

Unit 1: India: Similar Biologics

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Regulatory Aspects of Herbal and Biologicals, subject code MRA202T, is the second core subject of M.Pharm Regulatory Affairs, Semester 2. It carries 4 credits and 60 hours of theory, taught at 4 hours per week, for 100 marks. MRA201T taught how the world regulates the chemically defined drug: a molecule that can be fully characterised, copied exactly, and proved the same as its reference by analysis and a bioequivalence study. This subject is about the products for which none of that is straightforward. A biologic is made by a living system, is defined as much by its manufacturing process as by its structure, and can never be copied molecule for molecule; a herbal product begins as a variable plant material whose active constituents may not even be fully known. The regulator's answer in both cases is a distinctive body of law built on characterisation, comparability and vigilance rather than on identity, and this course is designed to impart fundamental knowledge on the regulatory requirements, licensing and registration, and the regulation of labelling of biologics in India, USA and Europe, covering in detail the regulatory requirements for biologics, vaccines and blood products. The units follow the logic of the field. Unit 1 studies India, and within India the governing text is the CDSCO and DBT guideline on similar biologics: the principles of development, the preclinical, clinical trial and market authorisation data packages, and the post market duties of pharmacovigilance, GMP and GDP. Unit 2 studies the United States: what biologics, biologicals and biosimilars are, how they differ from generic drugs, the laws, regulations and guidance that govern them, and the development and approval machinery of the IND, BLA and the neighbouring routes, closing with preclinical and clinical considerations and the advertising, labelling and packing rules. Unit 3 studies the European Union, the system that invented the biosimilar concept: its directives and scientific guidelines, comparability and biosimilarity assessment, the plasma master file, TSE and BSE control, and approval of investigational products and biosimilars. Unit 4 takes the two oldest biological product families, vaccines and blood products, across India, the US and the EU, including batch release, ISBT labelling and haemovigilance. Unit 5 turns to herbal products and compares quality, safety and legislation in India, the USA and the European Union. One habit pays off throughout: keep asking what evidence stands in for the identity proof that these products cannot give. For a generic, sameness is shown. For a biosimilar, similarity is built stepwise. For a herbal medicine, long use and controlled quality are made to carry part of the weight that trials carry elsewhere. Every system in this subject is a variation on that substitution.

1.1 Introduction: why biologics needed their own Indian framework

India is one of the world's largest makers of biotechnology medicines, and its regulatory problem arrived early: recombinant products such as insulin, erythropoietin, interferons and monoclonal antibodies were being manufactured domestically long before there was a settled answer to the question of how a follow on version of such a product should be judged. A chemical generic is approved by showing it contains the same molecule and delivers it to the body at the same rate and extent. A biologic cannot meet that test. It is a large, complex protein produced in a living cell line, folded and glycosylated in ways that depend on the cell, the medium and the purification train, and two manufacturers using different processes will produce molecules that are highly similar but never identical. The Indian framework therefore regulates the follow on product as a **similar biologic**: a biological product that is similar in terms of quality, safety and efficacy to an already authorised **reference biologic**, with the similarity demonstrated through a comparability programme rather than assumed. This unit teaches the architecture CDSCO built for that judgment: the applicable statutes and guidelines, the principles of development, and the data packages at the preclinical,

clinical and market authorisation stages, with the post market duties that follow.

1.2 Applicable regulations and guidelines, and who administers them

Similar biologics are drugs under the **Drugs and Cosmetics Act 1940** and the **Drugs and Cosmetics Rules 1945**, and a similar biologic is a new drug requiring permission and registration like any other new drug; the clinical trial and approval machinery now sits in the **New Drugs and Clinical Trials Rules 2019**, which MRA103T teaches in full. Because the product is made by recombinant DNA technology, a second statutory layer applies: the **Rules for the manufacture, use, import, export and storage of hazardous microorganisms and genetically engineered organisms or cells, 1989**, made under the Environment (Protection) Act 1986, with the recombinant DNA safety guidelines administered by the Department of Biotechnology (DBT). The guideline that organises the whole field is the **Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorization in India**, first issued in 2012 by the Central Drugs Standard Control Organization (CDSCO) together with the DBT, and revised in 2016; the revision is the operative text, and it is the document from which this unit's data requirements are drawn. Around it sit the CDSCO guidance documents on clinical trial applications, on quality information for biotechnological and biological products, and on post approval changes to biological products. Administration is shared, and knowing which desk holds which decision is part of the subject. **CDSCO**, through the Central Licensing Authority, is the licensing authority for the clinical trial permission and the market authorisation. The **Review Committee on Genetic Manipulation (RCGM)** in the DBT oversees the development and preclinical evaluation of recombinant products, acting through the Institutional Biosafety Committees at each facility. The **Genetic Engineering Appraisal Committee (GEAC)** in the environment ministry is the apex body under the 1989 Rules for environmental release matters. Manufacture itself is licensed by the State Licensing Authority under CDSCO oversight for this class of products, and the good manufacturing practice benchmark is Schedule M of the Drugs and Cosmetics Rules, met again at section 1.9.

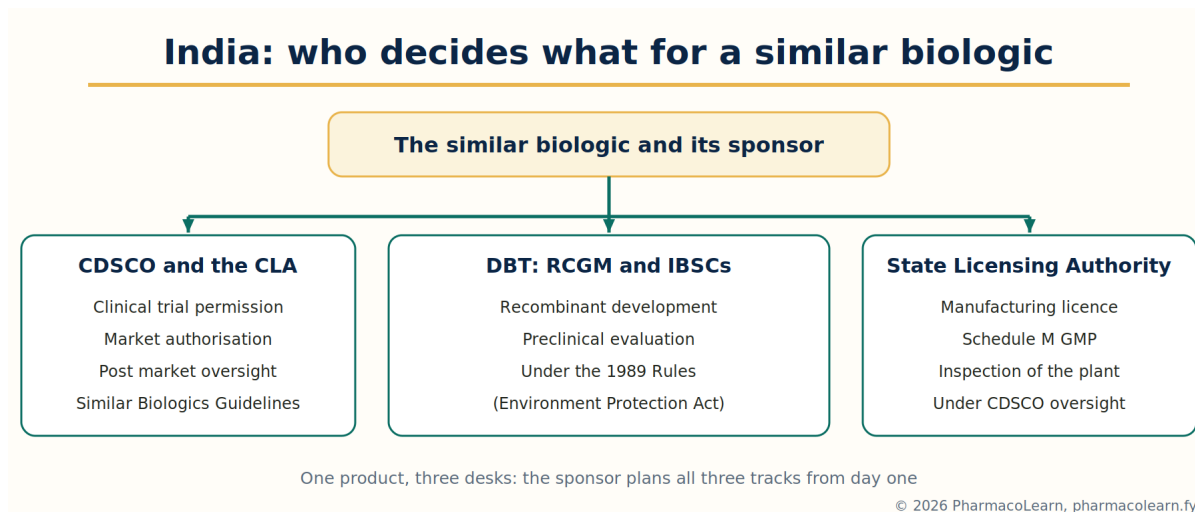
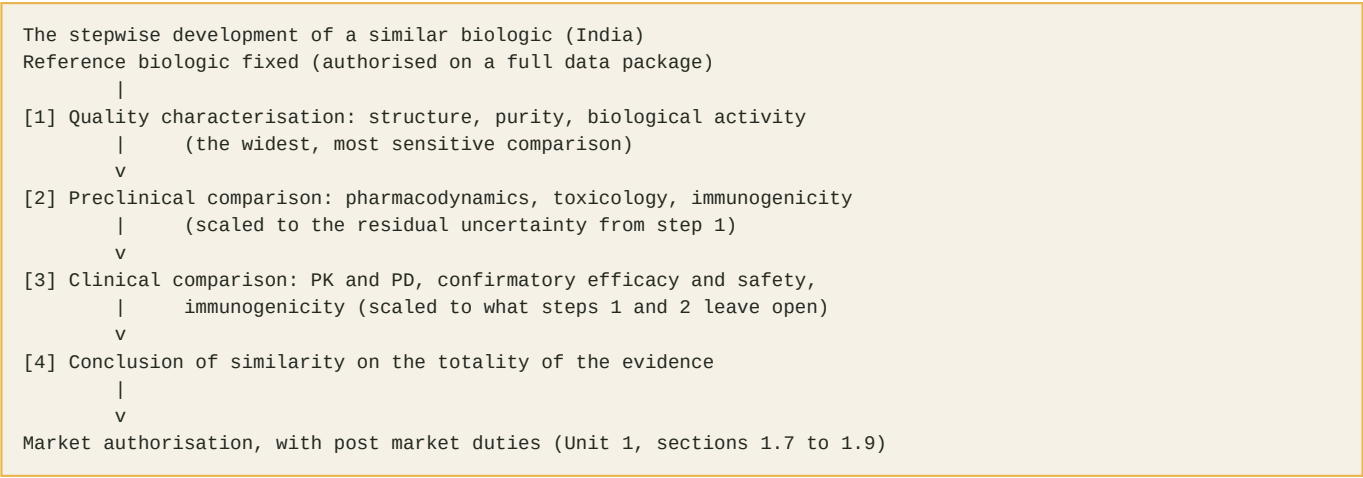


Figure: Who decides what for an Indian similar biologic: CDSCO and the Central Licensing Authority for trial permission and market authorisation, the RCGM and Institutional Biosafety Committees for recombinant development and preclinical oversight under the 1989 Rules, and the State Licensing Authority for the manufacturing licence (Unit 1, section 1.2).

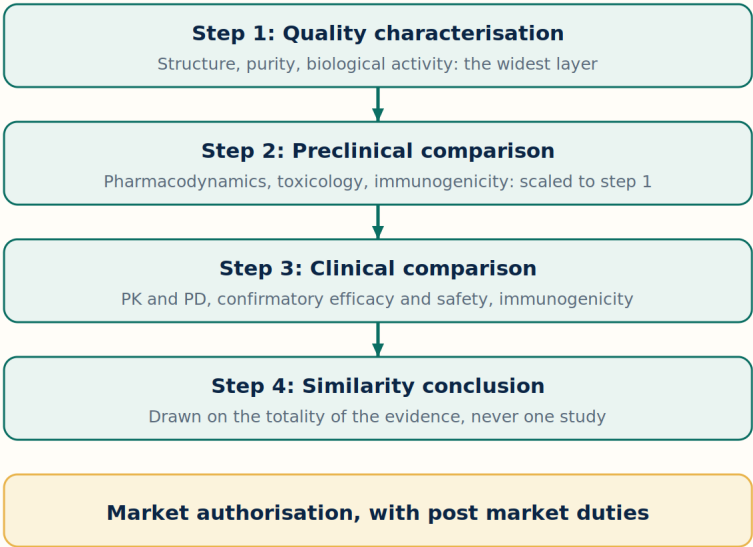
1.3 Principles for development of similar biologics

The 2016 guideline rests on principles that the whole of this subject, in every jurisdiction, then repeats in local language. First, the **reference biologic** must be a product authorised in India on a complete data package, or, where the guideline permits, authorised in a jurisdiction whose standards India accepts, and it must be used consistently as the comparator throughout development; similarity to a moving target proves nothing. Second, development is **stepwise**: the programme begins with extensive physicochemical and

biological characterisation of both products, and the amount of preclinical and clinical evidence then required is decided by what the analytical comparison leaves uncertain. A candidate that is analytically very close, with differences shown to be irrelevant, may need a reduced nonclinical and clinical package; a candidate with meaningful differences must earn its authorisation with more data, up to a full standalone package. Third, the standard is the **totality of the evidence**: no single study carries the application, and similarity is a conclusion drawn from the analytical, functional, preclinical and clinical layers together. Fourth, the similar biologic is developed against **one reference product for one route of manufacture**: the process used for the comparability batches must be the commercial process, because for a biologic the process defines the product, and a later process change reopens comparability. Fifth, **extrapolation** is possible but must be justified: if similarity is established rigorously in one studied indication, the product may be authorised for other indications of the reference biologic without a trial in each, provided the mechanism of action and the safety and immunogenicity profile support it. The stepwise logic is the single most examined idea in the unit, because it explains every data requirement that follows.



Stepwise development of a similar biologic



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Figure: Stepwise development: characterisation first and widest, then preclinical and clinical layers scaled to the uncertainty each earlier step leaves, concluding in a judgment on the totality of the evidence (Unit 1, section 1.3).

1.4 Data requirements for preclinical studies

The preclinical package exists to detect, before human exposure, any difference between the similar biologic and its reference that the laboratory comparison could not settle. Its first layer is **in vitro**: pharmacodynamic studies using the functional assays of the product, receptor binding and cell based potency assays, run head to head against the reference biologic, because these assays are often more sensitive to real differences than animal work. The **in vivo** layer compares pharmacodynamics in a relevant animal model where one exists, and the guideline expects the choice of species to be justified by relevance to the pharmacology, not by convenience. **Toxicology** is comparative and deliberately proportionate: typically a repeat dose toxicity study in a relevant species with the similar biologic and the reference side by side, examining local tolerance and any difference in the toxicity profile, rather than the full standalone toxicology programme of a new molecule, which would waste animals answering a question the comparability design asks better. **Immunogenicity** in animals is read with care: animals commonly respond to human proteins in ways patients do not, so animal antibody data are used to understand the products' relative immunogenic behaviour, not as a direct prediction of the human response. Two administrative features distinguish this stage in India. The recombinant origin of the product brings the **RCGM** into the preclinical phase: the development and preclinical evaluation of recombinant DNA products are overseen through the RCGM and the Institutional Biosafety Committee machinery under the 1989 Rules, alongside the CDSCO track. And the whole package is read as a **gate**: its function is to decide the size and design of the clinical programme, so unexplained preclinical differences enlarge, and clean preclinical comparability can support reducing, the clinical work of the next section.

1.5 Data requirements for the clinical trial application

The clinical trial application to CDSCO assembles the quality dossier on the product made by the final process, the complete preclinical comparison of section 1.4, and the protocols of the proposed studies, and permission is sought under the NDCT Rules 2019 with ethics committee approval, as MRA103T teaches. The clinical programme the guideline expects has a recognisable shape. It opens with **pharmacokinetic and pharmacodynamic comparison**: a study, usually in healthy volunteers where ethically possible and in patients where the product's pharmacology requires it, showing that exposure and the PD response of the similar biologic match the reference within prespecified margins. It proceeds to a **confirmatory clinical study** in a sensitive indication and population, designed as an equivalence (or, where justified, non inferiority) comparison of efficacy against the reference biologic, with safety collected throughout. **Immunogenicity** is assessed across the programme with validated assays for anti drug antibodies and neutralising antibodies, because the immune response is the risk that analytical similarity can least guarantee away, and it is followed for a period proportionate to the risk, commonly through and beyond the treatment course. The guideline also leaves room, used carefully, for a **reduced clinical package**: where the analytical and preclinical comparability is comprehensive and a sensitive PD marker exists, the extent of efficacy testing may be reduced, which is the stepwise principle of section 1.3 operating at the clinical layer. What the Indian framework does not contemplate is approval on quality data alone for this class: some clinical comparison is the price of the word "similar".

1.6 Data requirements for the market authorization application

The market authorisation application converts the comparability programme into a licence. Its quality layer is the largest: full characterisation data, the head to head analytical comparison against the reference biologic presented as a structured comparability report, the description and validation of the manufacturing process, evidence of **consistency** across batches made by the final commercial process, specifications with their justification, and stability data supporting the claimed shelf life and storage conditions, which for a protein product almost always means a controlled cold chain. Its scientific layer carries the preclinical and clinical comparison of sections 1.4 and 1.5 with their integrated conclusions, an explicit justification for any

extrapolation of indications sought beyond the studied one, and the proposed labelling, which follows the reference product's information as adapted to the similar biologic. Two features of the Indian decision deserve emphasis. The assessment is a **similarity conclusion**, not a re-proof of the reference product's benefit: CDSCO judges whether quality, safety and efficacy have been shown similar, and the authorisation is granted for the indications justified by that showing. And authorisation is accompanied by **post marketing commitments**, the subject of the next two sections: typically a Phase IV study or registry type follow up, periodic safety reporting, and product specific risk management measures, because a comparability judgment made on limited clinical exposure carries residual uncertainty that only wider use can close.

1.7 Post market data for similar biologics

Post market data in the Indian framework is not an afterthought; it is the fourth layer of the stepwise bargain. The guideline expects the marketing authorisation holder to generate data in real world use proportionate to the uncertainty left at approval, principally through **Phase IV studies** or structured observational follow up in the authorised indications, with attention to the endpoints the pre authorisation programme could not reach: uncommon adverse reactions, immunogenicity on repeated and long term exposure, and effectiveness in populations the trials excluded. These data feed **periodic safety update reports** submitted to CDSCO on the schedule the authorisation sets, and the findings can lead to label revision, additional studies or, in the limit, regulatory action. The professional point is continuity: the same comparability dossier that won the authorisation frames what must be watched after it, and a well built application names its own residual questions and proposes the post market work that answers them.

1.8 Pharmacovigilance

Pharmacovigilance for similar biologics runs through the **Pharmacovigilance Programme of India (PvPI)**, coordinated by the Indian Pharmacopoeia Commission, with adverse drug reaction monitoring centres collecting reports from hospitals and practitioners, and through the authorisation holder's own obligations to collect, assess and report adverse reactions to CDSCO, including expedited reporting of serious and unexpected reactions. Two disciplines are specific to this class of products and are examined accordingly. The first is **traceability**: an adverse event report for a biologic is scientifically useful only if it identifies the exact product, by brand name and batch number, because several similar biologics of the same reference may be on the market and their immunogenicity can differ; prescribing and reporting by brand and batch is therefore a pharmacovigilance measure, not a commercial preference. The second is **immunogenicity surveillance**: loss of efficacy or hypersensitivity appearing in use may signal anti drug antibody formation, and the pharmacovigilance plan must be able to detect and investigate such signals, which is why the immunogenicity assays validated during development remain part of the product's post market life.

1.9 GMP and GDP for biologics

Manufacture of a biologic is licensed against **Schedule M** of the Drugs and Cosmetics Rules, and the biologics plant carries the general GMP discipline of MRA101T plus the controls this class demands: validated aseptic processing for products that cannot be terminally sterilised, control and monitoring of the cell banks and starting materials from which every batch descends, environmental monitoring of clean areas, and viral and microbial safety built into the process design rather than tested into the finished vial. **Good distribution practice** closes the unit because a biologic's quality is perishable in transit: the product's authorised shelf life assumes an unbroken **cold chain**, typically refrigerated storage and transport with continuous temperature records, and GDP for biologics is therefore centred on qualified storage, validated shipping systems, temperature excursion handling, and distribution records that can execute a batch recall to the last consignment, the GDP principles of MRA101T applied to a product that heat

destroys silently.

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