

Unit 2: Dossier Preparation and Submission

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2.1 What a dossier is

A **dossier** is the assembled body of information a company submits to a regulatory authority to obtain and keep a permission: to test a drug in humans, to market it, to change it. Unit 1's documents are its raw material: the development report becomes the development sections, the master formula record stands behind the manufacturing description, the certificates and stability reports become the quality evidence. The dossier differs from the factory's document system in one way: it is written **for an external reader with legal power**, an assessor who will decide from the paper alone, who does not know the company, and who reads with structured scepticism. Everything in this unit, organisation, format, electronics, validation, serves that reader. The dossier's life also mirrors the product's: an investigational dossier opens development, a marketing dossier wins approval, and the supplements and reports of Unit 5 maintain it until withdrawal: the submission is a **lifecycle**, not an event, and regulatory writing is written for re-reading across decades.

2.2 Contents and organisation: binders and sections

Before format harmonisation, each authority prescribed its own dossier architecture, and the physical object was formidable: volumes of paper organised in **binders**, each binder a section of the application, tabbed, paginated and indexed by a master table of contents. Even today the intellectual structure the paper era imposed remains the skeleton of every format in this unit, and examinations still ask it plainly: a dossier is organised in **sections by discipline**, administrative information first (application forms, licences, certificates, labelling), then the summaries by which an assessor orients, then the three evidence bodies in their standard order, **quality** (chemistry, manufacturing and controls), **nonclinical** (pharmacology and toxicology), and **clinical** (the human studies), each section self contained, cross referenced rather than duplicated, and every claim in a summary traceable to data in a report. Compilation discipline, the order of volumes, the numbering of sections, the pagination and indexing, was the paper era's quality system for reviewability; the electronic formats of sections 2.5 onward automate exactly these virtues.

2.3 Compilation and review of the dossier

Compilation is the assembly of authored documents into a submission that satisfies a specific agency's format and content requirements for a specific application and market. Its working instruments are the **submission outline** (the target structure, module by module, with an owner and a status for every document), the **gap analysis** (what exists, what is missing, what is outdated, against the requirement list), and staged **review**: scientific review of the content by its authors and functions, regulatory review of format, consistency and cross referencing, and quality review of the finished assembly before it is released for transmission. The classic compilation failures are documentary, not scientific: a summary that quotes a study the report contradicts, a specification that differs between the quality summary and the method document, a study filed in the wrong module, a labelling text that does not match the approved wording. The review function exists because an agency's first deficiency letter is usually written out of exactly such inconsistencies, and each one costs the applicant a review cycle. Regulatory writing, in the compilation sense, is therefore an editorial discipline as much as a scientific one: one terminology, one set of numbers, one story, told identically in every module.

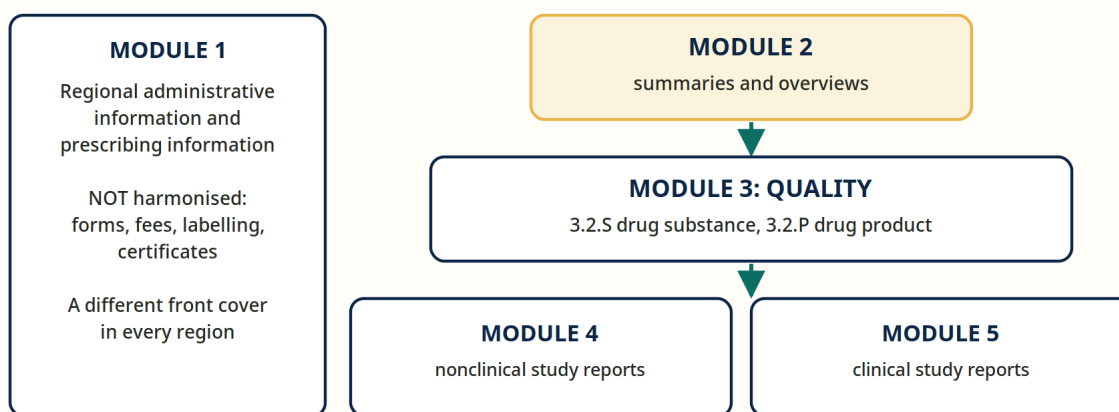
2.4 The Common Technical Document: overview and modules

The **Common Technical Document (CTD)** is the ICH harmonised format for a marketing application, defined by the **ICH M4** guideline family, and it is the centre of gravity of modern regulatory writing. One set of technical content, in one organisation, is accepted in substance by the ICH regions and most of the world, so the company writes once and adapts the regional module, instead of rewriting the whole dossier per country. The CTD has **five modules**:

Module	Content	Notes
Module 1	Regional administrative information and prescribing information	Not harmonised: forms, fees, labelling, certificates; differs by region
Module 2	Summaries and overviews	2.3 Quality Overall Summary; 2.4 Nonclinical Overview; 2.5 Clinical Overview; 2.6 Nonclinical Summaries; 2.7 Clinical Summaries
Module 3	Quality	3.2.S drug substance; 3.2.P drug product; manufacture, characterisation, control, stability
Module 4	Nonclinical study reports	4.2 study reports: pharmacology, pharmacokinetics, toxicology
Module 5	Clinical study reports	5.3 study reports and their data, written and structured around ICH E3 clinical study reports

Three reading rules reward memorisation. Modules 2 to 5 are the harmonised core; **Module 1 is regional**, the reason the same dossier still wears a different front cover in each market. Inside Module 2, the **overviews** (2.4, 2.5) are critical assessments written by experts, argument, not summary, while the **summaries** (2.6, 2.7) and the Quality Overall Summary (2.3) are factual compressions of Modules 4, 5 and 3 respectively. And the CTD is an **organisation of content, not itself an electronic format**: the same CTD content is what paper, eCTD, NeeS and ACTD all carry, each in its own mechanics, which is why this unit teaches the CTD before its electronic forms.

The CTD: Five Modules (ICH M4)



The harmonised core (ICH M4) is Modules 2 to 5; only Module 1 is regional.

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Figure: The CTD structure of ICH M4. Module 2, the summaries, sits above the three evidence modules like the apex of the classical CTD triangle; Module 1 stands apart as the regional administrative layer.

The CTD by the numbers (the structure an examiner expects)

- Module 1 : regional, not harmonised (forms, labelling, certificates)
- Module 2 : summaries - 2.3 quality, 2.4/2.6 nonclinical, 2.5/2.7 clinical
- Module 3 : quality - 3.2.S substance, 3.2.P product
- Module 4 : nonclinical reports - 4.2 by study type
- Module 5 : clinical reports - 5.3 by study, CSR built to ICH E3

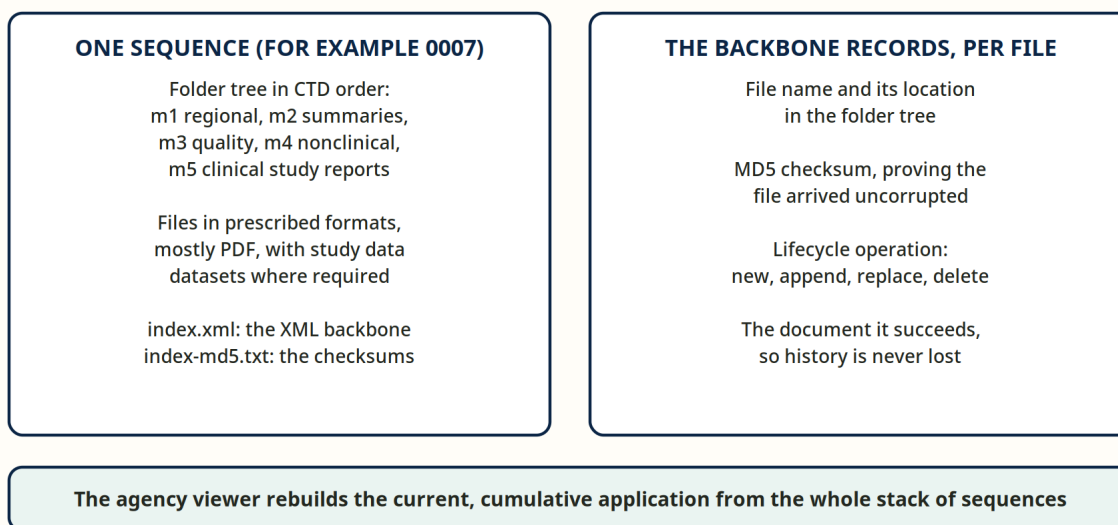
2.5 Paper submissions

The **paper submission**, bound volumes shipped to the agency, is the original form of the dossier and is retained in this syllabus because parts of the world, and parts of India's system, still run on it or on scanned paper logic. Its rules are physical: prescribed copies, prescribed paper and binding, signed original forms, a covering letter identifying the application and its contents, and a master index against which the agency checks receipt. Paper teaches two transferable lessons. The first is that the submission is a **manufactured object** with its own quality control: collation, pagination and completeness checks are batch records for a dossier. The second is why electronics won: paper cannot be searched, cross referenced automatically, amended cleanly or shared between an agency's offices, and a lifecycle of paper supplements degrades into archaeology. Agencies have accordingly moved market by market to mandatory electronic submission, the subject of the next sections, but the paper discipline of order, indexing and check listing survives inside every electronic standard.

2.6 The electronic CTD: structure and lifecycle

The **electronic CTD (eCTD)** is the electronic form of the CTD, specified by the **ICH M2** expert working group as the standard for transferring regulatory information from industry to agency. The content is the CTD's; the machinery is new. An eCTD submission is a **sequence**: a numbered transmission (0000, 0001, 0002 and onward) that carries, for one application, the documents added or changed since the last transmission, organised in the CTD folder structure. Its working parts are: files in prescribed formats (predominantly PDF for documents, with defined datasets for study data); a folder tree mirroring the modules; an **XML backbone**, the file index.xml, which lists every document in the sequence, its location, its checksum and its **lifecycle operation**; and checksums (the MD5 file) by which the receiving system proves nothing was corrupted in transit. The lifecycle operation is the eCTD's intellectual core: each document in a new sequence is marked **new**, **append**, **replace** or **delete** against the document it succeeds, so the agency's viewer can reconstruct the current, cumulative state of the whole application from the stack of sequences. Regulatory writing changes character here: granularity (how finely documents are split into files) follows the M4 granularity guidance, headings follow the backbone's fixed table of contents, and a misfiled document is no longer merely untidy but structurally wrong.

Anatomy of an eCTD Sequence



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Figure: One eCTD sequence: a folder tree in CTD order, an XML backbone that indexes every file with its lifecycle operation, and checksums that prove the transmission intact.

2.7 Planning, requirements and the submission process

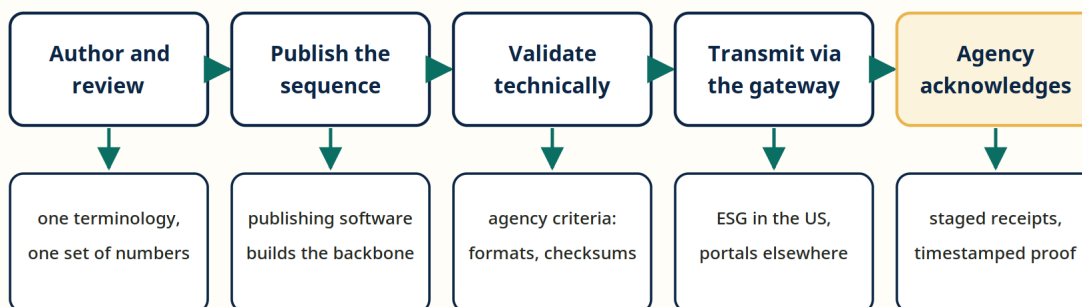
Because an eCTD is built by software, it is **planned** like a manufacturing process. **Electronic submission planning** begins with the publishing plan: which application, which sequence, which documents, authored to which templates and granularity, by whom and by when, and which regional requirements apply, for the module 1 content, file formats, and validation criteria differ by agency under the shared ICH standard (these agency specifications are the **regulatory bindings** the syllabus names: the regional rules that bind the harmonised format to a particular authority's systems). The **tools and technologies** are the publishing toolchain: document authoring and template systems, the eCTD publishing software that builds sequences and backbones, validators that test the build against the agency's technical criteria, and the transmission channel. The **submission process** then runs in a fixed rhythm: authoring and review of documents (section 2.3), publishing into a sequence, **technical validation** of the sequence (next section), transmission through the agency's gateway, receipt of the agency's acknowledgements, and archival of the exact transmitted package as the company's record of what the agency holds. Planning failures are as documentary as compilation failures: a sequence built against the wrong regional specification is a technically perfect submission to a door that cannot open.

2.8 Validation of the submission, and the Electronic Submissions Gateway

Validating the submission is the formal technical check that an electronic submission can be loaded, navigated and read by the agency's systems. It is done twice: by the applicant before transmission, with validator software applying the agency's published validation criteria (file formats and sizes, backbone integrity, checksum agreement, folder and naming rules, lifecycle references that resolve), and by the agency on receipt, where failure is a **technical rejection**: the submission is refused without scientific review, and the review clock never starts. The distinction examiners want is between technical validation (is the package well formed) and scientific assessment (is the product approvable): validation guards the door of the second. In the United States, transmission runs through the FDA **Electronic Submissions Gateway (ESG)**, the agency's single receiving system for electronic regulatory submissions, for which companies hold registered accounts and digital certificates; the gateway issues a staged series of **acknowledgements** as the package is received by the gateway, delivered onward, and accepted by the reviewing centre, so the

sender can prove, timestamp by timestamp, that the agency has its submission. Other regions run their own gateways and portals to the same design; the concept, one controlled door with receipts, is universal.

The Electronic Submission Pipeline



A technically invalid package is rejected before any scientific review begins.

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Figure: The submission pipeline of sections 2.3 to 2.8: authoring and review, publishing, technical validation, transmission through the gateway, and the agency's acknowledgements.

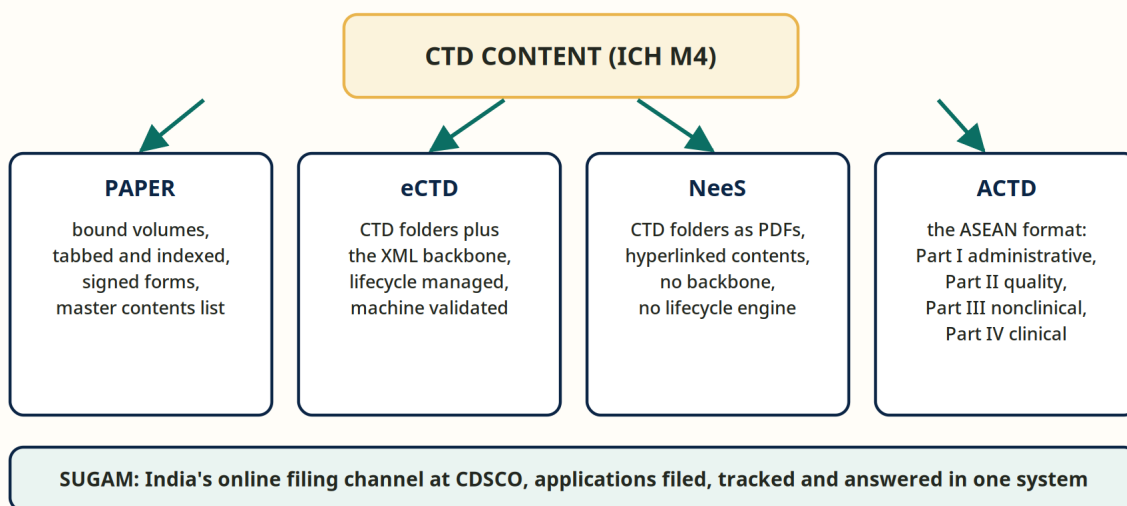
2.9 Non eCTD electronic submissions: NeeS

Between paper and eCTD stands **NeeS, Non eCTD electronic Submissions**: a dossier on electronic media (historically CD or DVD, now file transfer) in which the CTD folder structure and PDF documents are supplied **without the XML backbone**. Navigation is provided instead by hyperlinked tables of contents within the PDFs. NeeS was the European stepping stone format, accepted for national and some mutual recognition submissions while eCTD publishing capacity was scarce, and it survives where agencies permit it for smaller applications. Its teaching value is the contrast it sharpens: without a backbone there is no automated lifecycle management, no machine validation of structure, and no cumulative view across sequences, only a well organised set of documents; NeeS is the dossier as library, eCTD is the dossier as database. A regulatory writer must know which format a given market and procedure actually accepts today, for the same content, because filing NeeS where eCTD is mandatory is a technical rejection, and building eCTD where a simple format suffices is wasted effort.

2.10 The ASEAN CTD: ACTD

The **ASEAN Common Technical Dossier (ACTD)** is the regional format of the Association of Southeast Asian Nations, the format in which the ASEAN markets harmonised their applications on the CTD model with a structure of their own. The ACTD organises the same evidence in **four parts**: **Part I**, administrative data and product information (the regional front matter, like CTD Module 1); **Part II**, quality, carrying a quality overall summary with the quality documents; **Part III**, nonclinical, carrying the overview with the study reports; and **Part IV**, clinical, on the same pattern. The mapping onto the CTD modules is close enough that a company with a CTD core can republish into ACTD, which is precisely the regional design intent: harmonisation inside the bloc, convertibility outside it. For an Indian exporter, the ACTD matters practically, because the ASEAN markets are core destinations for Indian products, and the regulatory writer's craft includes knowing that the dossier family of this unit (CTD, eCTD, NeeS, ACTD, and India's own portal below) is one content in several bindings, and matching the binding to the market is a professional decision, not a clerical one.

One Content, Several Bindings



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Figure: The format family of Unit 2. CTD content is carried in paper, in eCTD with its XML backbone, in NeeS without one, and in the ASEAN four part arrangement; SUGAM is India's online filing channel.

2.11 Submission in the SUGAM system of CDSCO

India's filing channel is **SUGAM**, the online portal of the Central Drugs Standard Control Organization (CDSCO), through which applications for licences, registrations, permissions and approvals within CDSCO's remit are filed, tracked and answered. In the portal's logic, the applicant registers the organisation and users, selects the application type (for example import registration and licences, manufacturing related central approvals, clinical trial and bioequivalence permissions, and the filings that accompany them), completes the structured online forms, uploads the dossier documents in the prescribed arrangement (India's submissions follow the CTD pattern, with the country's own administrative requirements in front), pays the fee electronically, and then follows the application through queries and approvals inside the same system, with the authority's questions and the applicant's responses recorded against the file. SUGAM's significance for this subject is that it makes the Indian dossier a **tracked electronic lifecycle** rather than a paper file in a registry: the regulatory writer in India works in SUGAM as the American writer works in the ESG, and the virtues are the same, completeness at filing, validation before transmission, and an auditable trail of everything submitted and everything asked.

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