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Warning

• This presentation contains a mixture of
  • Reality
  • Aspirations
  • Authors’ vision for how we can greatly increase efficiency for product development
Agenda

- Background
- Implementing Data Standards/CDISC
- Starting with the End – “Tables First”
- Standards Implementation Strategy
- Standards from End to End
- Conclusion
Introduction

Wrong Question:
How can we implement CDISC standards to meet FDA submission requirements?

Right Question:
How can we use CDISC standards as part of a cost-effective product development strategy?
Current Status of Data Standards

- CDISC de facto standard
- Recent FDA draft guidance
- PDUFA V/FDASIA
- Communications with FDA
- FDA investment in CDISC
- Increased number of CDISC submissions
Data Standards: New Guidance

What does it mean?

- Promotes use of data standards
- Intent to propose new regulation
- Marketing Application
- IND/IDE

Promotes use of data standards
Pre-CDISC Clinical Trial Workflow

DMS  = Data Management System

DMS

setup

collection

lock

Data Management System (DMS)

Datasets

specs

program

Draft

final

Analysis

specification

program

Draft

final

Displays

specification

program

Draft

final

Time →
Workflow for CDISC Project

CDASH DMS
- setup
- collection
- lock

SDTM
- setup
- specs
- program
- draft
- "final"
- final

ADSNS ADaM
- specs
- program
- draft
- final

Displays
- specs
- program
- draft
- final

ADSNS = Analysis Datasets
## CDISC -> More Deliverables

<table>
<thead>
<tr>
<th>Non-CDISC Project Deliverables:</th>
<th>CDISC Project Deliverables:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Data Management data</td>
<td>• Data Management data</td>
</tr>
<tr>
<td>• CRT data</td>
<td>• SDTM datasets</td>
</tr>
<tr>
<td>• Analysis datasets</td>
<td>• ADaM datasets</td>
</tr>
<tr>
<td>• Dataset specifications</td>
<td>• Results-level metadata</td>
</tr>
<tr>
<td>• Annotated CRF</td>
<td>• 2 Annotated CRFs (DM, SDTM)</td>
</tr>
<tr>
<td>• Define.pdf for clinical and</td>
<td>• Define.xml and Define.pdf for SDTM</td>
</tr>
<tr>
<td>analysis databases</td>
<td>• Define.pdf for ADaM</td>
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<tr>
<td>• TLFs</td>
<td>• Additional validation/</td>
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<td></td>
<td>documentation</td>
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<td>• TLFs</td>
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</table>
Sponsor Impact: Short Term

- Need to assimilate standards into processes
- More project parts to consider in the timeline
- Need to build new tools
- Lots of training
- More coordination needed
- Legacy conversions

## Sponsor Impact: Long Term

<table>
<thead>
<tr>
<th>Development standards and tools established</th>
<th>Standardized datasets across studies and therapeutic areas</th>
<th>Facilitates data exchange with multiple partners</th>
</tr>
</thead>
<tbody>
<tr>
<td>More efficient work flow</td>
<td>Facilitates data integration</td>
<td>Faster and higher quality review</td>
</tr>
</tbody>
</table>

[Image: Rho logo]
Some Ugly Facts about Drug Development

Patent life of a new compound or treatment: 20 years

Typically:
• Time from patent to approval: > 12 years and growing
• Time available to recoup investment, make profit: < 8 years and decreasing
• Cost of developing a new product: estimates range from $0.6 billion - $1.2 billion. $1.0 billion is a typical number cited
Sponsor Impact: Poor Implementation

- More work
- Delays in timelines, assembling NDA, approval
- Lower quality submission
- Increased costs
- Less remaining time on patent
Sponsor Impact: Successful Implementation

- Faster, more efficient study set up
- No delays in current timeline
- Lower overall costs of development
- Submission easier to assemble, review
- Facilitates communication during review
- Warehousing and retrieval of information
- More remaining time on patent
CDISC FDA Implementation
Progress Report

- SDTM and ADaM most frequently used models
- ODM used as format for define file
- CDASH use not widespread, other models not frequently used
- Predominant use: Meet FDA requests for CDISC compliant databases
- Standards not part of an integrated product development strategy
How Do We Get There?

Implementation Strategies

- Tables first philosophy
  - “start with the end in mind”

- Data standards implementation plan
  - NO LEGACY CONVERSIONS!!

- Extend standards to the beginning and to the end
  - “from protocol to display”

- Take advantage of standards- “Make routine things routine”
  - Metadata libraries
Keys to Implementation

1. Start with the end in mind

2. Extend the Use of Standards end to end

3. Data Standards Implementation Plan
Start With the End in Mind

Key Concepts
- Use of data standards throughout the life cycle
- Use of adaptive study designs

ISE/ISS mock displays first
- Based on target product profile or draft label

What displays/analyses are needed to show safety and efficacy
- Determines what studies are needed
- Each study contributes to evidence needed for approval
Start With the End in Mind

For a given study:
- What displays are needed to meet goals of the study?
  - Generate mock displays, which ...
    - Identify required data

Mock displays are driving force
- Dictate data to collect
  - Identify what data streams are needed

After mock displays:
- Protocol
- CRFs
- DMS
- Analysis / displays

Rho
Giving flight to research.
Tables-First Data Flow

Time ➔

Pre Data Collection ➔ Mock Displays ➔ Protocol CRF ➔

DMS ➔ setup ➔

Analysis DSNs ➔

Displays ➔

specs ➔ program ➔ draft ➔

SUBMISSION READY ➔

Mock Displays ➔

spec setup collection lock
draft

program
draft

final

P&H Group
Giving flight to research.
Benefits of This Approach

- Overlap studies/phases
- Focused data collection
- Early start on analysis
- Earlier start on ISS/ISE

Work flow is more focused and efficient!
Extend Standards End-to-End: Part 1

Clinical Research Standards (Content)
(Protocol-driven Research; Protocol → Reporting)

Protocol
• Study Design
• Eligibility
• Registration
• Schedule
(PR Model)

Case Report Forms (CRF) (CDASH)
• Study Data

Lab Data
(LAB and PGx)

Tabulated CRF data (SDTM)
• Study Data
• Lab Data
• Study Design
• Schedule

FDA eSubmissions Analysis and Reporting

Analysis Datasets
(ADaM)

*Transport: CDISC and/or HL7

Underutilizing anything?
Protocol Representation Model (PRM)

- Relatively new; not often used
- Expedited drug development
- Efficient protocol development
- Facilitates data collection system set up
PRM: Benefits & Efficiencies

Regulatory Submission Preparation

- PIND/PIDE meeting package
- INDs and CTAs
- Annual Reports/DSURs/PSURs
- EOP2 meeting package
- Pre-NDA/BLA meeting package
- NDA/BLA/Marketing Authorisation Application
- 120-Day Safety Updates
Extend Standards End-to-End: Part 2

Clinical Research Standards (Content)
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Missing anything?
Extend Standards: Displays/Reporting

Standards not extended to reporting

Fewer papers/presentations using standards effectively

Many displays are common across numerous studies

Focus of FDA Working Group 5
Standards Now Truly End-to-End

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FDA eSubmissions Analysis and Reporting

Display/Results Meta-data

*Transport: CDISC and/or HL7
Implementation Plan

Company Size Matters!
- Size and diversity of skill sets
- Resources available

Business Model
- Taking current product to approval?
- Taking current product to proof of concept?
- Partnering as soon as possible?
- Selling as soon as possible?
Implementation Strategy

- Non-CDISC submission
- SDTM and ADaM for Ongoing Studies
- Extend to data collection -> CDASH
- Integrated product development strategy
- Legacy Conversions
- Non-CDISC submission
When to Implement

- Non-CDISC submission
- Legacy conversions for all studies
- SDTM and ADaM only for Phase III
- SDTM and ADaM for all studies
- End to End plan
Implementation Strategy

- Legacy Conversions
- Non-CDISC submission
- SDTM and ADaM for Ongoing Studies
- Extend to data collection -> CDASH
- Integrated product development strategy
Legacy Conversion

Pros

- Most organizations start here
- Gets the FDA what they want
- Responsibility of biostatisticians/programmers
- No investment in CDISC until success of drug likely
- Continued use of existing tools and processes
## Legacy Conversion

### Cons

- Lots of work in a short time
- EXPENSIVE!!!
- Must reproduce clinical and analysis db, displays, CSR
- Lower quality
- Diverts resources from ISS/ISE
- Possible submission delay
Legacy Conversion Post Phase III

Not a good strategy if:
- Working with multiple partners
- Long term goal is to take product to market or partner

Good strategy if:
- Goal is to sell ASAP
- Sell after proof of concept
- Staff does not have skill set to implement
- No $$ to implement CDISC early in development
Implementation Strategy

Legacy Conversions

SDTM and ADaM for Ongoing Studies

Non-CDISC submission

Extend to data collection -> CDASH

Integrated product development strategy
SDTM/ADaM: Implement for Ongoing Studies

- Gets the FDA what they want
- Responsibility of biostatisticians/programmers
- Long term efficiency and effectiveness
- ↓ cost of analysis/reporting up to 50%
- Common format
- Industry wide standard
Short term considerations:

- More work and less time to do it
- Could affect timelines
- Existing standards and processes
- Most drugs (90%) fail during phase I -> more work with risk of little in return
- Significant changes in internal processes and workflow
- Investment in training and software
- CDISC still not required
SDTM/ADaM: Implement for Ongoing Studies

Long term considerations:

- Good strategy if plan to take product to market or partner
- Requires staff with diverse skill set to implement CDISC
- Requires $$$ to implement CDISC
- FDA has invested heavily in CDISC
- Proposed regulation to require CDISC
SDTM/ADaM: Hybrid Strategy

Use CDISC standards only for adequate and well-controlled Phase 3 studies

Advantages

• Much higher probability at this stage that the drug will succeed
• Good chance you can negotiate with FDA to submit only pivotal studies in CDISC format

Disadvantages

• All studies will not be in a uniform format-annoy reviewers, increase difficulty of review
• Integration will be more difficult, especially for safety data
• The FDA may prefer non-pivotal studies in CDISC format
Implementation Strategy

- Non-CDISC submission
- SDTM and ADaM for Ongoing Studies
- Extend to data collection -> CDASH
- Integrated product development strategy
SDTM and ADaM + CDASH

- Same advantages as SDTM/ADaM Strategy
- Extends standards to data collection
- Global library of data collection elements
SDTM and ADaM + CDASH

**Advantages**

- Facilitates SDTM database creation
- Streamlines conversion of DM data to SDTM
- Faster and cheaper SDTM
- Package DM->SDTM
- Cost effective DM-> SDTM for Phase I/II studies
- Extends standards to Clinical Data Management (CDM)
- Improves communication between CDM and biostatistics
- Important for cost effectiveness in products being taken to market
Implementation Strategy

Non-CDISC submission

SDTM and ADaM for Ongoing Studies

Extend to data collection -> CDASH

Integrated product development strategy
End-to-End Standards Implementation

Clinical Research Standards (Content)
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Analysis Datasets (ADaM)

FDA eSubmissions
Analysis and Reporting

Displays / Reporting

*Transport: CDISC and/or HL7
End-to-End Standards Implementation

Extend standards implementation all the way upstream

Standards plan required at time of IND/IDE

Create a plan for entire product development life cycle

Start at protocol and end at display production

Rho
Giving flight to research.
End-to-End Standards Implementation

Protocol Representation Model (PRM) facilitates:

- Efficient protocol development
- Data collection system set up
- Expedited drug development
- SDTM database creation
End-to-End Standards Implementation

Advantages:
• Includes regulatory and clinical personnel
• Promotes cross-functional communication
• Facilitates regulatory review

Most cost effective when goal is:
• Bring product to market
• Partner (adds significant value)
End-to-End Standards Implementation

Standards implemented from the beginning

- Can save up to 60% of non-subject participation time and cost
- About half of the value is in the start up stages

Savings depends on several factors

- Existing use of proprietary standards
- Stage of implementation
- Training
- Type and size of study

Summary

Data Standards Plan expected at time of IND/IDE

Plan dependent on business strategy, company size, and resources

Successful implementation strategy can

• reduce time and cost
• facilitate regulatory review
• increase time remaining on patent
• increase communication
• increase quality
• “make routine things routine”
Summary

Change in mindset required

- Tables first
- Expedited Product Development
- Standards beyond biostatistics
- Standards from end-end

“If you are in the drug development business, you now are also in the CDISC Data Standards Business.”
Q&A

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Frank Dilorio (Frank@CodeCraftersInc.com)