whenever a suffix is added to an existing biologic. These administrators and pharmacists should, in turn, be encouraged to implement a system whereby every prescription for, or order to administer, the biologic should be flagged for review by the pharmacist before dispensing, in order to ensure that the correct product is administered. This would be a critical safeguard to ensure that patients who have been given at least one dose of a reference biologic are administered the same product after the name change has been implemented. The FDA also could encourage the development of an additional flagging mechanism within the electronic medical record at the point of prescribing, notifying physicians and other prescribing health care professionals of, and explaining, an affected product's name change and requiring confirmation of the name of the product to be prescribed.

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." At the time of publication of this draft guidance, WHO was still evaluating the comments received on its proposal. If 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 WHO proposal "Biological Qualifier — An INN Proposal" (latest draft June 2015) proposes, like the FDA, that a random four-letter qualifier, devoid of meaning, be assigned to every biologic on a prospective and, possibly, a retrospective basis (only "vaccines, impure mixtures, and complex biologically-extracted products" are exempted from this requirement).[12]

We believe that, in cases where the WHO has generated a four-letter biological qualifier for a product first approved outside of the U.S., the FDA should assign the same four-letter qualifier to biologics approved in the U.S., thus maintaining consistency in naming among the different countries in which a biologic is marketed. This approach has several advantages. It would ensure that adverse event reports to the FDA that originate from countries other than the U.S. are appropriately consolidated with U.S. reports related to the same product. It also would eliminate the possibility that an approved biologic manufactured abroad might be mistakenly imported into the U.S. with a four-letter suffix in the product label that differs from the suffix approved by the FDA for the biologic.[13]

Thank you for taking our comments into consideration.

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[12] World Health Organization. Biological Qualifier: An INN Proposal. INN Working Doc. 14.342. Draft 2.2 – June 2015. http://www.who.int/medicines/services/inn/bq_innproposal201506.pdf.pdf. Accessed October 14, 2015.

[13] Note that this comment refers only to approved, finished drug products imported into the U.S. by companies that have registered appropriately with the FDA. It does not encompass the illegal importation of unapproved drug products. For a discussion of the regulations that govern drug importation into the U.S., see: Nychis B. Import of Human Drugs and Human Drug Components. Food and Drug Administration. June 2011. http://www.fda.gov/downloads/AboutFDA/WorkingatFDA/FellowshipInternshipGraduateFacultyPrograms/PharmacyStudentExperientialProgramCDER/UCM259423.pdf. Accessed October 19, 2015.

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