SA18: Electronic Clinical Data Submissions Across Global Regulatory Authorities

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Abstract

Electronic submissions to global regulatory agencies, such as the FDA, EMA, PMDA, Health Canada and NMPA, are necessary to get approval for medicinal products. These agencies have different requirements for submissions. The FDA, EMA, and PMDA require technical compliance with the ICH's eCTD, but some regulators may have additional requirements. It is essential to contact regulatory agencies prior to submission to learn about their specific requirements. The FDA and PMDA mandate data submission in a standardized CDISC format, including SDTM for collected data and ADaM for analysis datasets. The PMDA strongly recommends including ARM, while it is optional for the FDA. Knowing these key regulatory requirements is important for planning, creation, and submission of clinical study data. The article details clinical data electronic regulatory submission requirements, regulatory data standards catalogs, similarities and differences between submission packages, recommendations, and essential resources for successful submissions.

Keywords

eCTD v3.2.2/v4.0; CDISC SDTM; ADaM; Define-XML; Reviewer's Guides; ARM; Validation; PMDA Forms A/B; NMPA Chinese labels; Health Canada eCTD.

Abbreviations

ADaM – Analysis Data Model; ARM – Analysis Results Metadata; aCRF – Annotated Case Report Form; cSDRG/ADRG – (Clinical/Analysis) Study Data Reviewer's Guide; CTD/eCTD – (electronic) Common Technical Document; EMA – European Medicines Agency; FDA – U.S. Food and Drug Administration; HC – Health Canada; ICH – International Council for Harmonisation; NMPA – National Medical Products Administration (China); PMDA – Pharmaceuticals and Medical Devices Agency (Japan); SDSP – Study Data Standardization Plan; SDTM – Study Data Tabulation Model; TLFs – Tables, Listings and Figures.

Introduction:

Global regulatory agencies including the FDA, EMA, PMDA, Health Canada, and NMPA require electronic clinical data submissions in **CDISC-compliant formats**, placing statistical programmers at the center of preparing the full suite of deliverables contained in **eCTD Module 5**, such as SDTM/ADaM datasets, Define-XML, reviewer's guides, and analysis programs. This paper provides clinical programmers and statisticians with practical guidance for planning and producing these components by outlining regulatory expectations, submission package structure, and cross-agency differences. The goal is to equip teams with effective strategies and best practices to create high-quality, globally compliant CDISC submission packages.

Global regulatory agencies:

FDA (Food and Drug Administration): Federal agency responsible for responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices.

CDER (Center for Drug Evaluation and Research): The Center within FDA that regulates over the counter and prescription drugs, including biological therapeutics and generic drugs.

CBER (Center for Biologics Evaluation and Research): CBER is the Center within FDA that regulates biological products for human use.

Standard Format for submissions: The eCTD is the standard format for submitting applications, amendments, supplements, and reports to FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER).

The US FDA will require applications to be submitted in eCTD 4.0 format by 2029.

EMA (European Medicines Agency): Agency of the European Union (EU). It is responsible for the scientific evaluation, supervision and safety monitoring of medicines.

Standard Format for submissions: The eCTD format is mandatory to use for all submission types related to Marketing Authorisation for products within all EU procedures.

PMDA (Pharmaceuticals and Medical Devices Agency): Japanese regulatory agency that protect the public health by assuring safety, efficacy and quality of pharmaceuticals and medical devices. PMDA conduct scientific reviews of marketing authorization application of pharmaceuticals and medical devices, monitoring of their post-marketing safety. Standard Format for submissions: Japan's Pharmaceuticals and Medical Devices Agency (PMDA) will require applications to be submitted in eCTD 4.0 format by2026.

National Medical Products Administration (NMPA):

China’s national regulatory authority responsible for overseeing drugs, medical devices, and cosmetics.

Responsible for regulating the safety, quality, registration, and post-market oversight of drugs, medical devices, and cosmetics, including setting standards such as the Chinese Pharmacopoeia and enforcing good practice guidelines like GLP, GCP, and GMP.

Center for Drug Evaluation (CDE) of NMPA:

Division under China’s National Medical Products Administration (NMPA) conducts technical reviews for drug clinical trial and marketing applications, assesses generics and emerging therapies, develops and implements drug review regulations and guidelines, coordinates inspection-related activities.

Standard Format for submissions: Applicants should prepare and submit the eCTD application as required by the eCTD technical documents.

Health Canada: Federal department responsible for national health policy in Canada, regulating the safety, efficacy, and quality of pharmaceuticals, medical devices, food, and other health-related products to protect and promote the health of Canadians.

Health Products and Food Branch: Health Canada's HPFB is the national authority that regulates, evaluates and monitors the safety, efficacy, and quality of therapeutic and diagnostic products available to Canadians. These products include drugs, medical devices, disinfectants and sanitizers with disinfectant claims.

Standard Format for submissions: Companies are required to file submissions electronically to Health Canada in Electronic Common Technical Document (eCTD) format.

Other Global Regulatory agencies:

Medicines and Healthcare products Regulatory Agency (MHRA): The Medicines and Healthcare products Regulatory Agency regulates medicines, medical devices and blood components for transfusion in the UK.

Therapeutic Goods Administration (TGA): Australia's government authority responsible for evaluating, assessing and monitoring products that are defined as therapeutic goods. They regulate medicines, medical devices and biologicals.

Central Drugs Standard Control Organisation (CDSCO): National Regulatory Authority (NRA) of India responsible for regulating the drugs and cosmetics.

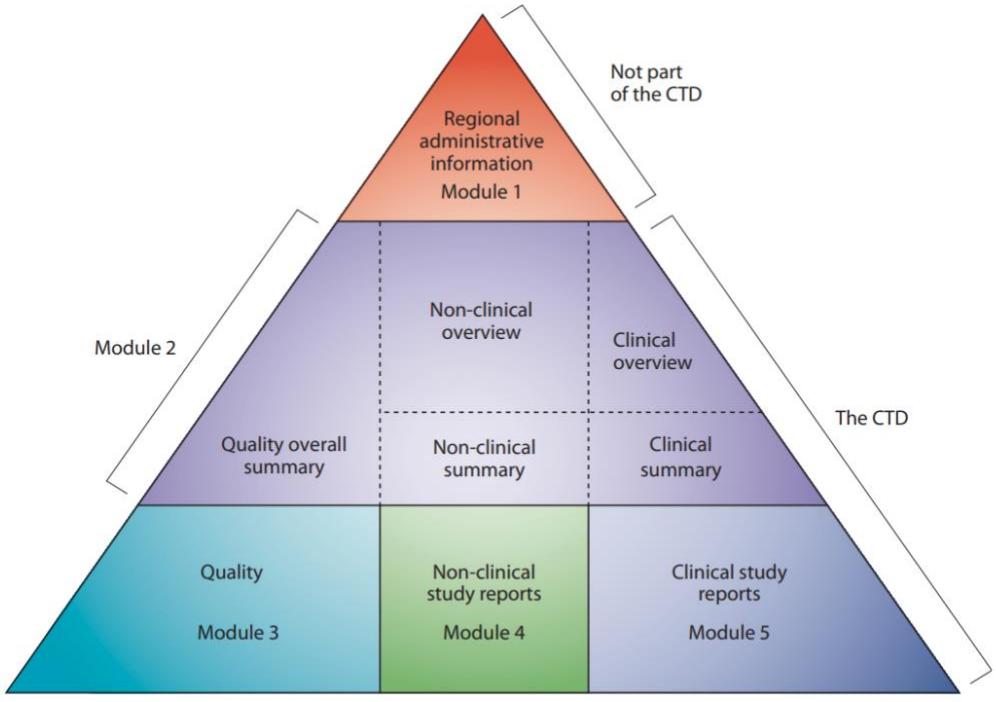
These Global Regulatory agencies require New Drug Applications applications to be submitted in eCTD format.

Electronic Common Technical Document (eCTD):

- The Electronic Common Technical Document (eCTD) is the standard electronic format for pharmaceutical companies submitting New Drug Applications (NDAs), Biologics License Applications (BLAs) and other regulatory reports to different regulatory agencies globally such as FDA, EMA and PMDA.

- eCTD includes the details about medicinal products such as New Drugs and Biologics to these regulatory authorities for getting the approvals to market these products.

- An eCTD submission typically consists of 5 modules.
    - Module 1: Regional Administrative information and prescribing information
    - Module 2: Overviews and Summaries (quality, nonclinical, clinical) of Modules 3–5
    - Module 3: Quality (CMC) information (pharmaceutical documentation)
    - Module 4: Non-clinical study reports (pharmacology/toxicology)
    - Module 5: Clinical study reports (clinical trials).



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

The Common Technical Document (CTD) provides a globally harmonized structure for regulatory submissions and forms the backbone of the electronic CTD (eCTD) used by FDA, EMA, PMDA, Health Canada, NMPA, and other agencies. While the CTD establishes a consistent high-level organization, each module serves a distinct regulatory purpose and carries implications for how statistical programmers prepare, validate, and package clinical data within Module 5.

Module 1 contains region-specific administrative content—such as application forms, labeling, and procedural documents—defined entirely by each regulatory authority. Although it sits outside the harmonized CTD, Module 1 is essential for the eCTD backbone because it includes region-specific XML files containing metadata about the application, product, and submission sequence, as well as the pointers that link to the technical files provided elsewhere in the dossier.

Module 2 provides high-level overviews and summaries of the Quality, Nonclinical, and Clinical components of the submission. It opens with a general introduction to the drug and includes structured summaries such as the Quality Overall Summary, Nonclinical Overview and Summaries, and the Clinical Overview and Clinical Summary. These sections present the rationale, key findings, and benefit–risk considerations that integrate the content of Modules 3–5. For programmers, Module 2 underscores the importance of well-organized clinical data, because reviewers rely on these summaries to contextualize datasets, derived variables, and statistical analyses.

Module 3 presents the Chemistry, Manufacturing, and Controls (CMC) information that describes the drug substance and drug product, including composition, manufacturing processes, analytical methods, and quality control data. Though primarily authored by CMC teams, the structure of Module 3 highlights the overall reporting discipline regulators expect—consistent heading structure, unaltered section numbering, and complete traceability—which parallels expectations for dataset documentation in Module 5.

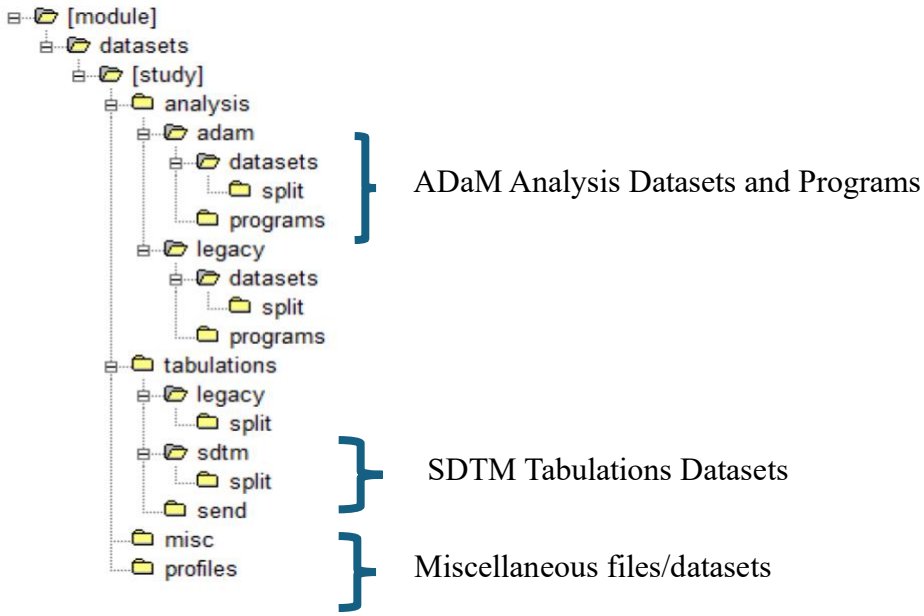
Module 4 compiles the nonclinical study reports across pharmacology, pharmacokinetics, and toxicology, following the format defined in ICH M4S. The standardized sectional structure (4.1–4.3) mirrors the organization expected in clinical data submissions and reinforces the importance of consistent metadata, file naming, and cross-referencing strategies used across Modules.

Module 5 the module of highest relevance to statistical programmers, contains the complete clinical data package, including Clinical Study Reports, biopharmaceutics reports, human PK/PD studies, pivotal efficacy and safety studies, pooled ISS/ISE analyses, BIMO materials, annotated CRFs, patient listings, and cross-study appendices. Module 5's structure is defined by ICH M4E and requires strict placement of each report based on primary study intent. Because Module 5 houses SDTM datasets, ADaM datasets, Define-XML, reviewer's guides, TLFs, and analysis programs, it is the focal point for CDISC standardization and traceability. The organization of this module underscores the need for disciplined dataset creation, transparent derivation logic, consistent metadata, and proper use of controlled terminology to support regulatory review.
Across all regions, Modules 1–5 together establish the regulatory and scientific narrative for product evaluation. For programming teams, understanding the purpose and expectations of each module ensures that clinical data deliverables in Module 5 align seamlessly with the broader

dossier, improving clarity, reducing reviewer queries, and strengthening the overall quality of the submission.

Module 5 Folder Structure:

Figure 1: Folder Structure for Study Datasets



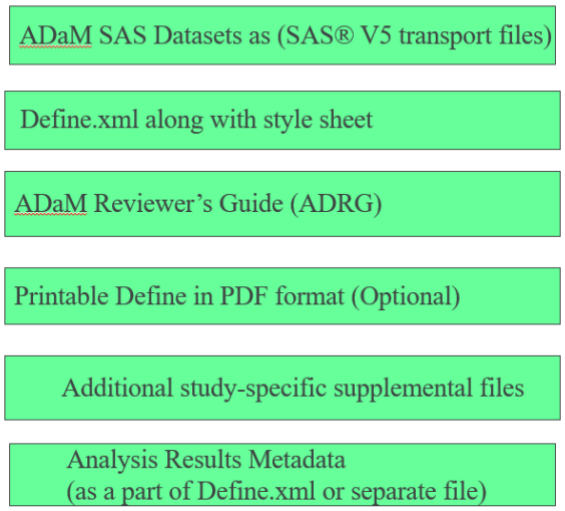
Components of Tabulations Folder: The Tabulations Folder contains all components required for an SDTM e-submission package. This includes SDTM datasets in SAS V5 XPORT format, the annotated CRF (aCRF), the Clinical Study Data Reviewer's Guide (cSDRG), and the full Define-XML with its stylesheet and optional PDF rendering. Any study-specific definitions or supplemental files are also stored here. In practice, sponsors rarely submit SDTM programming code because SDTM datasets are standardized, interpretable without SAS scripts, and the underlying raw data referenced by those programs are typically not part of the submission package.

Components of Tabulations Folder:

- SDTM SAS Datasets as (SAS® V5 transport files)
- Annotated CRF (aCRF)
- Define.xml along with style sheet
- SDTM Reviewer's Guide (cSDRG)
- Printable Define in PDF format (Optional)
- Additional study-specific supplemental files

Components of Analysis Folder: The Analysis Folder houses the ADaM portion of the submission, including ADaM datasets in XPORT format, the Analysis Data Reviewer's Guide (ADRG), the Define-XML, and any optional printable define files. This folder also contains analysis-related programs (ADaM derivation code, TLF programs, and supporting macros) provided in native ASCII SAS (.sas) or R (.r) formats. A frequent misconception is that programs must be renamed as ".txt" files; however, SAS and R scripts are inherently ASCII and can be submitted with their standard extensions. Together, these components ensure that regulators have complete visibility into the analysis datasets, derivation logic, and reproducibility of key results.

Components of Analysis Folder:



FDA Documents, Standards, and Tools:

The FDA's submission framework is built on the Data Standards Catalog, which defines acceptable versions of CDISC SDTM, ADaM, and controlled terminologies, and is supported by planning tools such as the SDSP, TAUGs, CRFs, and the BIMO/CDER Technical Conformance Guides. Core deliverables include XPT datasets, Define-XML, aCRF, cSDRG/ADRG, and (optionally) ARM, all of which must pass FDA validation and business rules. Together, these standards and tools ensure consistent, traceable, and review-ready eCTD submissions.

The FDA outlines clear expectations for standardized clinical data submissions through its CDISC data package requirements, the FDA Data Standards Catalog, and the Study Data Technical Conformance Guide, which define acceptable standards, versions, and technical specifications. Compliance is further ensured through FDA Business Rules, the Validator Rules v1.6, and the requirement for a Study Data Standardization Plan (SDSP), enabling consistent, traceable, and review-ready study data. Collectively, these documents form the foundation of FDA's regulatory framework and guide sponsors in preparing high-quality, standards-aligned eCTD submissions.

PMDA Documents, Standards, and Tools:

PMDA's regulatory framework is anchored by the PMDA Data Standards Catalog, supported by planning requirements such as Form A & B and CRFs, and standardized clinical data using CDISC SDTM, ADaM, and optional TAUGs. Submissions must include aCRF, XPT datasets, Define-XML, cSDRG/ADRG, programs, and PMDA strongly encourages ARM to enhance traceability, with conformance evaluated using PMDA's Study Data Validation Rules. PMDA further relies on global terminologies (MedDRA, WHODrug, CDISC CT) and sponsors engage through Clinical Trial and eData Consultations, ensuring data are review-ready and aligned with Japan's regulatory expectations.

PMDA Requirements for Regulatory Submissions:

PMDA's regulatory submission framework is defined by its Data Standards Catalog, Study Data Validation Rules, and the Technical Conformance Guide, which together specify the required standards, formats, and technical expectations for electronic study data. Sponsors must also complete Form A and Form B, which document the scope and structure of electronic study data planned for submission, ensuring transparency and traceability. These components collectively provide a clear, structured foundation for preparing CDISC-compliant, review-ready submissions for PMDA evaluation.

EMA Mandatory Files for Data Packages:

EMA requires that clinical study datasets be submitted primarily in SAS Transport (XPORT) format, though alternative formats such as XML or JSON may be accepted upon agreement. All submitted data must comply with CDISC SDTM and ADaM standards, accompanied by Define-XML, the Study Data Reviewer's Guide, the Analysis Data Reviewer's Guide, and the full set of analysis and dataset-generation programs, including those used for modelling and simulation. Together, these components ensure complete transparency, traceability, and reproducibility of the clinical evidence package for EMA scientific review.

EMA Optional Files for Data Packages:

EMA allows the inclusion of optional components in the data package when justified procedurally, including Analysis Results Metadata (ARM) strongly recommended for key efficacy endpoints—submitted in XML or PDF. Additional optional items such as BIMO datasets, annotated CRFs, ISS/ISE datasets, and pooled analyses packages can further enhance transparency, traceability, and regulatory assessment where relevant to the submission. These supplemental files strengthen the evidentiary package by enabling deeper methodological insight and supporting EMA's data-centric review processes.

EMA Requirements for Regulatory Submissions:

EMA's regulatory submission framework is grounded in guidance for data submission on investigational medicines and the ICH M4 (R4) CTD structure, which defines how pharmaceutical dossiers must be organized for EU review. Sponsors are also supported by

EMA's clinical study data proof-of-concept pilot resources, including Q&A and detailed procedural information, which together promote standardized, transparent, and data-centric submissions. These documents form the foundation for ensuring that clinical data packages are complete, well-organized, and aligned with EMA's scientific assessment expectations.

Health Canada Requirements for Regulatory Submissions:

Health Canada's regulatory framework is supported by guidance covering drug submissions, biologics, radiopharmaceuticals, and genetic therapies, along with detailed instructions for preparing clinical and bioequivalence data within the CTD structure. Sponsors must follow Health Canada's validation rules for eCTD transactions and the Electronic Common Technical Document (eCTD) format guidance, ensuring that dossiers are well-organized, standards-compliant, and technically validated before transmission. Collectively, these requirements provide a structured pathway for preparing high-quality, review-ready submissions for Canadian regulatory assessment.

Health Canada Validation Rules:

Health Canada enforces eCTD Format Validation Rules (v5.3) that check for structural and technical compliance, including errors for empty folders, unauthorized file/folder access, and sequence folder naming issues, as well as warnings or errors for exceeding maximum file size limits (e.g., 200 MB for PDF, 1 GB for SAS XPT). These rules ensure that submissions are technically sound, fully accessible, and organized correctly, preventing processing delays at the regulatory gateway. Collectively, they form a critical quality gate that sponsors must satisfy before Health Canada will accept an eCTD sequence for review.

NMPA Submission Components:

NMPA requires separate SDTM and ADaM submission packages, each containing XPT datasets, Define-XML, the respective reviewer's guides (cSDRG/ADRG), and the annotated CRF, with ADaM datasets typically encoded in UTF-8/EUC-CN. Sponsors must also provide statistical programs in readable TXT format—well-commented and free of macro dependencies—to ensure full transparency and reproducibility of analyses. Together, these components form the core of the NMPA eSUB package and support traceable, standards-aligned regulatory review.

NMPA-Specific Requirements:

NMPA mandates that key submission components—including dataset and variable labels, AE/CM/MH terminology, Define-XML descriptions and derivations, and aCRF content—be translated into Chinese to support local regulatory review. Sponsors must also provide Chinese translations of values or coding lists for efficacy indicators and ensure that both cSDRG and ADRG are submitted in Chinese. These requirements emphasize NMPA's focus on transparency, linguistic accessibility, and clear traceability across all standardized study data elements.

NMPA Dataset Requirements:

NMPA enforces strict structural and linguistic rules for submitted datasets, including dataset and variable names capped at 8 bytes, labels limited to 40 bytes, and variable lengths not exceeding 200 bytes, with all labels required to be translated into Chinese. Because UTF-8/EUC-CN characters can range from 1 to 4 bytes, sponsors must carefully validate byte-length to avoid submission failures. Additionally, when datasets are split, NMPA requires clear documentation of splitting and merging rules within the Data Reviewer's Guide to ensure transparency and traceability.

Conclusion:

Electronic submissions to global regulatory authorities—including FDA, EMA, PMDA, Health Canada, and NMPA—are essential for obtaining marketing approval and must follow each agency's specific technical and procedural requirements. While core expectations align around ICH eCTD and standardized CDISC datasets (SDTM and ADaM), some regulators impose additional expectations, such as PMDA's strong recommendation to include ARM. Understanding these regional nuances is crucial for effective planning, creation, and submission of high-quality clinical study data packages.

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