Response to:

US Food and Drug Administration Docket No. FDA – 2010-N-0477
Approval Pathway for Biosimilar and Interchangeable Biological Products
Section C. Patient Safety and Pharmacovigilance

Submitted by the
International Society for Pharmacoepidemiology

December 23, 2010

Introductory remarks:

The International Society of Pharmacoepidemiology (ISPE) is an international organization of pharmacoepidemiology professionals from academia, government and industry. ISPE's mission is to provide "a forum for the open exchange of scientific information and for the development of policy, education, and advocacy for the field of pharmacoepidemiology." Within ISPE, a biologics special interest group has explored theoretical and practical issues that arise when pharmacoepidemiologic approaches are applied to the study of biological products. These considerations are directly applicable to the evaluation of the safety of biosimilars, biosimilar products and interchangeable products. ISPE, through its policy committee and the Biologics Special Interest Group, is submitting these comments to the FDA Docket FDA-201-N-0477 to address questions concerning Patient Safety and Pharmacovigilance (Section C, 1 - 4).

Pharmacoepidemiologic methods underlie active surveillance strategies for early identification of emerging safety issues for marketed products and are of particular value for identifying changes in frequency or severity of known adverse events. ISPE's submission to this docket will focus on the information elements needed to facilitate optimal pharmacoepidemiologic approaches to the safety issues for these products.

Question 1. What factors unique to proposed biosimilar or interchangeable biological products and their use should the agency consider in developing its pharmacovigilance program for such products?

- Pharmacoepidemiologic approaches are essential to evaluating the safety of biological products.

Since much of the safety evaluation of biosimilar or interchangeable products has to do with assessing quantitative aspects of the safety profile, pharmacoepidemiologic methods will be critical. Spontaneous reporting systems can contribute little to understanding quantitative changes in severity or frequency of known adverse reactions.

- Proteins composing most biological products are large complex molecules that are vulnerable to structural change.

Such changes can alter both anticipated pharmacological action and safety. In addition to the primary amino acid sequence, tertiary structure is critical to function and immunogenicity but conformational changes can be introduced by a variety of often subtle factors. The vulnerability of biological agents to changes in structure is at the heart of the issues to be considered when planning for safety assessments of these products, since manufacturing, storage and even the mode of administration can alter these structures.

- Biological agents have the inherent potential to elicit immunologic responses that can

alter safety and tolerability as well as efficacy.

Immunologic response to a biological product will be affected by factors intrinsic to the product, factors related to its production, storage, and mode of administration, and host-related factors including prior exposures and overall immune competence. Clinical manifestations of immunologic responses vary greatly in nature, severity, time course and outcome.

- Indications for biological products and the populations receiving them are factors that must be considered in pharmacovigilance systems for biological products.

Important issues for pharmacovigilance surveillance include disease characteristics (e.g. prevalence, natural history) and the nature of the populations exposed (e.g. demographics, comorbidities, risk factors). Severely debilitating or life-threatening chronic diseases constitute a high proportion of the indications for biological products. In these cases, the ability to follow patients over time is important, particularly in settings where they may use more than one biological agent.

In addition, the size of the target populations ranges from a few hundred individuals (enzyme replacement therapies for ultra orphan lysosomal storage diseases) to hundreds of thousands (insulin dependent diabetics). For relatively large populations such as insulin dependent diabetics, claims data or electronic medical records may provide sufficient patient experience. For very small populations such systems may be insufficient and focused registries may be needed. Here indication-focused systems (e.g. disease registries) may be more informative than product-specific approaches, particularly if several biosimilar or interchangeable biological products are being used. .

- Biological products are commonly administered by parenteral routes under health care professional supervision.

Dispensing and administration may occur in physician offices, infusion centers or hospitals, although self administration is routine for subcutaneously injected products (e.g. insulin, interferons). Each setting has different implications with respect to available data for pharmacoepidemiology. Furthermore, payment modalities may alter the type of data available for pharmacoepidemiologic analyses, particularly with insurance claims data (e.g. drug costs are individually claimed vs. subsumed under a hospital reimbursement code).

- Biological products are frequently used for more severe disease not responsive to first line therapy.

This introduces the potential for channeling bias when comparing these patients to those receiving non-biological therapies or other biosimilar products. This can be challenging to address since subtle differences in patient characteristics must be taken into account in evaluating or contrasting the safety profile of a product. Sorting out such factors requires the use of sophisticated pharmacoepidemiologic methods.

In summary, when pharmacovigilance program for biosimilar or interchangeable biological products, the agency should consider:

- ⇒ Biological products are susceptible to structural changes altering both safety and efficacy;
- ⇒ Globalization of production has the potential to produce additional concerns related to product quality;
- ⇒ The immunogenic potential inherent in proteins has pleiotropic clinical manifestations;
- ⇒ Parenteral administration in diverse health care settings complicates the collection of essential patient safety data.
- ⇒ Disease indications and the characteristics of the recipient populations pose particular challenges for safety assessment and surveillance;
- ⇒ Pharmacoepidemiology will be a primary tool for evaluating safety and benefit-risk in the setting of biosimilar and interchangeable products.
- ⇒ Specific measures (as discussed below) can be instituted to optimize the contribution of pharmacoepidemiology to the evaluation of safety of biological product.

Question 2. What approaches can be undertaken by the agency, industry, or health care community to ensure appropriate pharmacovigilance for biosimilar and interchangeable products?

Pharmacoepidemiologic evaluation of biologic products is dependent on accurate ascertainment of exposure and the systematic identification and categorization of relevant adverse events, particularly those of immunologic origin.

- Accurate ascertainment of exposure

It will be critically important to put into place systems that allow tracking of individual biological products from their original components and manufacture through to final production, packaging, distribution and dispensing. There is precedent for this based on past responses to public health crises. In particular, the recognition of the role of blood products in the spread of AIDS and hepatitis led to the introduction of the current system, which allows such products to be traced from individual donors to individual recipients. Thus, several specific strategies would be recommended:

- o *Source Identification*. Biological products are produced and their components sourced throughout the world. Precise identification of the source of product is instrumental in monitoring safety and controlling risks. In 2008, adulteration of heparin from Chinese suppliers led to serious hypersensitivity reactions including fatal anaphylaxis in users of the final product.
- o *Tracking individual product lots*. Given the importance of manufacturing in defining the nature of even well-characterized biological products, the routine recording of the specific product and lot number into the patient record is essential if safety issues with biosimilar and interchangeable products are to be quickly identified and controlled. The

absence of lot number information in AERS case reports was specifically identified as a data limitation that hampered risk analysis. (GAO-11-95 FDA Response to Heparin Contamination, Oct 2010)

- *Bar coding and control of counterfeiting*. Concerns about the impact of theft and counterfeiting on the integrity of drug supply have led to the establishment of systems to track drug supplies through bar coding. The logical extension for costly and critical biological products would be to extend a similar system to the patient level.
- *Promote recording of lot number in patient records*. Vaccine lot numbers are routinely entered in the patient record. This practice is of proven utility and practicality, and provides a clear precedent. An analogous approach to biological products is needed to protect public health in the setting of biosimilar products and interchangeable products. The potential of bar-coding technologies and electronic patient records should be fully exploited to this end. Thus, while a unique non-proprietary name is a *sine qua non* for the identification of the product, it is not sufficient. Optimal use of pharmacoepidemiologic methods depends on the ability to accurately characterize patient exposure through unambiguous product identification and recording of actual administration not only in a medical record, but also in standard insurance claims (as in the US NDC system that designates individual products) to a specific biological agent and to identify relevant individual safety outcomes in the same patients. Full identification of a biologic product administered to a patient should include not only the manufacturer but also the specific lot number.

- Systematic identification and categorization of relevant adverse events, particularly those of immunologic origin

Given the inherent immunogenicity of biological products, manifestations of hypersensitivity are a universal feature of their safety and tolerability profile. These manifestations are diverse and reflect a variety of immunopathologic mechanisms. The ability to evaluate safety profiles of biosimilar and interchangeable biologic products depends on the development of consistent practices for collecting relevant adverse event data and further standardization of terminology and coding practices. Standards with respect to criteria for defining and coding conventions should be introduced in clinical development so that manifestations of hypersensitivity can be consistently evaluated across biological products as safety endpoints. The consequences of the lack of such standards are reflected current product labels for biological products, many of which carry black boxes for hypersensitivity reactions, but non-standardized and inconsistent terminology makes it impossible to understand the precise manifestations, their nature, severity or frequency.

Question 3. If each product were given a unique nonproprietary name, should a distinguishing prefix or suffix be added to the nonproprietary name for a related biological product that has not been demonstrated to be biosimilar, a biosimilar product, or an interchangeable product to

facilitate pharmacovigilance? What factors should be considered to reduce any negative impact on the healthcare delivery system related to unique nonproprietary names for highly similar biological products?

As suggested above it will be essential for safety surveillance to identify precisely the product administered to a patient, including not only the manufacturer but the lot number of the biosimilar or interchangeable product. This is of overriding importance for patient safety and for the conduct of pharmacoepidemiologic investigation. The logical consequence is that health care professionals should be to be fully informed as to the precise product administered, its relationship to the reference product and the identity of its manufacturer. An example would be the ability to identify the manufacturer of an interchangeable product for an adverse event report within AERS. Given the sensitivity of biologics to subtle changes in manufacturing, and the assumption of interchangeability in particular, biosimilar and interchangeable products must be subject to continuous assessment and reevaluation.

Question 4. What safeguards should the agency consider to assist the healthcare community when prescribing, administering, and dispensing biological products to prevent unsafe substitution of biological products?

Safety information relating to hypersensitivity should be presented in a uniform manner in the product label. It is likely however that the accrual of information will invariably be ahead of labeling changes. Consideration should be given to providing appropriate access to evolving post-marketing data on biosimilar and interchangeable biological products for methodologically sound pharmacoepidemiologic surveillance. How such an approach might work in practice could be informed by experience with the Sentinel Initiative and also with clinicaltrials.gov.

Conclusion

The International Society of Pharmacoepidemiology regards pharmacoepidemiology as critical to the safety monitoring, risk evaluation and risk mitigation for biosimilar and interchangeable biological products. To optimize the potential of observational studies, biological product exposure down to the manufacturer lot number should be recorded in the medical record at each administration. This approach builds on existing practices with blood products and vaccines.

Secondly, much of the safety profile and tolerability of biological products reflects immunological responses to exposure. Standards need to be set with regard to information collection, coding and terminology, data analysis, and presentation of clinical manifestations of immunological mechanisms in the product label. FDA can promote optimal pharmacovigilance practices for marketed biosimilar and interchangeable biological products by taking steps to support the availability of data needed for pharmacoepidemiologic analyses.