PDUFA V, 21st Century Review, CDER Data Standards, PhUSE/FDA and ADaM: Getting It All Right

Steve Wilson

Director, Division of Biometrics III

OTS/OBCDER/FDA

PhUSE SDE - Durham, North Carolina

Thursday, April 18th, 2013

11:30 am – 12:15 pm

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

Truth-in-Advertising

- CDER-centric
- Statistical reviewer-centric
- Don't like talking to screens
- Pardon my accent
- I'm just a "set-up" for Behrang

Acknowledgements

- Amy Malla
- Joy Mele
- Frank Newby
- Mary Ann Slack*
- Stan Woolen


NORTH
5
CAROLINA
NCAA

Getting It All Right

- FDASIA/PDUFA V
- 21st Century Review Initiative
- CDER Data Standards
- PhUSE/FDA and ADaM

FDASIA/PDUFA V

FDA Safety and Innovation Act (FDASIA)

- Reauthorizes the fifth instance of Prescription Drug User Fee Act (PDUFA V)
- Authorizes the new Generic Drug User Fee Act and Biosimilars User Fee Act
- FDASIA Section 1136:
  - Allows FDA to require standardized fully electronic submissions related to marketing applications
- Phased-in through guidance to industry according to an agreed timetable

Slack, 2013

Where We Started: PDUFA I

- The ***Prescription Drug User Fee Act*** (PDUFA-- law Congress in 1992 allowing FDA to collect fees to fund the new drug/ biologics approval process.
- CDER and CBER
- FDA is required to meet certain performance benchmarks, primarily related to the speed of certain activities within the NDA review process
- 5-year Plans -- PDUFAs I - IV

FDASIA/PDUFA V

PDUFA REAUTHORIZATION

PERFORMANCE GOALS AND PROCEDURES

FISCAL YEARS 2013 THROUGH 2017

http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf

PDUFA V Performance Goals FY 2013 – FY 2017

I. REVIEW PERFORMANCE GOALS

II. NEW MOLECULAR ENTITY NDA AND ORIGINAL BLA PERFORMANCE GOALS

III. FIRST CYCLE REVIEW PERFORMANCE

IV. REVIEW OF PROPRIETARY NAMES TO REDUCE MEDICATION ERRORS

V. MAJOR DISPUTE RESOLUTION

VI. CLINICAL HOLDS

http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf

PDUFA V Performance Goals FY 2013 – FY 2017

XII. IMPROVING THE EFFICIENCY OF HUMAN DRUG REVIEW THROUGH REQUIRED ELECTRONIC SUBMISSIONS AND STANDARDIZATION OF ELECTRONIC DRUG APPLICATION DATA

XIII. PROGRESS REPORTING FOR PDUFA V AND CONTINUING PDUFA IV INITIATIVES

XIV. INFORMATION TECHNOLOGY GOALS

XV. IMPROVING FDA PERFORMANCE MANAGEMENT

XVI. DEFINITIONS AND EXPLANATION OF TERMS

http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf

How Is This "Standards Thing" Going to Be Accomplished?

Later: CDER Data Standards

21st Century Review Initiative

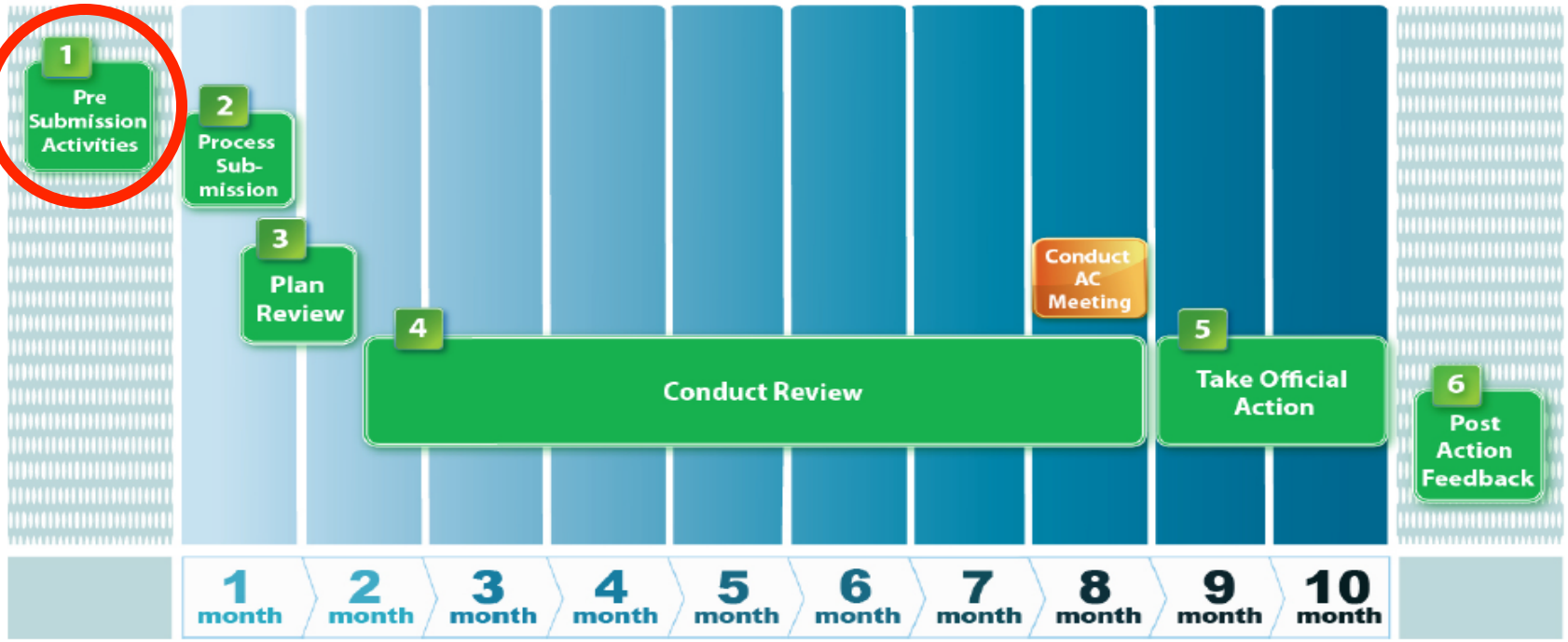
- Performance standards
- Meetings and timelines
- Goal is to make the drug review process more organized and integrated
- Ensure all decision makers are heard.
- Review team members are accountable for raising and addressing differing points in a timely manner (i.e., no surprises)

21st Century Playbook for Reviewers

http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM218757.pdf

CDER 21st Century Review Process

Desk Reference Guide



New Drug Application and Biologics License Application Reviews
(NDA/BLA Review Process)

Version: September 2012

21st Century Submission and Filing Review

- **All applications are expected to be complete at the time of original submission**
- Filing Review: For electronic submissions, reviewers also study the structure of data files and assess the overall navigation of the submission
- During the filing review, reviewers identify any substantive deficiencies or concerns that appear to have been inadequately addressed in the application and merit particular attention during the review process
- Discipline Filing Review Templates

Statistics: Filing Checklist

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: **Applicant:** **Stamp Date:**

Drug Name: **NDA/BLA Type:**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.				
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)				
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).				
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).				

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? _____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Stat Review: Confirmatory Study

- Confirmatory hypotheses – protocol, SAP
- Sponsor's work and reported results
- Locate, understand, "handle" the data
- Assess data quality/completeness
- Identify and validate important results reported by sponsor (label claims)
- Determine appropriateness of statistical methods
- Evaluate potential sources of bias
- Perform additional analyses (safety and efficacy)
- Create/maintain review audit trails
- Conclude and recommend – issue review

"Building" a Stat Review

- Protocol
- Statistical Analysis Plan (SAP)
- Need Both!:
  - "Raw"/"observed" data (Case Report Tabulations or CRTs) -- SDTM or legacy data
  - Analysis files -- ADaM or legacy datasets
- Metadata (including define.xml/pdf and programs)
- Study reports
- NDA/BLA

CDER Data Standards

Remember: FDASIA Section 1136 allows FDA to require standardized fully electronic submissions related to marketing applications

CDER's Data Standards Program - Operating Principles

- Process
  - Open and inclusive of stakeholders
  - Transparent
  - Predictable
  - Focused on near-term improvements and long-term goals
- Policies, Standards, Requirements
  - Practical
  - End-user oriented
  - Cost-sensitive
  - Sustainable

Slack, 2012

FDA's "Communication" Toolkit

Laws & Regulation

Guidance & Initiatives

Adapted from S. Woollen

Relevant PDUFA V Commitments

- … FDA shall consult with stakeholders … to issue draft guidance on the standards and format of electronic submission of applications by December 31, 2012.
- … Such final guidance … shall be binding on sponsors, applicants, and manufacturers no earlier than twenty-four months after issuance of the final guidance.
- Requirements for electronic submission shall be phased in according to the following schedule:
  - Twenty-four (24) months after publication of the final guidance: All new original NDA and BLA submissions … efficacy supplements and amendments … labeling supplements and amendments … manufacturing supplements and amendments, and all other new NDA submissions.
  - Thirty-six (36) months after publication of the final guidance: All original commercial INDs and amendments, except for submissions described in section 561 of the Federal Food, Drug, and Cosmetic Act.

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More Relevant PDUFA V Commitments

- Clinical Terminology Standards: Using a public process that allows for stakeholder input, FDA shall develop standardized clinical data terminology …
  - … FDA shall publish a proposed project plan for stakeholder review and comment by June 30, 2013.
- Development of terminology standards for data other than clinical <*trials*> data: … FDA will request public input … to develop new standards or refine existing standards.
- FDA shall periodically publish final guidance specifying the completed data standards, formats, and terminologies that sponsors must use to submit data in applications. In the case of standards for study data, new data standards and terminology shall be applicable prospectively and only required for studies that begin 12 months after issuance of FDA's final guidance on the applicable data standards and terminology

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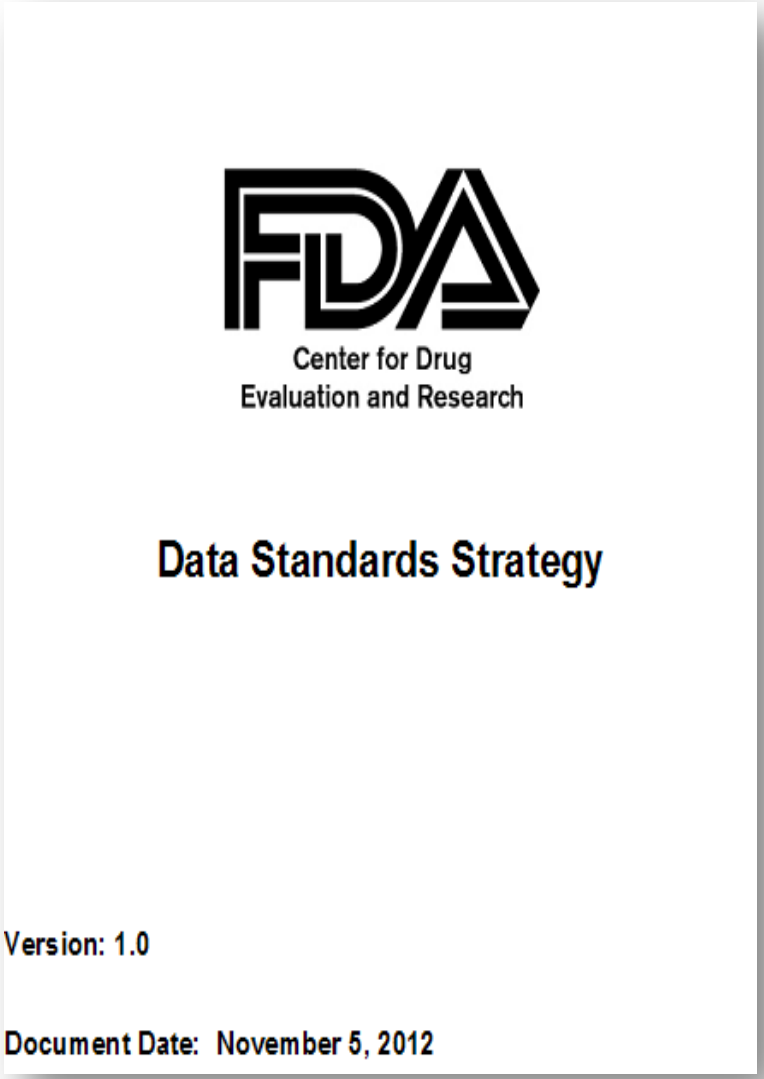
CDER Data Standards Strategy

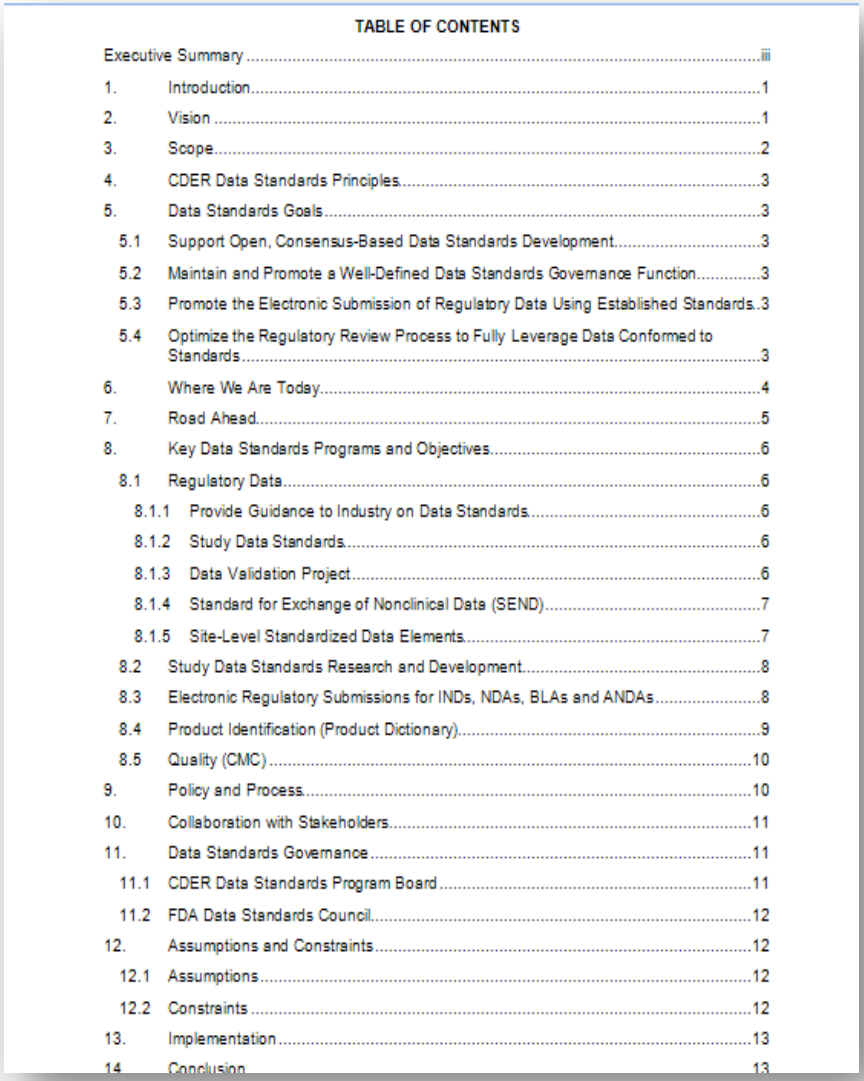


Center for Drug
Evaluation and Research

Data Standards Strategy

Version: 1.0

Document Date: November 5, 2012



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CDER Data Standards Action Plan

Just Published!

Initiatives align with the Center's data standards strategic goals:

- **Policy and Process** – Key activities to establish essential standards-related policy or process (e.g., standards development & adoption, guidance development and schedule, specific guidance)
- **Standards Development and Implementation** – Projects to develop, test, and implement a standard to meet a regulatory need
- **Study Data Standards** – Projects that develop, test, or implement advancements in study data terminology and content standards
- **Research and Development** – Projects to assess a potential approach to meet a standards-related need without immediate intent to implement; these are to inform future direction

Efforts Are "Risk Focused"

The standards activities and projects are defined with the major program risks in mind. This risk focus includes:

- Strong, consistent communications with stakeholders (e.g., SDOs, Industry, Academia, other government agencies, medical professional societies)
- Transparency through solicitation and receipt of public input
- Predictability through use of consistent process
- Assuring use-ability for regulatory review

A Sample of Relevant Efforts

- Published Communications Plan, Data Standards Strategy, and soon the Action Plan
- Executing requirements gathering and modeling for FDA "core" needs plus TAs
- Developing standards testing/readiness approach
- Conducting forward-looking activities (e.g., requirements and alternatives for data exchange needs, sustainability over time)

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FDASIA and PDUFA V – Some Key Guidance-Related Activities

(electronic submissions)

- Issue guidance for standardized electronic submissions (i.e. eCTD); draft by end of year, final within 12 months of receiving comments
  - **PUBLISHED**

Guidance will ultimately apply to all NDA, BLA, ANDA and commercial IND submissions (except for those described in section 561 of the FD&C Act)

FDASIA and PDUFA V – Some Key Guidance-Related Activities

(clinical/nonclinical study data)

- Develop plan for standardizing study data for Therapeutic Areas
  - **DRAFT, under internal review**
- Develop standardized clinical data terminology through open, consensus-based standards development organizations
  - **UNDERWAY**
- Periodically issue final guidance specifying the completed clinical data standards for use in sponsor application submissions
  - **"Parent" Guidance in DRAFT, anticipated release for public comment**

CDER's Grants Program

Objective:

- Expedite development of data concepts and terminology to support human drug development and evaluation

(additional details at http://grants.nih.gov/grants/guide/pa-files/PAR-11-209.html)

Goals:

- Advance the harmonization of data elements across the care continuum
- Support evolution toward better assessment of patient outcomes and a learning health system

To Date: Six (6) grants awarded (covering 5 different TAs)

- Cardiovascular (CV) Imaging
- CV Endpoints
- Schizophrenia
- Major Depressive Disorder
- Virology

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Current Activity – Study Data Standards

#	TA	Commenced	Start Date	Tier	Stage	Lead Group
1	Cardiovascular (CV)	Y		Tier 1	Development	CDISC
2	CV Imaging	Y			Development	DCRI
3	Pain	Y		Tier 1	Public Release, v1.0 Provisional	CDISC
4	Parkinson's	Y		Tier 1	Public Release, v1.0 Provisional	CDISC
5	Polycystic Kidney Disease	Y		Tier 1	Public Release	CDISC
6	Schizophrenia	Y		Tier 1	Development	DCRI
7	Tuberculosis	Y		Tier 1	Public Release, v1.0 Provisional	Critical Path Institute
8	Virology	Y			Public Release, v1.0 Provisional	CDISC
9	Anti-diabetic agents	N		Tier 1	Initiation	FDA/CFAST
10	Gastroesophageal Reflux Disease	N		Tier 2	Initiation	FDA
11	Major Depressive Disorder	Y	9/15/12	Tier 2	Development	DCRI
14	Acne	Y	10/1/12	Tier 1	FDA Requirements	FDA
29	Lipid-altering Drug Groups	N	January	Tier 2	FDA Requirements	FDA
32	Asthma	Y		Tier 2	Development	CFAST
42	Treatment of Hepatitis C	Y	1/10/13	Tier 1	FDA Requirements	FDA
45	Treatment of Overactive Bladder	Y	11/1/12	Tier 2	FDA Requirements	FDA
	Alzheimer's	Y		Tier 1	Public Release, v1.0	CDISC

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM297093.pdf

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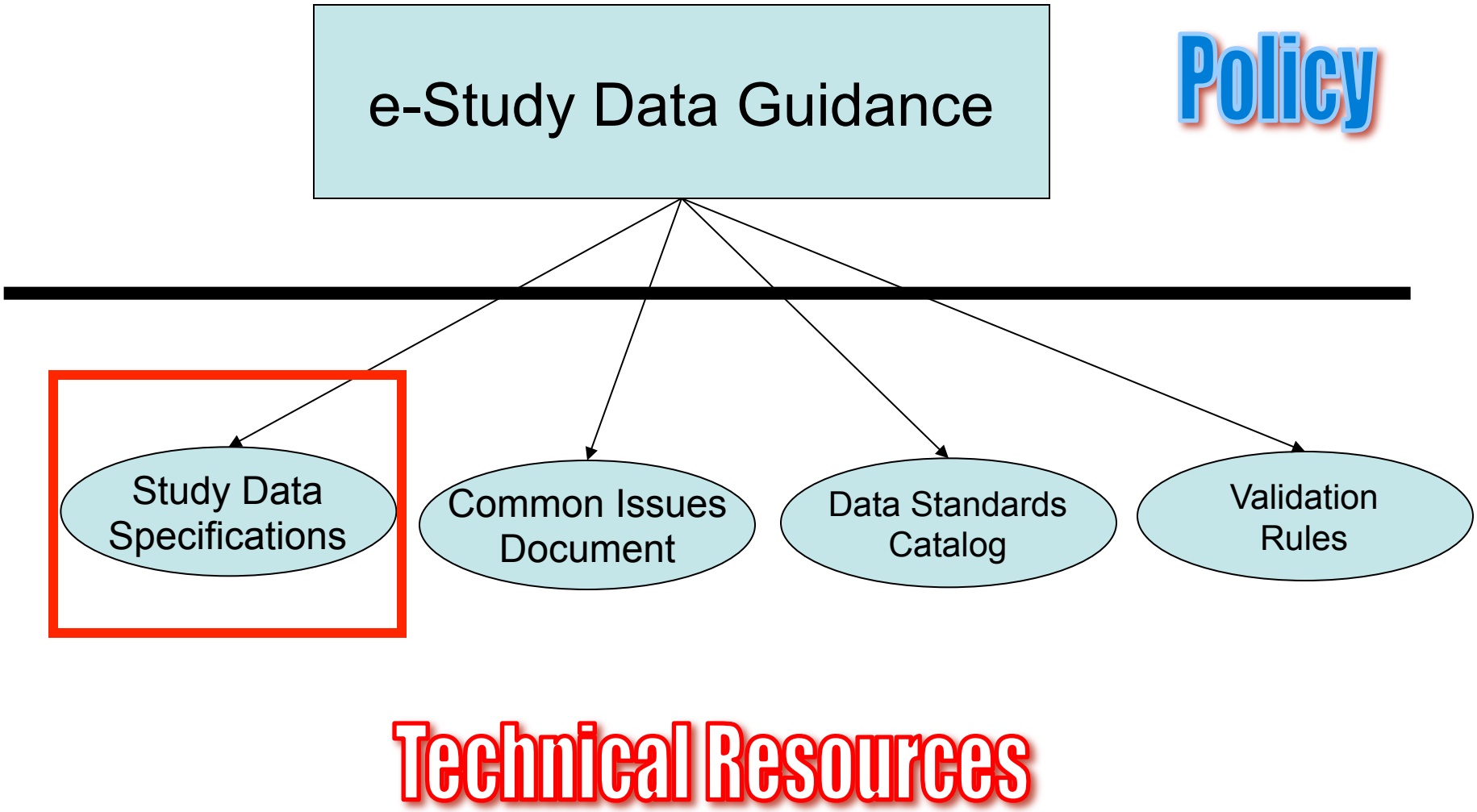
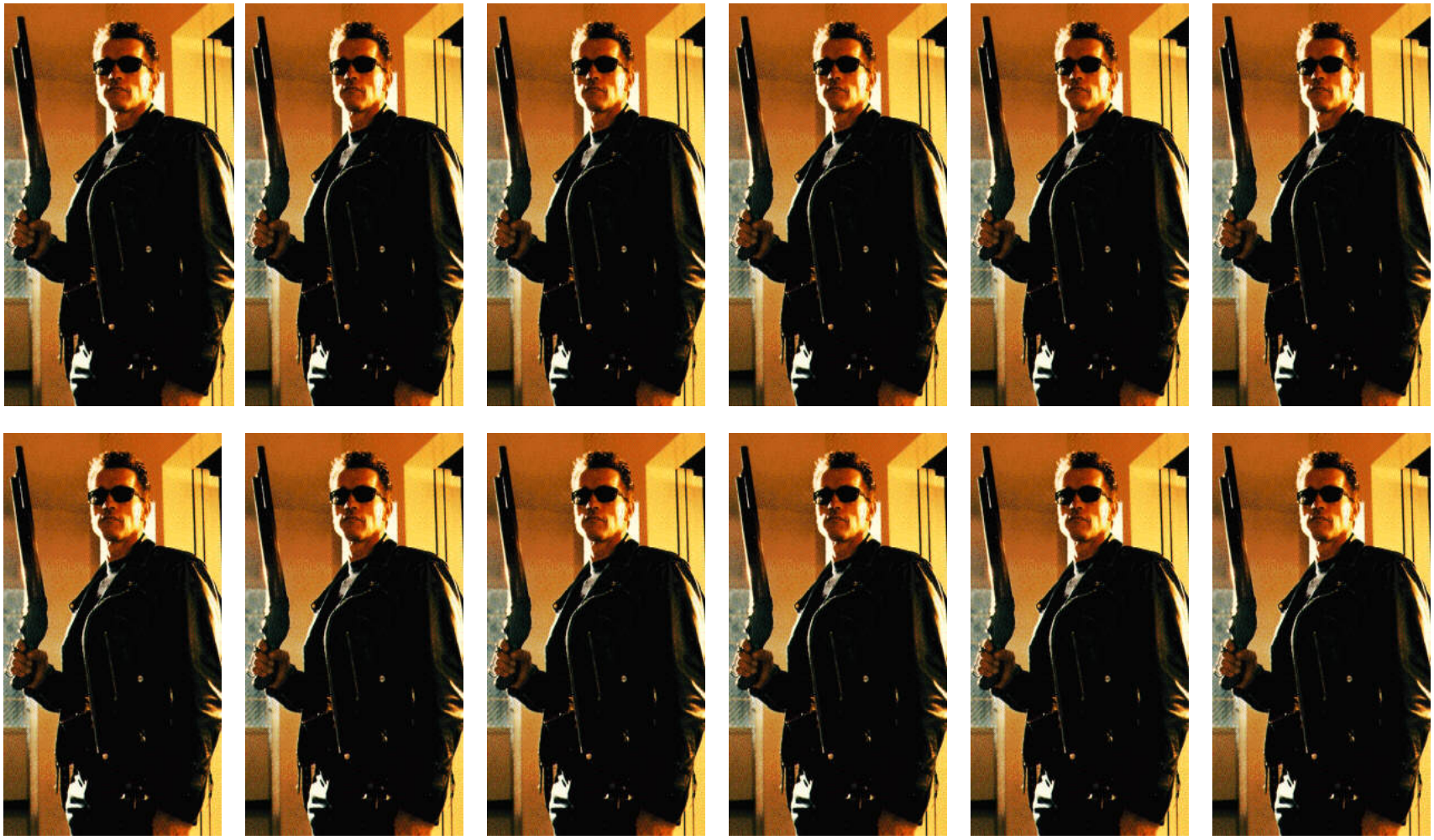
Moving Forward in PDUVA V



Specifications:
Another "Communication Tool"



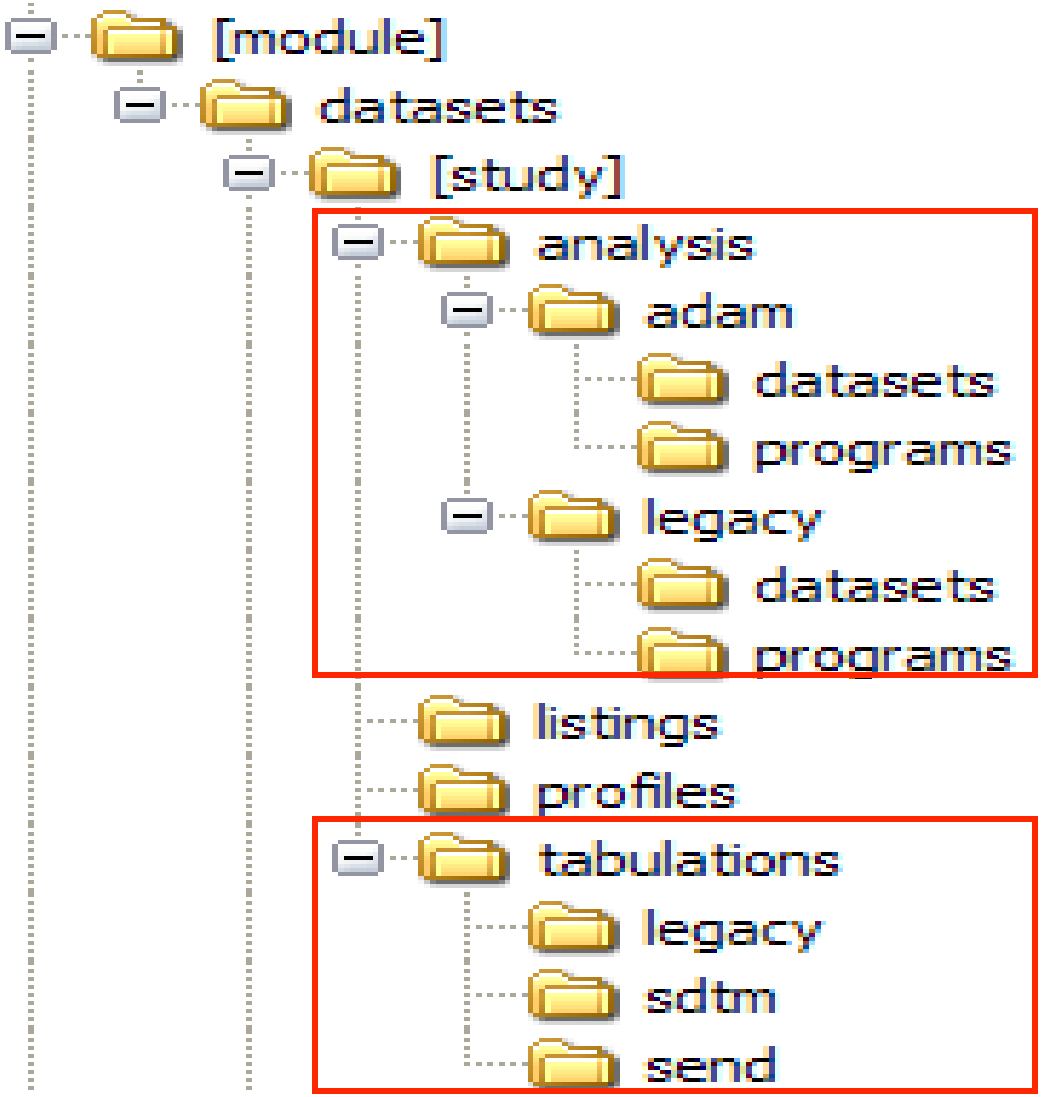
Study Data Specifications

Revision History

Date	Version	Summary of Changes
2004-07	1.0	Original version
2005-03-18	1.1	Addition of specifications for define.xml and SAS XPORT transport files specifications. Changes in document organization.
2006-03-04	1.2	Update information on annotated ECG waveform data. Delete ecg folder under Specifications for Organizing the Datasets.
2006-11-27	1.3	Addition of specifications for submitting tumor datasets (tumor.xpt) from rodent carcinogenicity studies.
2007-08-01	1.4	Addition of hyperlink to information for 3.1.1 datasets
2009-10-30	1.5	Modified introduction. Additional specifications for submitting data tabulation datasets. Additional specifications for analysis datasets. Revision of maximum file size restrictions. Addition of hyperlink to information for 3.1.2 datasets.
2010-01-04	1.5.1	Modified directory tree structure for organizing datasets and made minor technical corrections.
2011-06-22	1.6	Addition of specifications for general toxicology and carcinogenicity data tabulation datasets
2012-07-20	2.0	Reorganization , minor editorial changes

eCTD Study Data Folders

Source: Study Data Specifications Version 2.0 July 18, 2012
http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf



For More Information

Data Standards Website: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm249979.htm

Data Standards Catalog: http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

Questions: CDERDataStandards@fda.hhs.gov

PhUSE/FDA and ADaM

CDISC Analysis Data Model - ADaM

Provide data and metadata models along with examples of how to use analysis datasets to generate statistical results for regulatory submissions

Newby and Wilson, 2009

ADaM: Model & Guide

CDISC

Analysis Data Model (ADaM)

Prepared by the

CDISC Analysis Data Model Team

Notes to Readers

This is Version 2.1 of the Analysis Data Model (ADaM) Document. It includes modifications so that it corresponds to Version 1.0 of the Analysis Data Model Implementation Guide (ADaMIG).

Revision History

Date	Version	Summary of Changes
Dec. 17, 2009	2.1 Final	Released version reflecting all changes and corrections identified during comment period.
May 30, 2008	2.1 Draft	Draft for comment.
Aug. 11, 2006	2.0 Final	Final document
31 May 2006	2.0 Draft	Incorporate comments from public review
15 Feb 2006	2.0 Draft	Reformatted from General Considerations v1.0, incorporating Subject-level model, emphasizing requirements and naming and content rules and guidelines.

Note: Please see Appendix G for Representations and Warranties; Limitations of Liability; and Disclaimers.

CDISC

Analysis Data Model (ADaM) Implementation Guide

Prepared by the

CDISC Analysis Data Model Team

Notes to Readers

This Implementation Guide is Version 1.0 (V1.0) and corresponds to Version 2.1 of the CDISC Analysis Data Model.

Revision History

Date	Version	Summary of Changes
Dec. 17, 2009	1.0 Final	Released version reflecting all changes and corrections identified during comment period.
May 30, 2008	1.0 Draft	Draft for Public Comment

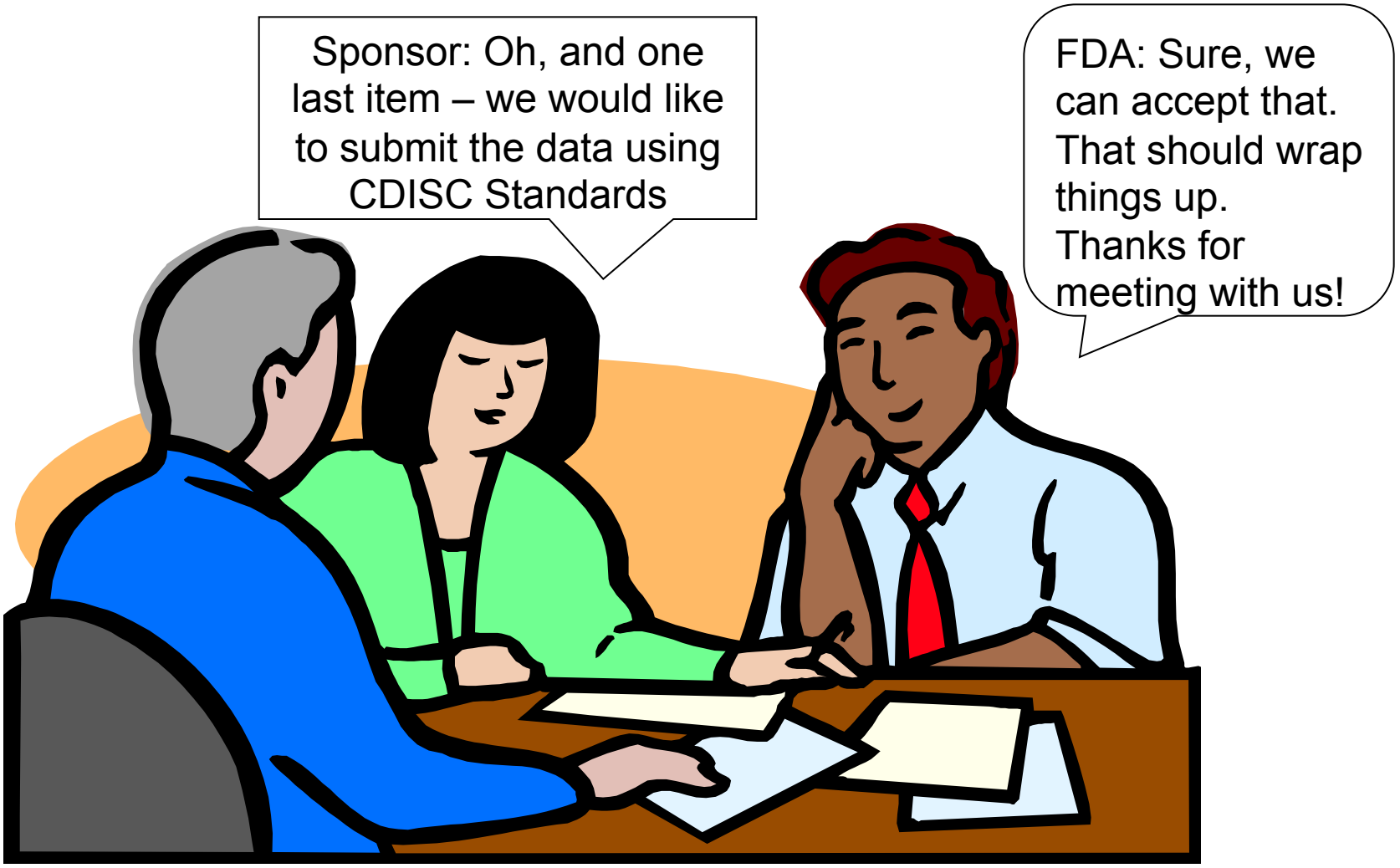
Note: Please see Appendix B for Representations and Warranties; Limitations of Liability, and Disclaimers.

SDTM and ADaM

- **SDTM**
  - Source data
  - No redundancy
  - Predominantly character variables
  - Each domain has a specific topic variable
  - Dates are ISO8601 character strings
  - Designed for data transfer and Interoperability
- **ADaM**
  - Source & Derived data
  - Redundancy is needed for easy analysis and may contain variables for supportive purposes
  - Numeric variables are often needed for analysis
  - Uses variables from multiple domains
  - Dates are numeric to allow calculation
  - Designed for communication of science

Newby and Wilson, 2009

Communiction: The FDA / Sponsor Data Submission Discussion



= DISASTER

Newby and Wilson, 2009

An ADaM Key Principle

Analysis datasets should:

Facilitate clear and unambiguous communication and provide a level of traceability

- Communicate two processes
  - Analysis Dataset creation
  - Analysis Results generation
- Clearly describe and document each process

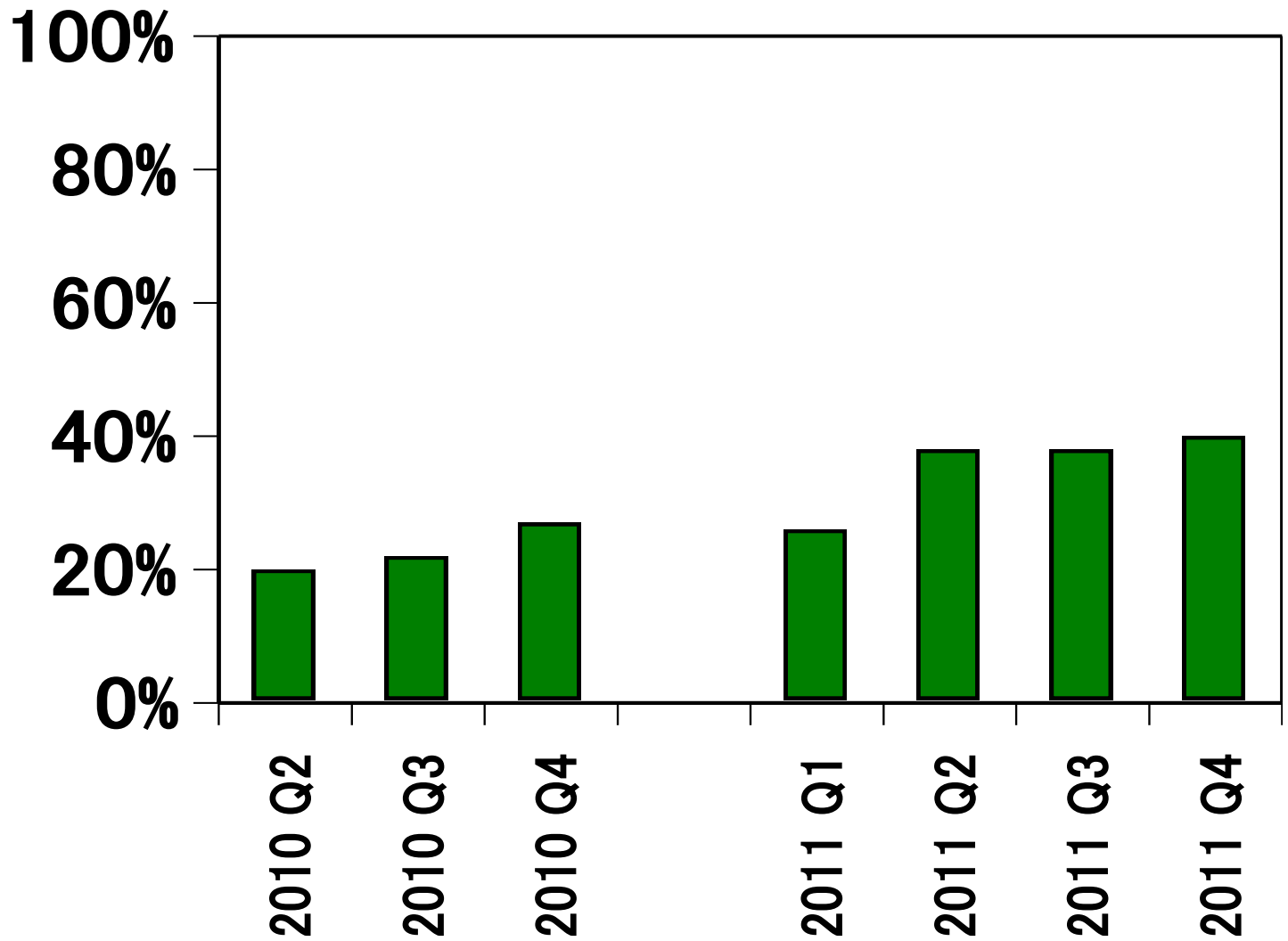
Adapted from Newby and Wilson, 2009

Specifications: Analysis Datasets

- Analysis datasets are datasets created to support results presented in study reports, ISS, ISE and other analyses that enable a thorough regulatory review.
- Analysis datasets contain both raw and derived data.
- CDISC/ADaM standards for analysis datasets (http://www.cdisc.org/adam) may be used if acceptable to the review team
- While the ADaM provides a valuable representation that may facilitate review, it does not always provide data structured in a way that supports all analyses needed for review.
- FDA review divisions may request non-standard analysis datasets to facilitate regulatory review.
- Prior to submission, sponsors should contact the appropriate center's reviewing division to determine the division's analysis dataset needs. [Talk to the Statistical Reviewer]

FDA Transparency Initiative

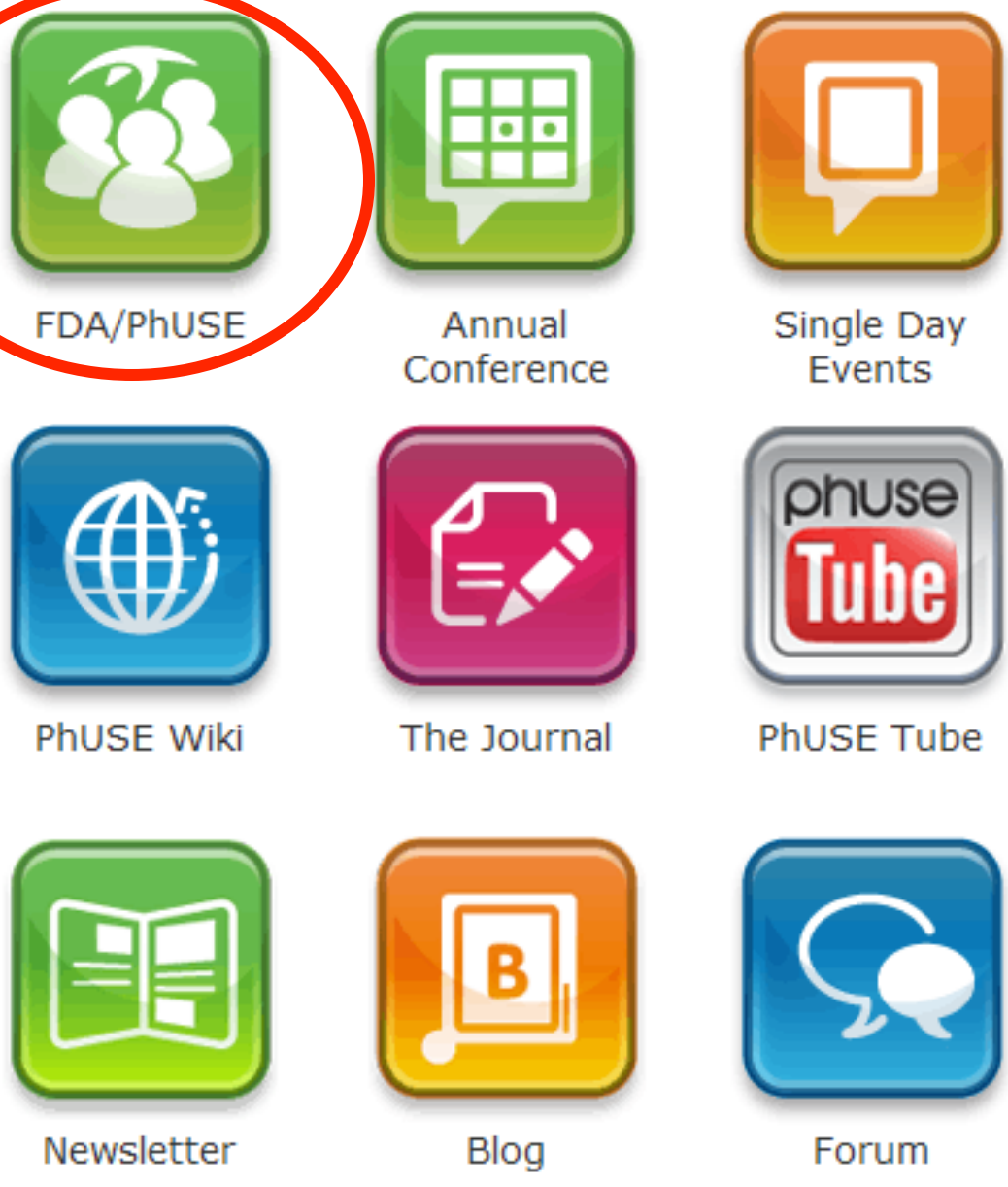
ADaM Submissions:2010 and 2011
as % of NDA submissions reviewed by OB



Mele, 2012

Collaboration: FDA/PhUSE

www.phuse.eu



Open Collaboration in a "Pre-Competitive" Space

2013 FDA/PhUSE Computational Science Symposium (CSS)

http://www.phuse.eu/css

Pharmaceutical Users Software Exchange

FDA/PhUSE | Annual Conference | Single Day Events

PhUSE Wiki | The Journal | PhUSE Tube

Newsletter | Blog | Forum

Archive | Members | About

Silver Spring Civic Center, Silver Spring Maryland, USA

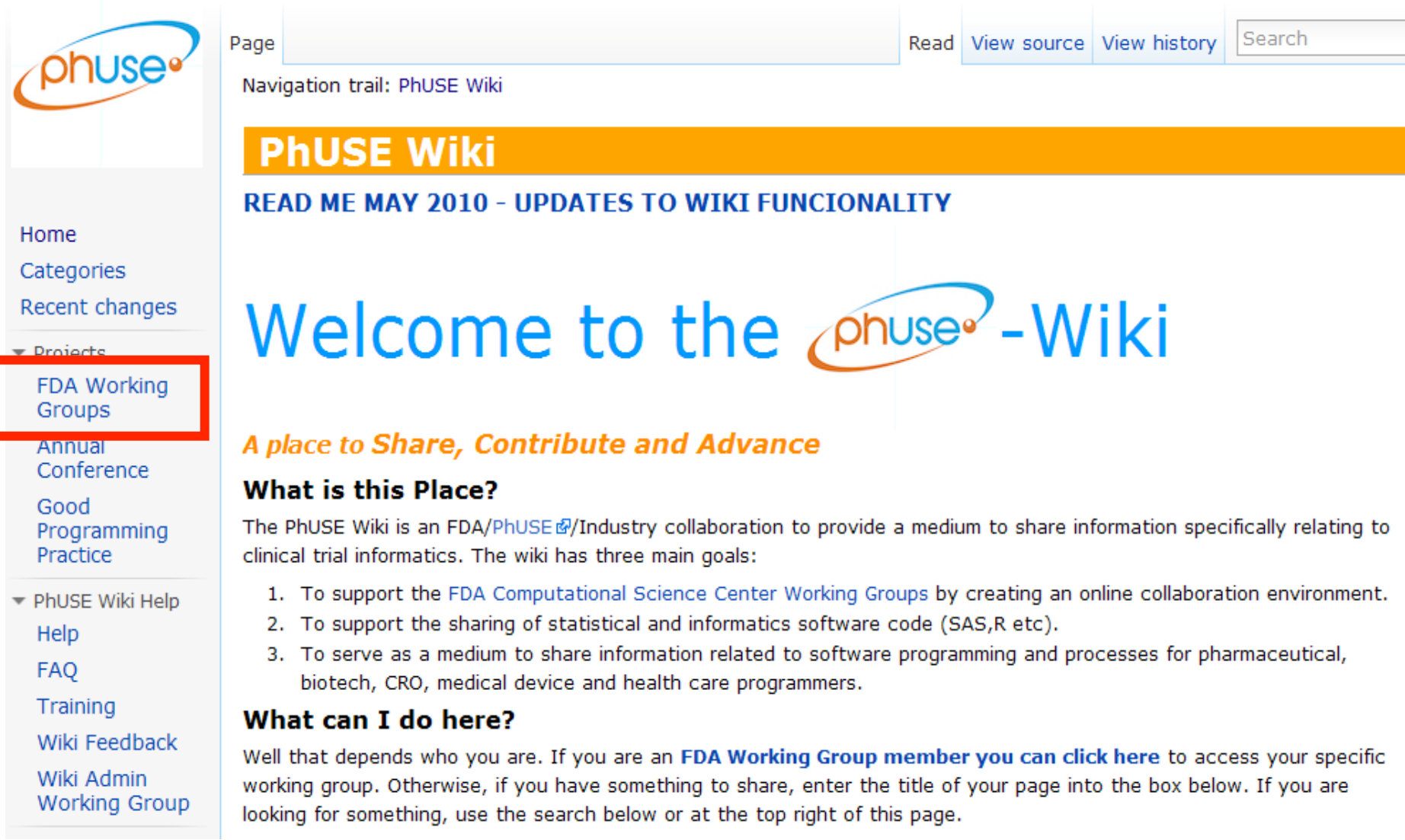
March 18th - 19th, 2013

The aim of the FDA/PhUSE annual Computational Science Symposium is to provide updates on collaborations with project groups to improve standards, tools and processes across regulatory review and computational science.

The annual Computational Science Symposium will bring FDA, industry and academia together for updates and work on collaborations established at previous symposiums and continued throughout the year. Additional collaborative projects will be created to address additional challenges related to the access and review of data to support product development. The groups will work on possible solutions and practical implementations with the goal of helping the broader community align and share experiences to advance computational science.

Working Groups:

The PhUSE Wiki



FDA/PhUSE Working Groups (WGs)

Optimizing the use of Data Standards Projects:

- Study Data Reviewer's Guide (SDRG)
- Traceability and Data Flow of Study Level Data
- (NEW) CDRH Pilot for the Electronic Submission of Medical Device Data in an SDTM-Based Format
- (NEW) Analysis Data Reviewer's Guide (ADRG)
- (NEW) SDTM Exceptions

Final SDRG Work Package!

http://www.phusewiki.org/wiki/index.php?title=Study_Data_Reviewer%27s_Guide

Overview & Scope

CGD-010: define.XML does not adequately document SDTM mapping decisions, sponsor-defined domains, sponsor-defined controlled terminology, and sponsor extensions to CDISC controlled terminology. A standardized Data Guide would help to address this documentation gap. The content of the Data Guide should be standardized and developed jointly between CDER, Industry, and CDISC.

Scope: The Study Data Reviewer's Guide (SDRG) will be proposed as a component of the eCTD's Module 5 SDTM data documentation. This document will be defined for SDTM data descriptions only. An Analysis Data Reviewer's Guide will be handled in a future project.

SDRG Core Team

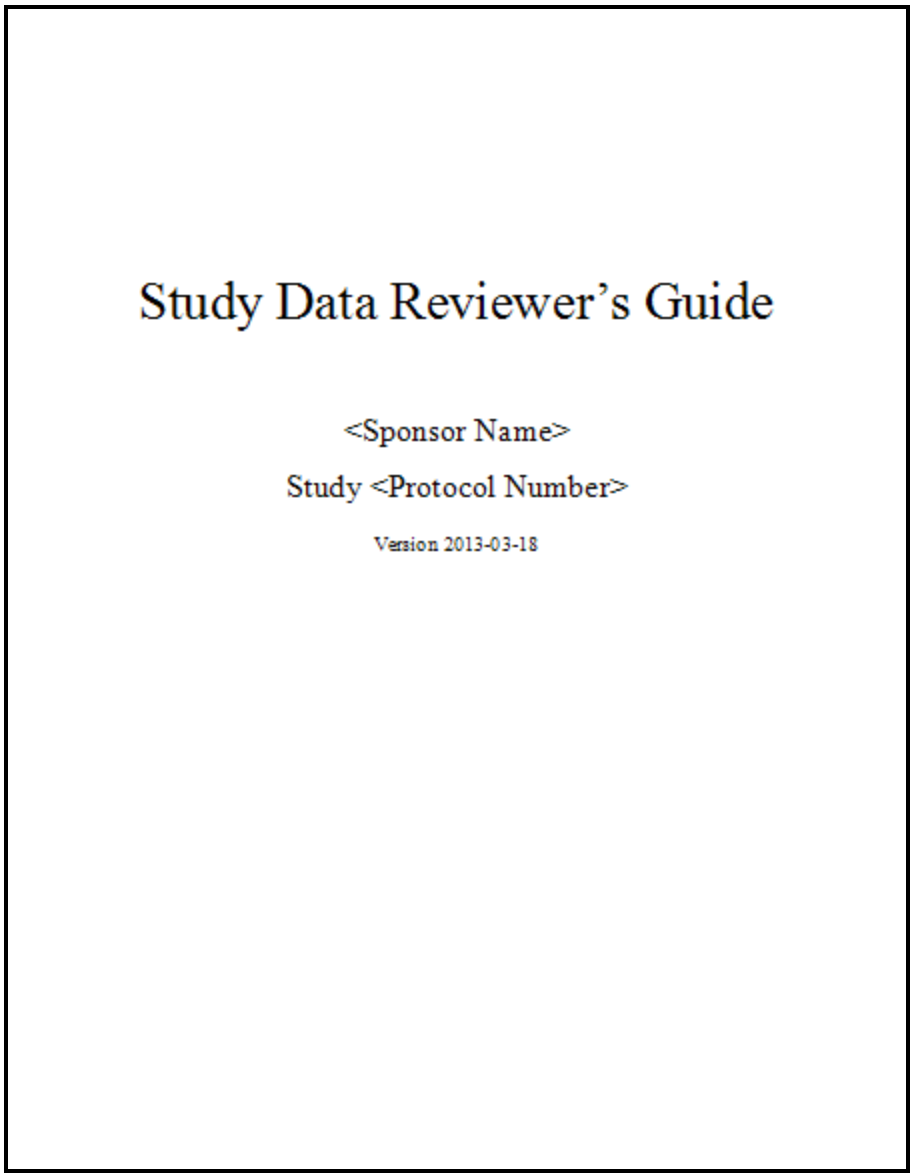
Helena Sviglin, FDA
Douglas Warfield, FDA
Gail Stoner GStoner@its.jnj.com, J&J
Joanna Koft joanna.koft@biogenidec.com, Biogen Idec
Scott Bahlavooni scottab@gene.com, Genentech
John Brega, Pharmastat

Final SDRG Work Package

Final SDRG Work Package v1.0 - Includes: SDRG Completion Guidelines, SDRG Template, and Example SDRGs
Please review Readme.txt for a complete description of all files in the work package.

Additional feedback can be provided by adding a comment to the Discussion Tab.

SDRG Template – Version 1.0!



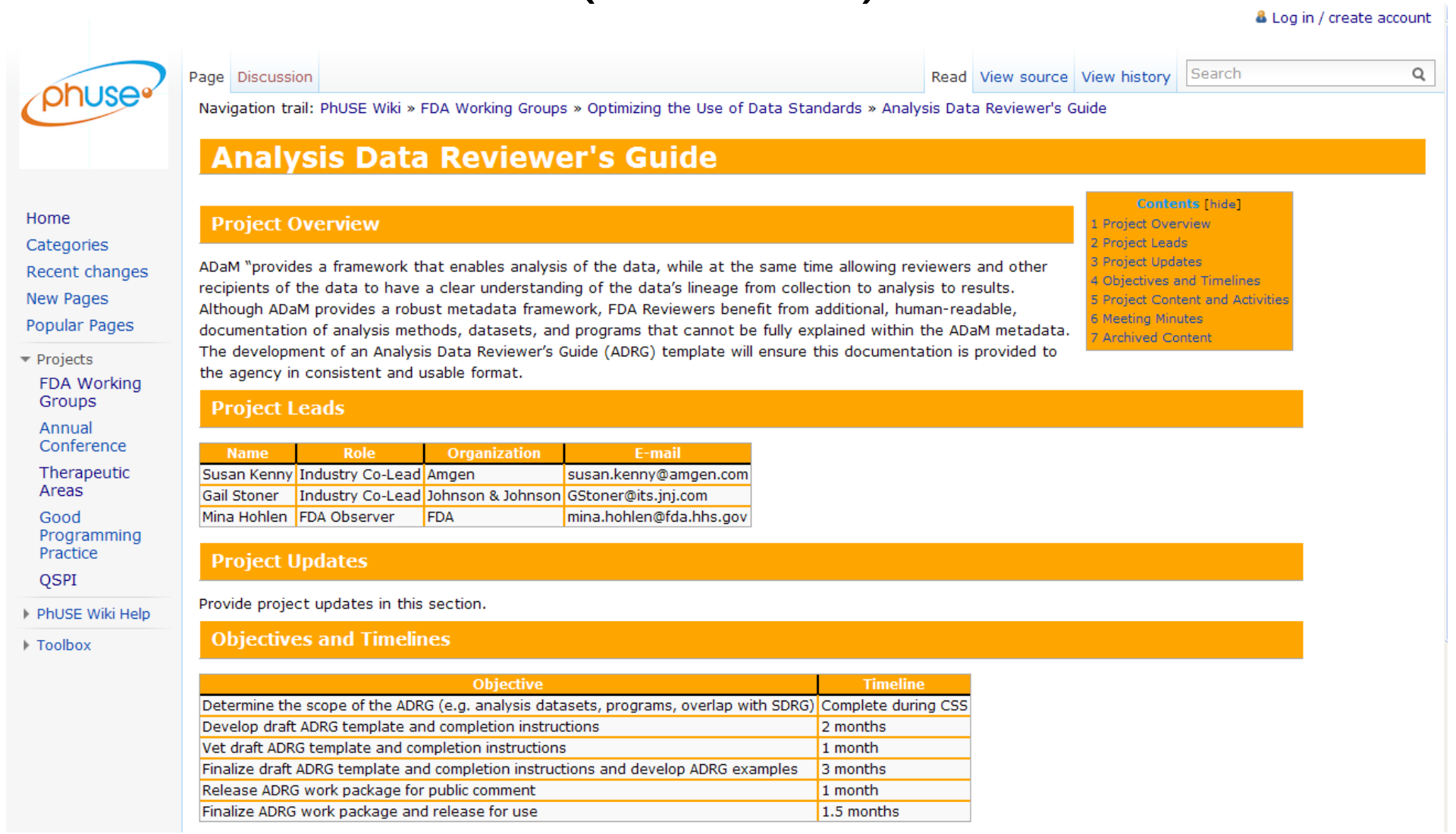
Study Data Reviewer's Guide

<Sponsor Name>

Study <Protocol Number>

Version 2013-03-18

Analysis Data Reviewer's Guide (ADRG)



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Navigation trail: PhUSE Wiki » FDA Working Groups » Optimizing the Use of Data Standards » Analysis Data Reviewer's Guide

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Analysis Data Reviewer's Guide

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2 Project Leads
3 Project Updates
4 Objectives and Timelines
5 Project Content and Activities
6 Meeting Minutes
7 Archived Content

Project Overview

ADaM "provides a framework that enables analysis of the data, while at the same time allowing reviewers and other recipients of the data to have a clear understanding of the data's lineage from collection to analysis to results. Although ADaM provides a robust metadata framework, FDA Reviewers benefit from additional, human-readable, documentation of analysis methods, datasets, and programs that cannot be fully explained within the ADaM metadata. The development of an Analysis Data Reviewer's Guide (ADRG) template will ensure this documentation is provided to the agency in consistent and usable format.

Project Leads

Name	Role	Organization	E-mail
Susan Kenny	Industry Co-Lead	Amgen	susan.kenny@amgen.com
Gail Stoner	Industry Co-Lead	Johnson & Johnson	GStoner@its.jnj.com
Mina Hohlen	FDA Observer	FDA	mina.hohlen@fda.hhs.gov

Project Updates

Provide project updates in this section.

Objectives and Timelines

Objective	Timeline
Determine the scope of the ADRG (e.g. analysis datasets, programs, overlap with SDRG)	Complete during CSS
Develop draft ADRG template and completion instructions	2 months
Vet draft ADRG template and completion instructions	1 month
Finalize draft ADRG template and completion instructions and develop ADRG examples	3 months
Release ADRG work package for public comment	1 month
Finalize ADRG work package and release for use	1.5 months

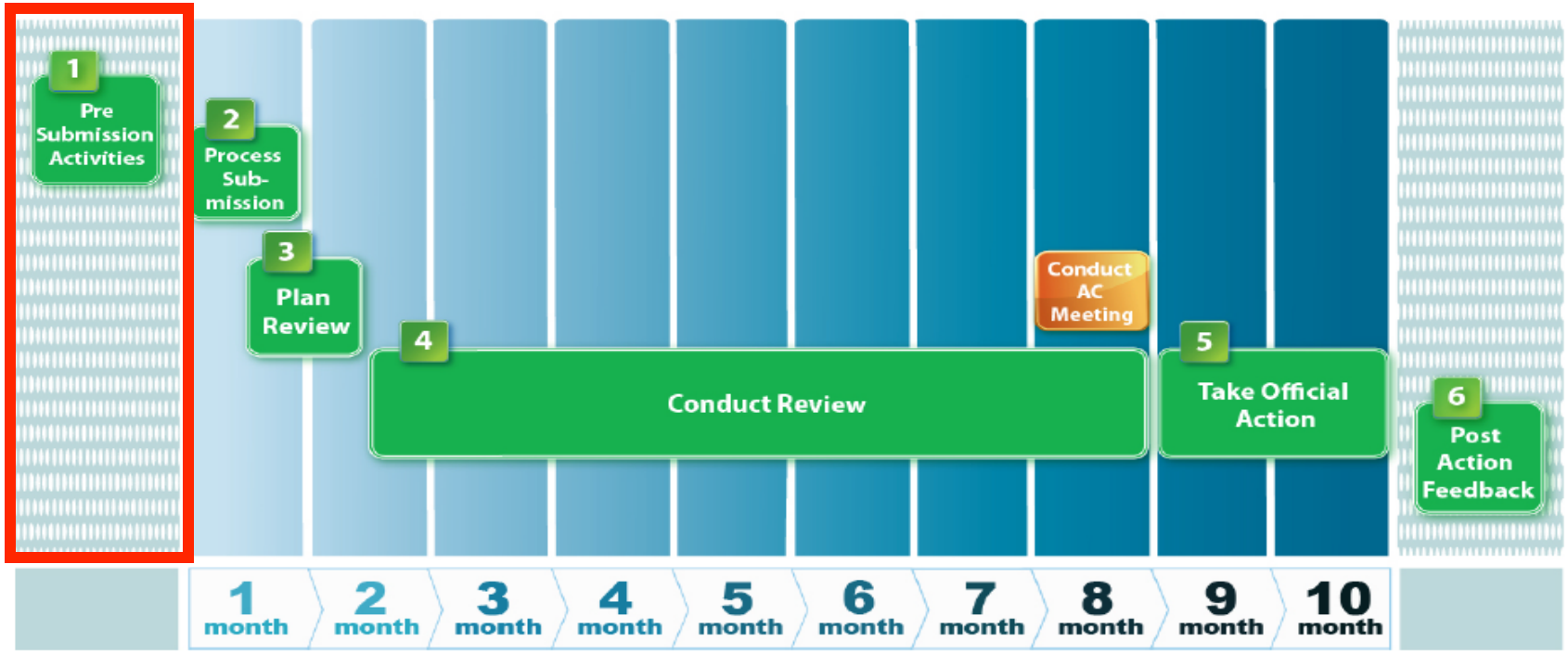
SDRG and ADRG –
Review Data “Communication Tools”

Here is Your Opportunity to Paint Some Communication Fences!

The Playbook for Reviewers and Sponsors!!!

CDER 21st Century Review Process

Desk Reference Guide



New Drug Application and Biologics License Application Reviews
(NDA/BLA Review Process)

Version: September 2012

We Need to Practice / to Get Better at Communicating! The NDA/BLA Analysis Data Pass

We All Want This to Work!


NORTH
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CAROLINA
NCAA


NDA

Conclusion

It's All About Communication!

Shameless Plugs: More Opportunities to Commuicate!

- 7th Annual FDA/DIA Statistics Forum – Bethesda, MD, April 28 – May 1, 2013
- DIA Annual Meeting, Boston, MA, June 23-27, 2013 (The Statistics Track includes an Data/ADaM Session)

THANK YOU FOR YOUR ATTENTION !!!

Take It Away Behrang!

(After Lunch)