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Understanding BLA/NDA Clinical Data Submission

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October 11, 2011

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Overview

- ✓ Drug Approval Process
- ✓ Data Submission
  - FDA Processes
  - Data Submission Specifications
  - Legacy Data
- ✓ Conclusions

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Statistical Programming Work

- ✓ Prepare Raw Data
- ✓ Generate Analysis Data
- ✓ Programming of TLGs
- ✓ aCRF & DEFINE
- ✓ What Happens with the Data???

Your RA Department

- ✓ RA= Regulatory Department
- ✓ Gatekeeper to Agencies
- ✓ Very Formalistic
- ✓ Get Involved
  - You Are the Expert!
  - Paradigm Shift
  - Start Discussions Early!

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Drug Approval Process

EMA FDA

Drug Development

License Application

Product Release

EMA= European Medicines Agency (formerly EMEA)

FDA= Food and Drug Administration

What's (in) the PI?

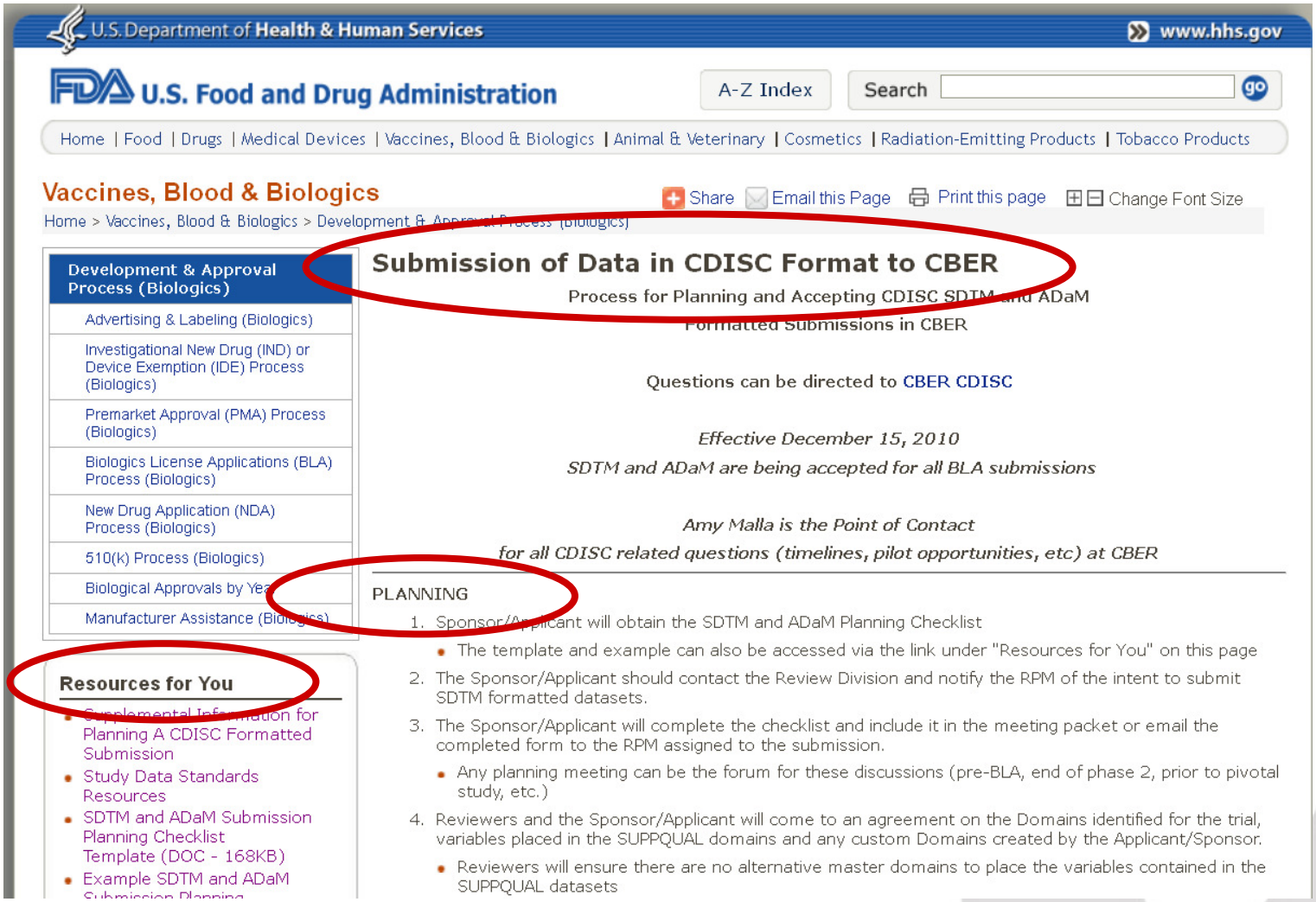
Pictures of safety and efficacy
tables from package insert
removed for publication

CBER – BLA / CDER – NDA

CBER	CDER
Center for Biologics Evaluation and Research	Center for Drug Evaluation and Research
e.g. Vaccines	e.g. "Traditional Drugs"
BLA= Biologics License Application	NDA= New Drug Applications
Number of BLAs in 2010: **6**	Number of NDAs in 2010: **87**

CDER and CBER Act Differently

CBER Submission Process



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U.S. Food and Drug Administration — A-Z Index — Search — go

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Vaccines, Blood & Biologics

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Home > Vaccines, Blood & Biologics > Development & Approval Process (Biologics)

Development & Approval Process (Biologics)

- Advertising & Labeling (Biologics)
- Investigational New Drug (IND) or Device Exemption (IDE) Process (Biologics)
- Premarket Approval (PMA) Process (Biologics)
- Biologics License Applications (BLA) Process (Biologics)
- New Drug Application (NDA) Process (Biologics)
- 510(k) Process (Biologics)
- Biological Approvals by Ye
- Manufacturer Assistance (Biologics)

Resources for You

- Supplemental Information for Planning A CDISC Formatted Submission
- Study Data Standards Resources
- SDTM and ADaM Submission Planning Checklist Template (DOC - 168KB)
- Example SDTM and ADaM Submission Planning

Submission of Data in CDISC Format to CBER

Process for Planning and Accepting CDISC SDTM and ADaM Formatted Submissions in CBER

Questions can be directed to CBER CDISC

Effective December 15, 2010

SDTM and ADaM are being accepted for all BLA submissions

Amy Malla is the Point of Contact

for all CDISC related questions (timelines, pilot opportunities, etc) at CBER

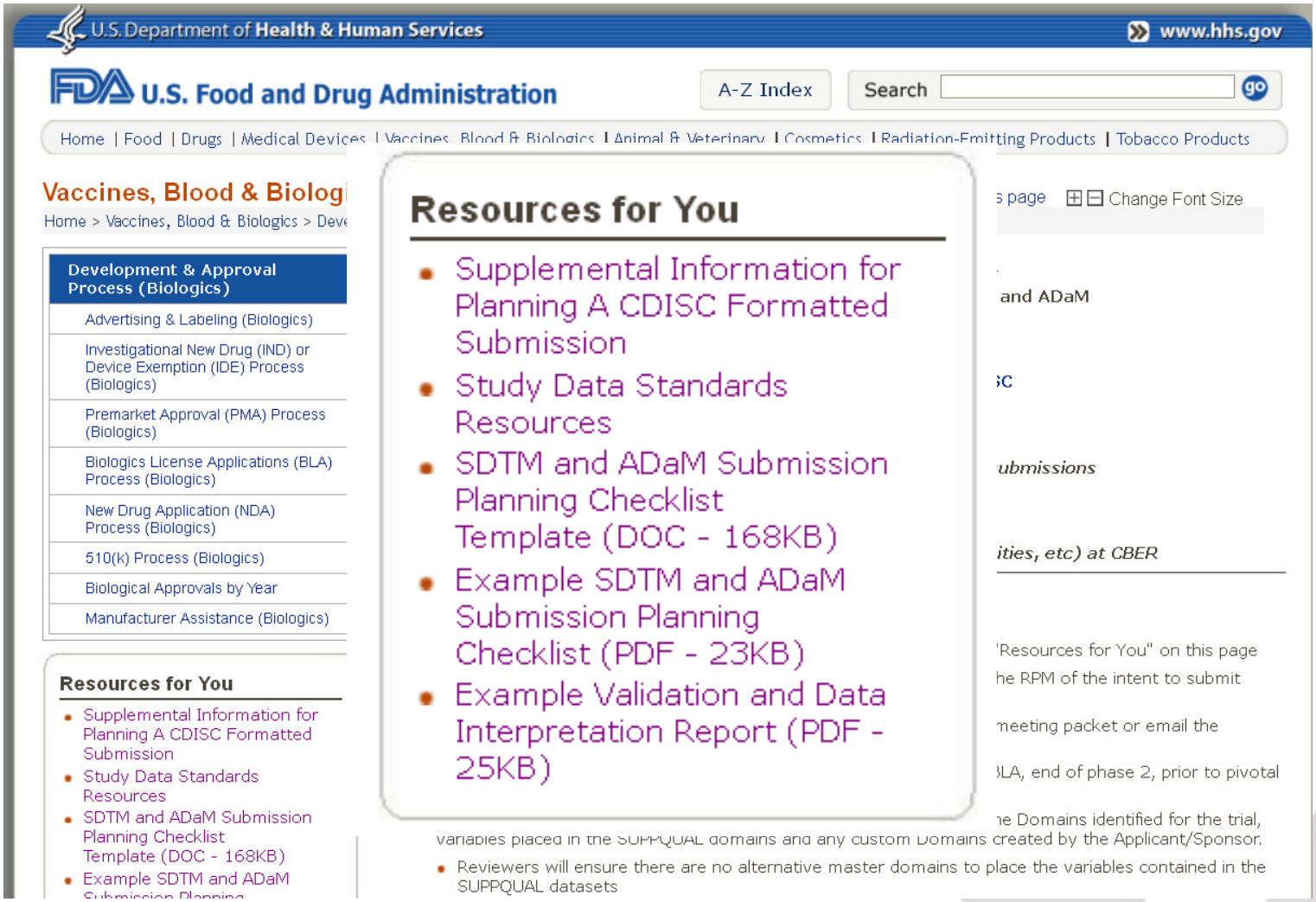
PLANNING

1. Sponsor/Applicant will obtain the SDTM and ADaM Planning Checklist
   - The template and example can also be accessed via the link under "Resources for You" on this page
2. The Sponsor/Applicant should contact the Review Division and notify the RPM of the intent to submit SDTM formatted datasets.
3. The Sponsor/Applicant will complete the checklist and include it in the meeting packet or email the completed form to the RPM assigned to the submission.
   - Any planning meeting can be the forum for these discussions (pre-BLA, end of phase 2, prior to pivotal study, etc.)
4. Reviewers and the Sponsor/Applicant will come to an agreement on the Domains identified for the trial, variables placed in the SUPPQUAL domains and any custom Domains created by the Applicant/Sponsor.
   - Reviewers will ensure there are no alternative master domains to place the variables contained in the SUPPQUAL datasets

http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/ucm209137.htm

(accessed 5Oct2011)

CBER Submission Process



http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/ucm209137.htm

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CBER Submission Process CDISC

- 4-Step Process Described on Website
- Planning (including demo)
- Validation (OpenCDISC)
- Submission (CD-ROM, electronic Gateway)
- Review
- Questions to: CBER.CDISC@fda.hhs.gov

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CDER Submission Process

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Drugs

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Home > Drugs > Development & Approval Process (Drugs) > Forms & Submission Requirements

- Development & Approval Process (Drugs)
  - Forms & Submission Requirements
    - Electronic Submissions to CDER
      - CDER Data Standards Program
      - Electronic Common Technical Document (eCTD)
      - Electronic Regulatory Review
      - Electronic Regulatory Submissions and Review Helpful Links
      - Electronic Submissions Presentations
      - Study Data Standards for Submission to CDER
      - Data Standards Manual (monographs)

Study Data Standards for Submission to CDER

CDER strongly encourages IND sponsors and NDA applicants to consider the implementation and use of data standards for the submission of applications. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. These resources are intended to assist submitters in the preparation and submission of standardized study data to CDER. This webpage will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

- **CDER Data Standards Common Issues Document** (PDF - 115KB) NEW - The goal of this document is to communicate general CDER preferences and experiences regarding the submission of standardized data to aid sponsors in the creation of standardized datasets. The document is not intended to replace the need for sponsors to communicate with review divisions regarding data standards implementation approaches or issues, but instead, it is designed to compliment and facilitate the interaction between sponsors and divisions.
- **Study Data Specifications (v1.6)** (PDF - 199KB) NEW - Study specifications for submitting animal and human study datasets in electronic format
- **CDISC Study Data Tabulation Model (SDTM)**
  - **SDTM Implementation Guide for Human Clinical Trials (SDTM IG)** - Developed by the Clinical Data Interchange Standards Consortium (CDISC), the SDTM IG is an implementation of the SDTM for clinical study data. The conceptual model and SDTM IG can be obtained from the CDISC web site at: http://www.cdisc.org/sdtm
  - **Standard for Exchange of Nonclinical Data Implementation Guide (SEND IG)** - Developed by the Clinical Data Interchange Standards Consortium (CDISC), the SEND IG is an implementation of the SDTM for

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

(accessed 5Oct2011)

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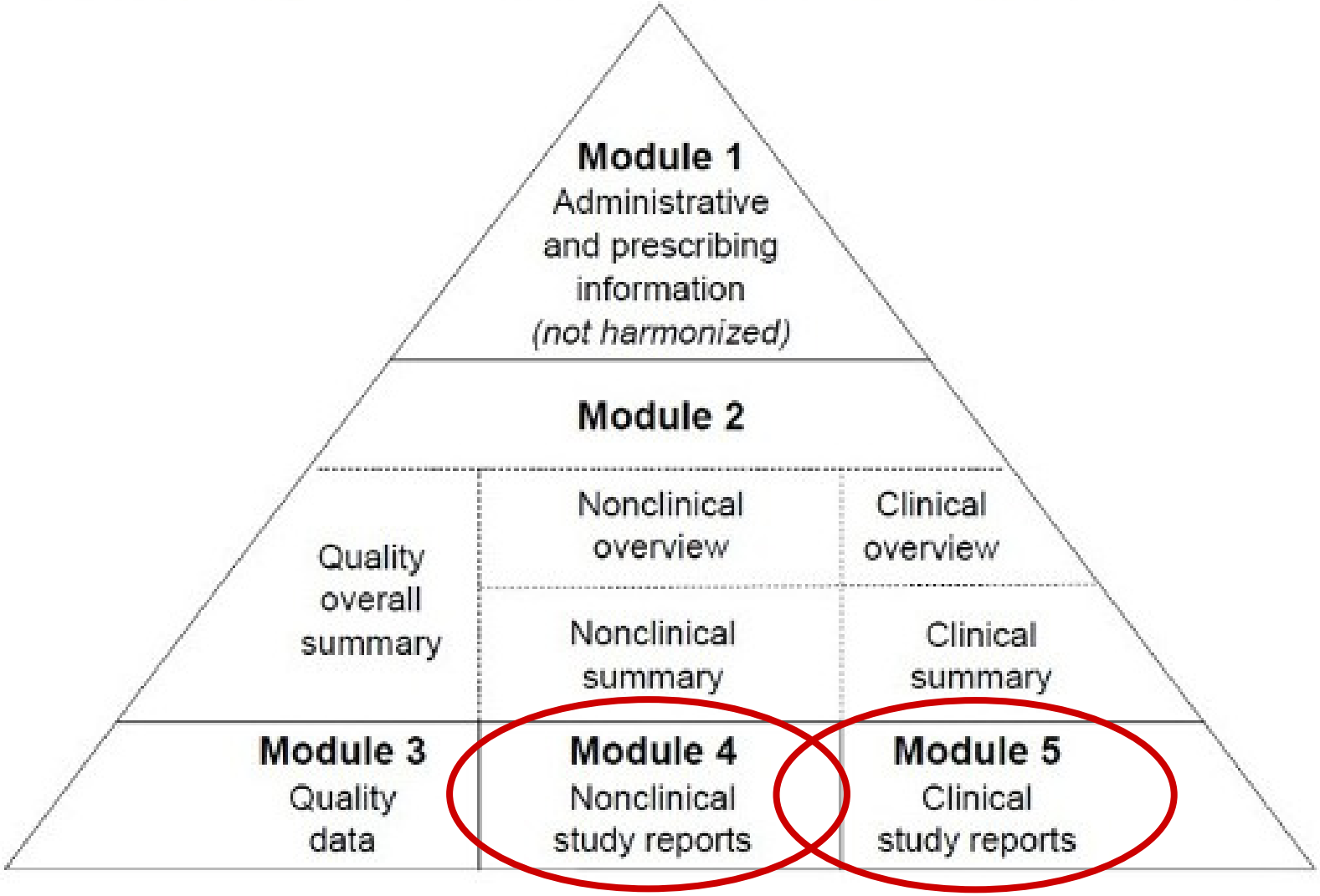
CDER Submission Process CDISC

- No Formal Process Published
- Internal Process will be Similar to CBER
  - But No Checklists Available
  - And No Demo Submission
- Questions to: cder-edata@fda.hhs.gov

Location of Data

- ✓ Location Defined in CTD / eCTD
- ✓ Harmonized Submission Structure
- ✓ Mandatory in EU & Japan
- ✓ Recommended for FDA
- ✓ 5 Modules

Modular Structure of Common Technical Document



Where are you going, Data?

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You can find me in Module M5

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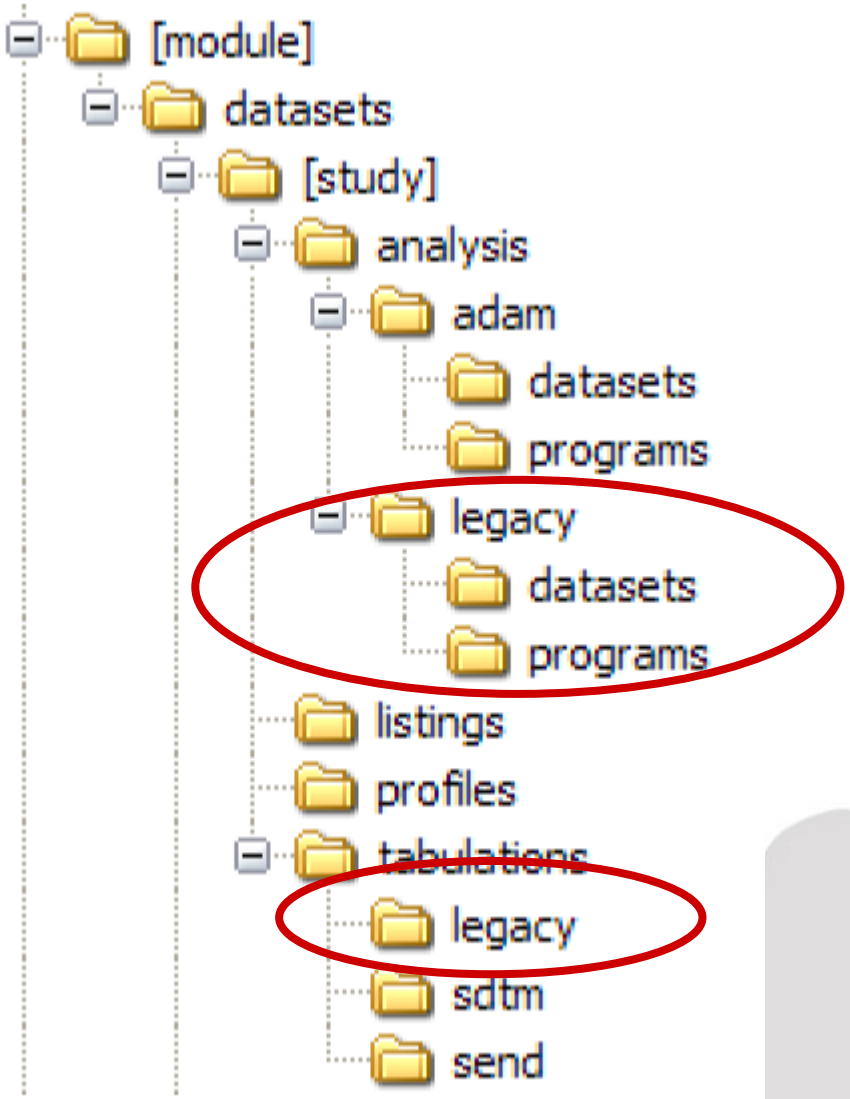
Study Data Specifications

- Study Data Specifications (FDA, 2004)
  - Based on CBER Guideline from 1999
  - Dataset Requirements (e.g. XPT)
  - Data Types
    - → Data Tabulation Datasets (SDTM)
    - → Data Listings
    - → Subject Profiles
    - → Analysis Datasets
  - Documentation (aCRF, DEFINE, ...)
  - Organization of Data (eCTD)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profiles
tabulations
legacy
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send

Required / Recommended Docs

- ✓ DEFINE Document (PDF / XML)
- ✓ Annotated CRF
- ✓ SAS Programs (Analysis & Data Prep)
  - Non-Executable
  - Clear and Understandable (GPP)
- ✓ Validation Programs
- ✓ Reviewer Guidance Document (see PhUSE Wiki)

Think About Your Customer

- ✓ Help Reviewer Understand Your Data
- ✓ Describe
  - Specialties
  - Deviations from Guideline
  - Explain Decisions
- ✓ Document, Document, Document

Errors & Discrepancies

You Discover Errors During Data Preparation

- No Formal Process in Place
- Prepare Document (e.g. Amendment)
- Describe Discrepancies
- Be Transparent
- **Don't Try To Hide Anything!**

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Legacy Data Submission

- ✓ Avoid Retrospective Mapping to CDISC
  - Perform Risk Assessment
  - Communicate Risks (internal & external)
- ✓ If Mapping is Required:
  - Recreate (Key) Results
  - Make Validation Transparent
  - Provide Scripts to Reviewers

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Programming Tips

- ✓ Work with Submission in Mind
- ✓ Minimum: XPT Restrictions
- ✓ Document Timely and Thoroughly
  - Not all Reviewers are Programmers!
- ✓ Keep Standards across Studies
- ✓ Ensure Traceability

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Conclusion (1/2)

- ✓ Guideline vs Law
- ✓ Every Submission is Different
- ✓ Be Transparent
  - Document What Was Done
- ✓ Discuss Requirements with FDA (Early!)
- ✓ Use CDISC if Possible

Conclusion (2/2)

- ✓ Ultimate Goal: Keep Scientific Integrity
- ✓ Process is in Transit
- ✓ Industry and FDA are Learning
- ✓ There will Always be Exceptions
- ✓ Don't Panic

Questions / Discussion

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