

China Center for Drug Evaluation, NMPA

Electronic study data submission Requirements

SA02



Wednesday, August 18, 2021

Majdoub Haloui

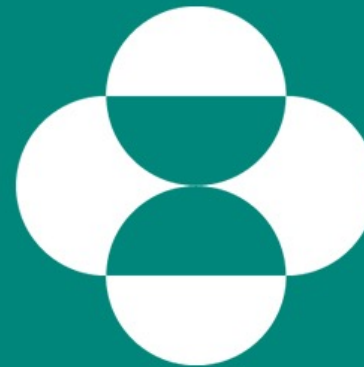
Prin. Scientist, Statistical Programming

Yanhong Li

Assoc. Dir, Statistical Programming

Hong Qi

Prin. Scientist, Statistical Programming



INVENTING
FOR LIFE

Objectives

- NMPA & CDE Introduction
- New CDE Guidance
- CDE Submission Components and Guidance
- Chinese Translation Requirements
- CDE and CDISC Standards
- Challenges from recent Filings



NMPA & CDE Introduction



NATIONAL MEDICAL PRODUCTS ADMINISTRATION

国家药品监督管理局

- **National Medical Products Administration (NMPA)**

- Chinese government's administrative body responsible for regulating pharmaceuticals, medical devices, and cosmetics in China.
- Grants permission for clinical trials to be conducted in China.
- In 2018 China's State Food and Drug Administration (CFDA China) was renamed to NMPA

- **NMPA's Center for Drug Evaluation (CDE)**

- Responsible for the evaluation of drug clinical trial applications, drug marketing authorization applications, supplementary applications, and overseas drug production registration applications.

New CDE Guidance

- **NMPA CDE Guidance on the Submission of Clinical Trial Data**

- First draft Guidance was published in **May 2020** for public review.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.

- **Where is the Guidance located**

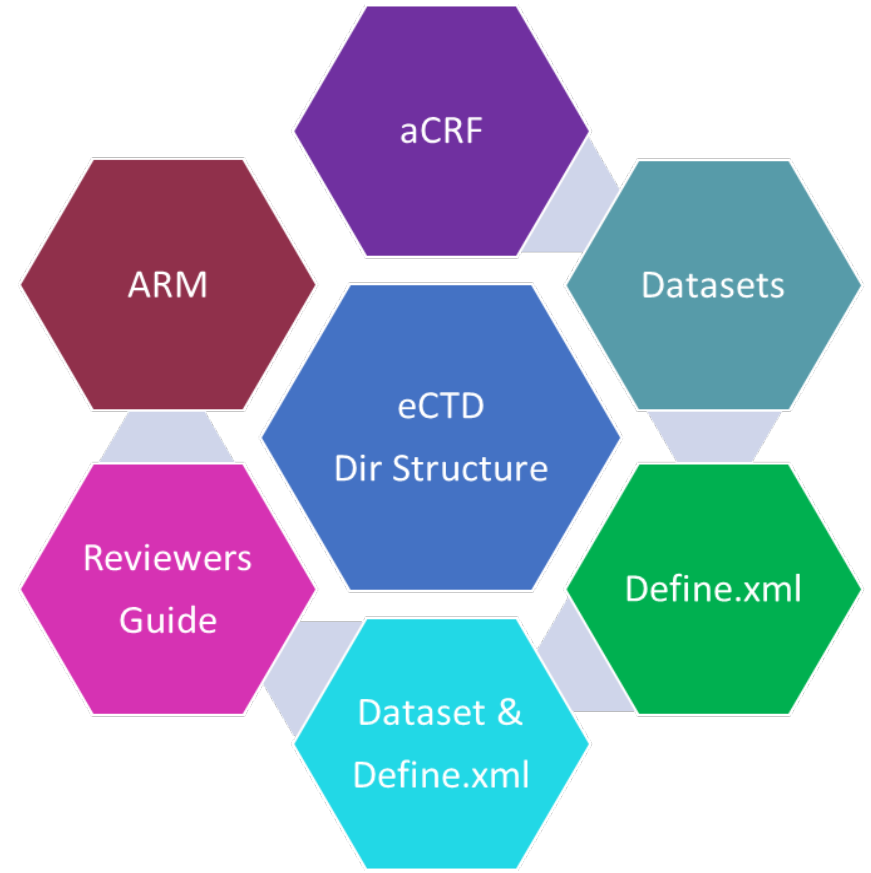
- **Chinese version:** <http://www.cde.org.cn/news.do?method=largeInfo&id=7a43c3abfde95950>
- **English version:** Not yet released but a vendor translated document is available

- **Sponsor responsibilities**

- Prepare the submission packages based on the requirements in this guidance document.
- Sponsor is encouraged to submit clinical trial data and the associated materials according to Clinical Data Interchange Standards Consortium (CDISC) standards.

Chinese Submission Components

- Annotated CRF (aCRF)
- SDTM Datasets
- ADaM Datasets
- SDTM and ADaM Define.xml
- Reviewers Guides (cSDRG and ADRG)
- Programs
- ARM (Not specifically specified in the guidance)



CDE Submission Components Guidance

- **Dataset and variable names and labels**

- Datasets should be in xpt format, DM and ADSL are required, other datasets if applicable.
- Dataset and variable names should not exceed 8 bytes.
- Variable labels should not exceed 40 bytes and Variable length should not exceed 200 bytes.
- Variable name can only contain upper case characters, underline and numbers, and must start with a letter.
- The length of each character variable should be set to the maximum actual value length of the variable across all datasets of the same study.

CDE Submission Components Guidance Cont ...

- **Dataset and variable names and labels**
 - If necessary, labels can contain English letters, underlines, or numbers, but cannot start with numbers
 - Labels can not include the following characters
 - Unpaired half-width/full-width single/double quotation marks
 - Unpaired half-width or full-width brackets
 - Special characters(e.g. '>','<')
 - The encoding used (UTF-8, EUC-CN, etc ...) should be described in reviewers guide

CDE Submission Components Guidance Cont ...

- **Split Datasets**

- Only submit the split datasets.
- Detailed rules for splitting and detailed steps for merging the datasets back should be specified in data reviewer's guide to ensure that reviewer can reconstruct the dataset.

- **Traceability of clinical trial data**

- Ensure that regulatory reviewers can use the study database (dataset) to derive the analysis database that is consistent with what the sponsor submitted.
- Analysis datasets should directly reproduce statistical analysis results that are also consistent with what the sponsor submitted.
- Traceability can be supplemented by providing a detailed data flowchart from the collection to the submission.

CDE Submission Components Guidance Cont ...

- **Data definition file (define)**

- Generally, Define.xml is accepted but define.pdf is also accepted.
- If define.xml is submitted, the corresponding stylesheet file should also be submitted.
- At least the following contents should be in Chinese:
 - Description/label and specification of each dataset in the database.
 - Description/label and derivation of variables in dataset; values or codes list of efficacy indicators.

- **Data reviewer's guide (csdrg.pdf & adrg.pdf)**

- DRGs in Chinese should be submitted in PDF format.

- **Annotated CRF (acrf.pdf)**

- At least the following contents should be in Chinese:
 - Description of questions designed to collect data.
 - Values or codes list of efficacy indicators.

SC = 受试者特征		DM = 人口学
Subject Assignment - Form Version: 15-Oct-2015 07:38		
Site:	Subject:	Subject No: SCGRPID = 'SA'
[REDACTED]		
筛选编号验证		
1. 筛选编号	SCTEST	SCORRES when SCTESTCD = 'FULLSCRN'
受试者分配		
2. 受试者是否满足所有合格标准?	☐ 否 [NOT SUBMITTED] ☐ 是 如“否”，请完成最终访视DS页面录入。	
3. 治疗/随机编号		SUBJID
4. 默沙东受试者编号		[NOT SUBMITTED]

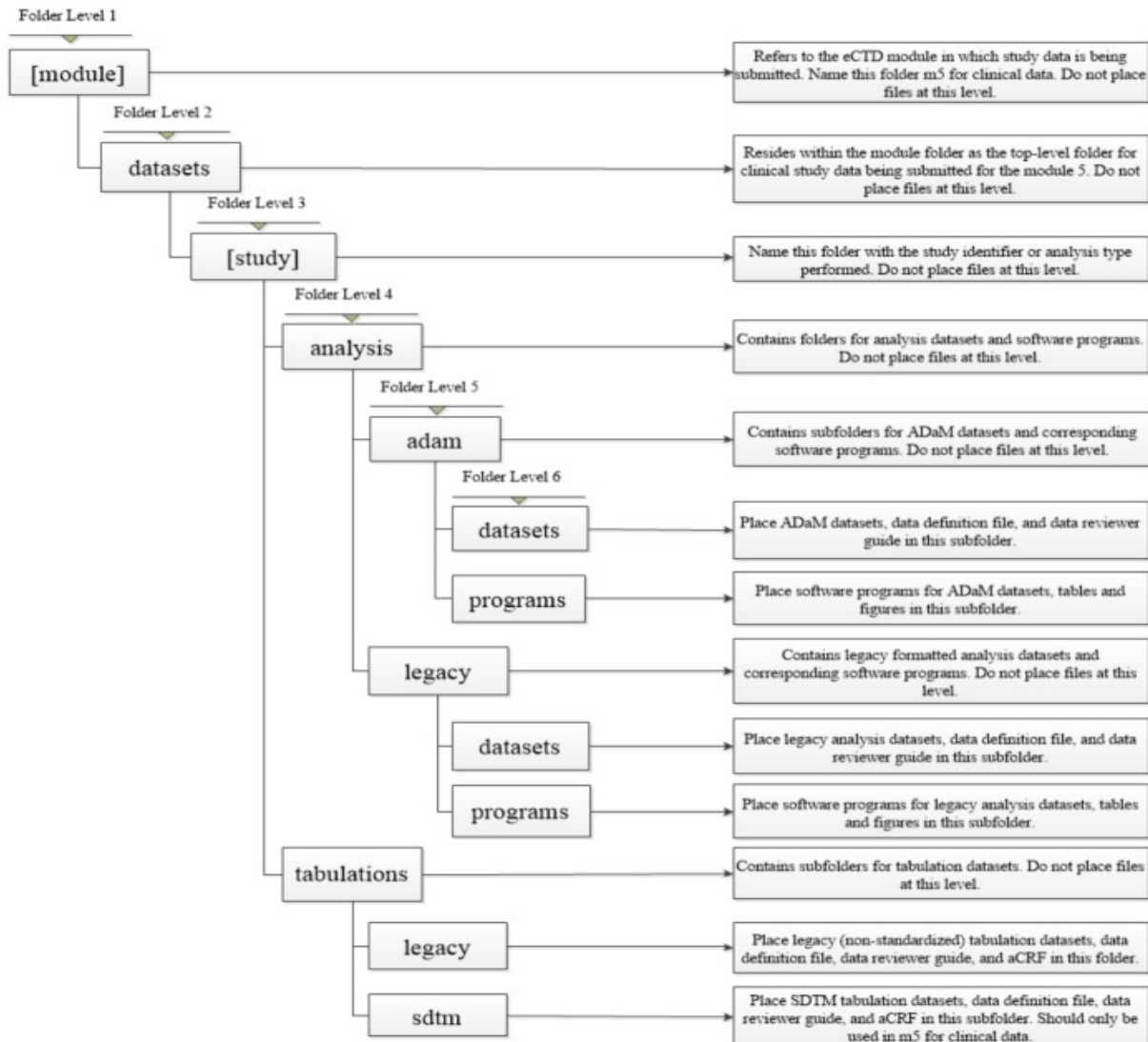
CDE Submission Components Guidance Cont ...

- **Programs**

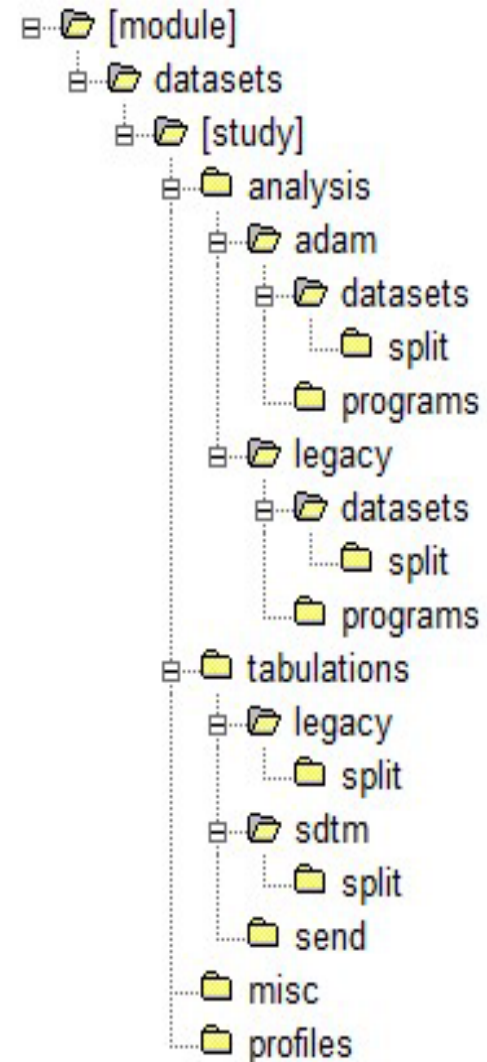
- Sponsor should submit programs for ADaM datasets as well as analysis results for the efficacy endpoints.
- Programs submitted in submission package should be readable (with comments), understandable.
- Programs should avoid using external macro programs.
- Programs in submission packages should be in TXT format.

CDE Submission Folder Structure (eCTD)

NMPA



FDA



CDE Translation Requirements

- The submission materials related to clinical trial data should be mainly in Chinese.
- Chinese translations should be consistent across all documents in submission packages.
- To improve the review efficiency, at least the following contents should be in Chinese:
 - **Datasets**
 - Dataset and variable labels
 - Adverse events terms, generic name of concomitant medications, medical history in CSR and other documents
 - **Define.xml**
 - Datasets and Variable labels
 - Derivations
 - Values or Codelist of efficacy indicators
 - **aCRF**
 - Description of questions designed to collect data
 - Values or codes list of efficacy indicators
 - **Reviewers Guide**
 - Data reviewer's guides should be submitted in Chinese

CDE and CDISC Standards

- **CDISC China is still working on Chinese translation of standards and terminology**
 - [SDTM-IG 3.2](#) is available, SDTM-IG 3.3 is in progress
 - [ADaM-IG 1.1](#) is available
 - CDISC CT translation for common codelists is in progress
- **Translation of other documents also needed**
 - Define.xml stylesheet (P21 has one available)
 - PhUSE Data Reviewer's Guide templates
- **NMPA CDE business rules as well as the data standard catalog are not available yet**

Challenges from Recent Filings

- **Time to comply with the requirements**

- The grace period from the requirements release to the effective date was only two months (July 20 to Oct.1, 2020)

- **Deliverables Creation**

- SDTM and ADaM Datasets: SAS applications needed to be configured with different encoding.
- SDTM and ADaM Defines: Pinnacle 21 Enterprise could not read our Chinese ADaM spec and had to use Community version.

- **Translation Deliverables**

- Multi-national Corporations, including Merck, need to first develop English version of the documents and datasets and then translate all into Chinese, which is time-consuming and will impact resources and the filing timelines.
- Translation consistency across documents in submission packages (cSDRG, ADRG, aCRF and define files)
- Translation companies are not fully familiar with CDISC data standards

Disclaimer: Proceed with Caution

- **NMPA CDE guidance and requirements are highly evolving**
 - Data Standard Catalog is not available.
 - Validation rules not yet available.
- **New CDISC metadata and CT are in progress**
 - SDTM IG v3.2 and ADaM IG v1.1 are available, others in progress.
 - CT is still in progress.
- **Pinnacle 21 Enterprise/Community Support**
 - NMPA CDE business rules are not finalized.
 - Pinnacle 21 released the first NMPA engine to validate CDE dataset and create CDE define.xml, however not all checks are supported.
 - Pinnacle 21 released a version of the style sheet to support CDE define.xml.





Majdoub Haloui

Prin. Scientist, Statistical Programming

Yanhong Li

Assoc. Dir, Statistical Programming

Hong Qi

Prin. Scientist, Statistical Programming

