PharmacoLearn

MRA202T Regulatory Aspects of Herbal & Biologicals, M.Pharm Semester 2

Unit 3: European Union: Biologics and Biosimilars

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3.1 Introduction to biologics in the European Union

The European Union was the first system to build a working biosimilar framework, issuing its overarching biosimilar guideline in 2005 and licensing the first biosimilar, a somatropin product, in 2006, years before the American pathway existed; Unit 3 therefore teaches the original design from which the concepts of Units 1 and 2 descend. The legal base is **Directive 2001/83/EC**, the Community code for human medicines, as amended for biologics, and **Regulation (EC) No 726/2004**, which makes the **centralised procedure** compulsory for medicines manufactured using specified biotechnological processes and for the advanced and innovative products EMA lists; in practice every biotechnology derived medicine and every biosimilar is authorised once, centrally, by the European Commission on the scientific opinion of the EMA's Committee for Medicinal Products for Human Use (CHMP), valid across the Union. The legal definition of a **similar biological medicinal product** lives in the Directive's data requirements: where a biological product does not meet the conditions of a generic, owing to differences in starting materials or manufacturing, the results of appropriate preclinical tests and clinical trials must be provided, which is the statutory sentence the entire biosimilar guideline structure elaborates.

3.2 Directives, scientific guidelines and guidance related to biologics in the EU

The framework is two layered. The **directives and regulations** set the gates: Directive 2001/83/EC for the dossier, authorisation and labelling of medicines; the variations and pharmacovigilance legislation met in MRA201T; the blood and tissues directives met in Unit 4; and the Clinical Trials Regulation for investigational products, at section 3.6. The **scientific guidelines** set the technical standard, and for biologics they form a deliberate architecture. At the top sits the overarching guideline on similar biological medicinal products, stating the principles: a stepwise comparability exercise, choice of reference product authorised in the EEA, and the possibility of extrapolation. Beneath it sit **quality guidelines** on the comparability of biotechnological products and on the quality data a biosimilar dossier must carry, and **non clinical and clinical guidelines** that translate the principles into study expectations. Beneath those sit **product class specific guidelines**, for insulins, erythropoietins, granulocyte colony stimulating factors, monoclonal antibodies, interferons and others, where the class experience is deep enough to prescribe the comparison in detail; the monoclonal antibody guideline, for the most complex class, is the natural capstone of the set. The professional reads the stack top down: principles first, then the class rule for the product in hand.

3.3 Comparability and biosimilarity evaluation

Two related exercises must be distinguished, because examinations confuse them. **Comparability**, codified in ICH Q5E, is the demonstration, after a change to a product's own manufacturing process, that the pre change and post change products are comparable in quality and that the change has no adverse impact on safety or efficacy; it is the originator's tool for living with process evolution, and it taught the biosimilar world its methods. **Biosimilarity** is the application of the same logic between two different manufacturers' products: an extensive head to head **comparability exercise** against the reference medicinal product across quality attributes, then non clinical comparison, then clinical comparison, in the stepwise order of Unit 1, with the extent of each later layer justified by the certainty of the layer before. The

EU adds two operational features. The reference product must be one **authorised in the EEA**, and data from a non EEA comparator may support the programme only through a scientific bridging comparison. And on substitution, the EU legislates the science and leaves the practice to the member states: EMA and the Heads of Medicines Agencies have stated that biosimilars approved in the EU are interchangeable with their reference products from the scientific point of view, while the decision on pharmacy level substitution rests with each member state's own rules, which differ; the EU thus has interchangeability as a scientific conclusion without the American legal designation of section 2.2.

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The EU comparability exercise for a biosimilar
[1] Quality comparison: physicochemical and biological characterisation
    against the EEA authorised reference product (widest layer)
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[2] Non clinical comparison: in vitro function, then in vivo work
    only where a residual question remains
        |
[3] Clinical comparison: PK and PD first; confirmatory efficacy,
    safety and immunogenicity in a sensitive population
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[4] Biosimilarity conclusion on the totality; extrapolation of
    indications justified mechanism by mechanism
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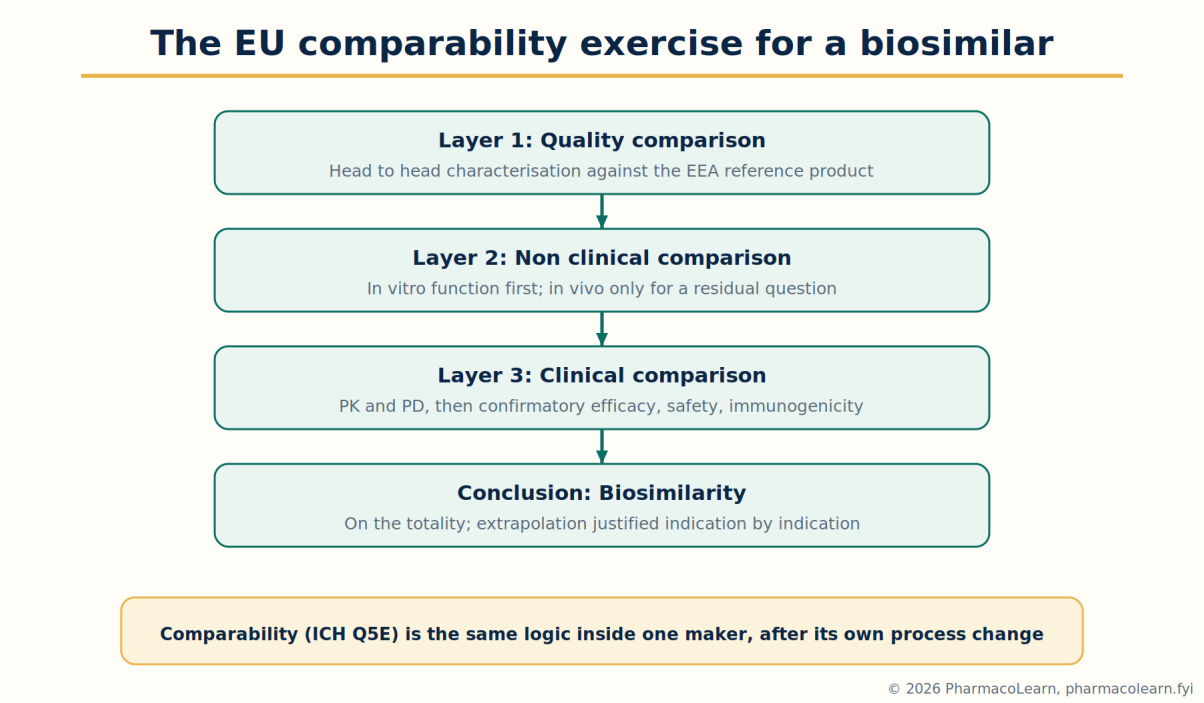

Figure: The staged comparability exercise: quality widest, non clinical targeted, clinical confirmatory, concluding on the totality with extrapolation justified separately (Unit 3, section 3.3).

3.4 The plasma master file

Plasma is the starting material of a whole family of biologics, albumin, immunoglobulins and clotting factors, and it is collected at many centres outside the marketing authorisation holder's own sites. The EU solves the resulting dossier problem with the **Plasma Master File (PMF)**: a standalone dossier of the scientific and technical data on the collection, testing and pooling of human plasma, separate from any product's marketing authorisation dossier. A PMF holder submits the file to EMA for **certification**: the Agency evaluates the PMF and issues a certificate of compliance, which the marketing authorisation holders whose products use that plasma then cite in their own dossiers, so the plasma data are reviewed once and relied on many times. The certificate is maintained by **annual recertification**, in which the holder submits the updated epidemiological data on the donor populations and infectious markers, the year's changes to

centres and tests, and the Agency re confirms compliance; product dossiers referencing the PMF are updated in step through the variations system. The PMF is the exact analogue, one level up the supply chain, of the ASMF of MRA201T: the master file device separates confidential, reusable source data from each product's own application.

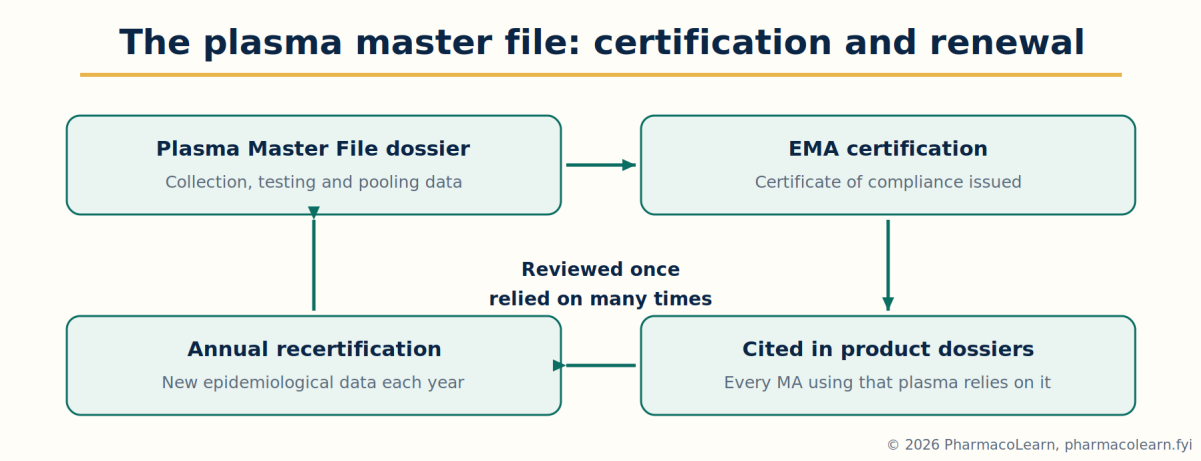

Figure: The PMF cycle: the plasma data dossier, EMA certification, citation by every marketing authorisation that uses the plasma, and annual recertification carrying the new epidemiological data (Unit 3, section 3.4).

3.5 TSE and BSE: evaluation and control

Transmissible spongiform encephalopathies, of which bovine spongiform encephalopathy (BSE) is the animal form and variant Creutzfeldt Jakob disease its human counterpart, are caused by prions that no routine inactivation or test can reliably remove from a biological starting material, so regulation works by **risk minimisation at the source**. The governing instrument is the EMA guideline on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products, which classifies materials by the infectivity of the **tissue** (from specified high risk tissues down to materials with no detectable infectivity), by the **species** and the geographical BSE risk of the country of origin, and by the manufacturing process's capacity to reduce prion load, and combines them into the acceptability judgment for each animal derived material in a product, gelatine, lactose, bovine serum and tallow derivatives being the everyday examples. For specified materials, compliance is evidenced through the **EDQM Certificate of Suitability** for TSE risk, the TSE counterpart of the CEP of MRA201T, cited in the dossier in place of raw data. The evaluation is a living one: a change of sourcing country, species or tissue reopens the assessment, and the pharmacovigilance of section 3.8 stands behind it as the detector of last resort.

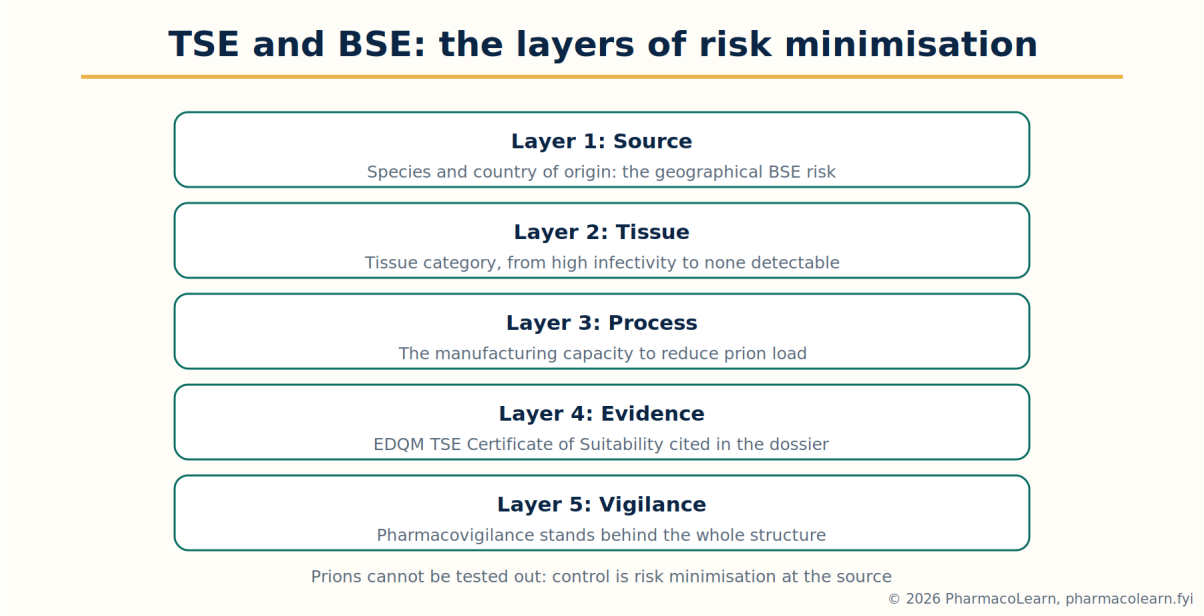

Figure: TSE and BSE control as layered risk minimisation: species and country risk, tissue category, process reduction, the EDQM TSE certificate as evidence, and vigilance behind the whole (Unit 3, section 3.5).

3.6 Development and regulatory approval: investigational products and biosimilars

A biologic enters European patients as an **investigational medicinal product (IMP)** under the Clinical Trials Regulation (EU) No 536/2014: one application through the EU portal, a coordinated assessment by the member states concerned with one state reporting, and the manufacturing of the IMP itself under GMP for investigational products with Qualified Person certification of each batch, the QP discipline of MRA201T carrying into the trial supply. The development programme is shaped in dialogue with EMA through **scientific advice**, the European habit of settling the comparability design with the regulator before the expensive studies run. Authorisation of the finished biologic is by the **centralised procedure** of section 3.1, applied for through a single dossier in CTD format in which the comparability exercise of section 3.3 is presented as an integrated, explicitly argued case: a quality module comparing the products attribute by attribute, the non clinical and clinical modules each prefaced by what the earlier layer left open, and the biosimilarity conclusion drawn across them. The CHMP opinion and Commission decision grant an authorisation for the indications the evidence supports, including extrapolated indications individually justified, and the product enters the post authorisation world of section 3.8 carrying a **risk management plan** as a condition of its licence.

3.7 Pre-clinical development considerations in the EU

European non clinical expectations for biosimilars state the stepwise principle in its most disciplined published form. The **in vitro** layer does the heavy lifting: a battery of functional assays reflecting every known mechanism of action of the product, run comparatively, because these assays are sensitive to differences that matter and spare animal use. **In vivo** animal studies are required only where an in vitro model cannot answer a remaining question, and where run, they are comparative, in a pharmacologically relevant species, designed for the question in hand: pharmacodynamics, a limited comparative toxicity assessment with toxicokinetics and antibody measurement, and local tolerance where the route demands it. Standalone safety pharmacology, genotoxicity and carcinogenicity programmes of the new molecule era are not expected for a biosimilar; the reference product's dossier has already settled those questions for the pharmacology in question. The design ethic is constant: every animal study must be able to change the decision, or it is not run.

3.8 Stability, safety and clinical evaluation

Stability of a biotechnological product is governed by ICH Q5C: because proteins degrade by pathways that accelerated conditions distort, the shelf life rests principally on real time, real condition data, with stress studies used to map degradation and prove the stability indicating power of the methods, and the cold chain conditions on the label are part of the stability claim itself. **Safety and clinical evaluation** post authorisation run through the EU pharmacovigilance system of MRA201T, with biologic specific sharpness: the risk management plan identifies immunogenicity and class risks as the standing concerns; periodic safety update reports follow the reference product's reporting cycle; and newly authorised biologics carry **additional monitoring**, marked by the black inverted triangle in the product information, inviting intensified adverse event reporting while experience accumulates. Traceability is a stated EU requirement for this class: brand name and batch number must be recorded in adverse reaction reports for biological medicines, the same discipline India teaches at section 1.8 and the US builds into its naming at section 2.8, because without product level identity a class level signal cannot be assigned to its source.

3.9 Advertising, labelling and packing of biologics in the EU

A European biologic is named by its **INN** with the company or brand name, in the invented name the centralised authorisation carries, and its identity in reporting and dispensing is anchored on that brand and batch, as section 3.8 sets out. The **product information** is the harmonised pair of the Summary of Product Characteristics for professionals and the package leaflet for patients, agreed centrally so that the same text serves every member state, with national additions confined to the blue box area of the pack. **Advertising** follows the medicines advertising rules of the Directive: prescription only biologics may not be advertised to the general public, professional promotion must accord with the SmPC, and no presentation of a biosimilar may claim a difference from its reference product that the authorisation does not establish. **Packing** carries the safety features of the falsified medicines framework, the unique identifier and anti tampering device by which each pack is verified at dispensing, together with the storage statement that keeps the cold chain promise of section 3.8 visible to every handler of the pack.

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