



Presenter Bio:

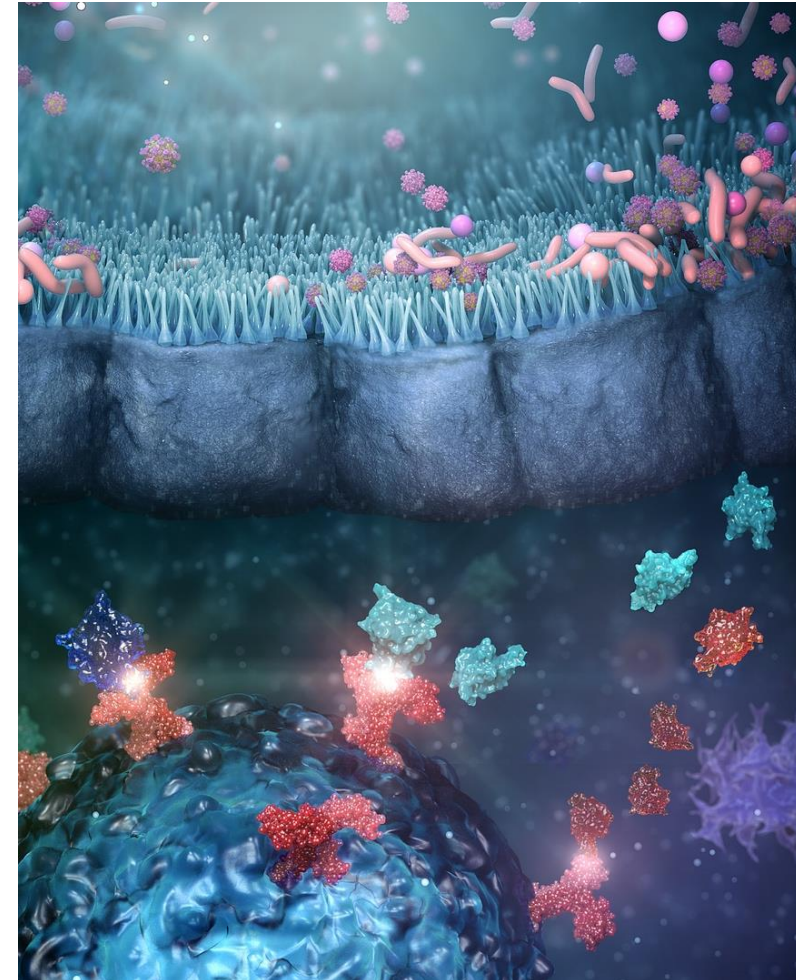
- ❖ I'm Statistical Programming Associate Director and Programming Portfolio Leader at AstraZeneca, with over **15 years of experience** in clinical data analysis and regulatory submissions.
- ❖ My expertise encompasses managing statistical programming projects, ensuring compliance with industry standards, and leading teams to execute quality clinical reports and regulatory submissions.
- ❖ In addition to my technical accomplishments, I have been actively involved in peer review and thought leadership in the clinical research community. I have served as Mentor and Judge at several Hackathons such as HackNC, Hack Ohio and SAS Hackathon.
- ❖ I have been actively involved in peer review and thought leadership in the clinical research community. I have judged 2025 Claro Awards for AI Excellence and served as a peer review panelist for various prestigious organizations, including the Society for Clinical Data Management (SCDM).
- ❖ I'm also a regular speaker and presenter, at PharmaSUG (Software Users Group of life science and health research professionals) Single-Day Event and SouthEast SAS® Users Group Conferences, SAS Life Sciences Community Connection.





Electronic Clinical Data Submissions Across Global Regulatory authorities

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AstraZeneca



Agenda:

- ❖ Introduction
- ❖ Global Regulatory Agencies FDA, EMA, PMDA, NMPA, Health Canada
- ❖ What is eCTD?
- ❖ Modules of eCTD
- ❖ Requirements for regulatory submissions: Similarities and Differences
- ❖ Conclusion



FDA, CDER, CBER:



- ❖ **FDA (Food and Drug Administration):** Federal agency in US 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.
- ❖ **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.

Source: <https://www.fda.gov/>
<https://www.fda.gov/about-fda/fda-organization/center-drug-evaluation-and-research-cder>
<https://www.fda.gov/about-fda/fda-organization/center-biologics-evaluation-and-research-cber>
<https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd>



EMA:



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- ❖ **EMA (European Medicines Agency):** Medicinal 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.

Source:

<https://www.ema.europa.eu/en/about-us>

<https://www.ema.europa.eu/en/guideline-use-ctd-format-preparation-registration-application-traditional-herbal-medicinal-products>

<https://esubmission.ema.europa.eu/ectd/>



- ❖ 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..
- ❖ 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 by 2026.

Source:

<https://www.pmda.go.jp/english/about-pmda/outline/0005.html>

<https://www.pmda.go.jp/files/000156431.pdf>

<https://www.pmda.go.jp/files/000251542.pdf>

<https://www.pmda.go.jp/files/000247157.pdf>



NMPA:



NATIONAL MEDICAL PRODUCTS ADMINISTRATION
国家药品监督管理局

- ❖ **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.
- ❖ **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.

Source: https://english.nmpa.gov.cn/2019-07/18/c_377587.htm
https://english.nmpa.gov.cn/2019-07/19/c_389169.htm
https://english.nmpa.gov.cn/2021-09/30/c_693017.htm



Health Canada :



Government
of Canada

Health Canada

- ❖ **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.

Source:

<https://www.canada.ca/en/health-canada/corporate/mandate/regulatory-role.html>

<https://www.canada.ca/en/health-canada/services/drugs-health-products.html>

<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/fact-sheets/drugs-reviewed-canada.html>

https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/draft_ebauche_ctdbe-eng.pdf

<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/filing-submissions-electronically.html>



Other Global 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 Organization (CDSCO):** It is the National Regulatory Authority (NRA) of India responsible for approval of Drugs, Conduct of Clinical Trials, laying down the standards for Drugs, control over the quality of imported Drugs in the country.

Source:

<https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency/about>

<https://www.tga.gov.au/>

<https://cdsco.gov.in/opencms/opencms/en/Home/>



Standard Format for submissions:

 **U.S. FOOD & DRUG**
ADMINISTRATION

[← Home](#) / [Drugs](#) / [Development & Approval Process | Drugs](#) / [Forms & Submission Requirements](#) / [Electronic Regulatory Submission and Review](#)
/ [Electronic Common Technical Document \(eCTD\)](#)

Electronic Common Technical Document (eCTD)

Electronic Regulatory Submission and Review

Electronic Common

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). Please refer to the [eCTD Guidance](#)

Quick Links

- [eCTD Guidance \(Final, Rev 8\)](#) (PDF -11 KB)



eCTD v3.2

[Home](#)
[Human eSubmission](#)
 [eCTD v3.2](#)
 [eCTD EU M1 specification](#)
[Veterinary eSubmission](#)
[eSubmission expert group](#)
[eSubmission expert group documents](#)
[External Links](#)
Systems:
 [Common Repository](#)
 [eAF](#)

The Common Technical Document (CTD) describes the organisation of modules, sections and documents to be used by an Applicant for a Marketing Authorisation for a medicinal product for human use agreed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). The electronic Common Technical Document (eCTD) allows for the electronic submission of the Common Technical Document (CTD) from applicant to regulator. While the table of content is consistent with the harmonised CTD, the eCTD also provides a harmonised technical solution to implementing the CTD electronically. In other words, an eCTD is the submission of PDF documents, stored in the eCTD directory structure, accessed through the XML backbone and with the files integrity guaranteed by the MD5 Checksum.

The current version of the eCTD specification to be used for CTD modules 2-5 is the [Electronic Common Technical Document Specification V3.2.2](#) (PDF). More information about the standard can be found at [the ICH eCTD webpage](#).

For eCTD submissions within EU, the EU Module 1 eCTD Specification (see link below) should be used.

The eCTD format is mandatory to use for all submission types related to Marketing Authorisation for products within all EU procedures (i.e. Centralised, Decentralised and Mutual Recognition Procedures). In accordance with the [eSubmission Roadmap](#), Mandatory eCTD format is also stepwise introduced for National Procedures.



Government
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> [Applications and Submissions - Drug Products](#) > [Guidance documents on applications and submissions for drug](#)

Filing submissions electronically

Companies are required to file submissions electronically to Health Canada in either Electronic Common Technical Document (eCTD) format or non-eCTD format, depending on the regulatory activity type. The sections below include links to documents that provide



What is 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 is the industry standard used extensively within Europe, USA, and Japan for the transfer of regulatory information. It is gradually being rolled out by other regulatory agencies around the world.
- ❖ eCTD includes the details about medicinal products such as New Drugs and Biologics to these regulatory authorities for getting the approvals to market human pharmaceutical products.
- ❖ The standard was developed by the International Conference on Harmonization (ICH) and defines the criteria that makes an electronic submission technically valid.
- ❖ It enables industry to communicate and exchange information with regulators in a consistent format.

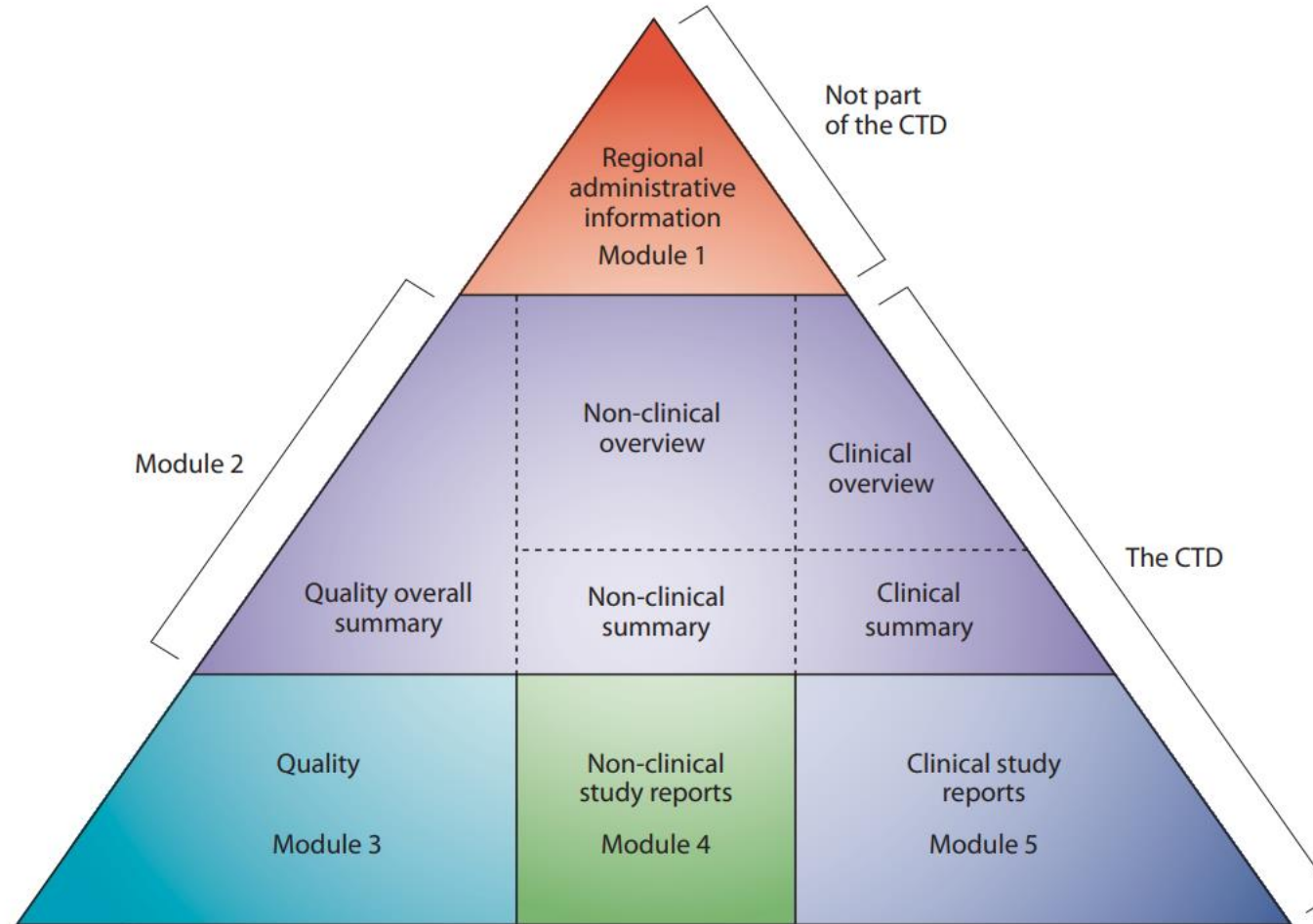


Modules of Electronic Common Technical Document (eCTD):

- ❖ eCTD dossier is divided into five main 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)**
- ❖ Statistical programmers focus on Modules 2 and 5, providing summaries and detailed data analyses critical for approvals.



CTD Triangle:



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.



Module 1: Regional Administrative information and prescribing information

- ❖ It contains documents that are specific to each region, e.g. application forms or the proposed label.
 - ❖ The content and format of this module is specific to individual Regulatory Authorities.
 - ❖ The relevant regulatory authorities specify the content and format of this module.
-
- ❑ 1.0 Cover letter.
 - ❑ 1.1 Comprehensive table of contents.
 - ❑ 1.2 Application form.
 - ❑ 1.3 Product information documents.
 - ❑ 1.4 Information about the experts.
 - ❑ 1.5 Specific requirements for different types of applications (if required).
 - ❑ 1.6 An Environmental risk assessment.
 - ❑ 1.7 Information relating to orphan market exclusivity (if required).
 - ❑ 1.8 Information relating to pharmacovigilance.
 - ❑ 1.9 Information relating to clinical trials (if required).
 - ❑ 1.10 Information relating to paediatrics.



Module 2: Common Technical Document Overviews and Summaries

- ❖ Provides an overall summary of the quality information. It contains seven sections:
 - ❑ 2.1 Table of Contents of Modules 2-5
 - ❑ 2.2 CTD Introduction
 - ❑ 2.3 Quality Overall Summary
 - ❑ 2.4 Nonclinical Overview
 - ❑ 2.5 Clinical Overview: provides a critical analysis of the efficacy and safety data of the medicinal product
 - ❑ 2.6 Nonclinical Written and Tabulated Summaries
 - ❑ 2.7 Clinical Summary
 - 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods
 - 2.7.2 Summary of Clinical Pharmacology studies
 - 2.7.3 Summary of Clinical Efficacy
 - 2.7.4 Summary of Clinical Safety
 - 2.7.5 References
 - 2.7.6 Synopses of individual studies



Module 3: Quality (pharmaceutical documentation)

- ❖ This module contains information pertinent to the Quality of the pharmaceutical substance and product.
- ❖ Module 3 presents the (CMC) Chemistry, Manufacturing and Controls reports of the drug/biologic substance and product.
- ❖ Sections on both drug substance and drug product are included in this module. The main headings in this section (that must not be altered) are as follows:
 - ❑ 3.1 Table of contents of Module 3
 - ❑ 3.2 Body of data
 - 3.2.S Drug Substance
 - 3.2.P+ Drug Product
 - ❑ 3.3 Literature references used in Module 3



Module 4: Non-clinical reports (pharmacology/toxicology)

- ❖ This module contains information on the non-clinical (pharmacological, pharmacokinetic and toxicological) evaluation of the drug/biologic substance and product.
- ❖ This information is typically provided in the form of study reports and publications.
- ❖ The main headings in this section (that must not be altered) are as follows:
 - ❑ 4.1 Table of contents of Module 4
 - ❑ 4.2 Study reports
 - 4.2.1 Pharmacology
 - 4.2.2 Pharmacokinetics
 - 4.2.3 Toxicology
 - ❑ 4.3 Literature references used in Module 4.



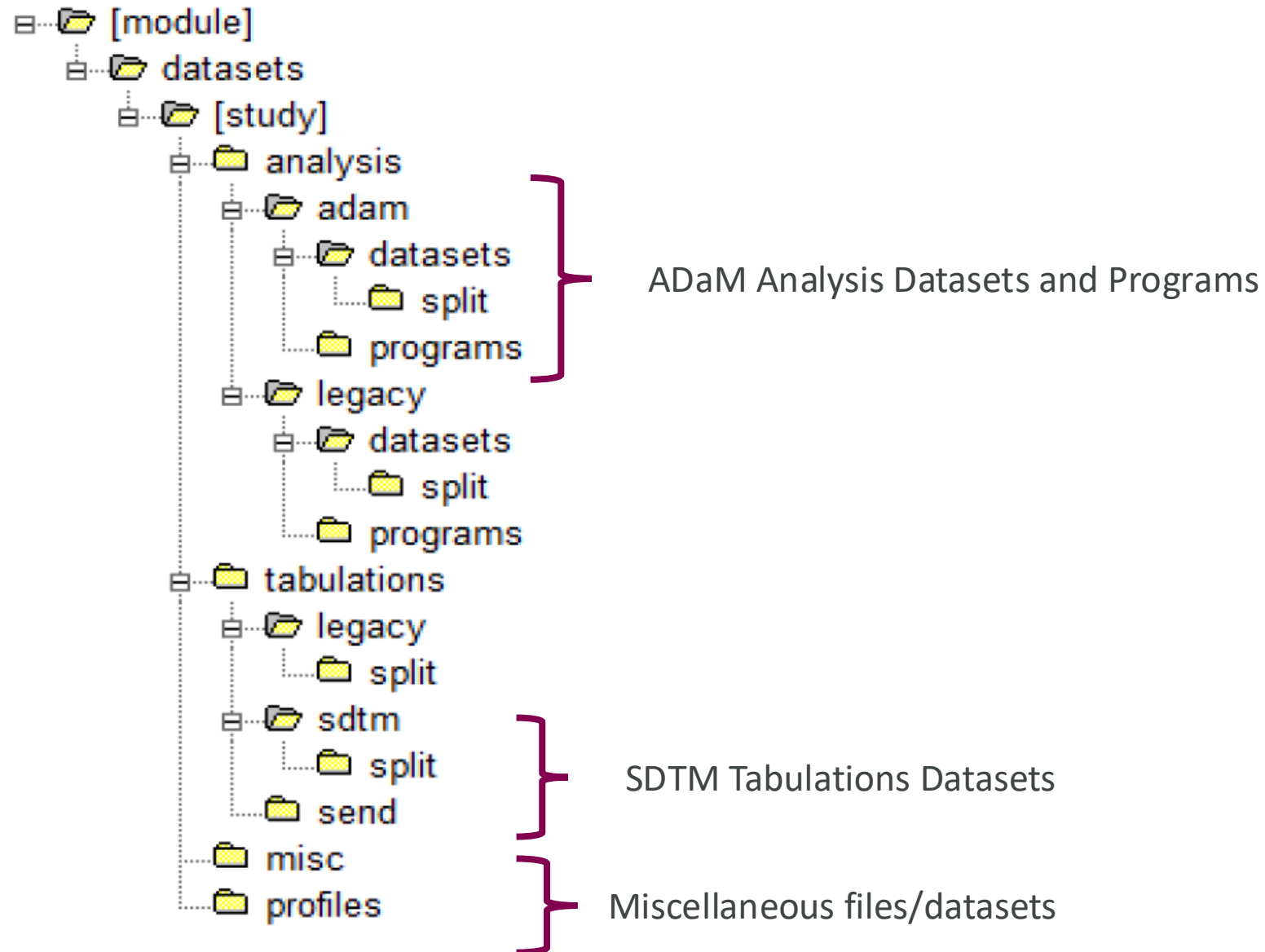
Module 5: Clinical study reports (clinical trials)

- ❖ This module Presents information on the clinical evaluation of the drug/biologic product. The main headings in this section are as follows:
 - ❑ 5.1 Table of contents of Module 5
 - ❑ 5.2 Tabular listing of all clinical studies
 - ❑ 5.3 Clinical study reports
 - ❑ 5.4 Literature references.
 - ❑ 5.3.5 Reports of efficacy and safety studies
 - 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
SDTM, ADaM datasets, Tables, Listings and figures
 - 5.3.5.2 Study Reports of Uncontrolled Clinical Studies
 - 5.3.5.3 Reports of Analyses of Data from More than One Study
 - Pooled safety analyses (ISS Tables, Listings and figures + CRT)
 - Pooled Efficacy Analyses (ISE Tables, Listings and figures + CRT)
 - 5.3.5.4 Other Study Reports (BIMO)



Module 5 Folder Structure:

Figure 1: Folder Structure for Study Datasets



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:

ADaM SAS Datasets as (SAS® V5 transport files)

Define.xml along with style sheet

ADaM Reviewer's Guide (ADRG)

Printable Define in PDF format (Optional)

Additional study-specific supplemental files

Analysis Results Metadata
(as a part of Define.xml or separate file)



FDA documents, standards and tools:

Mandates	➡	FDA Data Standard Catalog
Planning	➡	SDSP, Waiver, TAUGs, CRF, BIMO(CDER) TCG
Study Data Standards	➡	CDISC SDTM, ADaM and TAUGS
Tabulation	➡	acrf, xpt, Define-XML, csdrg
Analysis	➡	xpt, Define-XML, adrg, programs, ARM (optional)
BIMO (CDER)	➡	listings, clinsite.xpt, define.xml
P21	➡	P21 E v4.1.1
Validation Rules	➡	FDA Validation and Business Rules
Dictionaries/CT	➡	MedDRA, WHODrug Global, CDISC CT
Meetings	➡	Type A, B and C



FDA Requirements for regulatory submissions :

- ❖ **FDA requirements for CDISC submissions data packages:** <https://www.fda.gov/industry/fda-data-standards-advisory-board/study-data-standards-resources>
- ❖ **FDA Data Standards Catalog:** Contains specifications for the data standards and versions that the FDA supports. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/data-standards-catalog>
- ❖ **FDA Study Data Technical Conformance Guide:** Contains technical specifications for submission of electronic study data. <https://www.fda.gov/media/88173/download>
- ❖ **FDA Business Rules:** The [Business Rules v1.5 \(May 2019\)](#) help ensure that the study data are compliant, useful, and will support meaningful review and analysis.
- ❖ **FDA Validator Rules:** The [Validator Rules v1.6 \(December 2022\)](#) are used by the FDA to ensure data are standards compliant and support meaningful review and analysis.
- ❖ **Study Data Standardization Plan (SDSP):** Documentation of data standards discussions with FDA. Although a specific template is not specified, an example SDSP is available ([PhUSE SDSP Package](#)).



Study Data Standardization Plan (SDSP) Requirement :

2.1 Study Data Standardization Plan

For clinical and nonclinical studies, sponsors should include a plan (e.g., during the early stages of product development conducted under the IND) describing the submission of standardized study data to FDA. The Study Data Standardization Plan (SDSP) assists FDA in identifying potential data standardization issues early in the development program. Sponsors may also initiate discussions at the pre-IND stage. For INDs, NDAs, and BLAs, the SDSP should be located in eCTD sections 1.13.9 General Investigational Plan or 1.20 General investigational plan for initial IND. Although a specific template is not specified, an example SDSP is available.¹¹

In addition, for clinical studies that will be submitted to CBER, the SDSP appendix should be provided to the review office no later than the End-of-Phase 2 (EOP2) meeting. The CBER SDSP appendix should include tables of proposed SDTM domain/variable usage, supplemental domain usage and proposed analysis.

Source: FDA's Study Data Technical Conformance Guide



Study Data Standardization Plan (SDSP) Requirement :



For clinical and nonclinical studies, sponsors should include a plan (e.g., during the early stages of product development conducted under the IND) describing the submission of standardized study data to FDA.



An SDSP should be provided with pre-NDA and pre-BLA meetings.



For clinical studies that will be submitted to CBER, the SDSP appendix should be provided to the review office no later than the End-of-Phase 2 (EOP2) meeting.



The CBER SDSP appendix should include tables of proposed SDTM domain/variable usage, supplemental domain usage and proposed analysis.



Although a specific template is not specified, an example SDSP is available ([PhUSE SDSP Package](#)).



Study Data Standardization Plan (SDSP) Contents:

Introduction

General Sponsor Information

Product Information

List of Studies and Standards

- Clinical & non-clinical

Non-conformance to Supported Standards Justification

FDA Data Standards Discussions

CBER Appendix



Study Data Standardization Plan (SDSP) Sample Image:

Study Identifier	Brief Title	Study Design	Study Status	Study Start Date	Exchange Standards	Terminology Standards
Phase 3 Interventional Studies - Asthma						
ABC-AP-008	A Proof-of-Concept Trial in Patients with Severe, Difficult to Control, Non-atopic Asthma	Nonrandomized, Control None, Single Group Assignment, Open Label, Safety/Efficacy, Treatment	PLANNED	2018-06-09 (forecasted Informed Consent)	SDTM v1.4/ SDTM IG 3.2 SDTM define.xml 2.0 ADaM v2.1/ ADaM IG1.0 ADAM define.xml 2.0	CDISC SDTM Terminology 2017-06-30 MedDRA (Adverse Events/ Medical History) Initial 18.0 Final 18.0 WHO-DD (Medications) Enhanced B2 format 01JUN2016
ABC-AP-009	A Study of MyNewDrug in Adolescent Patients With Uncontrolled Asthma Who Are on Inhaled Corticosteroids and a Second Controller Medication	Randomized, Control Active, Crossover Assignment, Single Blind, Safety/Efficacy, Treatment	PLANNED	2018-08-10 (forecasted Informed Consent)	SDTM v1.4/ SDTM IG 3.2 SDTM define.xml 2.0 ADaM v2.1/ ADaM IG 1.0 ADaM define.xml 2.0	CDISC SDTM Terminology 2017-06-30 MedDRA (Adverse Events/ Medical History) Initial 18.1 Final 18.1 WHO-DD (Medications) Enhanced B2 format 01DEC2016

Source: [PhUSE SDSP Package](#)



PMDA documents, standards and tools:

Mandates	➡	PMDA Data Standard Catalog
Planning	➡	Form A & B, CRF
Study Data Standards	➡	CDISC SDTM, ADaM and TAUGS (optional)
Tabulation	➡	acrf, xpt, Define-XML, csdrg
Analysis	➡	xpt, Define-XML, adrg, programs, ARM (strongly recommended)
BIMO (CDER)	➡	Not Applicable
P21	➡	P21 E v4.0.2
Validation Rules	➡	PMDA Study Data Validation Rules
Dictionaries/CT	➡	MedDRA, WHODrug Global, CDISC CT
Meetings	➡	Clinical Trial and eData Consultation



PMDA Requirements for regulatory submissions:

- ❖ **Overview of PMDA requirements for regulatory submissions:** containing links to many useful documents and guidance for CDISC data submissions. <https://www.pmda.go.jp/english/review-services/reviews/0002.html>
- ❖ **PMDA Data Standards Catalog:** Contains specifications for the data standards and versions that the PMDA supports.
- ❖ **Study Data Validation Rules:** PMDA's validation rules for study data.
- ❖ **Technical Conformance Guide:** Contains technical specifications for submission of electronic study data. <https://www.pmda.go.jp/files/000215100.pdf>
- ❖ **Explanation of Electronic Study Data (Form A and Form B):** Describe the contents of electronic study data planned to be submitted to the PMDA.
- ❖ **Form A:** <https://www.pmda.go.jp/files/000247169.pdf>
- ❖ **Form B:** <https://www.pmda.go.jp/files/000247164.pdf>



PMDA Selecting Standards Version :

- ❖ Refer to “PMDA Data Standards Catalog” on the PMDA’s website for the versions that are acceptable.
- ❖ It is advisable to use the latest version when preparing the data.
- ❖ Datasets created using a version other than the acceptable one on applications must be converted using the acceptable version.
- ❖ Different versions of the CDISC standards may be used in different studies within the same application; however, a single version of the standards must be used within a clinical study or an analysis.
- ❖ If different versions are used for any parts of the same clinical study or the same analysis, it should be explained in the reviewer’s guide, with the reasons for the use of the different versions indicated.



PMDA Data Standards Catalog :

- ❖ Use planned filing date in conjunction with PMDA's data standards catalog to develop data standardization approach.

PMDA Data Standards Catalog (2025-03-14) - Data Exchange Standards						
Use	Data Exchange Standard	Supported Version(s)	Implementation Guide Version	Exchange Format	Date Support Begins (YYYY-MM-DD)	Date Support Ends (YYYY-MM-DD)
Clinical study datasets - Transport	SAS Transport (XPORT)	5	-	XPT	2016-10-01	
Clinical study datasets	SDTM	2.0	3.4	XPT	2025-04-01	
Clinical study datasets	SDTM	1.7	3.3	XPT	2023-04-01	
Clinical study datasets	SDTM	1.4	3.2	XPT	2016-10-01	
Clinical study datasets	SDTM	1.3	3.1.3	XPT	2016-10-01	
Clinical study datasets	SDTM	1.2	3.1.2 Amendment1	XPT	2016-10-01	
Clinical study datasets	SDTM	1.2	3.1.2	XPT	2016-10-01	
Clinical study datasets	ADaM	2.1	1.3	XPT	2024-04-01	
Clinical study datasets	ADaM	2.1	1.2	XPT	2024-04-01	
Clinical study datasets	ADaM	2.1	1.1	XPT	2022-01-01	
Clinical study datasets	ADaM	2.1	1.0	XPT	2016-10-01	
Clinical study data definition files	Define	2.1	-	XML	2024-04-01	
Clinical study data definition files	Define	2.0	-	XML	2016-10-01	
Clinical study data definition files	Define	1.0	-	XML	2016-10-01	2025-03-31



PMDA Validation of CDISC-conformant Data :

- ❖ PMDA will perform validation of CDISC-conformant data using Pinnacle 21 Enterprise.

Severity	Action
Reject	Rules which, if violated, <u>will cause the review to be suspended until corrections have been made.</u> Very basic rules such as the presence/absence of necessary datasets for each clinical study.
Error	Rules which, if violated, will require an explanation. In many cases, these rules are clearly stated in each standard and implementation guide, and if violated, <u>the applicant should explain in the reviewer's guide about the reason for the violation and the reason why it is not possible to correct it.</u>
Warning	Rules which, even when violated, will not necessarily require any explanation. The reason for the violation possibly is requested separately from the perspective of the quality of the clinical study data



PMDA Key Guidance Document Related to esubmission :

- [Revision of Notification on Electronic Study Data \[189KB\]](#)

Revision of Notification on Handling of Submission of Electronic Study Data for New Drug Applications (PSB/PED Notification No. 0408-3, by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare, dated April 8, 2024)

- [Q&A Regarding Notification on Electronic Study Data \[135KB\]](#)

Question and Answer Guide Regarding "Notification on Handling of Submission of Electronic Study Data for New Drug Applications" (Administrative Notice of the Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare, dated April 8, 2024)

- [Notification on Gateway Application \[284KB\]](#)

New Drug Applications Using the Gateway System (PSEHB/PED Notification No. 0401-7, by the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated April 1, 2022)

- [Revision of Technical Conformance Guide \[351KB\]](#)

Revision of Technical Conformance Guide on Electronic Study Data Submissions (PMDA/CPE Notification No. 1345 and PMDA/CRS Notification No. 21, by the Director of Center for Product Evaluation and the Director of Center for RS, Pharmaceuticals and Medical Devices Agency, dated April 8, 2024)

FAQs on Electronic Study Data Submission

This document summarizes inquiries on electronic study data submission received by the PMDA in a Q&A format.

- [FAQs on Electronic Study Data Submission \[813KB\]](#)

Please utilize these Q&A to resolve problems and questions related to electronic study data submission.

Notice: This is an English version of the following FAQs on electronic study data submission published on April 8, 2024.

Explanation of Electronic Study Data (Form A and Form B)

- [Explanation of Electronic Study Data \(Form A\) \[501KB\]](#)

- [Explanation of Electronic Study Data \(Form B\) \[450KB\]](#)

From October 1, 2023 (application date), PMDA does not require to submit "Explanation of Electronic Study Data (Form A)" and "Explanation of Electronic Study Data (Form B)", that describe the contents of electronic study data planned to be submitted to the PMDA, before electronic study data submission for the new drug application.

Please note that Form A and Form B still must be submitted to the PMDA for consultations related to submission of electronic study data for new drug applications.

Source: [New Drug Review with Electronic Data | Pharmaceuticals and Medical Devices Agency \(pmda.go.jp\)](https://pmda.go.jp)



PMDA CDISC Data Standards Validation :

- CDISC Data Validation Software

The software that PMDA is using is Pinnacle 21 Enterprise 5.1.2, and the engine corresponding to the validation rules are as follows.

- PMDA 1511.6 (Validation Rule Version 1.0)
- PMDA 1810.3 (Validation Rule Version 2.0)
- PMDA 2010.2 (Validation Rule Version 3.0)
- PMDA 2211.1 (Validation Rule Version 4.0)
- PMDA 2311.0 (Validation Rule Version 5.0)
- PMDA 2411.0 (Validation Rule Version 6.0)

On December 15, 2023, PMDA changed the engine from PMDA 2211.0 to PMDA 2211.1 for validation rule version 4.0. This change is intended to resolve an issue of report output and does not change validation results. Therefore, if the validation has been already performed using the previous PMDA 2211.0, there is no need to perform the validation again using the current PMDA 2211.1.

Source: [New Drug Review with Electronic Data | Pharmaceuticals and Medical Devices Agency \(pmda.go.jp\)](https://www.pmda.go.jp/english/press/2023/1215_01.html)



EMA Requirements for regulatory submissions:

- ❖ Data submission on investigational medicines: guidance for clinical trial sponsors
- ❖ <https://www.ema.europa.eu/en/human-regulatory-overview/research-development/clinical-trials-human-medicines/data-submission-investigational-medicines-guidance-clinical-trial-sponsors#data-submission-13885>
- ❖ ICH guideline M4 (R4) on common technical document (CTD) for the registration of pharmaceuticals for human use - organisation of CTD
- ❖ https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-m4-r4-common-technical-document-ctd-registration-pharmaceuticals-human-use-organisation-ctd-step-5_en.pdf
- ❖ Questions and Answers about the clinical study data proof-of-concept pilot for industry
https://www.ema.europa.eu/en/documents/other/questions-answers-about-clinical-study-data-proof-concept-pilot-industry_en.pdf
- ❖ Information about the clinical study data proof-of-concept pilot for industry
https://www.ema.europa.eu/en/documents/other/information-about-clinical-study-data-proof-concept-pilot-industry_en.pdf



EMA Mandatory files to be included in the data package:

- ❖ The data sets may be submitted in SAS Transport format (XPORT).
- ❖ However, the Agency will also consider other file transport formats such as Extensible Markup Language (XML) or JavaScript Object Notation (JSON) upon mutual agreement between the Agency and the applicant/MAH.
- ❖ The data sets from clinical trials should comply with Clinical Data Interchange Standards Consortium (CDISC) Analysis Data Model (ADaM) and CDISC Study Data Tabulation Model (SDTM) data standards.
- ❖ The data definition files in CDISC Define-XML format.
- ❖ The Analysis Data Reviewer's Guide and the Study Data Reviewer's Guide.
- ❖ The software programs for (i) creation of the ADaM datasets and (ii) related to the primary and secondary efficacy analyses including programs to generate figures and tables.
- ❖ The software programs used to generate datasets used for modelling & simulation, incl. PopPK, PKPD, ER, PBPK.
- ❖ Source: https://www.ema.europa.eu/en/documents/other/questions-answers-about-clinical-study-data-proof-concept-pilot-industry_en.pdf
- ❖ https://www.ema.europa.eu/en/documents/other/information-about-clinical-study-data-proof-concept-pilot-industry_en.pdf



EMA optional files to be included in the data package:

- ❖ The submission of additional files may be agreed upon on a procedural basis. For example, the following files are optional to be included in the data package that is submitted to the Agency.
- ❖ It is highly recommended to submit the Analysis Results Metadata (ARM) for the primary and key secondary endpoints. The ARM may be submitted in XML or in a non-machine-readable format such as PDF.
- ❖ The Bioresearch monitoring (BIMO) datasets and ancillary documents, with technical conformance guidance issued by the Office of Scientific Investigations (OSI), which are provided in FDA applications (link).
- ❖ The annotated case report forms (aCRF).
- ❖ Data on the Integrated Summary of Safety and Integrated Summary of Efficacy.
- ❖ Pooled data analyses packages, if they support the underlying submission.
- ❖ Source: https://www.ema.europa.eu/en/documents/other/questions-answers-about-clinical-study-data-proof-concept-pilot-industry_en.pdf
- ❖ https://www.ema.europa.eu/en/documents/other/information-about-clinical-study-data-proof-concept-pilot-industry_en.pdf



Health Canada Requirements for regulatory submissions :

- ❖ **Guidance on management of drug submissions and applications: Overview:**
- ❖ <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/management-drug-submissions-applications.html>
- ❖ **Biologics, radiopharmaceuticals and genetic therapies:**
- ❖ <https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies.html>
- ❖ **Drug products:** <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products.html>
- ❖ **Preparation of Comparative Bioavailability Information for Drug Submissions in the CTD Format"**
https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/draft_ebauche_ctdbe-eng.pdf
- ❖ **Validation rules for regulatory transactions in electronic Common Technical Document (eCTD) format**
- ❖ <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/ectd/notice-validation-rules-regulatory-transactions-submitted-health-canada-electronic-common-technical-document-format-2016-12-1.html>
- ❖ **Preparation of regulatory activities in the Electronic Common Technical Document (eCTD) format**
<https://publications.gc.ca/site/eng/9.882674/publication.html>
- ❖ https://publications.gc.ca/collections/collection_2021/sc-hc/H164-293-2019-eng.pdf



Health Canada Validation rules:

Health Canada eCTD format Validation Rules version 5.3

ID #	Rule Name	Rule Description	Severity
A – GENERAL			
A01	Empty Folders	Checks the sequence folder structure for any empty folders (folders without any files or subfolders).	Error
A02	File and Folder Security	Checks the sequence folder structure for any files or folders the user does not have access permission to.	Error
A03a	File Size	This rule's implementation checks for files that exceed the configured maximum size. Warning for PDF files between 150 MB and 200 MB. Warning for other file types larger than 100 MB (excluding SAS XPT).	Warning
A03b	File Size	This rule's implementation checks for files that exceed the configured maximum size (Max. size: 200 MB for PDF, 1 GB for SAS XPT).	Error
A05a	Sequence Folder Requirements	Checks the sequence folder name. Furthermore the rule will report a finding if the sequence seems to be the initial sequence for the application but its name is not 0000.	Error

Source: <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/ectd/notice-validation-rules-regulatory-transactions-submitted-health-canada-electronic-common-technical-document-format-2016-12-1.html>



NMPA CLINICAL DATA SUBMISSION GUIDELINE :

- ❖ The National Medical Products Administration (NMPA) has constantly improved and standardized the requirements of clinical trial data submission,

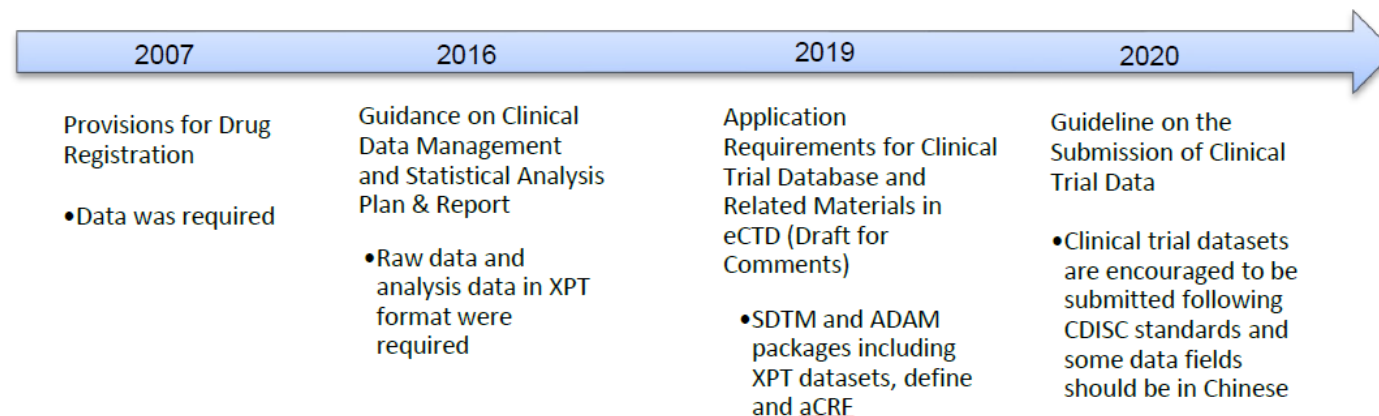


Figure 1. Evolution of Key Data Submission Requirements

- ❖ First draft Guidance was published in **May 2020** for public review.
- ❖ Final Guidance on the Submission of Clinical Trial Data (for Trial Implementation) was released on **July 20, 2020**.
- ❖ New Guidance went into effect on **Oct.1, 2020** for China NDA submission of drugs and biological products.



NMPA submission Components:

- This folder contains components for SDTM eSUB data package:
- **SDTM package:**
 - SDTM datasets in XPT format,
 - Data definition file (Define.xml/Define.pdf),
 - clinical study data reviewer's guide (cSDRG.pdf),
 - annotated case report forms (aCRF.pdf)
- **ADaM package:**
 - ADaM datasets in XPT format (usually using utf8/euc-cn encoding),
 - data definition file (Define.xml/Define.pdf),
 - analysis data reviewer's guide (ADRG.pdf),
 - statistical programs of datasets and reports in TXT format.
 - The programs should be comprehensive, readable, with enough comments and without references to macros.



NMPA specific requirements :

❖ There are specific requirements to the contents in the package, major one of them is the translation of the foreign language database to Chinese. The contents that should be translated to Chinese include:

❖ **Dataset:**

- Dataset and variable labels;
- Names of AE, CM and MH categories and terms as reported in CSR and other documents

❖ **Define:**

- Description of dataset;
- Description and derivation of variables;
- values or coding list for efficacy indicator

❖ **aCRF:**

- Description of the questions that were designed to collect data;
- Value or coding of questions for efficacy indicator

❖ cSDRG and ADRG: Data reviewer's guides should be submitted in Chinese.



NMPA Datasets Requirements:

- ❖ Dataset and variable names should not exceed 8 bytes
- ❖ Variable labels should not exceed 40 bytes
- ❖ Variable length should not exceed 200 bytes
- ❖ Dataset and variable labels should be in Chinese
- ❖ Depending on encoding a character may use 1-4 bytes
- ❖ When splitting datasets, make sure to provide rules for splitting and merging details in Data Reviewer's Guide.



Conclusion:

- ❖ 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.



QUESTIONS

