



BIO Principles on the Substitution of Biologic Products

Biologics are complex medicines manufactured from living organisms. Unlike traditional “small molecule” drugs, biologics are not chemically synthesized but rather are manufactured from living cells by programming a particular cell line to produce a desired therapeutic substance in a highly controlled sterile environment. Each individual biologic therapy is a complex, heterogeneous mixture, which in many cases cannot be well characterized by current science. Because of this complexity, even minor differences in manufacturing processes can cause variations in the end product. Consequently, two biologics made using different cell lines and differing manufacturing processes will rarely, if ever, be exactly the same.

Follow-on biologics, or “biosimilars,” are biologic products manufactured using different cell lines and manufacturing processes with the goal of closely mirroring the composition and treatment profile of an innovator product produced by another company. Due to the innate complexity of biologics in general, however, the production of biosimilar products will invariably lead to some differences between the composition of a biosimilar and the original innovator product, and these differences could potentially lead to clinical differences in a patient’s experience or reaction. In other words, unlike generic copies of traditional small molecule drugs, biosimilar biologic products will be therapies that are similar to, but not the same as, an innovator therapy.

Currently, the Federal Food and Drug Administration (the “FDA”) is developing guidance regarding the regulatory pathway for the approval of biosimilar and interchangeable biologic products. This approval pathway was established by federal law, and distinguishes clearly between biologic products that are “biosimilar” to an innovator biologic – meaning they are “highly similar” to an innovator product – and biologic products that meet a heightened standard to be deemed “interchangeable.” The standard for interchangeability in the law is a stringent one; one that is consistent with the FDA’s role in protecting patient safety. In order to deem a biologic product interchangeable with an innovator product, FDA must determine that a biologic is not only “biosimilar,” but also that it “can be expected to produce the same clinical result as the [innovator] product in any given patient.” Further, if a patient might be switched back and forth between two products, the FDA must determine that there is no additional risk in such switching compared to using the innovator product alone.

While FDA’s role in the approval of biologic and biosimilar medicines includes the designation of an interchangeable status, the policy on whether one biologic product may be substituted by dispensers when a different biologic product was prescribed is governed by state law. As such, the introduction of biosimilar and interchangeable biologics into clinical practice will present some new challenges that have not historically been present with small molecule generic medicines. In considering patient safety and pharmacovigilance monitoring, current state rules on substitution will very likely need to be updated or completely re-written in the context of biosimilar and interchangeable biologic medicines.

BIO believes that a sound policy in each state outlining parameters for safe substitution of interchangeable biologics is the best option to ensure patients have access to high-quality, safe, and effective biologic medicines. BIO’s core concerns are to safeguard patient safety and the primacy of the physician-patient relationship, recognizing that treating physicians and their patients are in the best position to determine appropriate therapies. BIO believes the FDA will develop appropriate standards for the approval of safe biosimilar and interchangeable biologic products in order to best protect patient safety. To ensure transparency and communication between patients and their treatment teams, however, BIO also believes that certain safeguards should guide substitution policies for interchangeable biologics under state law as well. The principal safeguards necessary for states to address include:



- Substitution should occur only when the FDA has designated a biologic product as interchangeable. Only in this situation can patients and their physicians be assured that all reasonable efforts have been undertaken to assess the possible adverse effects on a patient, in terms of diminished safety or effectiveness, when one biologic product is substituted for another. In these cases, the FDA will have more thoroughly evaluated the possibility for immunogenic reactions, side effects, and other safety or efficacy differences to help ensure that a patient will react favorably to a given treatment if there is a substitution of an interchangeable biologic for an innovator product, or vice versa.
- The prescribing physician should be able to prevent substitution. The prescribing physician is in the best position to evaluate a patient's treatment history and options, and thus it is important for the treating physician to be able to designate exactly which product he/she believes should be dispensed to the patient. Product determinations should include a patient's values and preferences following informed discussion of the interchangeable biologic product's risks, benefits, and uncertainties. By permitting prescription pads to contain the phrase "dispense as written," or "brand medically necessary," the physician can control the delivery of biologic products at the outset and be better able to manage potential patient side effects.

In addition to these two principal safeguards, which BIO believes to be a necessary inclusion for interchangeable biologics in every state, several other patient protections should be considered as well. Additional safeguards can help to ensure transparent discussion between the patient and pharmacist at the point of dispensing, as well as ensure all appropriate parties are included in the patient's care continuum so that any downstream reactions can be documented and appropriately addressed. These patient protections include:

- The prescribing physician should be notified of the substitution. Even though interchangeable biologics will be "expected" to produce the same clinical result, it remains the case that patients could react differently to an interchangeable biologic than if they were given the innovator product due to the complex nature of biologic products and how they work in the human body. In these circumstances, the treating physician must know that the products were substituted at the point of dispensing in order to appropriately assess a patient's experience and further treatment options. Moreover, it is in the interest of public health to be advised of which biologic is being administered as it will facilitate attribution to the proper product for adverse event reporting.
- The patient, or the patient's authorized representative, should, at a minimum, be notified of the substitution. Often times patients managing chronic medical conditions have tried multiple treatment regimens with their physician to get to a point of comfortably managing the condition while minimizing side effects to the greatest extent possible. In these cases, patients are generally aware of which treatments work best in their unique circumstances. Providing notice to the patient, or in some cases – depending upon current state law – requiring patient consent, of the intent to switch gives that patient the opportunity to discuss with the pharmacist or physician past treatment experiences so that any potential future problems can be avoided.
- The pharmacist and the physician should keep records of the substitution. Because many biologic medicines are used to treat chronic conditions that can change over time, it is important for a patient's treatment team to have records that document how and when a patient was treated with biologic therapies. These records will also provide insight down the road should an adverse reaction or disease evolution occur.

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