

Unit 2: USA: Biologics and Biosimilars

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2.1 Introduction to biologics

American law draws the map of this unit in one definition. A **biological product** is defined in section 351(i) of the Public Health Service Act (PHSA) as a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, applicable to the prevention, treatment or cure of a disease or condition of human beings. The definition is a list because it predates the science: it gathers everything medicine makes from living sources, and its modern weight falls on the word **protein**, under which the recombinant and monoclonal antibody products of today are licensed. Administration is split between two FDA centres. The **Center for Biologics Evaluation and Research (CBER)** holds vaccines, blood and blood products, allergenics, cellular and gene therapies and related products. The **Center for Drug Evaluation and Research (CDER)** holds the therapeutic proteins, monoclonal antibodies and most follow on biologics of the modern market, a transfer made in 2003 that is why the biosimilar programme of section 2.6 is run largely from the drug centre. Either way, the licensing instrument is the same: a biologics licence under section 351 of the PHSA, granted only when the product is shown to be safe, pure and potent, and manufactured in a facility that meets the applicable standards, a statutory triad, safety, purity and potency, that is the American shorthand for the whole biologics philosophy.

2.2 Biologics, biologicals and biosimilars: the vocabulary

Three words circulate in the sources and the syllabus lists them because examinations test their boundaries. **Biologics** is the American regulatory term of art: the class licensed under the PHSA as just described. **Biologicals** is the wider, older term used by WHO and in European and Indian usage, covering the same family of products, vaccines, sera, blood products, biotherapeutics, without implying a particular statute; the two words overlap almost completely in substance and differ in legal address. A **biosimilar** is a comparative claim, not a product class: under section 351(k) of the PHSA, a biological product that is **highly similar** to an already licensed reference product notwithstanding minor differences in clinically inactive components, and that has **no clinically meaningful differences** from the reference product in terms of safety, purity and potency. The United States adds one further grade that no other system in this subject has: an **interchangeable** biosimilar, for which the applicant additionally shows that the product can be expected to produce the same clinical result in any given patient and that switching between the biosimilar and the reference product creates no greater risk than staying on the reference; interchangeability is the designation that permits a pharmacist to substitute the biosimilar for the prescribed reference product without consulting the prescriber, subject to state pharmacy law. India's similar biologic (Unit 1) corresponds to the biosimilar idea without the interchangeability tier, and the EU biosimilar (Unit 3) sits between the two in its treatment of switching, a comparison drawn together at section 3.3.

2.3 Different biological products

The class the definition gathers is best learned by its families, because each family's regulation later in this subject follows from what the product is. **Preventive vaccines** immunise healthy populations, which sets their safety expectations; **blood and blood components** are donated human material, regulated through the blood establishment system of Unit 4; **allergenic products** are standardised extracts for diagnosis and immunotherapy; **cellular therapies and gene therapies** carry living cells or genetic material as the active

substance; **therapeutic proteins**, from replacement enzymes and growth factors to monoclonal antibodies, form the commercial centre of the class and nearly the whole of the biosimilar story; and a residue of products, toxins, antitoxins, sera and probiotics among them, descends from the original list. The recurring regulatory trait is that identity, purity and potency cannot be fixed by chemical specification alone: potency is measured by **biological assay** against reference standards, and batches are understood through the process that made them.

2.4 Difference between a generic drug and a biosimilar

This comparison is the conceptual centre of the unit, and it is stated precisely. A **generic drug** contains the **same** active ingredient as its reference, identical in structure, and is approved on pharmaceutical equivalence plus **bioequivalence**, the demonstration that it reaches the body at the same rate and extent; no clinical efficacy trial is needed because identity plus exposure is taken to settle the outcome. A **biosimilar** contains a **highly similar**, never identical, active substance, because no second living process reproduces a protein exactly; bioequivalence in the small molecule sense cannot settle the outcome, so approval rests on a **comparability programme**: extensive analytical and functional comparison, targeted animal and clinical work, and a dedicated immunogenicity assessment, scaled by the stepwise logic of Unit 1. The legal instruments differ accordingly, the ANDA under the FD&C Act against the 351(k) licence under the PHSA; the exclusivity landscape differs, Hatch-Waxman's patent and exclusivity settlement against the BPCI Act's 12 year reference product exclusivity; and substitution differs, the generic being rated therapeutically equivalent and freely substitutable, the biosimilar substitutable at pharmacy level only if separately designated interchangeable. A table fixes the contrasts.

Point	Generic drug	Biosimilar
Statute and route	FD&C Act, ANDA under section 505(j)	PHSA, licence under section 351(k)
Active substance	Same molecule, identical structure	Highly similar protein, never identical
Basis of approval	Pharmaceutical equivalence and bioequivalence	Totality of evidence from a comparability programme
Clinical efficacy trial	Not required	Confirmatory comparison usually required
Immunogenicity	Not a routine issue	Central assessment in every programme
Substitution at pharmacy	Yes, on therapeutic equivalence rating	Only if designated interchangeable
Reference exclusivity faced	Hatch-Waxman patent and exclusivity scheme	12 years of reference product exclusivity (BPCI Act)

Generic drug beside biosimilar: the core contrast

Generic drug	Biosimilar
Same molecule, identical structure	Highly similar protein, never identical
ANDA under section 505(j)	Licence under section 351(k)
Equivalence plus bioequivalence	Comparability programme, totality of evidence
No efficacy trial required	Confirmatory clinical comparison
Freely substitutable	Substitutable only if interchangeable

Identity settles the generic; similarity must be built, layer by layer, for the biosimilar

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Figure: Same molecule and exposure proof on the generic side; highly similar protein and a totality of evidence comparability proof on the biosimilar side, with interchangeability as the extra American grade (Unit 2, section 2.4).

2.5 Laws, regulations and guidance on biologics and biosimilars

The statutory frame has three layers. The **Federal Food, Drug, and Cosmetic Act** supplies the general machinery, adulteration and misbranding, establishment registration, inspection, and the IND system under which biologics are clinically developed. The **Public Health Service Act**, section 351, supplies the licence: subsection (a) for the originator's full licence application, and subsection (k), added by the **Biologics Price Competition and Innovation Act 2009** (the BPCI Act, enacted with the Affordable Care Act 2010), for the abbreviated biosimilar licence, with its 12 years of exclusivity for the reference product and a first interchangeable exclusivity for the first interchangeable biosimilar. The implementing regulations sit in Title 21 of the CFR: Part 600 and following for biological product standards and establishment licensing, Part 601 for licensing procedure, and Part 610 for the general biological product standards, including the lot release provisions met in Unit 4. Below statute and regulation sits the **guidance** layer, which for biosimilars does most of the technical work: FDA guidance on scientific considerations in demonstrating biosimilarity, on quality considerations, on clinical pharmacology data, on interchangeability considerations, and on the formal meetings between FDA and biosimilar sponsors at which the stepwise programme is agreed. The user fee system for this programme is the Biosimilar User Fee Act (BsUFA), under which FDA accepts performance goals for the review of biosimilar applications in return for industry fees, as PDUFA does for drugs. Purple Book literacy from MRA201T completes the picture: it is FDA's public list of licensed biological products with their biosimilars, interchangeables and exclusivity dates.

2.6 Development and approval: IND, BLA, and the routes the syllabus names

Development begins, as for drugs, under an **Investigational New Drug** application (21 CFR Part 312): the biologics IND assembles the manufacturing description of the investigational product, the preclinical pharmacology and toxicology, and the protocols, and the stepwise biosimilar programme is discussed with FDA through the biosimilar product development meeting series before and during the work. Approval for the originator is the **Biologics License Application (BLA)** under section 351(a), a full dossier proving safety, purity and potency from the applicant's own data, reviewed by CBER or CDER according to the product family of section 2.1, and granted together with the **establishment licence** judgment that the manufacturing facility meets its standards; approval carries post marketing duties, adverse event reporting

under Part 600.80, and changes controlled through supplements graded by their effect on the product, in the PAS, CBE and annual report ladder of MRA102T. The biosimilar applicant files an abbreviated BLA under **section 351(k)**, relying on the public knowledge that the reference product is licensed and on its own comparability programme rather than on a full independent proof of benefit. The syllabus names three further routes, and the student should place them exactly. The **NDA** appears because a defined set of protein products, insulin and human growth hormone among them, were historically approved as drugs under NDAs; in March 2020 those approvals were **deemed to be biologics licences** by operation of the BPCI Act transition provision, so the class now lives entirely inside the BLA system. The **PMA** (premarket approval) and **510(k)** (premarket notification) are the device pathways of MRA203T, administered by CDRH; they enter a biologics syllabus because some products in the biological family, diagnostic blood grouping and infectious disease screening tests and certain combination products among them, are regulated through the device framework, and because the regulatory professional must be able to route any given product to its correct gate. The teaching point is routing discipline: drug, biologic or device is decided by the product's nature and primary mode of action, and the pathway follows the classification, not the sponsor's preference.

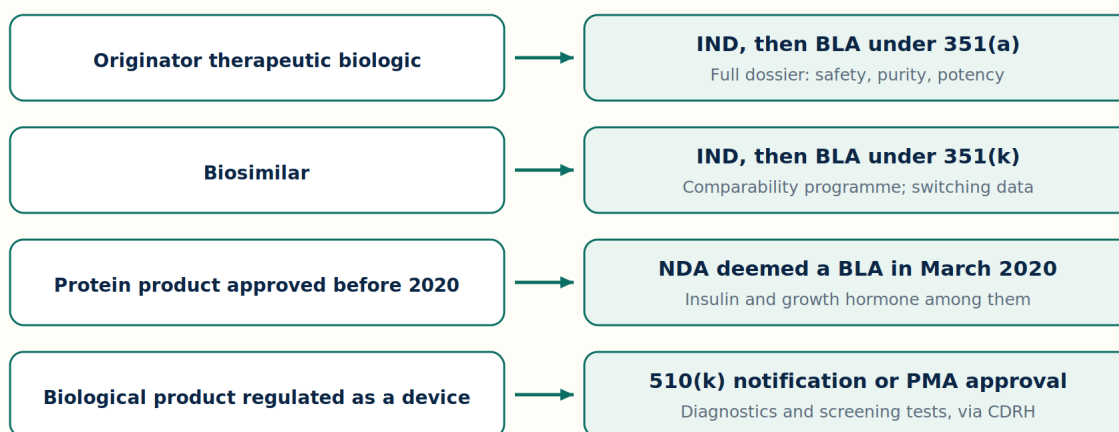
US approval routes named in this unit

Product under development

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|
+-- Therapeutic biologic, originator ..... IND, then BLA 351(a)
+-- Biosimilar ..... IND, then BLA 351(k)
|   (+ switching data for interchangeability)
+-- Protein product licensed before 2020 .... NDA, deemed a BLA
|   under the BPCI transition (March 2020)
+-- Biological product regulated as a device . 510(k) notification
|   (diagnostics, screening tests)           or PMA approval
  
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United States: the approval routes of this unit



Classification decides the gate: drug, biologic or device follows the product, not the sponsor

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Figure: The routes of section 2.6: the full BLA and the abbreviated 351(k) licence at the centre, the historical NDA population deemed licensed in 2020, and the device gates, 510(k) and PMA, through which device regulated biological products pass (Unit 2, section 2.6).

2.7 Pre-clinical and clinical development considerations

American expectations for the evidence mirror the stepwise principles of Unit 1, with three emphases of their own. First, **analytical similarity is the foundation** and is expected to be extensive: multiple lots of the biosimilar and of the United States licensed reference product, compared across structure, purity, charge and glycan profile and biological function with methods sensitive enough to find differences, because every

later reduction of animal or clinical work is argued from this base. Second, **animal studies are used sparingly and purposefully**, principally where they resolve a residual question of pharmacology or toxicity, reflecting both the comparability logic and the modern expectation that animal work must earn its place. Third, the **clinical** programme is built from a comparative pharmacokinetic and pharmacodynamic study where a PD marker exists, a confirmatory comparative clinical study in a population sensitive to differences, and an immunogenicity assessment with validated, drug tolerant assays, measuring anti drug and neutralising antibodies in both arms over a period adequate to the risk. For **interchangeability**, the additional evidence is a switching study: patients alternate between reference product and biosimilar, and the result must show no added risk and no diminished effect from the switching itself. Extrapolation to unstudied indications is permitted with scientific justification addressing mechanism and immunogenicity in each, as in India.

2.8 Advertising, labelling and packing of biologics

Naming is the first labelling rule and it is distinctive: FDA assigns each biological product a proper name consisting of a **core name** shared with related products and a distinguishing **four letter suffix** devoid of meaning for the originator and for biosimilars, so that adverse event reports and prescriptions can be traced to the exact product, the same traceability logic as India's brand and batch discipline at section 1.8; an interchangeable biosimilar shares the core name of the product it references. The **label** itself carries the US prescribing information in the standard format, with product specific warnings, and for REMS products the restricted distribution and communication elements FDA imposes. **Advertising and promotion** of biologics follow the prescription drug rules: promotional claims must be truthful, balanced and consistent with the approved labelling, a biosimilar may not claim superiority or difference the evidence does not support, and an interchangeable product's promotion must be consistent with its designation. **Packing** controls are the practical end of the same discipline: container closure integrity for a sterile protein, labelling that survives the cold chain, package level identification supporting recall and traceability, and the medication guide or patient labelling where the risk profile requires it.

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