INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Biosimilars and Interchangeables***
-October 2023-

Background:

Biologics are the fastest-growing class of medications in the United States and account for a substantial and growing proportion of health care costs. Examples of biologics include therapeutic proteins (e.g. insulins, monoclonal antibodies growth factors, enzymes), vaccines, blood and blood components. All FDA-approved biologics undergo a rigorous evaluation to help ensure their safety, effectiveness, and quality. There are two approval pathways for biologics under the Public Health Service Act. A biological product approved in a stand-alone biologics license application (BLA) under section 351(a) of the Public Health Service Act must contain data to demonstrate its safety and effectiveness and can serve as a reference product for biosimilar biological products. A biosimilar biological product is approved under a 351(k) BLA through an abbreviated pathway that generally avoids the need to conduct as many costly and lengthy clinical trials. A proposed biosimilar product is compared to and evaluated against a reference product to verify that it is highly similar to and has no clinically meaningful differences in terms of safety, purity, and potency (i.e., safety and effectiveness) from the reference product. FDA has approved biosimilars to treat many conditions such as chronic skin and bowel diseases, arthritis, kidney conditions, diabetes, multiple sclerosis, macular degeneration, and cancer. The intent of this review is to inform the Indian Health Service about the scientific and regulatory considerations for approving 351(k) products and to share helpful resources for healthcare providers.

Discussion:

Biosimilars must have the same route of administration, dosage form, and strength as the reference product. They must be manufactured according to standards designed to assure that the product is safe, pure, and potent- these quality standards are the same for all biological products. A biosimilar can only be approved for the same conditions of use (e.g., indications, dosing regimen) that were previously approved and described in reference product labeling. Biosimilars can have minor differences from their reference products in clinically inactive components (e.g., formulation excipients). They may also have a different presentation from that approved for the reference product. An interchangeable biosimilar product is a biosimilar that has been shown to meet other requirements under the law and may be substituted for the reference product without the requirement to consult the prescriber. The substitution may occur at the pharmacy, subject to state pharmacy laws which vary by state, a practice commonly called “pharmacy-level substitution” - similar to how generic drugs are substituted for brand name drugs. A biosimilar is as safe and effective as an interchangeable to the same reference product. *Interchangeability is not a higher standard than biosimilarity*. Rather, it incorporates additional assessments to support the potential for pharmacy substitution, which may not be relevant for every product class. Business or other reasons may influence whether manufacturers may seek interchangeability.

The FDA’s approval of a biosimilar product is based on a comprehensive review of scientific evidence demonstrating it is highly similar to and has no clinically meaningful differences with the reference product. This evidence includes comparisons of the products on an analytical level using an extensive battery of physicochemical and biological tests. These tests use reliable, precise methods to provide data which support the structural and functional similarity of the proposed product to the reference product and to evaluate the impact of any observed differences. Analytical studies are generally more sensitive than clinical studies in detecting differences between products, should differences exist. Comparative clinical studies are also conducted and may include clinical pharmacology studies to demonstrate that the proposed biosimilar moves through the body in the same way and provides the same effects as the reference product (e.g., pharmacokinetic or pharmacodynamic endpoint studies) and clinical immunogenicity studies to compare immune responses to the reference product or proposed biosimilar. Other comparative clinical studies may be conducted to address any remaining uncertainty about whether the proposed biosimilar has any clinically meaningful differences from the reference product. There is no one-size-fits-all approach to the clinical data that would support biosimilarity or interchangeability. The FDA has discretion to determine that certain assessments are unnecessary in a proposed application. For example, the FDA determined that comparative immunogenicity studies were unnecessary for biosimilar and interchangeable insulin products[1]. Applicants may choose to do or submit more to the FDA than what the FDA expects to support approval. More clinical data in an application does not mean that one biosimilar or interchangeable product is “better” than another approved biosimilar or interchangeable product. The FDA evaluates all the data and information together to determine whether the evidence supports biosimilarity.

The FDA may approve a biosimilar for indications or populations without direct clinical studies in those indications or populations because there is sufficient data and information in the application to support that the biosimilar or interchangeable will have the same treatment risks and benefits as the reference product in every indication that was previously approved for the reference product. The FDA encourages 351(k) applicants to seek licensure for all the

reference product's licensed conditions of use (e.g., indications) when possible. However, a variety of circumstances like orphan drug exclusivity or patent protection may be why a biosimilar is licensed for fewer indications than are approved for the reference product. If the FDA is concerned that a proposed product would not have the same risks and benefits as the reference product, it would not be approved as a biosimilar.

Biosimilars and interchangeables can be used in patients who have previously been treated with the reference product (i.e., treatment-experienced), as well as in patients who have not previously received the reference product (i.e., treatment-naïve). Since patients may be switched to a biosimilar once it becomes available, the FDA would not approve a biosimilar if there were concerns about switching. Misconceptions exist about increased safety risks when switching to a biosimilar. The FDA undertook a systematic review to add to the body of evidence that addresses these concerns. Herndon et al.[2] identified 5,252 patients who underwent at least one switch to or from a biosimilar and its reference biologic as part of randomized controlled studies or extensions of controlled studies and 5,770 patients who served as no switch controls. A meta-analysis from these studies was conducted and no differences in terms of major safety parameters such as deaths, serious adverse events, or treatment discontinuations were observed when patients were switched (to or from a biosimilar and its reference biologic) or not switched. Immunogenicity and immune-related adverse events were similar in switched and non-switched patients. Overall, this work adds to the publicly available information that supports there are no safety or immunological concerns when switching between a biosimilar and its reference product[3,4,5].

Nonproprietary names of biosimilar and interchangeable products have the same core name as their reference product plus an additional (or different) distinguishing 4-letter suffix devoid of meaning to help with product identification. Biosimilar and interchangeable labeling summarizes the information needed for safe and effective use. They are not required to have the same labeling as the reference product. For example, there may be some differences in how the reference product, biosimilar, or interchangeable should be prepare and stored. However, the labeling will incorporate other relevant data and information from the reference product labeling.

The Purple Book database of licensed biological products is a resource that provides key information about reference biologics, and any approved biosimilars and interchangeable[6]. Simple or advance search results summarize product information including: approved strengths, routes of administration, dosage form, approved labeling, and more.

The FDA is committed to developing effective communication about biosimilars and interchangeable to key stakeholders and, as such, has published educational materials for patients and healthcare providers in multiple languages[7], a curriculum for health care degree programs[8], and Medscape continuing education courses.

Findings:

Supporting a competitive marketplace for biologics, including biosimilar and interchangeable products, is essential for improving patient access to medicines and potentially reducing health care costs. The FDA's scientific experience with biosimilar and interchangeable products has grown, and with it, expectations about data to support approvals continues to evolve. Biosimilars and interchangeables are as safe and effective as the reference product to which they were compared, regardless of the amount of clinical data described in the reviews which supported approval. Biosimilars and interchangeables have the same treatment risks and benefits as their reference product. All FDA-approved biological products (biologics), including biosimilars and interchangeable, undergo a rigorous evaluation so that health care providers and patients can be confident of the safety, effectiveness, and quality of these products.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

References:

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6. Database of Licensed Biological Products: https://purplebooksearch.fda.gov/
7. Biosimilar Overview for Health Care Professionals: https://www.fda.gov/drugs/biosimilars/overview-health-care-professionals
8. Biosimilar Curriculum Materials for Health Care Degree Programs: https://www.fda.gov/drugs/biosimilars/curriculum-materials-health-care-degree-programs-biosimilars