



Summary of Lilly Position on Biosimilars

Biological products are medicines that are manufactured using a living system. A biosimilar is a subsequent version of an original biological product that is similar to the original product but not identical to it. Biosimilars are approved based on an abbreviated data package, in contrast to the full testing required of the originator biological product. Lilly supports the development and approval of new medical technology such as biosimilars that can benefit patients. However, given the difficulty and complexity of developing and manufacturing biological products, policies for approval of these products with an abbreviated data package must proceed carefully with patient safety at the forefront and respect for the innovator's intellectual property.

This summary document sets forth Eli Lilly and Company's positions on matters of public policy related to biosimilars. We recognize that emerging laws and regulations for biosimilars may be inconsistent with Lilly's policy positions in some respects. When developing or commercializing a biosimilar, Lilly will follow applicable laws and regulations as required and consistent with Lilly's priority to protect patient safety.

Regulatory Approval

Biosimilar products have an important role to play in the healthcare system for the benefit of patients, provided that they are approved based on rigorous, science-based standards. The regulatory approval pathway for biosimilars should be transparent, and the policies applicable to development and commercialization of biosimilars should be developed with input from relevant stakeholders. The timing of bringing a biosimilar to market must account for the valid intellectual property of the original (or "reference") biological product.

Biosimilarity

Biologics are large, complex medicines produced in a living system. These large molecules are especially sensitive to changes in the process used to manufacture the active component, the formulation and the conditions associated with enclosing and storing the finished product. Therefore, biosimilar versions of these large-molecule medicines cannot be based on the same type and amount of comparative data needed for approval of generic copies of simpler small-molecule medicines. Rather, in order to ensure patient safety, biosimilarity requires much more extensive comparative assessments, including non-clinical and clinical data, to demonstrate that the respective biological products are similar with no clinically meaningful difference in safety or efficacy. The biosimilar should have the same route of administration, dose form and strength as the reference biological product. The delivery device for the biosimilar may differ from the reference biological product provided that the differences have no impact on efficacy or safety.

Countries with Insufficient Regulatory Standards

Many countries and regions have enacted or are considering laws to authorize a pathway for regulatory approval of biosimilar medicines. Most major markets have adopted standards that are generally in line with World Health Organization (WHO) recommendations on biosimilars. However, some countries have policies or practices to approve an alternative version of a brand name biologic, whereby the alternative version may be marketed as a "similar" version of the branded biologic, but without requiring a sufficiently rigorous comparative evaluation. Without such an evaluation, these products pose risks to patient safety and should not be considered as "biosimilar."

Intellectual Property

Lilly supports strong laws for patent procurement and enforcement, as well as meaningful periods of data exclusivity for all medicines, including biologics. Patient access to biosimilars must be appropriately balanced with policies that protect

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intellectual property and provide incentives for research and innovation. When developing and commercializing our products, including biosimilars, Lilly will respect the valid patent and data exclusivity rights of third parties.

Active Component

The active component is the portion of the biological molecule or protein that is responsible for the intended pharmacological effect of the medicine. As one aspect of demonstrating **biosimilarity**, it is generally expected that analytical and structural data would show that the primary sequence of amino acids for the protein is the same as for the reference biological product. Therapeutic proteins also may have other important structural characteristics, including secondary and other higher order structures that may determine the protein's biological effect. To achieve biosimilarity, there should be no meaningful differences identified in any higher order structures, although it may not be possible to rule out such differences for two biologics made by unrelated manufacturers. This potential limitation in fully characterizing higher order structures for proteins is one reason that the active ingredients of two biologics produced by unrelated manufacturers cannot be considered to be identical.

Compendial Monographs

Product-specific monographs typically provide a set of specifications that are meant to determine the identity and quality of a particular medicine. For biological products, it is possible that two medicines made by unrelated manufacturers could meet the specifications of the same monograph. This might give the impression that the products are the same, whereas in fact the products are at most similar. Therefore, Lilly opposes the development of product-specific compendial monographs in situations where a single monograph can apply to biological active ingredients made by unrelated manufacturers.

Bioequivalence

Biosimilar products are not "bioequivalent" to the reference product. Bioequivalence is based on a comparative assessment of two products with the same active ingredient. In the case of biological products, two or more respective products produced by unrelated manufacturers are not considered to be the same. Therefore, "bioequivalence" is not an appropriate term to use in reference to biosimilar studies, even though biosimilar development may include comparative pharmacology trials that are designed based on scientific standards and criteria associated with small molecule bioequivalence studies.

Comparability versus Similarity

A sponsor that makes a change to the manufacturing process for its approved biologic product must demonstrate that there is no meaningful difference in the product as produced before and after the process change. If there is no meaningful difference, the product has demonstrated "comparability" and will continue to be distributed with the same name and label after the process change. The manufacturer's ability to do this comparability assessment and continue marketing the same product with no change in product information relies on the proprietary knowledge and experience of the manufacturing process and how process changes relate to quality, safety and efficacy over time.

Although many of the process steps are the same, the comparability exercise is fundamentally different than the biosimilarity exercise. Biosimilarity involves a comparative assessment of a biological product to a reference biological product in which the biosimilar is produced by a manufacturer that is unrelated to the manufacturer of the reference product. The biosimilar manufacturer lacks the proprietary information and processes regarding the reference product that would be needed to demonstrate comparability. Therefore, demonstrating biosimilarity can establish that the product is similar but not "comparable" and not the same. A similar product must be distributed with differences in the product information (see **Naming** and **Labeling** sections below) so that healthcare professionals and patients can clearly distinguish the similar product from the reference product.

Naming

Non-proprietary names, sometimes referred to imprecisely as the "generic name," for biosimilars should be distinguishable from the non-proprietary name of the reference biological product or other biological products. Having a similar but distinguishable name for the biosimilar product is consistent with the key principle of biosimilarity that the

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active component is similar, but not the same as, the reference product. Distinguishable names also will help to avoid inadvertent product substitution. As an additional measure to avoid inadvertent substitution at the point of dispensing, each biosimilar product should have its own brand name, and prescriptions for biological products should be based on brand names rather than non-proprietary names.

Substitution

Substitution is the practice of dispensing a biosimilar to a patient who was prescribed the reference biological product, or dispensing the reference product to a patient who was prescribed the biosimilar, without the consent of the prescriber. For example, this could occur upon a patient's initiation of therapy with the biological medicine, or at a later time upon dispensing or administration of a biosimilar to a patient who has been receiving the reference product for some period of time. Unless a regulatory authority determines the biosimilar to be **interchangeable** based on scientific data, Lilly opposes substitution because it deprives the physician and patient of making the decision of which product(s) are best for the patient. Biosimilars are similar, but not the same as the reference biological product, and therefore the prescriber and patient should determine whether the biosimilar is an appropriate treatment for the patient. Most countries and regulatory authorities do not recommend substitution of biosimilars.

Interchangeability

Interchangeability can have varying meaning around the world. In the U.S., interchangeability is a scientific determination made by the governing regulatory authority (FDA) to facilitate "automatic substitution," which occurs when a pharmacy receives a prescription for the originator biological product but dispenses the biosimilar in place of the originator product. Automatic substitution may be done without the prior consent of the prescribing physician and without medical supervision. In the U.S., interchangeable biological products must be shown to produce the same clinical result as the reference product in **any given** patient. Risks of alternating or switching between use of the proposed interchangeable product and the reference product must not be greater than the risk of using the reference product without alternating or switching. In the EU and most other regions and countries, "interchangeability" means that prescribers can safely switch to a biosimilar in place of the reference biological product at the initiation or during a course of therapy. In Europe a decision on "interchangeability" is not made formally by the European Medicines Agency but it is left to the local authorities. Many countries do not have specified data requirements or a process to formally evaluate data for interchangeability. Switching a patient's therapy in this situation would include medical oversight by the prescriber. The practice of pharmacy substitution of biosimilars without medical oversight, or "automatic substitution," is prohibited in most EU member states. There are no widely accepted criteria or processes to determine when automatic substitution of biosimilars is appropriate, although a small number of countries permit this practice without any formal laws or guidelines.

Lilly's position is that interchangeability determinations should be based on a higher scientific standard than biosimilarity, including a clinical demonstration of safety for patients who are switched back and forth between the biosimilar and reference products without their knowledge. In addition, interchangeability should be considered only when the biosimilar product has first obtained approval under principles of biosimilarity for all indications approved for the reference product. Also, interchangeability should be considered only when the biosimilar can demonstrate a safety profile in line with the reference product after a substantial period of post-marketing experience with the biosimilar. Interchangeable biosimilars also should have a delivery device that is functionally equivalent with, and has essentially the same instructions for use as, the reference product device.

Access to Biosimilars

Health care payers make policy that determines what medicines will be available within a health system, and how those medicines will be priced and reimbursed. Many factors influence these policy decisions, including science, cost and other practical issues. Policies on access to biosimilars should be patient-centered, grounded in science and compatible with continued incentives for innovation. Also, policies should not be adopted if they have the effect of forcing providers and patients to switch among **non-interchangeable** versions of biological products. A decision to switch to a biosimilar product should be based upon a decision by the prescriber and patient. Pricing, payment and access practices or policies that effectively remove the ability of the prescriber and patient to choose among the reference biological product and biosimilar are not in the best interests of patients.

Labeling

The labeling or other available product information for a biosimilar should identify the product as having been approved under biosimilarity standards, and should include summaries of the comparative clinical and non-clinical data essential to approval. The labeling or other available product information for a biosimilar also should explain the extent to which any indications were approved based on extrapolation, and should summarize the scientific justification for extrapolation. The labeling or other available product information also should highlight any approved indications of the reference product for which the biosimilar is not approved. Otherwise the biosimilar label and other available product information should be consistent with the reference product.