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MSD

Are You Ready to Face the Challenges for FDA NDA Filing

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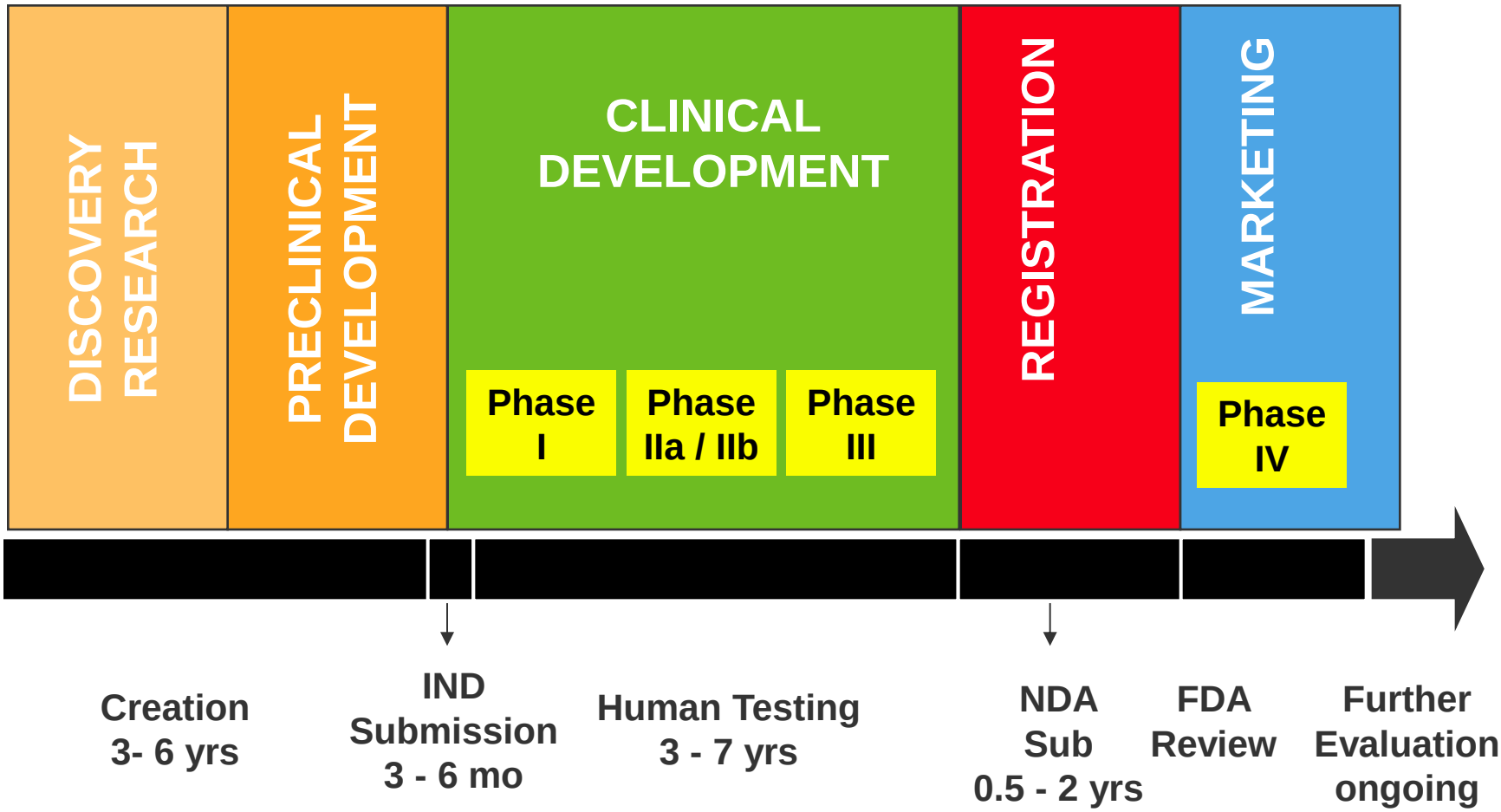
Drug Development

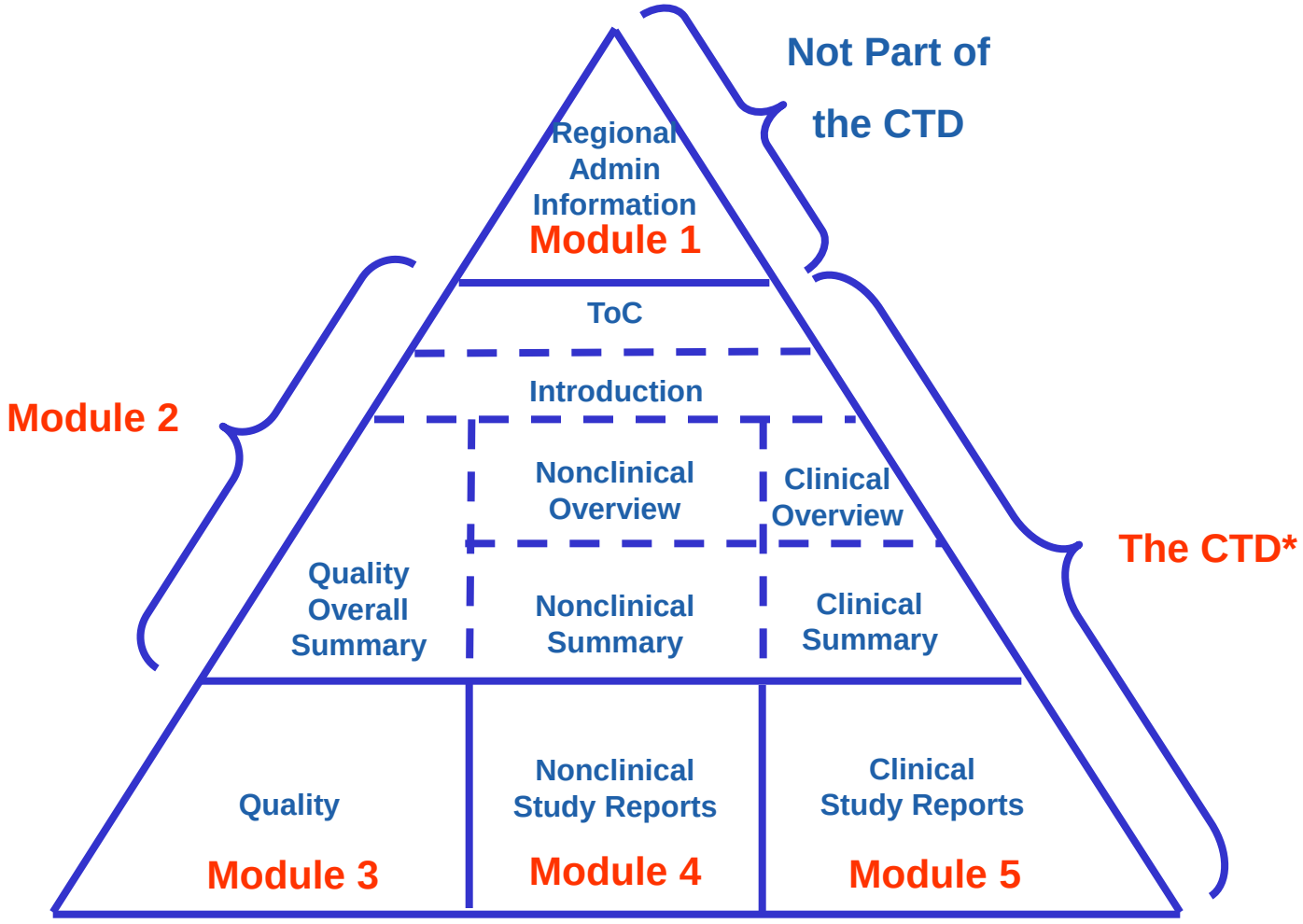


NDA Submission

- The NDA application is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S.
- The goals of the NDA are to provide enough information to permit FDA reviewer to reach the following key decisions:

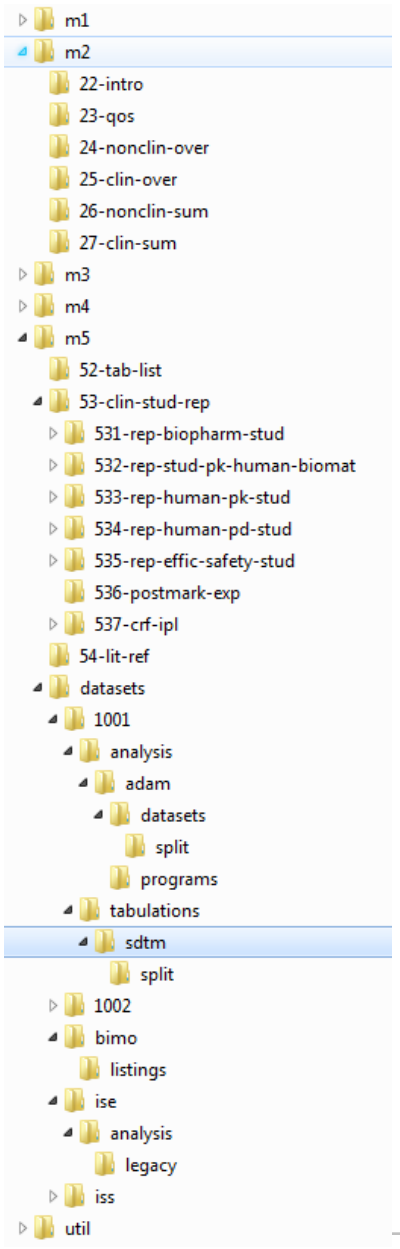
  - Whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks.
  - Whether the drug's proposed labeling (package insert) is appropriate, and what it should contain.
  - Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity.

The CTD Triangle



*ICH M4 Organization of the Common Technical Document (CTD)

eSub Packages Using the eCTD Specifications



- 2.5 Clinical Overview
- 2.7.3 Summary of Clinical Efficacy
  - ISE – intext TLFs
- 2.7.4 Summary of Clinical Safety
  - ISS – intext TLFs
- 5.2 Tabular Listing of All Clinical Studies
- 5.3 Clinical Study Reports
- 5.3.5.3 Reports of Analyses of Data from More than One Study
  - ISE – appendix TLFs
  - ISS – appendix TLFs (phase 1, phase 2-3)
- Datasets
  - analysis
  - tabulations
    - sdtm
      - define.xml + define.pdf, SDRG.pdf, blankcrf.pdf, XPT files
  - **bimo**

Submission Deliverables in Scope

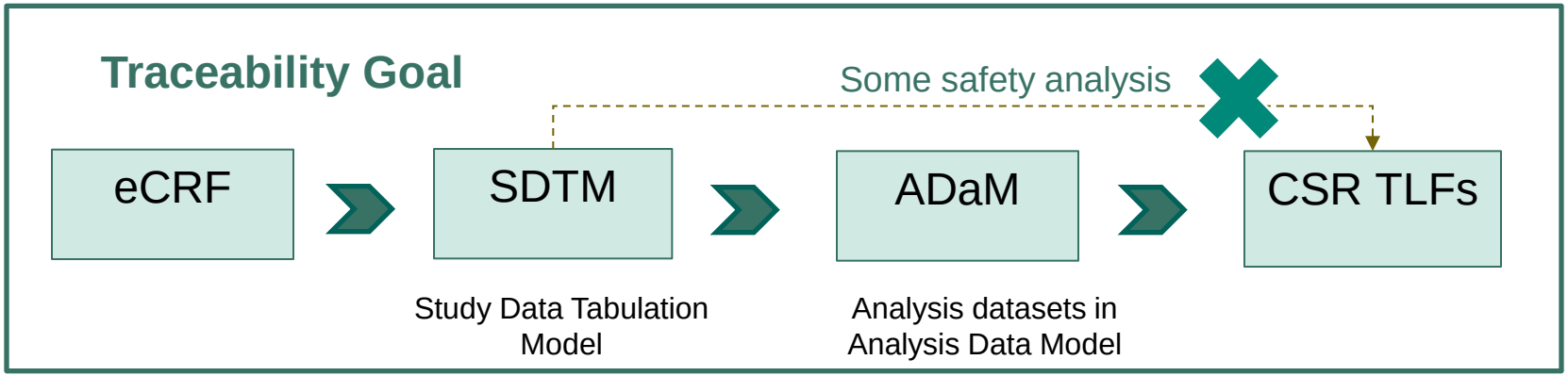
- TOC & Patient eCRFs with hyperlinks
- SDTM CRT (Case Report Tabulations) package
  - SDTM datasets (XPT files)
  - Define.XML(+Define.pdf)
  - Annotated CRF (acrf.pdf)
  - SDRG (reviewersguide.pdf, Study Data Reviewer's Guide with links to Define.XML)
- Analysis package
  - Analysis datasets
  - Analysis Define (Define.pdf(XML))
  - Analysis programs
  - ADRG (Analysis Data Reviewer's Guide with links to Define.pdf(XML))
- OSI (Office of Scientific Investigation) deliverables (Bioresearch Monitoring (BIMO))
  - Datasets (clinsite.xpt)/define.pdf
  - OSI a to j listings

Points to Consider in eSub Preparation

Pre-NDA Meeting

- To determine the adequacy of the sponsor's dossier for the submission of an NDA
- To agree on format and content of the application (any specific needs?)
- To determine status of ongoing studies to address pediatric safety and efficacy
- Early discussions on priority or standard review, and need for Advisory Committee meetings
- May include discussion on the need for REMS (Risk Evaluation and Mitigation Strategies) plans and proposed observational studies

Study Data Traceability in CSR TLFs

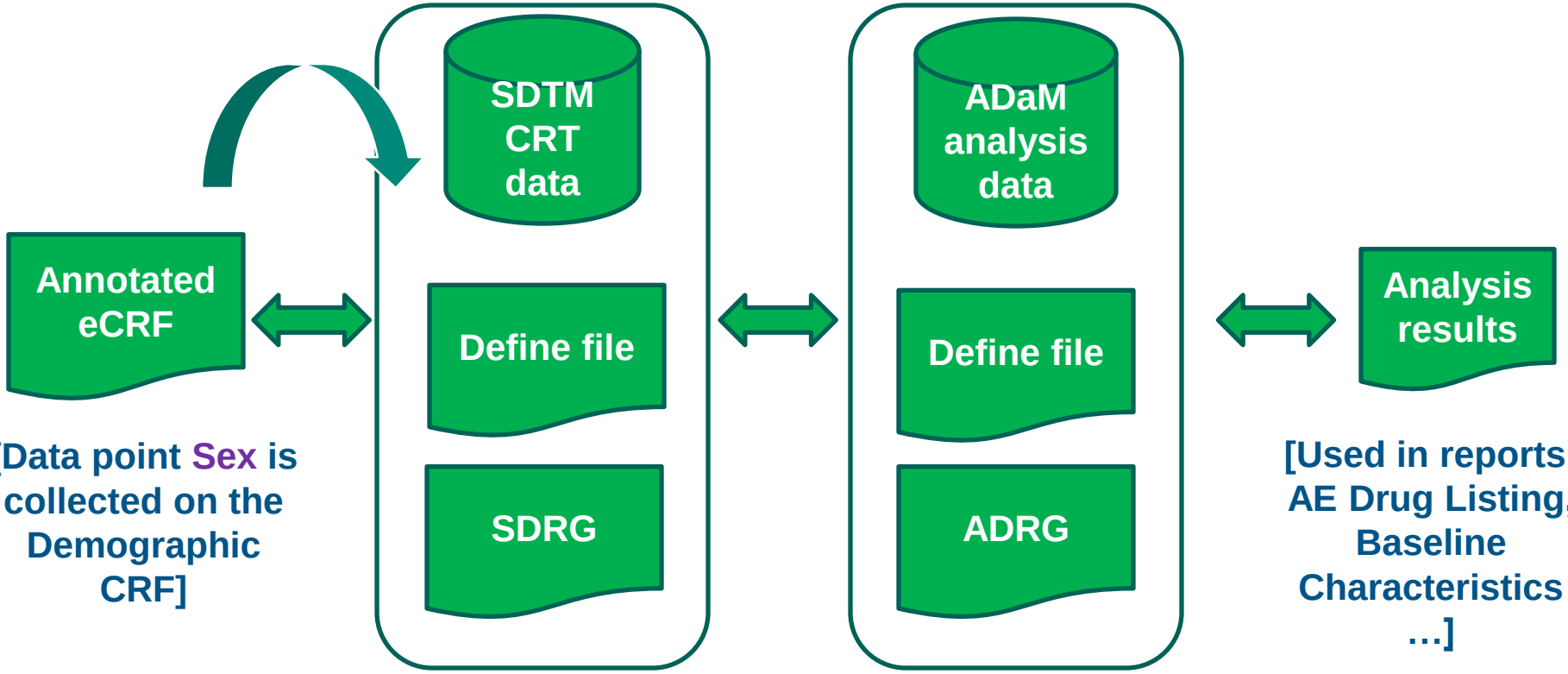


Study Data Technical Conformance Guide

An important component of a regulatory review is an understanding of the provenance of the data (i.e., traceability of the sponsor's results back to the CRF data). Traceability permits an understanding of the relationships between the analysis results, analysis datasets, tabulation datasets, and source data.

"Based upon reviewer experience, establishing traceability is one of the most problematic issues associated with legacy study data converted to standardized data. If the reviewer is unable to trace study data from the data collection of subjects participating in a study to the analysis of the overall study data, then the regulatory review of a submission may be compromised."

What is Traceability?



Points to Consider to SDTM CRTs Packages

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- Study Data Validation (OpenCDISC/ *WebSDM*™)
  - Conformance validation
    - Ensure that the data conform to the data standards
  - Quality checks
    - Ensure the data will support meaningful analysis

- Dataset Size
  - Datasets greater than 1 G in size should be split into smaller datasets no larger than 1 G.
  - Submit these smaller datasets, in addition to the larger non-split datasets .
  - The split datasets should be placed in a separate sub-directory labeled “split” .
  - The explanation regarding how these datasets were split needs to be documented in SDRG.

- Use of Controlled Terminologies

Points to Consider to SDTM CRTs Packages (Cont'd)

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- The Study Data Reviewer's Guide (SDRG)
  - is recommended as an integral part of a standards-compliant study data submission
  - describe any special considerations or directions that may facilitate an FDA reviewer's use of the submitted data
  - help the reviewer understand the relationships between the study report and the data

- The SDRG includes
  - Study protocol title, number, and version
  - Study design
  - Standards, formats, and terminologies and their versions
  - Description of study datasets
  - Data standards validation rules, versions, and issues
  - Description of all sponsor decisions related to data standard implementations

Points to Consider to Analysis Packages

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- FDA's feedbacks from recent submissions
  - Reviewers are requesting ADaM datasets for all data (both safety and efficacy)
  - All reporting programs should be using ADaM as the source, analysis ready, and not directly point to SDTM+
  - Sponsors should be submitting the code used for all TLFs including safety reporting. Does not need to be executable.
  - Create occurrence data structure (OCCDS) analysis dataset for Adverse Events (ADAE)

Points to Consider to Analysis Packages (Cont'd)

- FDA guidance requires all new studies starting on or after December 17, 2016 will be required to submit ADaM datasets
- Analysis Package comprises of four (4) components:

- Analysis datasets
- Includes all ADaM datasets (both safety and efficacy)

- Analysis programs
- Submits all TLFs programs including safety reporting. Does not need to be executable.

- Define.pdf (.xml)

- Analysis Data Reviewer's Guide
- Provides FDA Reviewers with additional context for analysis datasets (AD) received as part of a regulatory submission.

Points to Consider to Analysis Packages (Cont'd)

- The **Analysis Data Reviewer's Guide** (ADRG) provides FDA Reviewers with additional context for analysis datasets (AD) received as part of a regulatory submission.

Adobe Acrobat Document

- The ADRG is intended to describe analysis data submitted for an individual study in the Module 5 clinical section of the eCTD.

- **The ADRG has 8 sections :**
  - Introduction
  - Protocol Description
  - Analysis Considerations Related to Multiple Analysis Datasets
  - Analysis Data Creation and Processing Issues
  - Analysis Dataset Descriptions
  - Data Conformance Summary
  - Submissions of Programs
  - Appendix (optional)

Points to Consider to Analysis Packages (Cont'd)

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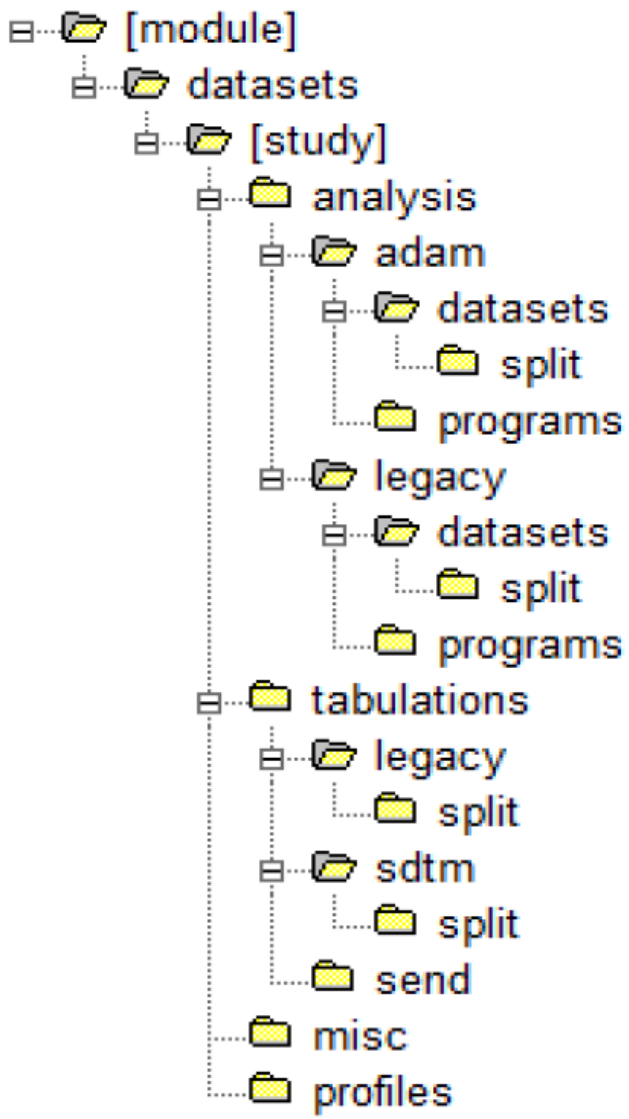
- Therapeutic Area Standards
  - ADaM or analysis datasets associated with a therapeutic area, refer to FDA guidance or communicated with FDA in Pre-NDA meeting

    e.g., HCV RAVs dataset and AMIS-like efficacy dataset

- Dataset Size
  - Datasets greater than 1 G in size should be split into smaller datasets no larger than 1 G.
  - Submit the smaller split files in the "split" sub-folder in addition to the larger non-split file in the original data folder.
  - No need for a second define.pdf(xml) file to be submitted within the split subfolder

Folder Structure for Study Datasets



datasets	2	Resides within the module folder as the top-level folder for study data (nonclinical or clinical) being submitted for the specified module (m4 or m5). Do not place files at this level.
[study]	3	Name this folder with the study identifier or analysis type performed (e.g., study123, iss, ise). Do not place files at this level.
analysis	4	Contains folders for analysis datasets and software programs; arrange in designated level 6 subfolders. Do not place files at this level.
adam	5	Contains subfolders for ADaM datasets and corresponding software programs. Do not place files at this level.
datasets	6	Place ADaM datasets in this subfolder.
split	7	Place any split ADaM datasets in this subfolder.
programs	6	Place software programs for ADaM datasets, tables and figures in this subfolder.
legacy	5	Contains legacy formatted analysis datasets and corresponding software programs. Do not place files at this level.
datasets	6	Place legacy analysis datasets in this subfolder.
split	7	Place split legacy analysis datasets in this subfolder.
programs	6	Place software programs for legacy analysis datasets, tables and figures in this subfolder.
tabulations	4	Contains subfolders for tabulation datasets. Do not place files at this level.
legacy	5	Place legacy (non-standardized) tabulation datasets in this folder.
split	6	Place any split legacy tabulations datasets in this subfolder.
sdtm	5	Place SDTM tabulation datasets in this subfolder. Should only be used in m5 for clinical data.
split	6	Place any split SDTM files in this subfolder.

OSI (Office of Scientific Investigation) Deliverables

- The Office of Scientific Investigation at FDA has the responsibility of verifying the integrity of the clinical efficacy and safety data submitted to CDER in support of new applications and supplements.

- OSI is also responsible for determining whether clinical trials are conducted in accordance with FDA regulations and that the rights and welfare of trial participants is protected.

- Based on the information provided to them, OSI uses algorithms to identify high risk sites and conduct site inspections.

OSI (Office of Scientific Investigation) Deliverables (Cont'd)

- Part 1 Tabular Listings of Site Information
  - Protocols and Annotated CRFs for each study (PDF)
  - This is included within Module 5.2 Summary level Clinical Site Information template

- Part 2 Line Listings by Site
  - Subject data listings organized by site for each study (PDF)
  - 10 Listings (a to j) x number of sites

- Part 3 Site-Level Data set
  - Single site level summary data for site selection tool across all pivotal studies (clinsite.xpt) (Pool all the individual DE dataset and name "clinsite")
  - Additional request from FDA for OSI in Pre-NDA meeting

Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

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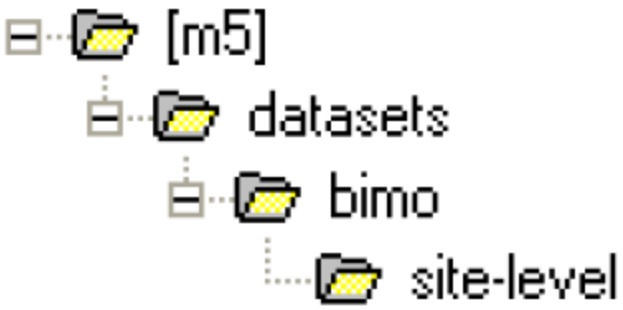
OSI Pre-NDA Request Item	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

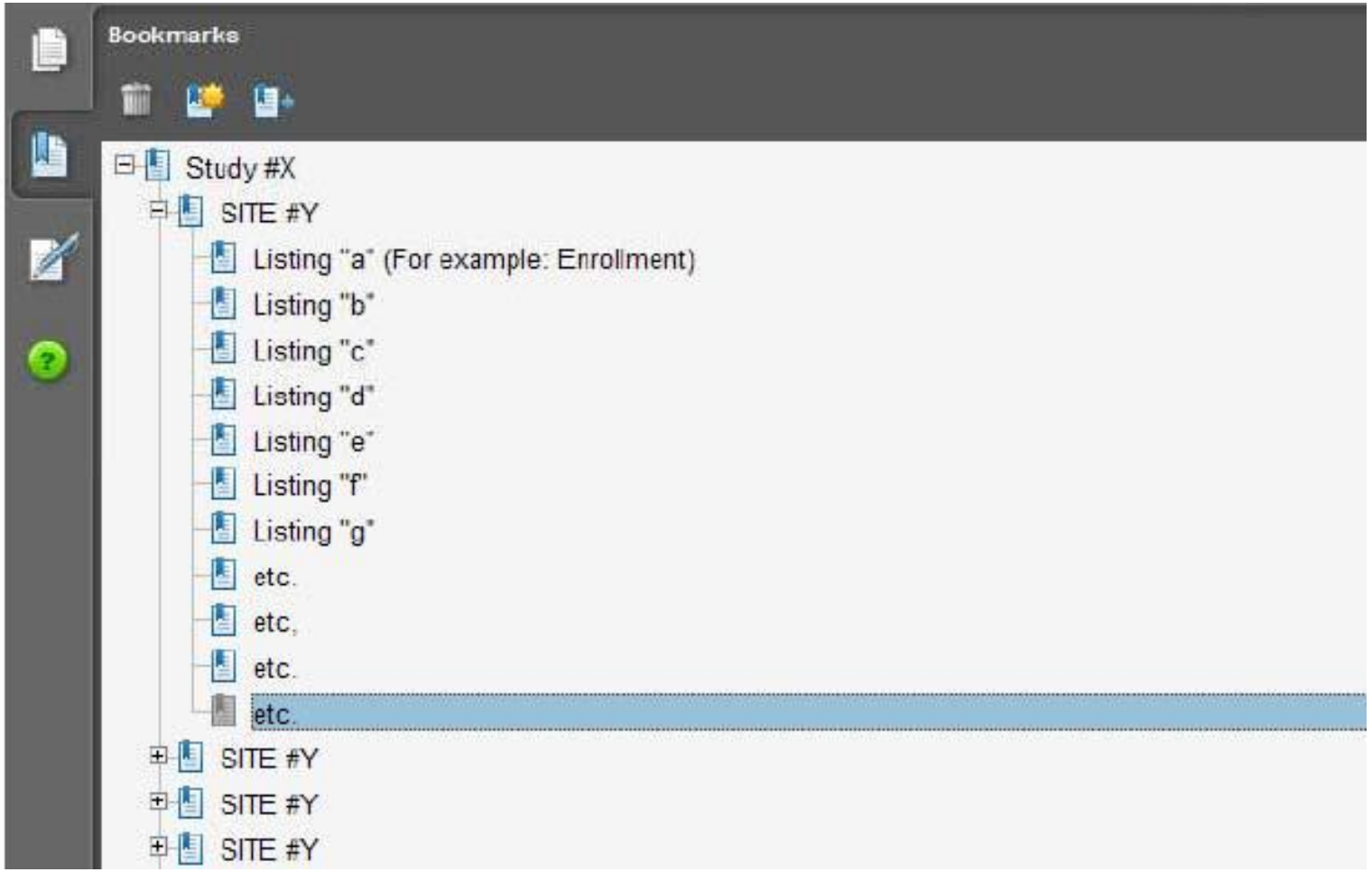
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format (Cont'd)

- Data submitted for OSI review belongs in Module 5 of the eCTD
  - Pool all the individual DE dataset and name "clinsite.xpt" and place it in the bimo folder
  - Place item III site-level dataset and listings in bimo folder across all pivotal studies
  - Place item III one define file in bimo folder across all pivotal studies



Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format (Cont'd)

- FDA requests that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format



References

- Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015);

- Providing Regulatory Submissions In Electronic Format — Standardized Study Data http://www.fda.gov/downloads/Drugs/.../Guidances/UCM292334.pdf

- Study Data Technical Conformance Guide (Technical Specifications Document) Oct 2015
- http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf

- Summary Level Clinical Site Data for CDER's Inspection Planning

  http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf

- ICH M4 Organization of the Common Technical Document (CTD)

Questions?

Thank You