



September 29, 2014

Raffaella Balocco Mattavelli, Ph.D., Pharm.D.
Manager, International Nonproprietary Name Programme
World Health Organization
Attn: Department of Essential Medicines and Health Products
1211 Geneva 27
Switzerland

Dear Dr. Balocco,

ASHP is pleased to submit comments to the World Health Organization (WHO) on the proposed biological qualifier to International Nonproprietary Names (INNs) for similar biotherapeutic products (biosimilars).¹ ASHP represents pharmacists who serve as patient care providers in acute and ambulatory settings. The organization's more than 40,000 members include pharmacists, student pharmacists and pharmacy technicians. For over 70 years, ASHP has been on the forefront of efforts to improve medication use and enhance patient safety. A core activity in those efforts has been ASHP's almost 60-year history of publishing authoritative, federally recognized drug information that serves a unique role in establishing medically accepted uses of drugs.

ASHP has been actively engaged on the issue of biosimilars for over a decade, with policies supporting a legislative and regulatory pathway for biosimilars in the U.S. and encouraging the development of safe and effective biosimilar medications in order to make such medications more affordable and accessible to patients. ASHP supported legislation enacted in the U.S. as part of the Affordable Care Act that gives the Food and Drug Administration (FDA) the authority to approve biosimilar medications as well as interchangeable biologics. The latter medications are those biosimilars determined by FDA to be interchangeable with their reference product

¹ INN Working Doc. 14.342, Revised draft July 2014.
(http://www.who.int/medicines/services/inn/bq_innproposal201407.pdf?ua=1)

and that therefore may be substituted for the reference drug product without the intervention of the original prescriber.²

ASHP has been extensively engaged with ANSI-accredited standards development organizations (SDOs) in the U.S. (e.g., National Council for Prescription Drug Programs, NCPDP) and with other stakeholders concerning standard naming and data coding practices for all medications, including biologics and biosimilars, advising FDA, the U.S. Federal Trade Commission (FTC), and others. Through all of these activities, ASHP strongly supports WHO's INN naming practice whereby biological substances are assigned INNs by the general principles applicable to all INNs and by a specific framework developed especially for them.³

ASHP opposes efforts advocating unique nonproprietary names for biosimilars. While ASHP recommends that nonproprietary names for biosimilar products be the same INN without modification, we do not oppose the use of separate suffixes or other qualifiers in addition to INNs if established as essential and superior for pharmacovigilance. However, we do not believe that alternative methods (e.g., data fields or systems) already in place have been shown to be ineffective or that the use of suffixes or other qualifiers in addition to INNs has been proven to serve an essential need for this purpose. Despite the opinions of some to the contrary, there currently is a lack of evidence that WHO's current system of unmodified INNs is inadequate for biosimilars.⁴

ASHP also recognizes that drug names should not be used inappropriately for regulatory purposes such as to imply interchangeability or for traceability, as acknowledged by FDA in WHO's 2006 consultation on biosimilar INNs.⁵ However, WHO's proposal for creation of biological qualifiers to complement the INN for a biological substance as a unique means to identify the manufacturer and manufacturing site of the active substance suggests that some may in fact use this for traceability. Therefore, if adopted, ASHP believes that WHO should state clearly that its biologic qualifier is not intended as a substitute for other means (e.g., the

² ASHP Policy Position Numbers 0519, 1218, and 1409.

³ INN Working Document 05.179, Update 2013
(<http://www.who.int/medicines/services/inn/BioRev2013.pdf>)

⁴ McCamish M, Gallagher AM, Orloff J. Biosimilar by name and biosimilar by nature. Elsevier Business Intelligence, the RPM Report. Jul/Aug 2013. (Available at http://www.ftc.gov/system/files/documents/public_comments/2014/03/00037-88739.pdf)

⁵ INN Working Document 07.211
(http://www.who.int/medicines/services/inn/BiosimilarsINN_Report.pdf)

standardized numerical identifier, SNI; global trade item number, GTIN) in track and trace solutions, which should be left to regulatory authorities such as the FDA in the US to establish.⁶

ASHP applauds WHO for addressing the current uncoordinated actions of various regulatory authorities around the world who have been adding nonproprietary modifiers to INNs in order to distinguish similar biotherapeutic products from the reference product and other follow-on products. However, we are concerned about WHO's proposed solution of randomly assigned, four-character (all consonants) biological qualifiers that are not meaningful and unpronounceable. Further, since the qualifiers are to be specific to the manufacturing site and not simply the product, the possibility of confusion is magnified.

ASHP recommends that WHO delay finalization of its current proposal on biological qualifiers pending engagement of a broader base of experts and stakeholders. For example, we are concerned that WHO's biological qualifiers may be used as part of the nonproprietary name rather than simply as a series of codes. While WHO's intent is that the biological qualifiers not be considered a part of the INN, it is difficult to see how that will be avoided, particularly considering some of the uses described at the end of WHO's proposal. In fact, WHO itself uses the term "names" to describe "epoetin alfa bbbb" and "epoetin alfa cccc" as examples of its proposed solution. As such, WHO should address how word-based applications of its proposed INN plus random vague or confusing code construct can be avoided, and if they cannot, develop sound evidence supporting their use from a human cognition perspective. Even if they are not employed as names, human cognition considerations must be addressed in the context of various use cases.

FDA recently deviated from standard practice by establishing the generic name of several biologic and biotechnology derived products by introducing prefixes independent of the USAN Council or INN Programme. The introduction of these prefixes has caused confusion, including within FDA itself (e.g., separate names for filgrastim and tbo-filgrastim but identical unique ingredient identifiers) and across agencies (e.g., FDA versus the National Cancer Institute and

⁶ Food and Drug Administration. Guidance for industry: Standards for securing the drug supply chain—standardized numerical identification for prescription drug packages. Final guidance. 2010 Mar.
(<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM206075.pdf>)

National Library of Medicine for preferred names) and has raised safety concerns. One such deviation from standard practice (ado-trastuzumab emtansine) by FDA actually resulted in the issuance of an FDA warning about potential medication errors, an Institute for Safe Medication Practices (ISMP) Medication Safety Alert,⁷ and a National Alert Network (NAN) alert.⁸ Because of the demonstrated risk and confusion of deviation from standard drug naming and coding practices, ASHP agrees in principle with WHO's position that a consistent centralized international mechanism must be maintained to meet the needs of certain regulatory authorities that consider distinct biosimilar names important.

Concerns

ASHP agrees with WHO's stated intent to create a single global scheme of unique qualifiers/identifiers to avoid proliferation of separate and distinct national qualifier systems for biologicals for regulatory authorities that consider such modification essential. However, ASHP is greatly concerned that WHO's proposal for biological qualifiers employs unrecognizable and unpronounceable four-consonant codes that are not meaningful in and of themselves. In fact, the reference product also is not identical to itself over time but instead shares the concept of biosimilarity chronologically with various batches.⁹ While WHO characterizes these biological qualifier codes as means to identify the source and site of manufacturing and not a part of the INN, the reality as described in WHO's own use cases (e.g., for use in prescriptions) is that the resulting combination of INN and biological qualifier will be treated as a single name in many applications. That it may be treated as a single name in some applications but not others, compounds the problem.

Humans are good at recognizing, recalling, and understanding well-formed standardized names but not at recognizing, recalling, and interpreting codes, especially randomly formed ones that are not meaningful. In reaching our conclusions and recommendations, ASHP sought the advice of several leading health literacy and cognition experts. These experts agreed with ASHP's concerns.

⁷ ISMP Acute Care Medication Safety Alert! Safety brief: Confusion between two HER2-targeted monoclonal antibodies. Vol 18, Issue 5. 2013 Mar 7.
(<https://www.ismp.org/newsletters/acutecare/issue.aspx?id=42>)

⁸ National Alert Network (NAN) alert. Confusion regarding the generic name of the HER2-targeted drug Kadcyra (ado-trastuzumab emtansine). 2013 Apr 17.
(<http://www.ashp.org/DocLibrary/Policy/PatientSafety/NAN-Alert-April-2013.pdf>)

⁹ Schneider CK. Biosimilars in rheumatology: the wind of change. *Ann Rheum Dis.* 2013; 72:315-8.

From a human behavior and cognition perspective, employing randomly assigned four-consonant modifiers that cannot be pronounced as a complement to an INN will make it difficult to recognize or recall the intended distinction in the name. Likewise, it would be highly unlikely that one could associate the modified INN with the respective product, and thus it would add little to the ability of patients, prescribers, pharmacists, and others to report potential adverse effects or other product-specific effects in a reproducible way. By comparison, humans can readily recognize distinctions in products represented by trade (brand) names or specific manufacturer names.

For example, human brains will have little if any ability to recognize and recall “dxvk” as a randomly assigned qualifier/modifier to complement an INN as part of the following hypothetical “generic” drug name: “filgrastim dxvk”. There are no meaningful cues in this example for practitioners and patients to use to help them recognize and recall the name, let alone apply any intended conceptual distinction between two biosimilar products such as “filgrastim dxvk” versus “filgrastim ztgl”. One would simply know that when viewed together the names were different but would not be able to easily associate these modified generic names with their respective brand names or manufacturer’s products.

In addition, this random consonant schema may result in transpositional errors because there is no way of recognizing and preventing errors associated with the wrong sequence of these random consonants as part of the qualified/modified INN. As a result, it will be extremely difficult for humans to recognize data entry errors. In addition to the associated risk of medication errors, this INN plus random code construct likely will lead to disruption in normal prescription work flows, such as increased call backs to prescribers seeking clarification or confirmation of the prescription intent.

If WHO’s intent is simply to create a codified system for drug product identification, there are better options than combining elements of a generic drug name (INN) with random letters as modifiers. Further, the approach outlined by the WHO is limited only to a single group of drugs—biologicals. In describing potential use cases at the end of the proposal, it would seem that a single system applicable to all drugs would be preferable to one limited solely to biologicals.

ASHP understands the challenge WHO faces in attempting to reign in the current uncoordinated modification of biosimilar INNs in various countries and serve as the arbiter of a

standardized international process that could be used by those regulatory authorities that consider modification necessary. ASHP agrees that adoption of any system of standardized qualifiers must be completely voluntary, leaving it to the individual regulatory authorities to determine whether they simply go with WHO's identical INN for biosimilars or decide to add the modifier. Therefore, any such standardized modified name will become "official" (e.g., for use in labeling) only in the countries that decide to follow the latter path. ASHP applauds WHO's goal of avoiding the proliferation of separate and distinct national qualifier systems by overseeing a single global scheme under the direction of the WHO INN Expert Group and WHO INN Secretariat. It is the proposed scheme that is problematic.

Recommendations

If the expectation is that the combination of INNs with biological qualifiers will result in humanly recognizable constructs that can be readily applied for specific biosimilar product identification, then WHO should engage health literacy, human cognition, and other experts to determine whether its proposal can achieve those goals. Consideration also should be given to engagement of the National Academies Institute of Medicine Roundtable on Health Literacy to explore this issue further.

If the expectation is that the combination of INNs with biological qualifiers will serve as a *codified data system* for drug product identification, particularly one that would be specific not just to the product but to the manufacturing site, then WHO should engage more extensively electronic drug database and standards experts as well as other stakeholders to determine whether its proposal can achieve its goals. Under this scenario, WHO should explore further whether a codified system applied to a single group of drug products—biologics—makes sense in the context of existing codified systems used for product identification. In addition, it must establish that such alternative codified data systems would be inadequate and that its proposed system that would employ a confusing combined INN plus random code construct would be superior before going down the path of creating yet another drug data system.

Of the use cases given by WHO in their proposal, those most likely to be achievable via the INN plus random biological qualifier construct would be ones that are codified data-, rather than name-driven. Examples would include use as a database of sites of biological active substances manufacturing, as a database of approved biological substances, as an additional means of identifying substances and products in reimbursement systems, or as a tool in pharmacovigilance systems. However, this raises the questions as to whether or not this new

data system would add substantially to the ability of existing codified drug data systems in meeting these needs. If it cannot be shown to be superior to such alternative data systems, then WHO should more clearly articulate its justification, specific roles, and limitations. As part of this articulation, WHO should emphasize more clearly the preferred approach of following WHO naming policies that rely on unmodified INNs and discourage the application of biological qualifiers unless such use is considered essential. WHO should also consider whether a standardized name (INN) plus random code construct meets contemporary data structure principles.

For use cases dependent on human cognition such as for prescribing by physicians, as aids in assessing product-specific patient response, and as facilitation of decision making, the random non-meaningful nature of the code presents important challenges concerning true usefulness of the INN plus code construct. We have articulated our concerns above, and believe that they are serious enough to warrant additional solicitation of expert advice by WHO and well-designed testing before the current proposal can be advanced.

ASHP appreciates the opportunity to provide our perspective on the WHO proposal for a biological qualifier to INNs for biosimilar medications. Please contact us if you have any questions or wish to discuss our comments further. We can be reached via e-mail at ctopoleski@ashp.org or gmcevoy@ashp.org.

Sincerely,

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