Key Terms & Concepts

Level 1: Biosimilar Foundational Concepts

Key Terms & Concepts Related to Biosimilar and Interchangeable Products

Term or Concept	Definition
351(a) Pathway	The regulatory pathway for originator biological products evaluated for licensure (approval) under Section 351(a) of the Public Health Service Act. A reference product is approved in a standalone 351(a) biologics license application (BLA), which must contain all data and information necessary to demonstrate the product's safety and effectiveness and generally includes data from clinical trials conducted in the relevant patient populations for each of the treatment indications being sought by the manufacturer. Upon approval, an originator biologic may later be used as the reference product against which a proposed biosimilar product is evaluated under the 351(k) abbreviated pathway.
351(k) Pathway	Abbreviated pathway for approval of biosimilar and interchangeable biosimilar products established by the Biologics Price Competition and Innovation Act in 2010. The goal of a biosimilar development program is to demonstrate biosimilarity between the proposed biosimilar and its reference product, not to independently establish the safety and effectiveness of the proposed biosimilar. This generally means that biosimilar manufacturers do not need to conduct as many expensive and lengthy clinical trials. A biologics license application (BLA) submitted for licensure (approval) of a biosimilar under section 351(k) of the Public Health Service Act includes information which aims to demonstrate that the biosimilar or interchangeable biosimilar product: • Is highly similar in structure and function to an FDA-approved reference product notwithstanding minor differences in clinically inactive components • Uses the same mechanism(s) of action for the proposed condition(s) of use – but only to the extent the mechanism(s) are known for the reference product • Proposes condition(s) of use that have been previously approved for the reference product • Has the same route of administration, dosage form, and strength as the reference product • Is manufactured, processed, packed, or held in a facility that meets standards designed to assure that the biologic continues to be safe, pure, and potent
Biological Product (Biologic)	Biologics are generally large, complex molecules that are made from living sources such as bacteria, yeast, and animal or plant cells. This makes biologics different from other medications, which are typically made from chemicals. Biologics include a wide range of products such as vaccines, monoclonal antibodies, blood components, allergenics, gene therapy, tissues, and proteins. They are used to treat a variety of diseases and conditions, such as cancer, kidney diseases, and autoimmune diseases.
Biologics License Application (BLA)	An application for FDA approval of a biological product (biologic). A BLA submission contains specific information on the manufacturing processes, chemistry, pharmacology, clinical pharmacology, and medical effects of a biologic product. If the information provided meets FDA requirements, the application is approved and a license is issued allowing the firm to market the product. All FDA-approved biological products including biosimilars and interchangeable biosimilars, undergo a rigorous evaluation so that health care providers and patients can be confident of the safety, effectiveness, and quality of these products.

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Biosimilar Product (Biosimilars)	A biologic medication that is highly similar to and has no clinically meaningful differences in terms of safety, purity, and potency (safety and effectiveness) from an existing FDA-approved biologic, called a reference product.
Comparative Analytical Assessment	The data analysis from comprehensive, robust comparative physicochemical and functional studies (e.g., biological assays, binding assays, enzyme kinetics) conducted by the manufacturer to evaluate and compare quality attributes identified in the proposed biosimilar product and the reference product. These highly sensitive assays help provide information and assurance about the identity, quality, safety, purity, and potency of the proposed biosimilar in comparison to the reference product.
Formulary	A list of prescription drugs (including biologics) covered by a prescription drug plan or another insurance plan offering prescription drug benefits. Also called a drug list.
Generic Drugs	A generic drug is a medication created to be the same as an already marketed brand-name drug in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use. The main difference between biosimilars and generic drugs is that the active ingredients of generic drugs are generally smaller, simpler, and more straightforward to copy.
Immunogenicity	The propensity of a therapeutic protein product or applicable drug product (e.g., peptides, oligonucleotides) to generate an immune response to itself, a related structure, or product complex or to induce immunologically related adverse clinical events.
Interchangeable Biosimilar Product (Interchangeable)	A biosimilar that, depending on state pharmacy laws, may be substituted for the reference product at the pharmacy without the intervention of the prescribing health care professional (similar to how generic drugs are routinely substituted for brand-name drugs). Not all biosimilars are interchangeable. Companies must submit an application with adequate information to support an interchangeability determination for their product to be approved as an interchangeable biosimilar. In addition to establishing biosimilarity, interchangeable biosimilar manufacturers generally conduct a switching study in which patients alternate between the reference product and the proposed interchangeable biosimilar multiple times over a specific period of time and are compared to patients who are just being treated with the reference product. The results must show no decrease in effectiveness or increase in risk associated with switching between the products.
Lot-to-Lot Variation	Variation inherent in biologics and impacted by the manufacturing process wherein different lots of biological products contain millions of slightly different versions of the same protein or antibody. Inherent variations occur in both reference products and biosimilars, where the same protein may have many slightly different versions in a single lot (e.g., variation typically occurs in glycosylation). These slight differences between manufactured lots of the same biological product (i.e., acceptable within-product variation) are normal and expected within the manufacturing process. As part of its review, FDA assesses the manufacturing process and the manufacturer's strategy to control within-product variations. These control strategies are put in place to help ensure that manufacturers produce biological products with consistent clinical performance.

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Nonproprietary Name (Proper Name)	A name unprotected by trademark rights that is in the public domain. The proper name of a biological product is a combination of the *core name* and a distinguishing suffix that is devoid of meaning and composed of four lowercase letters (e.g., -cznm, -hjxf). *Core name* refers to the component shared among an originator biological product and any related biological product, biosimilar product, or interchangeable biosimilar product as part of the proper names of those products. Two examples of a core name are “filgrastim” and “epoetin alfa.”
Orthogonal Methods	Independent techniques for measurement of the same quality attribute. Biosimilar product manufacturers use multiple orthogonal methods for assessment of quality attributes with high sensitivity and accuracy.
Pharmacodynamics (PD)	The study of (or data on) the relationship between drug exposure, such as dosage levels, and the body’s subsequent response.
Pharmacokinetics (PK)	The study of (or data on) how the body absorbs, distributes, metabolizes, and excretes a product.
Pharmacovigilance	The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.
Product-related Substances and Product-related Impurities	Molecular variants of the desired product formed during manufacture or storage which are active and have no deleterious effect on the safety and efficacy of the drug product. These variants possess properties comparable to the desired product and are not considered impurities. Certain molecular variants of the desired product (e.g., precursors, some degradation products) do *not* have properties comparable to those of the desired product with respect to activity, efficacy, and safety. These variants are considered product-related impurities.
Proprietary Name (Brand Name)	The trademark or brand name of a product.
Process-related Substances	Impurities that are derived from the manufacturing process. They may be derived from cell substrates (e.g., host cell proteins, host cell DNA), cell culture (e.g., antibiotics, media components), or downstream processing (e.g., processing reagents).
The Purple Book Database of Licensed Biological Products (“The Purple Book”)	An online, searchable database that contains information about FDA-licensed (approved) biological products (biologics). The Purple Book also contains information about whether there are any licensed biosimilar and interchangeable products for a given reference product. The Purple Book database contains information on all FDA-licensed (approved) biological products regulated by the Center for Drug Evaluation and Research (CDER), including licensed biosimilar and interchangeable products, and their reference products. The Purple Book also contains information about all FDA-licensed allergenic, cellular and gene therapy, hematologic, and vaccine products regulated by the Center for Biologics Evaluation and Research (CBER).
Quality Attributes	Physical, chemical, and biological characteristics that should be within an appropriate limit, range, or distribution to ensure the desired product’s quality. For biosimilar and interchangeable biosimilar products approved through the 351(k) abbreviated approval pathway, these attributes are carefully selected to support FDA’s assessment whether a proposed biosimilar is highly similar in terms of its molecular structure, bioactivity, and purity to its reference product.

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Reference Product	A reference product is a biological product that has been approved in a stand-alone application that contains all data to demonstrate the product's safety and effectiveness for each of the indications being sought by the manufacturer and is the product against which a proposed biosimilar is evaluated. Biosimilars are evaluated for approval based on all the evidence presented by the manufacturer.
Route of Administration	A way of administering a drug to a site in a patient (e.g., intravenous, subcutaneous).
Totality of the Evidence	The approach used by FDA to evaluate the applicant's structural, functional, and clinical data collectively to determine whether no clinically meaningful differences exist in a proposed biosimilar product's quality, safety, or efficacy as compared with the reference product.