

Nomenclature of New Biosimilars Will Be Highly Controversial

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Biopharmaceuticals, including products approved as biosimilars, must be clearly defined, identified, and named to ensure accuracy in writing and filling prescriptions (1–4). The US biosimilars law enacted last year enables the Food and Drug Administration (FDA) to approve abbreviated biosimilar biologics license applications (bBLAs) or 351(k) filings based largely on their sponsors proving structural, composition, and clinical similarities with an approved biologic (reference product), much like generic drug approvals (5). The agency has yet to disclose how it will implement biosimilar approvals. Factors to take into consideration include types of clinical trials, required data, and names to be officially designated and allowed for product labeling, inserts, and marketing.

The established (also referred to as *compendial, nonproprietary, or official*) names to be designated by the FDA and used for biosimilars are likely to be highly controversial. The agency will have to make difficult choices such as

- whether to assign either unique, similar, or generic (the same as reference product) names to biosimilars
- whether and how biosimilarity relationships, structures, product class, and other information should be reflected in biosimilar names
- whether there should be any system and predictability to names.



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Hardly anyone, even many people within the industry, is yet very knowledgeable concerning biosimilars, a totally new class of products and approvals. Established names will be the first identifier or piece of descriptive information regarding these products that users will encounter (other than registered trademarks, which are often meaningless and convey no information). So the established names to be adopted will profoundly affect the core perceptions of biosimilar products (e.g., whether the products are generic) and so affect their use, branding, and marketing.

PROBLEMS WITH OFFICIAL NAMES

Unique, dissimilar names help prevent prescription mix-ups, and reporting

and tracking adverse events while using identical or similar names may contribute to prescription mix-ups and complicate postmarketing surveillance. With the FDA having clearly signaled that it will be quite some time before it is ready to approve interchangeable biosimilars and automatic substitution among biosimilars and reference products (as with generic drugs), the agency will surely treat each biosimilar as a unique product. But what names will be used?

Identical, biosimilar (obviously related), and fully unique names each present advantages and problems for different user communities. Generic names greatly facilitate biosimilar marketing — which in the extreme may not involve any marketing, as with most generic drugs. Identical names make it easy for pharmacists and payers to substitute biosimilars for prescribed reference products. Generic names greatly facilitate information retrieval of related products. Nonidentical, unique names force biosimilars to be marketed like branded products, make prescription substitution and related cost-savings much more difficult, and complicate information organization and retrieval. So, the type of names the FDA designates for biosimilars will greatly affect their marketing, including how much costly marketing is required to establish brand identity and gain product sales to compete with reference products.

But the names to be designated for use by the FDA — whether they be fully unique but meaningless, generic and the same as the reference product, or a biosimilar name (a stem or name portion in common with the reference product along with modifiers) — remains unknown. FDA, marketers, pharmaceutical references, insurers, formularies, pharmacists, physicians, media, the general public, and other communities all have different needs and uses for product names. For example, essentially every pharmaceutical reference treats products as generically as possible such as handling related products in a single monograph, whereas unique product identifiers are obviously needed for prescription purposes.

DIFFICULTIES IN NAMING

Biopharmaceuticals are the most complex of all medical products. The biotechnology in their manufacture invariably leads to products being unique and largely defined by their processing (7). The new US biosimilars law recognizes this fact and does not consider products approved on the basis of similarity as fully identical. By contrast, generic drugs — composed of much simpler chemical substances as small molecules — are generally presumed to be identical to their reference products for all practical purposes, including prescriptions. So they receive the same generic names based on their active ingredients. Biosimilarity and approval of small molecules are relatively easy compared with the task of determining what is unique and different, the relevance of differences, and how to define, name, and describe biosimilars for various users and constituencies.

Defining a distinct biopharmaceutical — such as one deserving its own name — is a very difficult and subjective task. No one uses the same criteria to define unique products nor the changes in a product that would require that it be considered “new.” Active agents and products can be named on the basis of their structures, approvals (considering each full approval a unique product),

and/or how they are marketed. Naming a biopharmaceutical involves identifying the changes in an established product that require considering it a new, unique product that requires a new name. Many users would consider a product with a new formulation, significantly altered processing, new full approval, new trade name, different manufacturer or marketing company, or other changes to be a “new” product that requires a new name. Others would consider those products the same (enough) and expect them to retain the same name, particularly if new products are approved as clinically comparable with prior products.

Biopharmaceutical products are so complex, and the information that ideally — depending on users and uses — should be conveyed is so much that short, usable, descriptive names are impossible. So all biopharmaceutical nomenclature involves compromises, and various types of names may or may not be suited for various uses and user communities. For example, most existing pharmaceutical references and information systems probably not bother to modify their own nomenclature systems primarily oriented to drugs (chemical substances) simply to better handle a few biopharmaceuticals.

PROBLEMS SELECTING OFFICIAL NAMES

Selection of an established name has almost always involved the FDA's adoption of a US adopted name (USAN, assigned by the American Medical Association, with the *US Pharmacopeia* formerly involved). USANs are almost always the same as and often first granted by the parent International Nonproprietary Nomenclature (INN) system. However, the INN system is controlled by the World Health Organization (WHO), part of the United Nations (UN), with its committees dominated by lesser-developed countries. Those countries' main interests are in granting mostly generic-type names, which allows unrestricted substitution of less-expensive generic drugs/biosimilars in

place of more costly original Western-manufactured reference products. INNs and USANs work well for generic drugs but not biopharmaceuticals, for which even the most similar products must be considered different and unique, particularly in more affluent and highly regulated markets where safety is valued over cost savings.

INN/USAN nomenclature systems for biopharmaceuticals are a jury-rigged patchwork, with little or no consistency and predictability (e.g., each product class has its own naming conventions). Recently, INNs and USANs are adding numbers and Greek letters as modifiers to make biopharmaceutical names “more unique.” However, even those names are not unique, and the same name is still often used for multiple products (with different manufacturers, bioprocessing, formulations, delivery systems, and so forth). For example, “interferon beta-1 α ” applies to multiple US-marketed products. As the number and diversity of biopharmaceutical products increase, including multiple biosimilars being approved for most every successful biopharmaceutical, INNs/USANs will become more irrelevant for many or most uses, including for FDA-established names.

OTHER TYPES OF NAMES

In addition to regulatory-assigned names, there are many other types commonly used for biopharmaceuticals.

Trade names are almost always the registered trademark and are generally, but not always, unique to each product. Trademarks are among the few good options for unique biopharmaceutical names and will probably be the most-used type (but with the established name also required with it in any product marketing). However, trademarks are owned by their registrants, so they technically, cannot be widely used by others without permission. Their use as established names would make every mention of products — including biosimilarity comparisons — sound like advertising.

Table 1: Example of FDA-issued names

Trade Name	New Name	Old Name
Botox	OnabotulinumtoxinA	Botulinum toxin type A
Botox Cosmetic	OnabotulinumtoxinA	Botulinum toxin type A
Dysport	AbobotulinumtoxinA	Botulinum toxin type A
Myobloc	RimabotulinumtoxinB	Botulinum toxin type B

Systematic names are assigned by organizations, including the Chemical Abstracts Service (CAS), often along with other identifiers (e.g., CAS registry numbers). These are designed for indexing and retrieval of chemical substances in bibliographic databases, not for identifying commercial products. Such highly descriptive names are based solely on the primary structures of the active agents, and similar products are all assigned the same inherently generic name. In addition, such names are generally too long to be of much practical use in prescription writing. For example, Centocor's Remicade product, which contains a recombinant antibody, has the name "Immunoglobulin G, anti-(human tumor necrosis factor) (human-mouse monoclonal cA2 heavy chain), disulfide with human-mouse monoclonal cA2 light chain, dimer." Infliximab is the established and USAN/INN name for the active agent and final product.

Trivial names are common names. Unlike other types of names discussed above, no organizations are proposing or controlling them. Because users often make descriptive or other names to satisfy their own needs, these trivial names can often be short and either generic or unique. Remicade examples include "tumor necrosis factor-alpha monoclonal antibody," "chimeric IgG1 anti-human TNF mAb cA2," and "TNF-alpha mAb cA2." Trivial names that eventually become widely used — such as for popular and media use — can profoundly affect the perception of a product and its marketing.

National Drug Codes (NDC) identify approved products down to their specific dosage and packaging. NDCs are the best available choice for identifying specific marketed products, but numbers are not usable in most cases (e.g., writing prescriptions). But even NDCs do not reflect different bioprocessing, formulations, trade

names, manufacturers, and other changes, any one of which may define a new product (or version) deserving a new name/identifier for different uses.

NOMENCLATURE SOURCES

The types of names for agents and products are often organized as lists in formal registries (directories), including the public ChemIDplus Web database (<http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp>) and the CAS registry system. However, current registries generally compile and mix active-agent and finished-product names of all types, including collecting inaccurate names used by others, with none designed to cover either biopharmaceutical active agents or finished products. No registry relates different names to clearly different but similar active agents and products. And none relate agent and product names or provide useful explanations about their proper definitions and use.

The best single source for biopharmaceutical nomenclature is the BIOPHARMA database (www.biopharma.com), the only reference and information resource specializing in biopharmaceuticals, which generally provides more relevant information (9). But even this resource is not authoritative because its information is not peer-reviewed. For biopharmaceuticals, the only authoritative information originates from manufacturers, including product inserts, labeling, and downstream regulatory disclosures.

Very little information is ever publically available about products' up- and downstream processing, final product specifications (chemistry, manufacturing, and controls, CMC), or basic information such as purity. So, in many respects, biopharmaceuticals remain black boxes with insufficient information available to fully describe, characterize, and differentiate them. Biosimilar development will probably

compound those problems, especially when multiple biosimilars for every established biopharmaceutical enter the market. The biopharmaceutical industry will need to deal with this near total lack of transparency, oversight, or access to substantive product information to prevent widespread public distrust — such as what now plagues vaccines (8).

Currently, companies consider even the most basic final product specifications inherently proprietary. But the prevailing industry hoarding of product-related information (other than regarding product use) may begin to change as more biosimilars are marketed. Reference product innovators that have manufactured and marketed their products for more than a decade or even two will probably use information and its dissemination to their advantage, including to show that their legacy products remain competitive and high-tech. Biosimilar manufacturers (many using optimally efficient current methods such as improved expression and purification systems) can be expected to often proclaim increased purity or other objective improvements compared with reference products. That could include disclosing CMC information and comparisons with reference products. After filing biosimilar BLAs (bBLAs), biosimilar sponsors are required (by the new biosimilars law) to give their entire applications, including CMC sections, to reference product manufacturers as part of the mandated patent dispute resolution process. Thus, their worst and most-established competitors will know absolutely everything about their product. In this context, biosimilar companies have nothing to lose and everything to gain by publishing information about their products and comparisons with reference products.

FDA's Approach: The FDA is far from ready to consider biosimilars to be identical to their reference products. The agency initially will surely grant only unique names for biosimilars. But how unique will they be? The renaming of botulinum toxin products in 2009 may provide a hint of FDA's approach. Responding to problems with prescription mixups,

the agency issued new names for those products as (Table 1). It collapsed the prior established/USAN names and added meaningless prefixes to make each unique, and the two Botox products that contain the same active agent retain the same new name. The new names make it harder to mix up these products but confound their being retrievable and other uses. For example, none of the new names appear jointly in alphabetical lists; their references can not be easily remembered, and searching based on the toxin requires embedded text retrieval, which is rare. As a result, in the real world (other than sponsors' uses subject to FDA regulation), many uses and users will probably retain their existing ways of identifying those products, adding cross-references as needed, and will not adopt as primary names any arcane FDA-specified names. Allergan, manufacturer of Botox products, appears to have come out the winner, with its trademark now the only one similar to any familiar descriptive name. Competitors now have both trade and established names no longer readily identifiable as botulinum toxin products. Dysport and Myobloc marketers now have to put more resources into marketing and branding just to keep physicians, pharmacists, consumers, and other communities aware of their products.

For established names, the FDA will have to decide whether biosimilar names will reflect biosimilarity — that is, be fully or partially identical or be fully unique. Choices include fully unique meaningless contrived names (as many currently are) with no relationships discernible among biosimilar products or unique biosimilar names. Those are the most likely choices. Other possibilities include unique names based on adding commercial descriptors to USANs or biosimilar stems such as a manufacturer's name or trade name; and biosimilar or unique names based on product class such as mechanism of action. For example, potential names for a new biosimilar version of Epogen and Procrit products (US recombinant erythropoietin with the same active

agent and established name, epoetin alfa, and approvals) could include a meaningless but pronounceable multisyllable word, epoetin alfa-x1, aboepoetin alfa, epoetin alfa/XYZ Co., and erythropoiesis stimulator theta1 or erythrostim theta1. Each name presents different advantages and problems for marketing, prescriptions, product surveillance, and information organization and retrieval.

The FDA will need to decide whether and how reference products and/or other products with full BLAs might need to be (re)named to show their status (e.g., that they are not biosimilars). With biosimilars likely to outnumber reference products and potentially be perceived as second-class derivative approvals and low-quality products, reference product manufacturers and other communities may call for names somehow differentiating full BLA from sBLA approvals.

RESOLVING CONTROVERSIES

The FDA's names and nomenclature for biosimilars are likely to be very controversial with names profoundly affecting cost savings, marketing requirements and costs, and health care and consumer perceptions of such products. Options for the agency include ignoring the issue and granting names on a one-off basis, with no consistency or system; adopting INN/USANs with all of their problems (continuing the status quo), including using jury-rigged INN/USANs to be biosimilar but unique; and developing rational nomenclature systems with at least some rules and predictability. In the near-term, the first two options seem most likely (i.e., the FDA will most likely avoid nomenclature issues for as long as it can).

Otherwise, none of the usual organizations that should be involved — such as those currently in drug nomenclature and monograph development and trade associations — appear to want to get involved with biosimilars nomenclature and/or have existing conflicts of interest. Because naming and tracking biosimilars is a

thankless task, lacking publishing or other profit potential, there is no incentive for private-sector involvement. Incredibly, the US biopharmaceutical industry lacks its own trade association(s) that otherwise would already be involved in those issues. The few relevant ones avoid such technical issues involving members' specific products. Thus, no established organizations are either seeking or capable of getting involved in resolving biosimilar nomenclature, particularly concerning specific products.

I propose a US Biopharmacoepia Registry of Biopharmaceutical Products as an industry-based and -funded collaborative effort to help resolve biosimilar and broader biopharmaceutical nomenclature issues (see www.biopharmacoepia.com). It might be modeled after the CTFA Dictionary (Cosmetics Trade Association, now the Personal Care Products Council), in which industry-based committees propose product ingredient names — International Nomenclature Cosmetic Ingredient (INCI) names — that are almost always adopted by the FDA for cosmetic product labeling (10). The US Biopharmacoepia project will propose candidate unique, biosimilar, (bio)generic, and other needed types of names for selective adoption by regulatory agencies, reference works, formularies, media, and other diverse uses and users; and will provide a public registry website relating names for active agents and products. Ideally, one or more trade associations, forward-thinking companies, and/or the FDA might fund this or a similar program.

No one knows how to portray, classify, identify, or name biopharmaceutical products, including biosimilars. Biopharmaceutical nomenclature is too important to leave fully in the hands of the FDA and governments, and rightfully the industry should have input or even control of its products' names. The "US Biopharmacoepia" is proposed as one of a variety of ways for industry to get involved and help resolve biosimilar and broader

biopharmaceutical nomenclature issues.

REFERENCES

- 1 Rader RA. What Is a Generic Biopharmaceutical? Biogeneric? Follow-On Protein? Biosimilar? Follow-On Biologic? Part 1: Introduction and Basic Paradigms. *BioProcess Int.* 5(3) 2007: 28–38.
- 2 Rader RA. What Is a Generic Biopharmaceutical? Biogeneric? Follow-On Protein? Biosimilar? Follow-On Biologic? Part II: Information, Nomenclature, Perceptions and the Market. *BioProcess Int.* 5(5) 2007: 20–28.
- 3 Rader RA. (Re)defining Biopharmaceutical? *Nature Biotech.* 26(7) 2008: 743–751.
- 4 Rader RA. What Is a Biopharmaceutical, Part 1: (Bio)Technology-Based Definitions. *BioExecutive Int.* March 2005: 60–65.
- 5 Rader RA. What Is a Biopharmaceutical, Part 2: Company and Industry Definitions. *BioExecutive Int.* May 2005: 42–49.
- 6 Biologics Price, Competition and Innovation Act (BPCIA), *Patient Protection and Affordable Care Act*, H.R. 3590, enacted by Congress on 23 March 2010; www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf.
- 7 Copmann T, et al. One Product, One Process, One Set of Specifications: A Proven Quality Paradigm for the Safety and Efficacy of Biologic Drugs. *BioPharm Int.* 14(3) 2001: 14–24.
- 8 Rader RA. Biopharmaceuticals: Lack of Information Disclosure Confounds Public Trust, Particularly in the Context of Biosimilars. *BioWorld Perspectives* 2(18) 2008.
- 9 Rader RA. *BIOPHARMA: Biopharmaceuticals in the US and European Markets*, 10th ed. Biotechnology Information Institute; www.biopharma.com.
- 10 *International Cosmetic Ingredient Dictionary & Handbook, Personal Care Products Council*, 13th ed.; www.cosmeticsinfo.org/fdapartner_cid.php. 🌐

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