

Understanding BLA/NDA Clinical Data Submission

Dirk Spruck

Accovion, Germany

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Overview

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

Statistical Programming Work

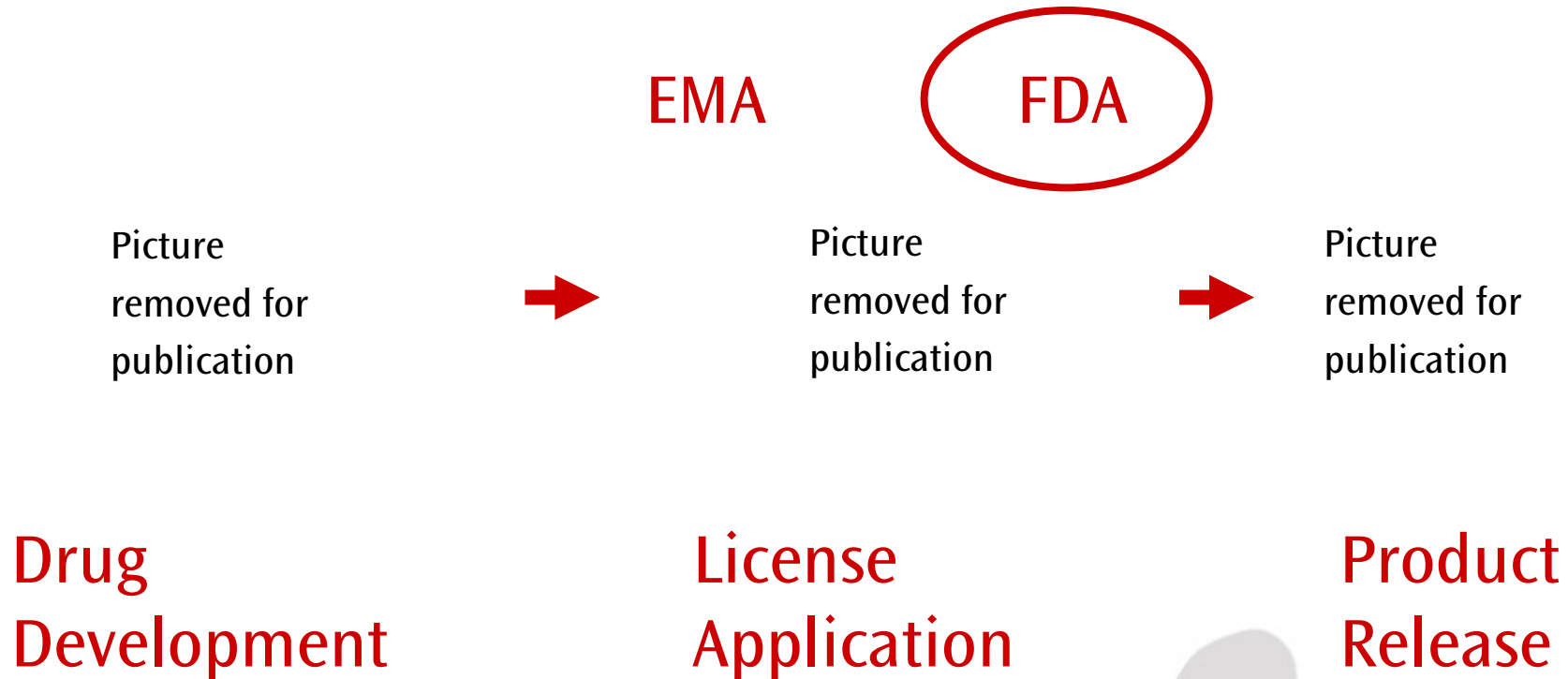
- ✓ Prepare Raw Data
- ✓ Generate Analysis Data
- ✓ Programming of TLGs
- ✓ aCRF & DEFINE
- ✓ What Happens with the Data???

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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publication

Drug Approval Process



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

U.S. Department of Health & Human Services | www.hhs.gov

FDA U.S. Food and Drug Administration

Home | Food | Drugs | Medical Devices | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Radiation-Emitting Products | Tobacco Products

Vaccines, Blood & Biologics

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

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 SUPQUAL 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 SUPQUAL datasets

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](#)

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

CBER Submission Process

The screenshot shows the FDA website interface. At the top, it says 'U.S. Department of Health & Human Services' and 'www.hhs.gov'. Below that is the 'FDA U.S. Food and Drug Administration' logo and a search bar. A navigation menu includes 'Home', 'Food', 'Drugs', 'Medical Devices', 'Vaccines, Blood & Biologics', 'Animal & Veterinary', 'Cosmetics', 'Radiation-Emitting Products', and 'Tobacco Products'. The main content area is titled 'Resources for You' and lists several links:

- 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 Checklist (PDF - 23KB)
- Example Validation and Data Interpretation Report (PDF - 25KB)

On the left side of the screenshot, there is a sidebar with a 'Development & Approval Process (Biologics)' section containing links like '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 Year', and 'Manufacturer Assistance (Biologics)'. Below this is another 'Resources for You' section with a smaller version of the same list.

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

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

CDER Submission Process

U.S. Department of Health & Human Services www.hhs.gov

FDA U.S. Food and Drug Administration [A-Z Index](#)

[Home](#) | [Food](#) | [Drugs](#) | [Medical Devices](#) | [Vaccines, Blood & Biologics](#) | [Animal & Veterinary](#) | [Cosmetics](#) | [Radiation-Emitting Products](#) | [Tobacco Products](#)

Drugs

[Home](#) > [Drugs](#) > [Development & Approval Process \(Drugs\)](#) > [Forms & Submission Requirements](#)

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>

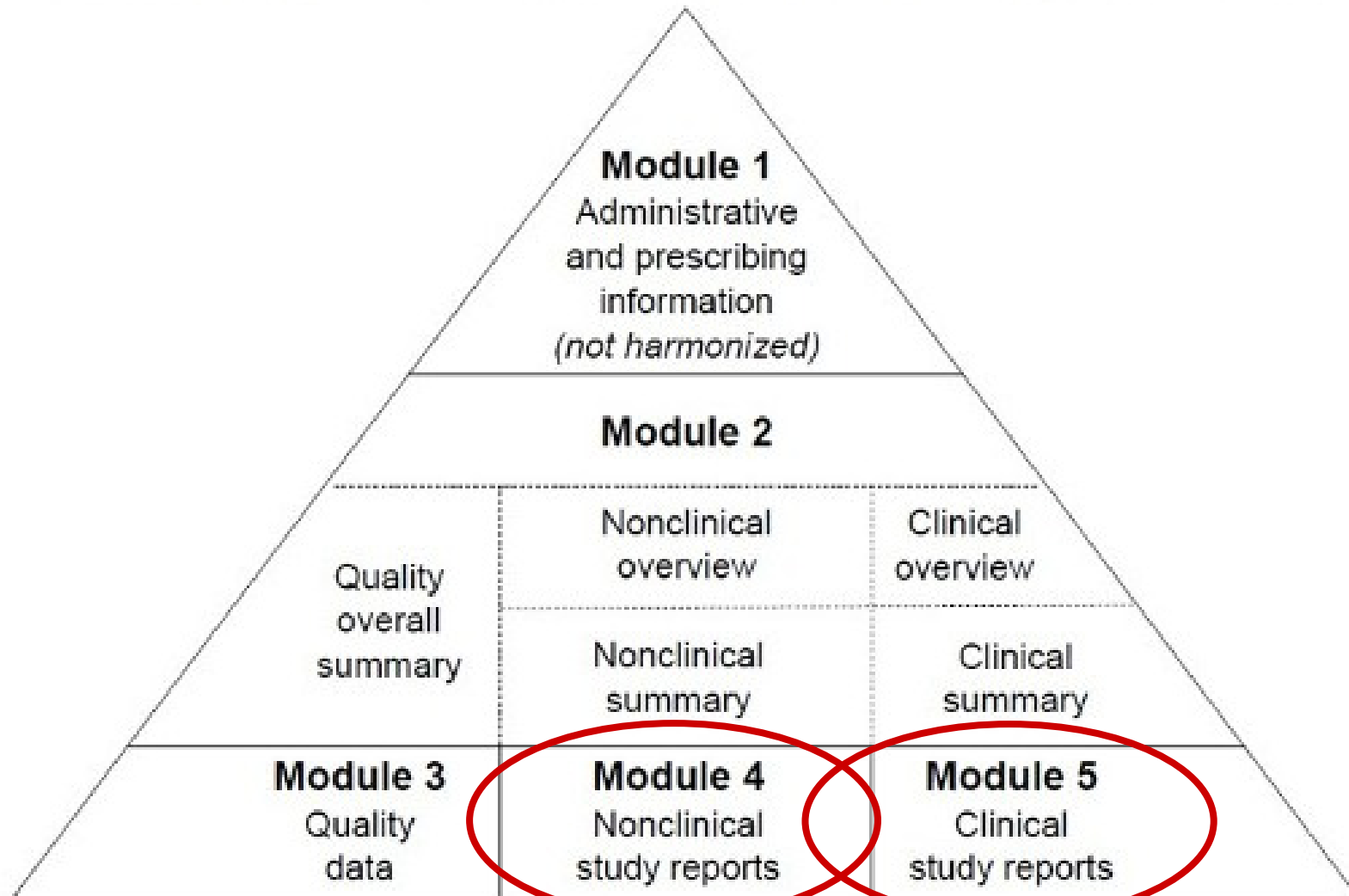
CDER Submission Process CDISC

- ✓ 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?

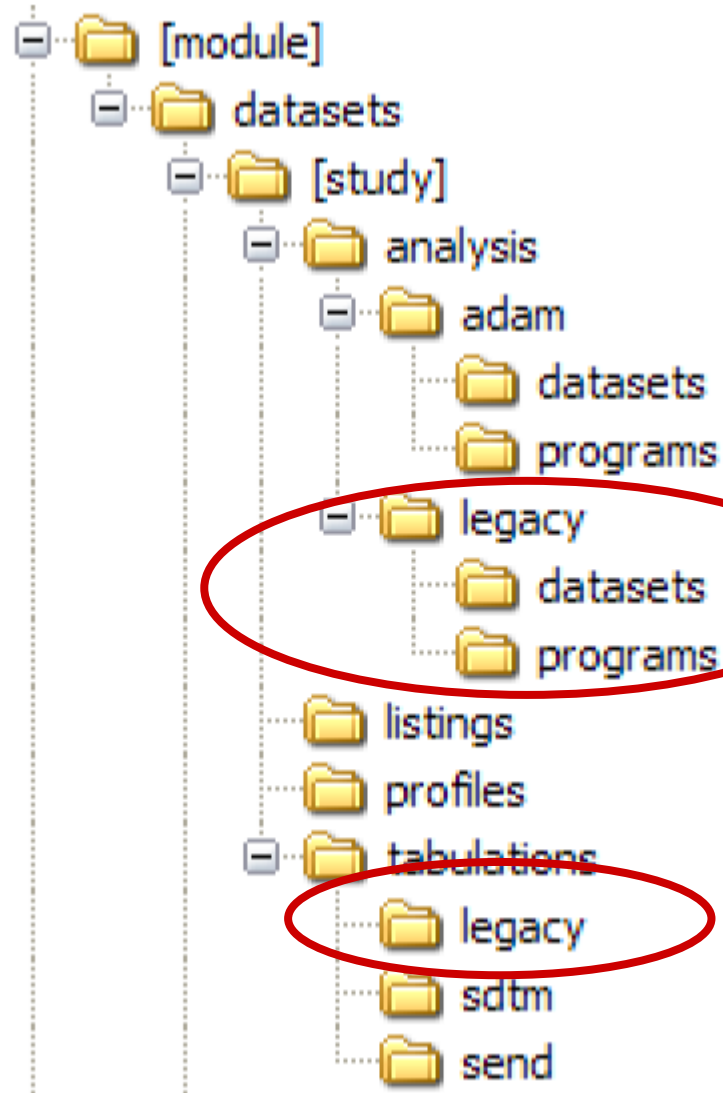
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You can find
me in
Module M5

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)



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)



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!**

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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publication

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

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

Dirk.Spruck@accovion.com