Understanding BLA/NDA Clinical Data Submission

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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!
Drug Approval Process

EMA  FDA

Drug Development  License Application  Product Release

EMA= European Medicines Agency (formerly EMEA)
FDA= Food and Drug Administration

Picture removed for publication

10/24/2011
What’s (in) the PI?

Pictures of safety and efficacy tables from package insert removed for publication
# CBER – BLA / CDER – NDA

<table>
<thead>
<tr>
<th><strong>CBER</strong></th>
<th><strong>CDER</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Center for Biologics Evaluation and Research</td>
<td>Center for Drug Evaluation and Research</td>
</tr>
<tr>
<td>e.g. Vaccines</td>
<td>e.g. “Traditional Drugs”</td>
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<tr>
<td>BLA= Biologics License Application</td>
<td>NDA= New Drug Applications</td>
</tr>
<tr>
<td>Number of BLAs in 2010: 6</td>
<td>Number of NDAs in 2010: 87</td>
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CDER and CBER Act Differently
CBER Submission Process


10/24/2011

(accessed 5Oct2011)
CBER Submission Process


(10/24/2011)
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

Study Data Standards for Submission to CDER

CDER strongly encourages NDA 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)**  - 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 standard 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)**  - 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 website at: [http://www.cdisc.org/sdtm](http://www.cdisc.org/sdtm)
  - **Standard for Exchange of Nontclinical Data Implementation Guide (SEND IG)**  - Developed by the Clinical Data Interchange Standards Consortium (CDISC), the SEND IG is an implementation of the SDTM for nonclinical data.

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: cdер-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

Module 1
Administrative and prescribing information (not harmonized)

Module 2
- Nonclinical overview
- Clinical overview

Module 3
- Quality overall summary
- Quality data

Module 4
- Nonclinical summary
- Nonclinical study reports

Module 5
- Clinical summary
- Clinical study reports
Where are you going, Data?

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)
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
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

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