PharmacoLearn

MRA201T Regulatory Aspects of Drugs & Cosmetics, M.Pharm Semester 2

Unit 2: European Union and Australia

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2.1 The EMA and the European network model

The European system is a **network**, not an agency with branches, and understanding that single fact organises the whole unit. The **European Medicines Agency (EMA)**, established in 1995 and seated in Amsterdam since 2019, coordinates the work of the national competent authorities of the member states; it does not itself employ most rapporteurs, who are experts drawn from the national agencies. Its scientific committees do the deciding: the **Committee for Medicinal Products for Human Use (CHMP)**, whose opinion is the scientific verdict on a centralised application; the **Pharmacovigilance Risk Assessment Committee (PRAC)**; the **Committee for Orphan Medicinal Products (COMP)**; the **Paediatric Committee (PDCO)**; the **Committee for Advanced Therapies (CAT)**; and the Committee for Herbal Medicinal Products. The legal act of authorization belongs not to the EMA but to the **European Commission**, which converts a CHMP opinion into a decision binding in all member states. Beneath this sits the two layer legislation of the Union: **Regulation (EC) No 726/2004**, which lays down the centralised procedure and the EMA itself, and **Directive 2001/83/EC**, the Community code for human medicines, which governs national authorizations, mutual recognition, manufacturing, wholesale, labelling and pharmacovigilance, implemented in each member state's own law. The working style of the system is shared work and reliance: one state assesses, others recognise, the committees arbitrate, and the Commission decides.

2.2 EDQM and the European Pharmacopoeia

The **European Directorate for the Quality of Medicines and HealthCare (EDQM)** is a different body from the EMA in both law and home: it is a directorate of the Council of Europe, seated in Strasbourg, not an EU institution, and its pharmacopoeia binds well beyond the Union. The EDQM elaborates the **European Pharmacopoeia**, whose monographs and general chapters are legally binding quality standards in the signatory states; it runs the network of Official Medicines Control Laboratories; it manages the standard terms for dosage forms and routes; and it operates the **certification of suitability** procedure of section 2.10. Where EMA answers whether a medicine may be marketed, EDQM answers whether the substance in it meets the public standard: an application quotes pharmacopoeial monographs it does not re-prove, and a substance maker holding a certificate of suitability need not file its full data again in every dossier.

2.3 The legal base and general guidelines

A European dossier is written against three layers of texts. At the top sit the Regulation and the Directive (section 2.1), amended over time, notably by the 2010 pharmacovigilance legislation and the Falsified Medicines Directive 2011/62/EU with its safety features on packs. In the middle sits **EudraLex**, the collected library of EU pharmaceutical law and guidance treated in section 2.14. At working level sit the **Notice to Applicants** volumes, which state the procedural and format expectations for applications, and the CHMP and ICH guidelines on quality, safety and efficacy topics. Applications are filed in the CTD, electronically as eCTD, and the Notice to Applicants systematises the legal bases of the application: full, generic, hybrid (the EU counterpart of the 505(b)(2) idea), well established use on bibliographic evidence, fixed combination, and informed consent applications. Data and market protection rewards the full application: eight years of data protection and two further years of market protection, with a possible

additional year for a significant new indication, the **8+2(+1)** formula, against which generic and hybrid applications are timed exactly as ANDAs are timed against the Orange Book.

2.4 The ASMF system in the European Union

The **Active Substance Master File** is the EU counterpart of the US Drug Master File: the active substance manufacturer files its confidential know how once, in a document split by design into an **Applicant's Part**, shared with the applicant whose product uses the substance, and a **Restricted Part**, which the assessor sees and the applicant never does. The ASMF is not authorized on its own; it is assessed as part of each marketing authorization or variation that references it, under the responsibility of the applicant, who must have access to the open part and must declare that the product is made with the substance the file describes. The EU adds one refinement the US system lacks, the **ASMF worksharing procedure**, under which a single ASMF used in several procedures is assessed once and the outcome shared across the concerned authorities.

Feature	US DMF	EU ASMF	Japan MF
Filed by	Substance or material maker	Active substance manufacturer	Substance or material maker
Confidential closed part	Whole file closed to applicants	Restricted Part, assessor only	Yes, in principle as US
Open part for applicant	None	Applicant's Part	Limited
Standalone approval	Never; reviewed when referenced	Never; assessed within each procedure	Registered with a certificate
Typical subject	Substances, excipients, packaging	Active substances	Substances, excipients, packaging
Reference mechanism	Letter of Authorization	ASMF reference and access letter	MF registration number

2.5 The IMPD: content and approval process

Before a medicine is authorized it must be trialled in Europe too, and the trial dossier is the **Investigational Medicinal Product Dossier**: the quality, manufacture and control of the investigational product, the non clinical pharmacology and toxicology, previous clinical experience, and the overall risk and benefit assessment, filed with the protocol and investigator material. Since 31 January 2022 the authorisation of clinical trials is governed by the **Clinical Trials Regulation (EU) No 536/2014**, applied through the single **Clinical Trials Information System (CTIS)**: one application, one portal, a coordinated assessment led by a reporting member state for the scientific part and a national part for each concerned state, replacing the patchwork of separate national filings under the old Directive. The IMPD itself survives the reform as the quality and evidence core of the application, in full or simplified form where the product is already authorized elsewhere in the system. MRA103T treats the ethics and conduct framework; the IMPD is its dossier face in Europe.

2.6 The four marketing authorization procedures: the map

Europe offers four roads to a marketing authorization, and choosing between them is a founding decision of a European regulatory strategy. The **centralised procedure** produces one authorization from the Commission, valid everywhere in the EU and the EEA states. The **mutual recognition procedure** converts an existing national authorization into authorizations in other member states. The **decentralised procedure** obtains first authorization in several member states at once, none holding it yet. The **national procedure** authorizes in one state only. Section 2.7 to 2.10 take each in turn; the comparison follows.

Procedure	Who assesses	Where valid	Typical use
Centralised	CHMP (rapporteur and co-rapporteur)	All EU and EEA states	Biotechnology products, orphan medicines, advanced therapies and other mandatory scope; major innovation
Decentralised	Reference member state leads, concerned states join	The states named in the application	New products aimed at several states, none yet authorized
Mutual recognition	Reference member state (holder of the first authorization) leads	Further states recognising the first approval	Extending an existing national authorization
National	One national authority	One state	Local products, first step toward mutual recognition

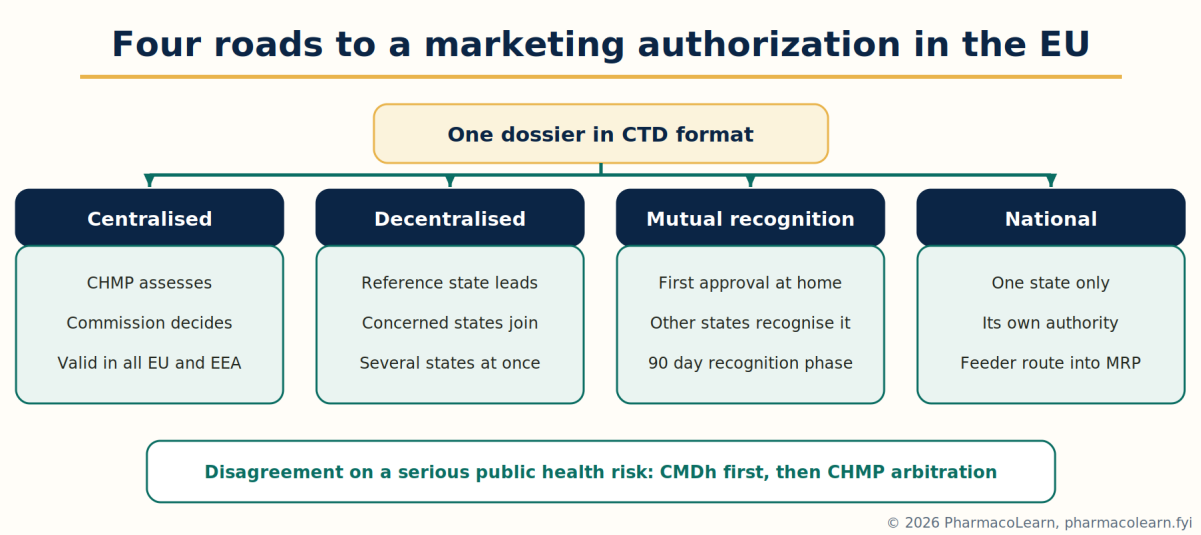

Figure: Four roads to a European authorization: the centralised procedure decides once for all states, the decentralised and mutual recognition procedures spread one assessment across chosen states, and the national procedure stays home (Unit 2, section 2.6).

2.7 The centralised procedure

The centralised procedure is **mandatory** for a defined scope: medicines derived from biotechnology processes, orphan medicines, advanced therapy medicinal products, and medicines for specified major disease areas; it is **optional** for other new active substances and significant innovations. The applicant files one dossier with the EMA; the CHMP appoints a rapporteur and co-rapporteur from member state agencies; and the assessment runs on a **210 day** clock for the committee's opinion, not counting **clock stops** during which the applicant answers the consolidated list of questions, so the elapsed calendar time is longer than the active clock. PRAC reviews the risk management plan in parallel, the PDCO the paediatric position, and inspections may be requested of the manufacturing sites. The CHMP opinion passes to the European Commission, whose decision, with the agreed product information in all Union languages, creates the single authorization; the summary of product characteristics, labelling and package leaflet approved here are the texts every member state then uses. Renewal falls due after five years, the variations of section 2.11 carry the authorization through commercial life thereafter, and the centralised authorization is maintained in one place, which is the practical prize the procedure offers a global company.

2.8 Mutual recognition and the decentralised procedure

The **mutual recognition procedure (MRP)** starts from an authorization that already exists in one member state, the **reference member state**, whose assessment report other, **concerned member states** are asked to recognise, ordinarily within a 90 day recognition phase. A concerned state may refuse only on the narrow ground of a **potential serious risk to public health**, and unresolved disagreement escalates first to

the coordination group (CMDh) and then, if needed, to a CHMP arbitration whose outcome binds all. The **decentralised procedure (DCP)** is the same machinery run before any authorization exists: the applicant chooses a reference member state, which prepares a draft assessment report and draft product information on the procedure's timetable, the concerned states comment, and the procedure closes with national authorizations issued in step in each participating state. The craft lies in choosing the reference state and in answering divergent national questions without fracturing the single text. Both procedures rest on mutual recognition with a public health escape, the compromise that built a single market in medicines without a single national regulator.

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The centralised procedure
Eligibility check and intention to submit to the EMA
        |
        v
Rapporteur and co-rapporteur appointed by the CHMP
        |
        v
210 active days of assessment, clock stops for applicant answers
        |
        v
PRAC, PDCO and inspection inputs in parallel
        |
        v
CHMP opinion (positive or negative)
        |
        v
European Commission decision, valid in all EU and EEA states
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2.9 National authorization, transfers and the life of the authorization

The **national procedure** authorizes in one member state under the Directive alone; it survives because some products are genuinely local, and as the feeder route into mutual recognition. Once granted, an authorization is an asset with its own conveyancing: a **marketing authorization transfer** moves it to a new holder, in the centralised system by a Commission decision on the transfer application, the dossier, manufacturing arrangements and pharmacovigilance system passing to the transferee, who steps into every duty from the transfer date. The authorization also has statutory lifelines to respect: it must be **renewed** after five years, after which it ordinarily remains valid indefinitely, and it lapses under the **sunset clause** if the product is not placed on the market within three years of authorization, or is absent for three consecutive years, subject to public health exemptions. Extensions of the authorization itself (a new strength, form or route that changes the terms fundamentally) are treated not as variations but as **extensions**, full applications in miniature (section 2.11).

2.10 The Certificate of Suitability: outsourcing substance proof to a monograph

Where the European Pharmacopoeia carries a monograph for an active substance, its manufacturer may prove compliance once, centrally, through the **Certificate of Suitability (CEP)**, granted by the EDQM after assessment of the substance dossier submitted to Strasbourg. The certificate states that the monograph, suitably supplemented by the annexes and conditions recorded on it, adequately controls the substance's quality. A marketing authorization application then cites the CEP number instead of filing the full substance data, exactly as an ASMF is referenced, but with the assessment already done and portable across every procedure and state. The certificate is maintained like an authorization: revisions for changes, renewal on its five year cycle, and suspension or withdrawal where inspection or data show the monograph no longer controls the material. For Indian API exporters the CEP is a familiar commercial instrument: one EDQM assessment, backed by periodic EDQM inspections of the manufacturing site, against the alternative of defending the substance file separately in each customer's dossier.

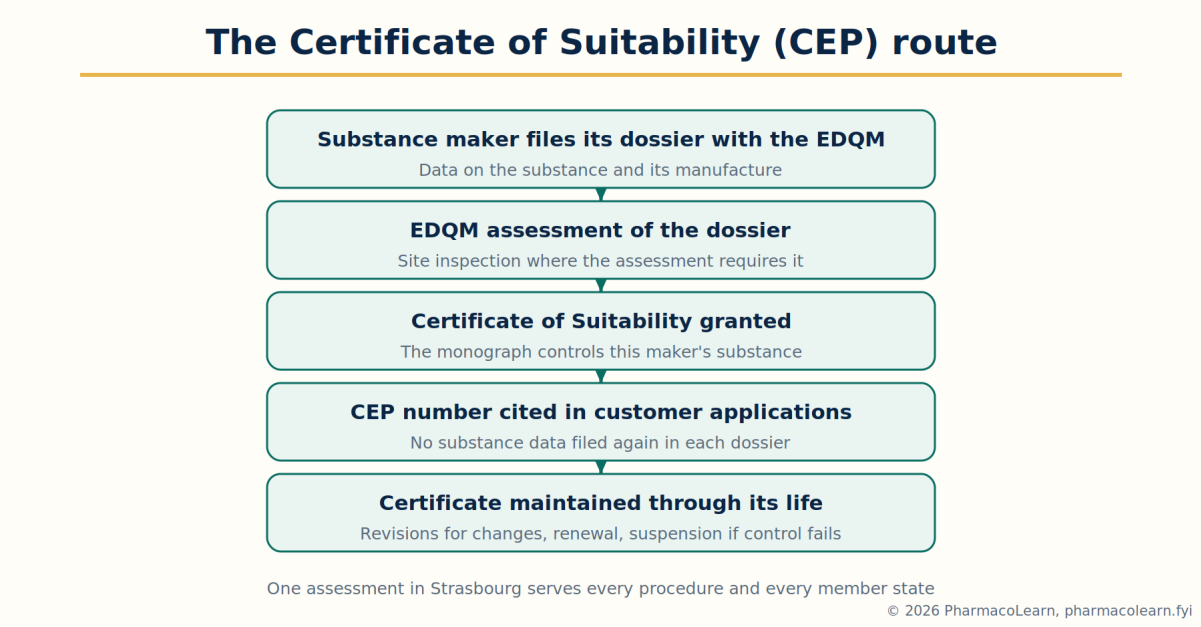

Figure: The CEP route: the substance maker applies to the EDQM, the dossier and, where needed, the site inspection support assessment, and the granted certificate is then cited in place of substance data in every customer's application (Unit 2, section 2.10).

2.11 Variations and extensions: grading change in the EU

Post approval change in the Union is governed by the **Variations Regulation (EC) No 1234/2008**, whose ladder mirrors the American one in spirit and differs in letters. **Type IA** variations are minor changes of no or minimal impact, handled on a do and tell basis: the holder implements and notifies within 12 months, with the **Type IAIN** subtype notified immediately after implementation where the regulation so requires (certain administrative and identity changes). **Type IB** variations are minor changes that are neither IA nor II: tell, wait and do, the authority having 30 days to object before the change may be implemented. **Type II** variations are major changes that may significantly affect quality, safety or efficacy: a full assessment, ordinarily 60 days of active review, ending in approval before implementation. **Extensions**, as noted, change the authorization's fundamental terms and are assessed as new applications under the variations regulation's annex. Related changes may be **grouped** in one application, and the same change across many authorizations may be filed as a single **worksharing** procedure with one lead authority. The classification guideline that accompanies the regulation lists, change by change, which rung applies and what evidence it demands; as in the US, the first professional act is classification.

Class	Weight	Procedure	Implement when
Type IA	Minor, no or minimal impact	Do and tell, annual window (IAIN immediately)	Before notification
Type IB	Minor, not IA or II	Tell, wait 30 days, do	After the wait without objection
Type II	Major, may affect quality, safety or efficacy	Full assessment, ordinarily 60 days	Only after approval
Extension	Change of fundamental terms	Assessed as a new application	Only after approval

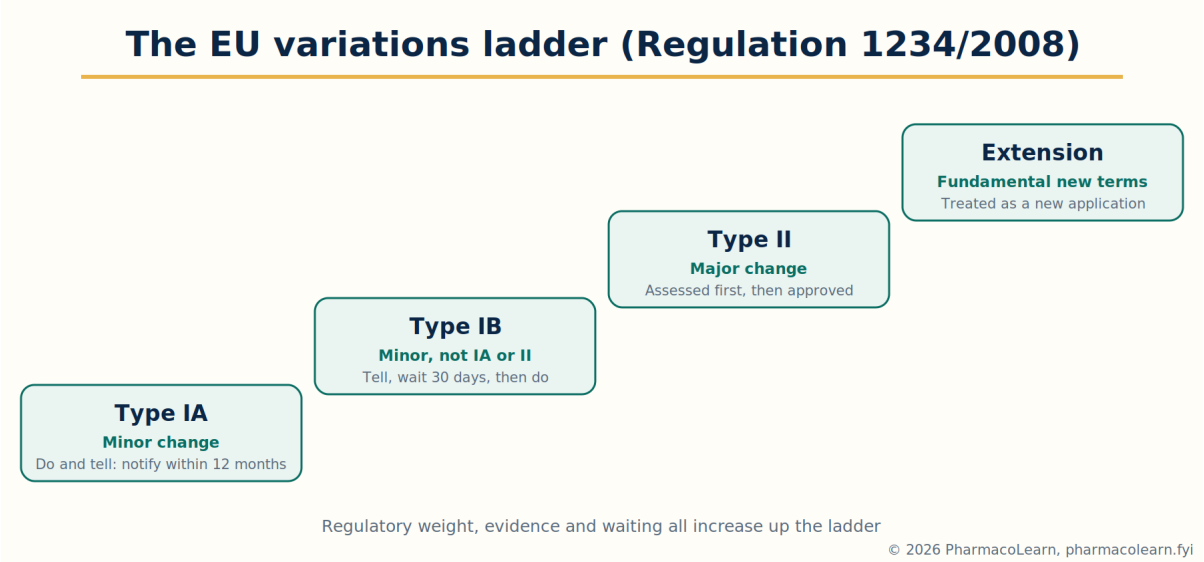

Figure: The ladder of the Variations Regulation: rising regulatory weight from the do and tell Type IA, through the tell wait do Type IB, to the assessed Type II and the extension treated as a new application (Unit 2, section 2.11).

2.12 The Qualified Person

The **Qualified Person (QP)** is the European system's signature institution: a named individual, meeting the Directive's qualification requirements in pharmacy, medicine, chemistry, biology or a cognate discipline plus defined practical experience, whom the manufacturing authorization holder names as personally responsible for certifying that **each batch** was manufactured and checked in compliance with the law, the GMP and the marketing authorization, before it may be released. Batch certification by the QP is the legal act of release in the EU; no quality unit, however senior, replaces the QP's personal certification, and the QP's duties, including defect handling and release of imported batches after the required tests, are detailed in GMP **Annex 16**. Set beside the American system, where release is a quality unit function under Part 211, the QP shows the EU's characteristic move: duties that other systems assign to organisations are pinned in Europe to an identified, qualified person, the same instinct that creates the cosmetics Responsible Person in section 2.15.

2.13 Manufacturing, packaging and labeling in the EU

Manufacture in the Union requires a **manufacturing and importation authorization** for the site, operation under the EU GMP of EudraLex Volume 4 (MRA101T), QP certification, and, for third country manufacture, importation by an authorized importer with testing in the EEA unless a mutual recognition agreement on GMP applies. **Packaging and labelling** run through the product information agreed in the authorization: the **Summary of Product Characteristics** as the professional reference text, the outer and immediate labelling of Title V of the Directive, and the package leaflet written in lay language and tested for readability with patient groups. Member state specific additions are confined to the **blue box** on the outer pack (local particulars such as price and reimbursement), the product name must also appear in **Braille** on the pack, and the Falsified Medicines safety features, a unique identifier in a two dimensional barcode plus an anti tampering device, must be carried by most prescription packs and verified through the European medicines verification system. As in the US, the pack and its texts are part of the authorization, not of the marketing plan.

2.14 EudraLex: the library of the system

EudraLex is the collected body of EU pharmaceutical law and guidance, arranged in ten volumes that the practitioner should be able to navigate by number: Volume 1, the pharmaceutical legislation for human

medicines (the Directive and the governing regulations); Volume 2, the Notice to Applicants and regulatory guidance on applications; Volume 3, scientific guidelines; Volume 4, the GMP guidelines including the annexes this branch keeps citing; Volume 5 and Volumes 6 to 8, the veterinary legislation and its application and guidance counterparts; Volume 9, pharmacovigilance guidelines (the GVP modules of MRA101T and MRA103T); and Volume 10, clinical trials guidelines. EudraLex is not a single instrument: it is the shelf on which the instruments live, and citation by volume is the profession's shorthand for where a requirement sits in the legal order.

2.15 Cosmetics in the European Union: Regulation 1223/2009

European cosmetics law is a single directly applicable Regulation, **(EC) No 1223/2009**, and its model is notification wrapped in personal accountability. Every cosmetic product placed on the EU market must have a designated **Responsible Person** established in the Union who answers for its compliance. Before placement, the Responsible Person must ensure a **cosmetic product safety report** has been drawn up by a qualified safety assessor and hold a **Product Information File** (product description, the safety report, manufacturing method and GMP statement, proof of claimed effects, animal testing data) available to authorities at the address on the label. The product is then **notified** through the **Cosmetic Products Notification Portal (CPNP)**: notification is not approval, but no lawful placement precedes it. Around this core the Regulation builds the substantive fences: annexes listing prohibited and restricted substances and the positive lists of permitted colourants, preservatives and UV filters; special rules for **CMR substances** and for **nanomaterials**, which require their own notification and labelling; claims discipline under the common criteria Regulation (EU) No 655/2013; manufacture under cosmetic GMP (ISO 22716 being the harmonised standard); and market surveillance by member states. Import into the EU makes the importer the Responsible Person unless it designates another, which is the practical point at which Indian cosmetic exporters meet the Regulation.

2.16 Cosmetics in Australia

Australia regulates cosmetics at the boundary of chemicals law and consumer law. Cosmetic ingredients are **industrial chemicals** under the **Australian Industrial Chemicals Introduction Scheme (AICIS)**, which replaced NICNAS in 2020: ingredients must be authorized for introduction under AICIS categories based on risk, and many are controlled through the **Poisons Standard** scheduling system, which restricts or prohibits listed substances in cosmetic use. A finished cosmetic is not registered as a medicine would be, unless it crosses the therapeutic boundary: products making therapeutic claims, and primary sunscreens among them, fall to the **Therapeutic Goods Administration** as therapeutic goods, while ordinary cosmetics remain in the chemicals and consumer law world, where labelling standards and the Australian Consumer Law apply and ingredient names follow the INCI style. The comparison the syllabus intends is triangular: the EU notifies with a safety assessment and a responsible person, North America notifies with substantiation duties after MoCRA, and Australia controls the ingredient, largely leaving the finished product to chemicals and consumer law unless its claims make it a medicine.

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