October 27, 2015

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

Re: Docket No. FDA-2013-D-1543—*Non-Proprietary Naming of Biological Products*

Teva Pharmaceutical Industries Ltd. ("Teva") is pleased to provide the following comments in response to the above-captioned Federal Register notice and associated *Draft Guidance For Industry—Nonproprietary Naming of Biological Products* (August 2015) (the "Draft Guidance").

Teva is a global leader in biopharmaceuticals and has one of the broadest product portfolios in the industry. Teva also develops and manufactures innovative medicines and is the world's leading provider of generic medicines. At the heart of Teva's mission is a commitment to develop and manufacture high-quality, safe, and efficacious products that promote global good health and well-being. Teva appreciates FDA's efforts in developing the proposals set forth in its Draft Guidance, and welcomes the Agency's thoughtful efforts to enhance patient safety in this emerging area.

GENERAL COMMENTS

Teva agrees that it is important for healthcare providers to be able to distinguish among non-interchangeable biological products and that the proper identification of distinct biological products can facilitate accurate pharmacovigilance reporting and useful pharmacovigilance analysis by industry, the Agency, and independent researchers. Nonetheless, Teva does not believe that the addition of a four-letter suffix to the nonproprietary name (or "proper name") of a given biological product is necessary to avoid the "inadvertent substitution" of non-interchangeable biological products and/or to reduce the risk of medication "dosing errors," *see* Draft Guidance at 5, or that the use of such suffixes is likely to produce a substantial improvement in the quality and accuracy of pharmacovigilance reporting. *Id*. at 6. To the contrary, requiring manufacturers to append a four-letter suffix to the nonproprietary name of a biosimilar product may well undermine the goals of the Biologics Price Competition and Innovation Act of 2009 ("BPCIA") without advancing the principal objectives outlined in the Draft Guidance. Indeed, that seems particularly likely if FDA finalizes its proposal to require the use of "non-meaningful" four-letter suffixes, because busy practitioners are unlikely to recall the kind of random four-letter sequences proposed in the Draft Guidance and because such inherently confusing names are subject to the possibility of transcription errors. *See id*. at 8 (suggesting exemplary nonproprietary names such as "replicamab-*cznm*" and "replicamab-*hixf*") (emphasis added). That introduces a substantial risk that healthcare practitioners could make

mistakes when prescribing appropriate therapies, tracking patient-level information, and submitting adverse event reports.

As for the Draft Guidance's concerns regarding the possibility of inadvertent product substitution and medication/dosing errors, our experience is that most prescriptions are written using the licensed product's proprietary name and include both appropriate dosing information and proper instructions for use, including both product strength and treatment (dosing) regimen. That is especially true for biological products that are intended for self-administration outside the immediate supervision of a licensed healthcare professional (and, thus, where concerns about medication/dosing errors would be most acute) . Moreover, we believe that the prospect of inadvertent product substitution and/or dosing errors seems highly unlikely given the Agency's publication of the *Purple Book* and the integration of that publication into pharmacy database services. For that reason, we believe that there is at best a marginal risk (if there is any appreciable risk at all) that patients might "inadvertently receive a product with a different delivery system or route of administration than was prescribed." Draft Guidance at 5.

We likewise believe that the Draft Guidance's expectation that the use of a four-letter suffix would enhance pharmacovigilance efforts is overstated. As the Draft Guidance explains, individual drug products already are distinguishable and readily identifiable in a variety of ways other than their proper name, including by the proprietary names, manufacturer identities, NDC numbers, and lot numbers disclosed on the approved product labeling; through patient medical records; and in the billing records and billing codes tracked in both insurance and pharmacy databases. *Id*. at 6. To the extent that some, *but not all*, of those characteristics may not be "routinely recorded" or "are often not included in adverse event reports," *id*. (discussing NDC numbers and proprietary names), the Draft Guidance provides no basis for its expectation that patients and healthcare practitioners would be more likely to routinely record or include yet another identifying characteristic in their systems and reports (especially one as difficult to recall as a random, four-letter suffix).

Make no mistake: Teva fully shares the Agency's concerns regarding pharmacovigilance and is deeply committed to ensuring that pharmacovigilance systems are structured and implemented in a manner that can help product manufacturers, healthcare practitioners, independent researchers, and FDA identify and respond to safety signals that may be associated with biopharmaceuticals. Our view is simply that gaps in current pharmacovigilance systems are best addressed directly—by educating healthcare professionals about the need to record the information they already possess and by conducting appropriate follow-up when adverse event reports lack the specificity needed to be useful—rather than indirectly and in a manner that seems unlikely to meaningfully advance the Agency's praiseworthy objectives.

That having been said, we recognize that the Agency appears committed to proceeding with the addition of a four-letter suffix, and the remainder of this document addresses the specific questions FDA has raised in connection with that proposal.

SPECIFIC QUESTIONS RAISED BY THE AGENCY

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?**

To the extent FDA proceeds with its proposal, we believe that two basic principles should govern the Agency's approach. First, as the Draft Guidance explains, *every* biological product should be required to use a four-letter suffix in its proper name regardless of its licensure pathway. Any other approach would lead to "inaccurate perceptions of the safety and effectiveness of" follow-on biological products and "will adversely affect use of these new products by health care providers and patients." Draft Guidance at 6.

Second, we believe that license holders should have maximum flexibility to select a four-letter suffix—whether devoid of meaning or meaningful, or unique to each biological product or unique to the licensee—provided only that the licensee's proposed suffix does not undermine the objectives of the Draft Guidance, run afoul of the Draft Guidance's proposed prohibitions, *see id.* at 10, or otherwise violate the standards FDA applies to manufacturer-selected product names, *see, e.g.*, 21 C.F.R. § 299.4(d) (incorporating the guidelines set forth in USAN, "Guiding Principles for Coining U.S. Adopted Names for Drugs"); *id.* § 299.4(e)(1) (cautioning against the use of product names that are "unduly complex or … not useful for any other reason"); *id.* § 201.10(c) (barring the use of certain "fanciful" names and those that are "similar in spelling or pronunciation" to others); *see also* FDA, *PDUFA Pilot Project: Proprietary Name Review—Concept Paper* 11-17, 25 (Sept. 2008); *Guidance for Industry—Contents of a Complete Submission for the Evaluation of Proprietary Names* (Feb. 2010). We note that this proposal is broadly consistent with the overall approach of the Draft Guidance, which stresses that sponsors should retain the flexibility to propose their own suffixes. Draft Guidance at 9, 10, 11.

We believe such flexibility is particularly important because each of the proposed approaches to crafting a four-letter suffix has advantages and disadvantages. For instance, and as we noted earlier, suffixes that are devoid of meaning can be difficult to remember and inherently are subject to the possibility of transcription errors throughout the distribution chain. As a result, the use of non-meaningful suffixes could lead prescription information to be inaccurately recorded by busy healthcare practitioners on prescriptions; in patient and pharmacy records; and/or in adverse events reports later submitted to the Agency. We also fear that the use of non-meaningful suffixes could generate confusion at other points in the product's chain of custody (i.e., from the point of manufacturing to ultimate patient use and disposal). Given those

concerns, we believe there is an appreciable risk that many non-meaningful four letter suffixes could undermine the core objectives of the Draft Guidance, and that the use of seemingly random letter combinations like the ones suggested in the Draft Guidance would add to the burdens prescribers, providers, and patients already face given the complexity of many nonproprietary names for biological products.

By contrast, using more meaningful suffixes (as the Agency approved for Sandoz's Zarxio® ("filgrastim-sndz")) seems likely to avoid those problems. In our experience, meaningful product names have been proven in the marketplace to help foster better product understanding because stakeholders can tie their training and educational materials to a clear and easy-to-associate name. More meaningful product names also are easier to remember, both for busy healthcare providers and especially for patients. Accordingly, the use of meaningful product names, including ones tied to the name or ownership of the licensee, seem more likely to facilitate accurate and useful adverse event reporting. But the use of meaningful suffixes that are tied to the licensee's name or ownership group also raises its own concerns—particularly in an industry undergoing widespread transactional activity, where an acquiring company might seek to alter the nonproprietary name of an established product's suffix in the middle of the product's lifecycle.

Forced to choose between imperfect alternatives, Teva believes that the disadvantages of requiring the use of non-meaningful suffixes likely present a greater public-health risk than those associated with the use of meaningful suffixes—where the identifiable downsides appear principally to be commercial in nature. Yet we also believe that there is no need for the Agency to mandate a "one size fits all" approach to this complex issue. So long as the licensee's chosen suffix would support the product differentiation and identification goals giving rise to the Draft Guidance without causing potential confusion; does not violate the guidelines set forth in the Draft Guidance; and complies with the principles FDA generally enforces when it reviews proposed proprietary names, we see no reason for the Agency to force an approach on the industry. Just as the Agency's regulations grant manufacturers wide latitude to select proprietary names, we believe the Agency should grant stakeholders broad discretion to adopt the approach they think is best—not least of all because mandating a naming convention that is not strictly tethered to the avoidance of false or misleading statements could raise significant First Amendment concerns. *See, e.g.*, *United States v. Caronia*, 703 F.3d 149, 164 (2d Cir. 2012).

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? Your response should consider that FDA's publicly available electronic resource, the *Purple Book*, 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?**

Teva expects that the overwhelming majority of follow-on biological products will be licensed and marketed as biosimilars under PHSA § 351(k)(3)(A)(i)) before they receive an interchangeable rating from the Agency under PHSA §§ 351(k)(3)(A)(ii) and (k)(4). In our view, name changes for previously marketed products can be (A) confusing to both practitioners and patients and (B) highly disruptive to ongoing commercial operations, and these problems are likely to be particularly significant when when a licensed or approved product has been on the market for a considerable period of time (as we expect to be the case given the 10-month BSUFA timeframe for FDA to act on a supplement seeking approval to convert from biosimilar to interchangeable status). Teva therefore does not believe that the Agency should mandate name changes for previously licensed biosimilar products if and when they are deemed interchangeable.

We also do not believe that there is a compelling rationale for mandating such changes. As the Draft Guidance acknowledges, the *Purple Book* clearly denotes the status of a given biological product as biosimilar ("B") or interchangeable ("I"), Draft Guidance at 11 ("The Purple Book also enables a user to readily see whether a biological product licensed under section 351(k) of the PHS Act has been determined by FDA to be biosimilar to or interchangeable with a reference product."), and as with the *Orange Book*, the Purple Book's listings already have been incorporated into the major electronic database services that wholesalers and pharmacists routinely consult.[1] As a result, wholesalers and pharmacies will be made immediately aware of any change in a biological product's status as soon as the *Purple Book* is updated, rendering a name change for the underlying product superfluous.

In addition, we believe that requiring name changes may undermine one of the Draft Guidance's principal objectives. Insofar as the Agency's proposal is motivated by pharmacovigilance concerns in connection with potential product switching, the use of shared product suffixes could be self-defeating: Precisely because the issuance of an interchangeable rating is likely to encourage product switching, it may be particularly important for patients and healthcare providers to identify which interchangeable product was used in the event of an adverse report (though Teva reiterates that currently-used product identification metrics like the manufacturer's name, proprietary name, and NDC codes likely are sufficient for those purposes without requiring the use of a suffix).

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**

[1] We believe that the Purple Book could be further enhanced by adding columns designating whether a licensed product is a reference product under PHSA § 351(i)(4), and, for biosimilars and interchangeable biologics, the identity of the reference product cited in the licensee's application under PHSA § 351(k).

the option of retaining its original suffix or adopting the same suffix as the reference product?

As set forth above, Teva believes that this is the most likely context in which problems could arise, particularly where a licensed biosimilar product has been on the market for a considerable period of time before obtaining an interchangeable rating. *See supra* at 4-5. And consistent with the views Teva previously expressed, we believe that the Agency should provide licensees with maximum flexibility in selecting the nonproprietary name associated with a given product—provided that the licensee's selection of a given four-letter suffix does not undermine the objectives of the Draft Guidance, run afoul of the proposed prohibitions set forth in the Draft Guidance, or otherwise violate the standards FDA typically applies or enforces when addressing manufacturer-selected product names. *See supra* at 3-4.

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?**

To the extent there are gaps in current pharmacovigilance systems, we believe that current adverse event reporting forms (including MedWatch's Form FDA 3500B) could be modified to provide better instructions to both patients and healthcare providers—directing consumers, for instance, to contact their pharmacist if they no longer have the product packaging or cannot recall details regarding the product, and emphasizing the importance of providing as much information as possible. Consumer reporting forms also could be modified to ask patients to identify the pharmacy or pharmacies where they filled their prescriptions and seek patient permission to contact the pharmacy to obtain missing information about the product that is the subject of the report.

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?**

As Teva previously explained, we believe that name changes for previously licensed products are likely to be confusing for patients and providers and highly disruptive to ongoing commercial operations—effectively requiring licensees to retool their production systems, re-educate customers and consumers, and re-launch products that have not been tied to safety or efficacy issues. *See supra* at 4-5. We therefore believe that previously marketed products and any

biosimilars that reference such products should be "grandfathered in," with the Agency's final guidance on this issue taking effect on a purely prospective basis. We further note that this approach is consistent with the one FDA previously mandated when it revised its drug labeling content and format regulations in 2006 (i.e., by allowing older NDAs to maintain their prior labeling and ordering ANDA applicants to replicate the reference product's old-format labeling, despite new content-and-format regulations that otherwise would govern the labeling for newly-approved ANDA products). *See Final Rule: Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, 71 Fed. Reg. 3922, 3928 (Jan. 24, 2006); *see also Proposed Rule: Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels*, 65 Fed. Reg. 81082, 81098 (Dec. 22, 2000)

In the event the Agency nonetheless proceeds on a retroactive basis, we believe that the pertinent FDA Review Division should work with each affected licensee to individualize a timetable for selecting and implementing a modified nonproprietary name. Such a case-by-case approach is essential to minimize the possibility of supply chain disruptions and potential drug shortages for these proven therapies, and we are confident that licensees can and would work collaboratively with the Agency to devise a reasonable timetable that mitigates the potential disruptions that would be be associated with the retroactive application of these new standards.

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

Once again, we do not believe that the retroactive application of the proposed naming convention (whether for previously-approved innovator biological products or forthcoming biosimilar products that reference previously approved biologics) is necessary in the absence of proven safety or efficacy issues with the previously approved products. To the extent the Agency proceeds, however, its prioritization should be driven by current safety and utilization metrics, with individualized timeframes that are designed to minimize supply chain disruptions and potential drug shortages.

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 we previously explained, it is critical that the Agency avoid creating or exacerbating drug shortages during the implementation this proposal and therefore that the deadlines for implementation be individualized and product-specific. In the absence of proven safety or efficacy problems, licensees should be permitted to exhaust current inventories of previously manufactured and distributed products and afforded an adequate period of time to implement any changes requested by the Agency.

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

FDA already has significant experience in notifying stakeholders about important safety information and labeling changes, as well as educating stakeholders about risk-management programs. In this context, we believe that public meetings, participation in stakeholder conferences, and the use of interactive communication tools that facilitate stakeholder participation (e.g., question-and-answer sessions, webinars) are feasible and time-tested options for the Agency.

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?**

Subject to Teva's prior comments, we believe it is important for FDA to align its final Guidance with the eventual WHO standards in order to facilitate global pharmacovigilance efforts and minimize the inefficiencies that would result from adopting U.S-specific standards for products being developed and marketed on a worldwide basis. As a result, we urge the Agency to confer with its counterparts at WHO and defer finalizing its Guidance until their proposals can be fully aligned.

If you have any questions about the information in this submission, I may be reached at (610) 786-7192.

Sincerely,

/s/ Penny S. Levin, M.S.

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