

3.1 Chemistry, Manufacturing and Controls (CMC)

CMC is the quality third of every application: the evidence that the product is the substance it claims to be, made the same way every time, and stable for its shelf life. In CTD terms it is Module 3 (Section 3.5), and it is organised in two halves:

- **Drug substance (3.2.S):** manufacture and characterisation, control of materials, critical steps and intermediates, specifications and analytical procedures with their validation, reference standards, container closure, and stability with the proposed retest period.
- **Drug product (3.2.P):** composition and pharmaceutical development, manufacture and process controls, control of excipients, specifications and analytical validation, batch analyses, characterisation of impurities, container closure, and stability supporting the shelf life and storage statement.

CMC is described as the part of the dossier the company will live with longest: every later change to process, site, specification or pack must be filed against the approved CMC baseline, which is why post approval affairs (next section) is mostly applied CMC.

3.2 Post approval regulatory affairs

Approval freezes an authorised baseline of the product. Everything that moves away from that baseline afterwards is a **post approval change**, and regulatory affairs work after approval is the disciplined filing of those changes, plus the routine reporting that keeps the licence alive. In the US system for NDAs and ANDAs the filing routes are graded by risk under 21 CFR 314.70:

Filing route	Kind of change	When the change may be implemented
Prior approval supplement (PAS)	Major change with substantial potential to affect identity, strength, quality, purity or potency (for example a new manufacturing site, a qualitative formulation change)	Only after FDA approval of the supplement
Changes being effected supplement (CBE, including CBE-30)	Moderate change (for example certain process or specification changes within guidance limits)	On submission, or 30 days after FDA receipt for CBE-30, as specified for the change
Annual report	Minor changes and the year's accumulated record (minor changes, stability data, labelling updates already permitted, complaint and adverse event summaries)	Reported once a year after implementation

The SUPAC levels of Unit 1.12 are the development side of the same grading. In the EU the same work is done through the **variations** system: minor Type IA notifications, Type IB minor variations, and Type II major variations that need prior approval, with extensions for genuinely new products. Post approval affairs also includes periodic safety reporting, licence renewals where they apply, and responses to agency questions and inspections throughout the product's life.

3.3 Regulation of combination products

A **combination product** combines two or more regulated components, for example a drug with a device (a drug eluting stent, a prefilled syringe, an inhaler), a drug with a biologic, or a biologic with a device. Its regulation starts from the **primary mode of action**: the single mode of action that provides the most important therapeutic action of the combination. In the US, the primary mode of action decides which FDA centre leads the review (drugs, biologics or devices), with the Office of Combination Products assigning the lead and coordinating the other centres; the GMP rule for combination products lets a manufacturer comply through a streamlined combination of the drug GMP and device quality system requirements. In the EU, a medicinal product with an integral device part is regulated as a medicinal product, with a notified body opinion on the device part where the rules require it. The examination point is simple: a combination product is not regulated twice in full; it is regulated once, under the lead system, with the other system's requirements drawn in.

3.4 Regulation of medical devices

Medical devices are regulated on a risk ladder. In the US:

- **Class I** devices (low risk, for example simple dressings) are subject to general controls and most are exempt from premarket notification.
- **Class II** devices (moderate risk, for example powered infusion pumps) usually reach the market through the **510(k) premarket notification**, which clears a device by showing substantial equivalence to a legally marketed predicate device.
- **Class III** devices (high risk, for example heart valves and implantable pacemakers) need **premarket approval (PMA)**, a full evidence review of safety and effectiveness similar in spirit to an NDA.

In the EU, devices carry the CE mark under the Medical Devices Regulation, with conformity assessment by notified bodies graded by device class (I, IIa, IIb, III). For this subject the device block matters mainly where it meets the drug side: combination products (previous section) and devices supplied with drug delivery systems.

3.5 The Common Technical Document (CTD)

The **Common Technical Document** is the ICH agreed format for assembling an application so that the same core dossier can be submitted in the US, EU and Japan and widely beyond. It has five modules:

Module	Title	Contents
Module 1	Administrative information and prescribing information	Region specific: application forms, labelling, certificates; the only module that differs by region
Module 2	Common technical document summaries	Quality overall summary, non clinical overview and summaries, clinical overview and summaries; the expert's written interpretation of Modules 3 to 5
Module 3	Quality	The full CMC documentation (Section 3.1)
Module 4	Non clinical study reports	Pharmacology and toxicology reports (Unit 4)
Module 5	Clinical study reports	Clinical protocols, reports and data (Unit 5)

The logic to remember: Modules 2 to 5 are the common core, and Module 1 wraps them for each region. The dossier is usually drawn as a triangle or stacked layers with Module 1 at the regional edge and the evidence deepening through Module 2 summaries into the full reports of Modules 3, 4 and 5.

The Common Technical Document: Five Modules

Module 1	Administrative and prescribing information (region specific)
Module 2	Summaries and overviews of quality, non clinical, clinical
Module 3	Quality: the full CMC documentation
Module 4	Non clinical study reports
Module 5	Clinical study reports

Modules 2 to 5 are common to all regions; only Module 1 is region specific.

Figure: The five CTD modules: Modules 2 to 5 form the common evidence core and only Module 1 is region specific.

3.6 The eCTD

The **electronic CTD (eCTD)** is the electronic implementation of the CTD, the standard ICH M2 format in which applications are submitted to FDA and EMA and many other authorities. Instead of paper volumes, the applicant submits a structured electronic sequence: each document placed in the module folder structure, tied together by an XML backbone that acts as the table of contents, with hyperlinks and bookmarks inside documents and checksums that let the agency verify file integrity.

- **Sequences and lifecycle:** each submission (original application, supplement, amendment, annual report) is sent as a numbered sequence, and documents across sequences can replace, append or delete earlier documents, so the eCTD builds the complete current dossier over the product's life.
- **Validation:** submissions are checked against technical validation criteria before review; a technically invalid sequence can be refused, so publishing quality is a regulatory skill in itself.
- **Benefits:** one publishing standard serves several regions, reviewers can navigate the whole history of the product, and companies stop printing and shipping paper dossiers.

3.7 Industry and FDA liaison

Regulatory work is not done by dossier alone; it includes formal **liaison** between the company and the agency. Its main instruments:

- **Formal meetings:** the development calendar is punctuated by scheduled meetings with FDA: pre-IND meetings before first human studies, end of phase 2 meetings to agree the pivotal programme, pre-NDA or pre-BLA meetings to agree the application's contents, and mid cycle and late cycle review meetings during assessment (in the PDUFA programme). Meetings are requested in writing, supported by a briefing package sent in advance, and closed by official minutes, which are the record both sides work to.
- **Written correspondence:** information requests and discipline review letters from the agency during review, complete response letters at the end of a cycle, and the applicant's amendments in reply. Good liaison practice means every agency question gets a traceable, complete answer in the sequence it belongs to.

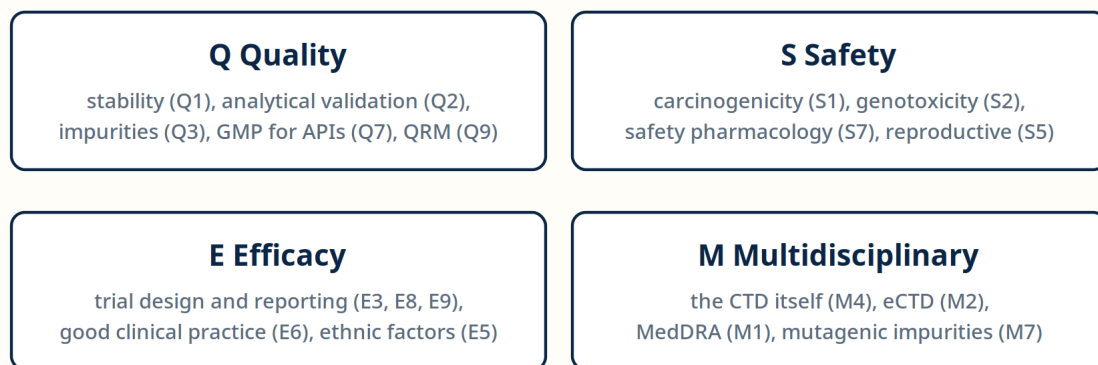
- **Informal scientific advice:** in the EU the same role is played by EMA and national scientific advice procedures; early advice is sought because a late disagreement about the evidence needed is far more expensive than an early one.

3.8 ICH and its guideline families

The **International Council for Harmonisation (ICH)** brings regulators and industry from the major regions together to write single technical guidelines accepted across regions, so that one development programme can support applications in all of them. Its guidelines are grouped in four families, and the syllabus names all four:

- **Q, Quality:** the pharmaceutical quality series. Includes stability testing (Q1), analytical validation (Q2), impurities (Q3), specifications (Q6), GMP for APIs (Q7), pharmaceutical development (Q8), quality risk management (Q9), pharmaceutical quality system (Q10), development and manufacture of drug substances (Q11) and lifecycle management (Q12).
- **S, Safety:** the non clinical series, covering carcinogenicity (S1), genotoxicity (S2), safety pharmacology (S7), immunotoxicity (S8), reproductive toxicology (S5), biotechnology product testing (S6) and similar topics that shape the Unit 4 programme.
- **E, Efficacy:** the clinical series, covering study design and reporting (E3, E8, E9), dose response (E4), ethnic factors (E5), good clinical practice (E6, the governing standard of Unit 5), and special populations such as geriatrics (E7) and paediatrics (E11).
- **M, Multidisciplinary:** topics that cross families: the CTD itself (M4), its electronic form the eCTD and electronic standards (M2), the MedDRA terminology (M1), evaluation of mutagenic impurities (M7) and electronic transmission standards such as E2B safety reporting under the E family implementations.

ICH Guideline Families: Q, S, E and M



One guideline set accepted across the ICH regions: one development programme, many applications.

Figure: The four ICH guideline families, Q, S, E and M, with the guidelines students meet most often in each.

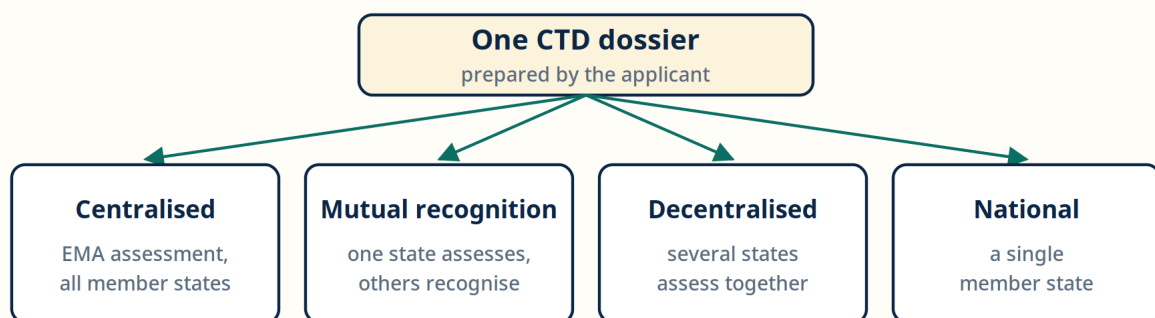
3.9 Regulatory requirements of the EU

The European system is a network: national authorities plus the **European Medicines Agency (EMA)** and the European Commission, which issues the legal decision for centralised products. Four routes lead to a marketing authorisation:

- **Centralised procedure:** one application to EMA, scientific assessment led by the Committee for Medicinal Products for Human Use (CHMP), and one Commission decision valid in all member states. Mandatory for biotechnology products, orphan medicines, and medicines for defined major disease areas, and available for other innovative products.
- **Mutual recognition procedure:** a product already authorised in one member state (the reference member state) seeks recognition of that authorisation by other member states, which rely on the reference state's assessment report.
- **Decentralised procedure:** for products not yet authorised anywhere in the EU, one reference member state assesses and the others accept the outcome, so several states authorise together.
- **National procedure:** authorisation for a single member state only.

The dossier is the same CTD, with an EU Module 1 (application form, product information in the common EU format, and local requirements). Conditional marketing authorisation and authorisation under exceptional circumstances exist for products where complete data cannot be provided at once, with specific obligations afterwards.

Four Routes to an EU Marketing Authorisation



For centralised products the European Commission issues the legal decision.

Figure: Four routes to an EU marketing authorisation from a single CTD dossier.

3.10 MHRA, TGA and the rest of the world (ROW)

- **MHRA (United Kingdom):** the Medicines and Healthcare products Regulatory Agency authorises medicines for the UK market. Since the UK left the EU it runs its own national licensing through its own assessment, and it also operates recognition style routes that can rely on the work of trusted partner regulators for suitable applications. The dossier remains CTD based, so a global dossier needs a UK Module 1 rather than a new evidence base.
- **TGA (Australia):** the Therapeutic Goods Administration registers medicines on the Australian Register of Therapeutic Goods (ARTG). Prescription medicines require full evaluation of quality, safety and efficacy data in CTD format, and TGA also uses comparable overseas regulator pathways that can rely on assessment reports from recognised regulators to shorten its own work.
- **ROW countries:** the rest of the world is not one system. Many countries accept the CTD dossier with a local Module 1, registration of the manufacturing site, local agent or subsidiary as the applicant, and legalised certificates such as the Certificate of Pharmaceutical Product (CPP) issued under the WHO certification scheme from the country of origin. Reliance and recognition of approvals by stringent regulators is a growing ROW pattern, and WHO prequalification serves products aimed at UN and donor procurement. The examination point is that the evidence core (Modules 2 to 5) travels globally; the administrative wrapper, site registration and labelling language are what change.

One dossier, many doors (the CTD idea)

Modules 2 to 5 written once -> quality, non clinical, clinical evidence

Module 1 prepared per region -> forms, labelling, certificates, local agent

Same core submitted to -> FDA (US), EMA and national agencies (EU),
MHRA (UK), TGA (Australia), CDSCO (India),
and ROW authorities with local requirements