

OVERVIEW OF BIOLOGICS AND BIOSIMILARS

Drugs are typically manufactured through chemical synthesis and generally have well defined structures. Generic drugs are approved following the brand drug, having the same active ingredient, strength, dosage form, route of administration, and bio-equivalency. The FDA then determines if the generic is therapeutically equivalent to the brand drug allowing interchangeability. In contrast, biologics are manufactured in living sources, and are often very large, complex molecules such as proteins. Therefore, the "generic" versions or biosimilars of these biologic products are more complex when manufacturing and thus being able to determine therapeutic equivalence. This overview highlights certain characteristics of biologics and biosimilars.

	Biologics	Biosimilars
Definition	<ul style="list-style-type: none"> A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings Referred to as the reference, pioneer, or innovator biologic 	<ul style="list-style-type: none"> The biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences* between the biological product and the reference product in terms of the safety, purity, and potency of the product Referred to as follow-on biologic
Properties	<ul style="list-style-type: none"> Derived from living sources such as cells Complex mixtures whose active ingredients (usually proteins) are hundreds of times larger than the compounds found in most pills Mostly given by injection due to unstable environmental conditions 	<ul style="list-style-type: none"> The active ingredient of biosimilars closely resemble the reference biologic However, they are not identical, generic equivalents due to differences in manufacturing processes, protein source, and extraction/purification processes
Approval Process	<ul style="list-style-type: none"> Submitted through the BLA process Requirements: <ul style="list-style-type: none"> Applicant information: Includes name and addresses of manufacturing facilities Product/Manufacturing information: Source material/raw material; manufacturing process and controls; formulation; facility information; contamination/cross-contamination information; environment assessment or categorical exclusion Pre-clinical studies: Safety, efficacy, and use Clinical studies: Safety, efficacy, and use Labeling: Safety, efficacy, and use 	<ul style="list-style-type: none"> 2012 FDA Draft Guidance recommends a step-wise approach to demonstrate biosimilarity, submitted through an abbreviated BLA Requirements (<i>unless FDA deems unnecessary</i>): <ul style="list-style-type: none"> Structural analyses: Determine structural characteristics of the protein, post-translational modifications, and/or other potential variants Functional assays: Evaluate the pharmacologic activity of the protein (eg, potency and MOA) Animal studies: Include toxicity, PK and PD measures, and immunogenicity Clinical studies: Human pharmacology data, clinical immunogenicity assessment, and clinical safety and efficacy data to demonstrate safety, purity, and potency for the condition(s) the reference product is licensed and intended to be used for
Pharmacovigilance	<ul style="list-style-type: none"> Typically required to have postmarketing safety monitoring Includes the detection, assessment, understanding and prevention of adverse effects after the launch of the biologic onto the market 	<ul style="list-style-type: none"> Biosimilars should include postmarketing surveillance to address immunogenicity and potential rare adverse events when seeking approval May undergo more strict monitoring due to limitations of clinical data compared to the reference product

CLINICAL CONSIDERATIONS

Substitution: The FDA allows for generic substitution of chemical drugs if two products can be deemed therapeutically equivalent. Due to the complex nature of biologics and the potential for differing properties and characteristics forming between biologics and their respective biosimilars, it is important to make informed decisions about substituting biologics.

NOTES

Key: BLA = biologics license application; MOA = mechanism of action; PD = pharmacodynamic; PK = pharmacokinetic

*Clinically meaningful differences could include a difference in the expected range of safety, purity, and potency of the proposed and reference products. By contrast, slight differences in rates of occurrence of adverse events between the two products ordinarily would not be considered clinically meaningful differences.

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