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Edith Ramirez
Chairwoman
Federal Trade Commission
Office of the Secretary
600 Pennsylvania Avenue, NW
Room H-113 (Annex X)
Washington, DC 20580

Re: Workshop on Follow-On Biologics: Project No. P131208

Dear Chairwoman Ramirez:

On behalf of the physician and medical student members of the American Medical Association (AMA), I appreciate the opportunity to provide comments and recommendations in response to the questions posed by the Federal Trade Commission (FTC) in its notice concerning the Workshop on Follow-On Biologics: Project No. P131208. The FTC has raised key questions in this emerging area of critical importance to physicians and patients. The varied presentations at the FTC workshop collectively underscored that a number of issues exist that require clarification and additional analysis before a long-term state and federal regulatory framework should be adopted. Specifically, U.S.-based physicians have not, yet, had experience with follow-on-biologics (FOB), as no such products have emerged from the Food and Drug Administration (FDA) regulatory approval pathway established by the Biologics Price Competition and Innovation Act (BPCIA). Implementation, therefore, remains a work in progress.

The European Union (EU) has made substantial progress in developing an FOB market through the European Medicines Agency. Although various analogies, distinctions, and conclusions were offered at the workshop based on experiences with FOBs in the EU, their experience is limited to biosimilars all having the same International Nonproprietary Name (INN), with products distinguished by unique trade names. In the EU, shared INNs between a biosimilar and the reference biologic product are based on a scientific regulatory assessment that meaningful clinical differences between these products do not exist. With few exceptions, biosimilar products are not interchangeable in the EU. Adoption at the country level has been uneven based on national payer and/or drug selection policies, although the overall experience has been positive with little evidence of serious safety issues. In light of the foregoing, many of the presentations at the workshop were based on conjecture concerning the practical and clinical implications of FOBs for patients and physicians in the U.S.

Background

The AMA strongly supported the establishment of the BPCIA as an FOB approval pathway to improve patient access to these cutting-edge innovative treatments and reduce the financial burden of these costly treatments on patients and the health care system. At the time, the AMA was mindful of the unique safety challenges posed by the manufacturer of complex biologicals and the corresponding challenges for FOBs. The AMA remains committed to the overall goal of developing policies that promote and protect patient access to FOBs and patient safety in a manner that preserves market competition and innovation. This is especially important given the anticipated growth in healthcare costs associated with biologics and the emergence of FOBs in the U.S. as a market-forming event characterized by substantial uncertainty.

Our comments do not directly address disputes about the relevance of comparability exercises following manufacturing changes compared with full scale biosimilar development, nor are specific recommendations offered about the explicit and prevailing need to improve post marketing surveillance activities in the U.S. Additionally, other issues that will likely influence competition in the emerging FOB market, such as the extent to which extrapolation of clinical data is allowed and how FOB product labeling might be distinctive, are not addressed.

Accordingly, the AMA's comments reflect consideration of current conditions and limitations in the existing regulatory regimes and what we reasonably believe would be applicable to FOBs in clinical practice in the U.S. The two most relevant questions to physician's practices and access for their patients are addressed below and reflect the organizational framework of the workshop. Although the influence of naming conventions is a distinct topic, they also are relevant for state substitution issues. For the purpose of clarity, the term biosimilar or interchangeable biosimilar will be used to reflect the reality of the two-tiered framework for approval of FOBs established by the BPCIA in the U.S.

How Naming Conventions May Affect FOB Competition

The BPCIA is silent on the naming of FOBs. The "intent of Congress was to provide the FDA the flexibility to establish a science-based policy for non-proprietary naming of drug substance, and not to encourage the FDA to adopt a policy of either identical or differentiated naming."¹

Background

The AMA has a unique perspective on this issue because it administers the United States Adopted Name (USAN) program in collaboration with the American Pharmacists Association and United States Pharmacopeia, with FDA representation. USAN facilitates the identification of pharmaceutical substances in development, including active pharmaceutical ingredients that are eventually marketed. Eventually, the USAN becomes an official name adopted by the USP, incorporated into their compendia monographs, and used in product labeling approved by the FDA. The FDA retains the statutory authority to establish a different non-proprietary name under various circumstances or conditions, and has done so recently for three distinct biological substances. A similar naming process is used by the International Nonproprietary Names (INN) Programme administered by the World Health Organization (WHO). USAN and INN engage in reciprocal process to ensure international harmonization of nonproprietary names (including

¹ Letter to Margaret A. Hamburg, MD, Commissioner of the Food and Drug Administration from Senators Orrin Hatch, Lamar Alexander, and Michael Enzi and Congressional representatives Anna Eshoo, Joe Barton, and Kay Hagan. November 13, 2013.

biologics)² among member countries, although certain countries (e.g., Australia, Japan) may take a different approach. Of note, the WHO is currently contemplating a post-hoc unique identifier process for biologics. It is critically important that FDA issue Guidance on the naming of biosimilar products in the U.S. that emanate from the BPCIA pathway. Adoption of different naming conventions for biosimilar products would create confusion on the global platform, bearing in mind that adverse events are also reported to U.S.-based companies from foreign physicians and healthcare providers.

The USAN or INN identifies the active substance, is designed to be shared among products, and not intended to identify a specific product. Different INNs denote products with different active ingredients, and the prevailing view (based on simple compounds, as well as the European experience with biologics) has been that they should not be used to differentiate products with the same active ingredient when evidence is available to conclude that no relevant pharmacologic or clinical differences exist. However, serial batches of complex biologics are not “identical,” even among originator products. This is a normal feature of the biotechnology processes used to create biologics, subject to analytical control and verification of product attributes within current technical and scientific limitations. Nevertheless, analytics have improved and evolved to the point where different manufacturers can develop biologic compounds that are highly similar to one another with respect to relevant structural and functional aspects.

In the U.S., the USAN is important in pharmacovigilance efforts, prescription writing and substitution practices (see below), and what it infers to the prescribing physician about the active ingredient in prescription drug products. From this point forward the term INN will be used to refer to nonproprietary names to the extent that it is synonymous with the USAN.

Pharmacovigilance

Pharmacovigilance is extremely important for assuring patient safety and in maintaining brand and product integrity. Two distinct elements comprise pharmacovigilance: (1) an effort to detect a safety signal through adverse event reporting; and (2) attribution of the adverse event to a specific drug substance or active ingredient or, in certain cases, a specific batch or lot number.

The INN is one piece of information that is part of a comprehensive identification system for products including the manufacturer name, batch and lot number, trade name, a National Drug Code (NDC number) and, within billing systems, the NDC or a unique J-code. Each NDC is a unique 10-digit, 3-segment number which identifies the labeler, product, and trade package size. Similar INNs allow the aggregation of postmarketing surveillance data across products, and facilitate the detection of safety signals associated with a specific active ingredient for simple compounds.

Manufacturers of biologics are concerned, however, about misattribution of an adverse event that could harm their brand (or lead to product recalls) when such aggregation occurs based on similar INNs, if the specific causative product(s) cannot easily be identified or isolated. This concern is based, to a degree, on the fact that many biologic products are long acting, adverse events related to immunogenicity (including loss of efficacy) may be latent, and manufacturing changes commonly occur over the lifecycle of biologic products. Once a biologic product is approved as interchangeable with a reference product, products that undergo manufacturing changes may theoretically begin to diverge with respect to product characteristics.

² INN Working Document 05.179. International Nonproprietary Names for biological and biotechnological substances. World Health Organization. 2013.

Manufacturers must convince the FDA that their new manufacturing process creates a product that is highly similar to the previous version through a “comparability” exercise that includes analytical comparisons, and sometimes additional clinical data requirements.

The other significant issue is the continuing heavy reliance in the U.S. on spontaneous adverse event reporting, and whether that process (as currently constructed) can adequately capture the necessary information for product attribution in the absence of a unique identifier for each biosimilar product. Some case studies were offered at the workshop demonstrating high capabilities for specific patient/product identification within a defined pharmaceutical benefit management system (Express Scripts), ePrescribing platform (SureScripts), or when brand names were used in reporting. Other studies showed that reliance on the nonproprietary name as the primary identifier was, in fact, unreliable, and the NDC, despite its highly informative construct, is virtually never included in adverse event reports. The surveillance issue is complicated by that fact that biologics are administered in various settings outside of traditional retail pharmacy, mostly in clinics and hospitals, as well as via mail order/self-administration.

Physician Attitudes

Several concerns have been raised about how different INNs, or INNs with unique modifiers for interchangeable biosimilars, might affect physician attitudes and, therefore, their potential willingness to prescribe or authorize substitution (see below). These potential concerns can be briefly summarized as follows.

Nonidentical INNs may:

- suggest to the prescriber that the active ingredient in products is different;
- create the (false) impression that interchangeable biosimilars have important, clinically relevant, distinguishable effects; and
- reduce uptake and substitution of interchangeable biosimilar products.

Available survey data to inform how U.S. based-physicians would interpret or view identical or non-identical nonproprietary names of biosimilars, whether interchangeable or not, is sparse, incomplete, and (like all surveys) is significantly influenced by the level of understanding, instructions, and the questions themselves. In the absence of robust, focus-group type activities on this issue, reliable predictions or recommendations cannot be made on how naming conventions may influence prescriber behavior regarding biosimilar products.

How State Substitution Laws May Affect the Development of FOB Competition

Although much attention has been devoted to the fact that “biosimilars are not generics,” one fundamental similarity exists. The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch Waxman Act) has been successful in establishing a regulatory platform leading to a largely seamless, scientifically-based system for generic substitution, based on state substitution laws that preserve physician autonomy in product selection, but otherwise allow automatic substitution of drug products that the FDA has deemed to be therapeutically equivalent. This determination of interchangeability of products containing the “same” active ingredients is a regulatory decision based on adequate and credible analytical and clinical data. In a similar fashion, the BPCIA created the framework for a science-based process to

establish interchangeability of biosimilar products using a high threshold that, once met, directs that they can be substituted without the intervention of a healthcare provider (i.e., automatic substitution).

It is instructive to note, that even after 30 years of generic substitution of bioequivalent, interchangeable A-rated generic products, a segment of physicians do not believe that such products are therapeutically equivalent and insist on prescribing and maintaining their patients on proprietary products, particularly for certain drugs with a narrow therapeutic index. In some states where additional requirements are in place for generic substitution (i.e., patient consent, physician authorization), substitution rates are reduced. Therefore, it seems reasonable to assume that additional recordkeeping or notification requirements may serve as a barrier to uptake of interchangeable biosimilars, but this supposition also remains speculative. Discussion about potential liability issues associated with physician notification requirements also has been lacking, as they relate to product substitution and market development for FOBs.

Limited survey data of US physicians indicates a low level of understanding about: (1) distinctions between generic equivalents of simple organic compounds and biosimilar products; (2) the difference between biosimilars and reference biologics; and (3) the current regulatory approval pathway for biosimilars. Familiarity is increased among practitioners who regularly use biologic products in their practice.³ The vast majority of U.S. physicians refer to biological medicines by proprietary names for medical records and adverse event reporting.⁴ As expected, physicians want to retain the authority to designate which biologic product is dispensed when choices are available. The AMA strongly supports the view that physician autonomy be preserved in directing which biologic product, including those that are deemed interchangeable, be dispensed, and that state pharmacy practice acts limit interchangeable products to those that have been designated as such by the FDA. It is our view that physician attitudes about biosimilar products, especially those that may be interchangeable, is poorly characterized. However, based on experiences with simple generic products, a substantial educational effort to avoid unintended barriers will be required when biosimilar products become available on the US market.

In consideration of the above discussion, the AMA makes the following recommendations:

With respect to state substitution laws:

1. Physicians and other prescribers must retain authority to determine which biosimilar product is dispensed.
2. Only biosimilar products deemed interchangeable by the FDA can be substituted. Such substitution could occur either when prescribers expressly authorize substitution or consent is implied by remaining silent (i.e., expressing no preference).
3. To facilitate awareness of prescribers and dispensing pharmacists, the FDA should compile and maintain an official compendium of biosimilars, biologic reference products, and their related interchangeable biosimilars as they are developed and approved for marketing by the FDA.
4. Further data and analysis are needed to determine the impact of prescriber notification requirements on prescriber behavior, as well as potential liability.

³ North American Center for Continuing Medical Education. CME Survey on Biosimilars. May 24, 2013.

⁴ Alliance of Safe Biological Medicines survey. September 13, 2012.

With respect to naming conventions and other issues:

5. The FTC should urge the FDA to finalize its Guidance on naming conventions for biosimilar products, including those deemed interchangeable. Clarity in this regard would go a long way to simplifying discussion at the state level regarding pharmacy practice acts governing substitution and interchange.
6. Any change in current nomenclature rules or standards should be informed by a better, and more complete, understanding of how such changes, including requiring a unique identifier for biologic INNs would impact prescriber attitudes and patient access, and affect postmarketing surveillance. Actions that solely enhance product identification during surveillance activities but act as barriers to clinical uptake are counterproductive.
7. If unique identifiers for biologic INNs are required, they should be simple and the resulting name should reinforce similarities, rather than differences.
8. Focused educational activities must precede and accompany the entry of biosimilars into the U.S. market, both for prescribers and patients.

We appreciate the opportunity to provide our comments and recommendations on follow-on biologics. We look forward to working with you further on our recommendations. Should you have any questions on this letter, please contact Cybil Roehrenbeck, Assistant Director, Division of Federal Affairs, at cybil.roehrenbeck@ama-assn.org or (202) 789-8510.

Sincerely,



James L. Madara, MD