Optimizing Standards Implementation for Successful eData Submissions to the FDA

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PhUSE SDE

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GILEAD

Advancing Therapeutics.
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Dhananjay (DJ) Chhatre, MS, RAC, PMP

Experience

- Senior Manager, Gilead Sciences (2015 – Present)
- FDA Data Standards Lead, Booz Allen Hamilton (2013 – 2015)
- Operations Research Analyst, FDA/CDER/OBI/eData (2009 – 2013)
- Research Fellow, NIH/NIDCD (2007 – 2009)

Industry Presence

- Working Group Lead, PhUSE "Optimizing the Use of Data Standards" (2014 – Present)
- Steering Committee Liaison, PhUSE Computational Science Symposium (2014 – Present)
- Working Group Lead, PhUSE "Data Validation and Quality Assessment" (2012 – 2013)
- Planning Committee and Track Chair, RAPS Annual Conference (2012 – 2013)
- Speaker, Panelist, and Session Chairman at various international conferences and webinars

PhUSE SDE

This SDE will focus on planning processes and data management workflows among sponsors and CROs for high quality regulatory e-data submissions with reduced costs.

There will be presentations from the FDA on their experiences with submissions to date with feedback on common errors observed in CDISC SDTM datasets. Presentations from sponsors, CROs and vendors will feature processes and capabilities that are being established for compliance with the FDA's implementation of CDISC-based electronic data submissions for both clinical and nonclinical studies.

Agenda Topics

1. Relevance & Importance of Standards
2. Governance Structure & Processes
3. Implementation Plan
4. Metadata
5. PhUSE WGs

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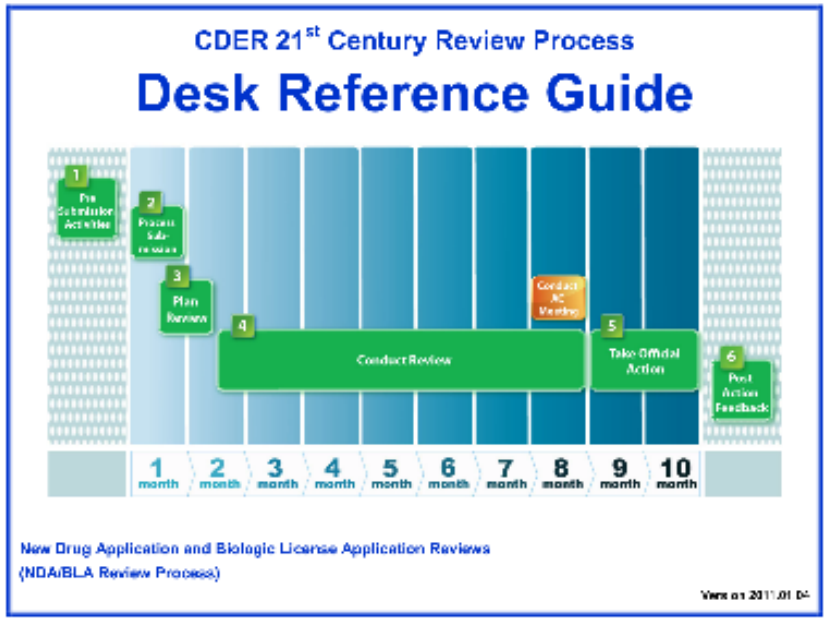
Data standards allow FDA reviewers to more effectively and efficiently review regulatory submissions, which already contain a variety of data use types, structures, and exchange formats

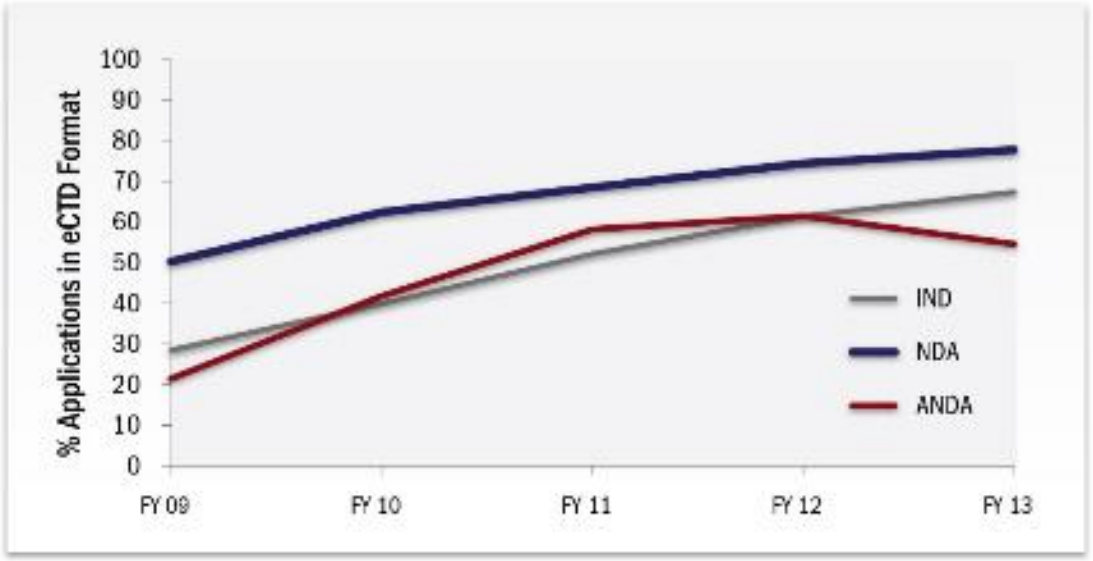
- FDA regulatory submissions contain data with various data use types, data structures, and data exchange formats
- Variances across submissions severely limit the Agency's ability to conduct cross-study, cross-product, retrospective, and cross-indication analyses during data-driven medical product reviews
- Standardized submissions will allow for smooth flow of study data through the human drug review process across the stages of 21st Century Review

Diversity of FDA Data Submissions	
Data Use Types:	Multiple use cases for data content, such as clinical study, nonclinical study, analysis, and adverse event data
Data Structure:	Various data structure types, from Sponsor-specific to ISO standards
Data Exchange Formats	FDA must manage and review data in paper, electronic, and hybrid submissions



Section 745A of the FD&C Act, amended by FDASIA, requires applications be submitted electronically 24 months after publication of final guidance

Proportion of CDER Applications in eCTD Format by Fiscal Year (FY)



Increasing amount of electronic data in eCTD format across application types is indicative of industry's ability to adapt and implement new requirements despite implementation changes to internal technologies

- FDASIA, signed on July 9, 2012 expanded FDA's authorities
  - Reauthorization of MDUFA III and PDUFA V
  - Authorization of GDUFA and BSUFA
  - FDA may issue "**guidance**" documents which are **binding**

- FD&C Act's Title XI Section 1136 addressed Electronic Formats of Applications
  - 745A(a)(1): Requires electronic submissions **24 months** following issuance of final guidance
  - 745A(a)(2): Guidance Contents
    - **Timetable** of further standards
    - Criteria for waivers and exemptions

http://www.gpo.gov/fdsys/pkg/BILLS-112s3187enr/pdf/BILLS-112s3187enr.pdf

FDA published binding guidance documents on 12/17/2014 which require regulatory submissions be submitted electronically and contain study data in conformance with CDISC standards

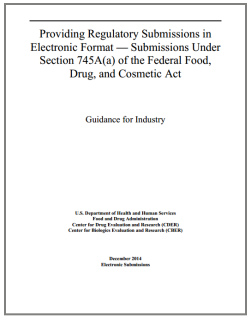
- FDA published 2 guidance and 4 technical specification documents on 12/17/2014
  - eCTD technical specification published in 05/2015
  - Study Data Technical Conformance Guide: Technical Specifications Document (SDTCG) updated 10/26/2015

1. *Providing Regulatory Submissions in Electronic Format – Submissions Under Section 745(a) of the Federal Food, Drug, and Cosmetic Act*
   - Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

2. *Providing Regulatory Submissions in Electronic Format – Standardized Study Data*
   - Data Standards Catalog (DSC)
   - SDTCG
   - FDA-specific SEND Validation Rules
   - FDA-specific SDTM Validation Rules

*"The submission of standardized study data **enhances** a **reviewer's ability** to more fully understand and characterize the **efficacy and safety** of a medical product."*

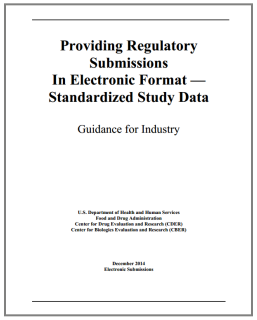
*"FDA **does not** foresee the **replacement** of CDISC standards for study data."*


Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2014
Electronic Submissions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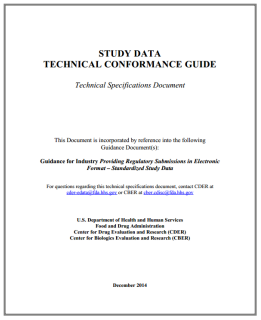

STUDY DATA
TECHNICAL CONFORMANCE GUIDE

Technical Specifications Document

This Document is incorporated by reference into the following Guidance Document(s):

Guidance for Industry ***Providing Regulatory Submissions in Electronic Format – Standardized Study Data***

For questions regarding this technical specifications document, contact CDER at sdtcg-edata@fda.hhs.gov or CBER at sdtcg-ebla@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

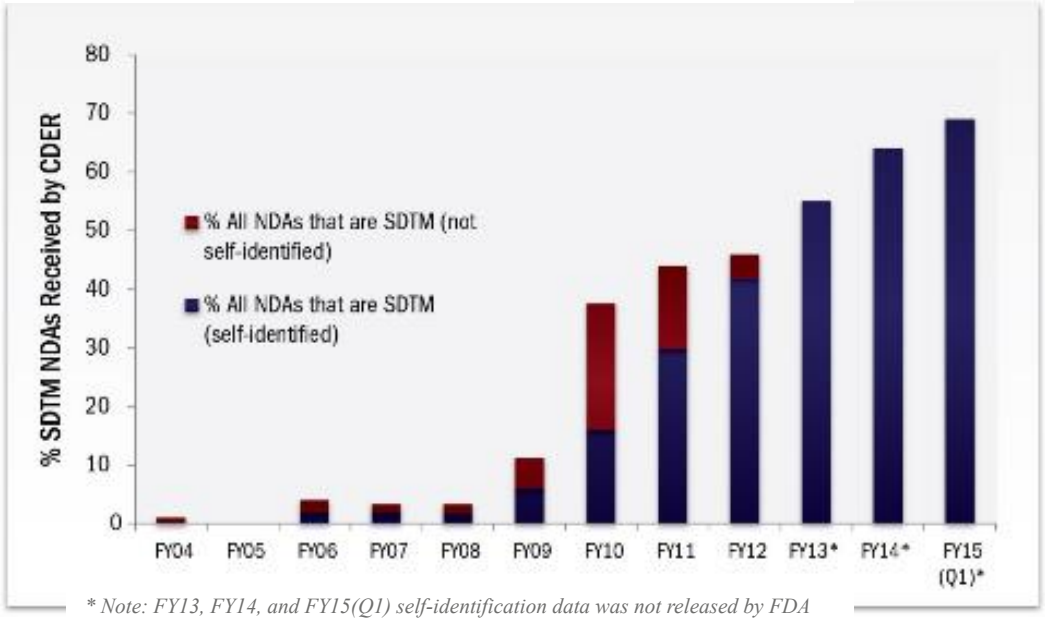
December 2014

http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM384686.pdf
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf
http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf

Clinical and Non-Clinical Studies, in support of regulatory submissions to the FDA, which start after December 17, 2016, must comply with all data standards and versions listed in FDA's DSC

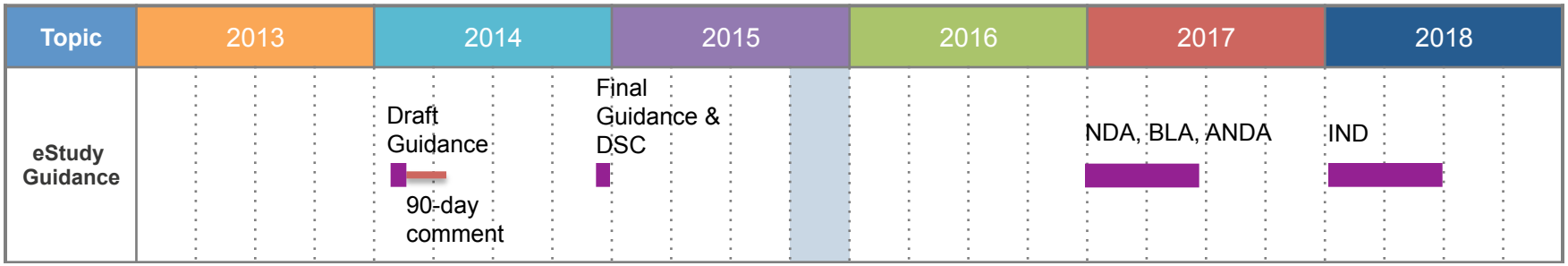
- Increasing numbers of NDAs received by CDER contain 1+ study with CDISC-formatted study data
- Growing number of sponsors labelling submissions as "CDISC"
- Rise in CDISC/SDTM adoption suggests confidence in data quality in face of additional FDA validation & compliance checks

Proportion of CDER SDTM NDAs by Fiscal Year (FY)



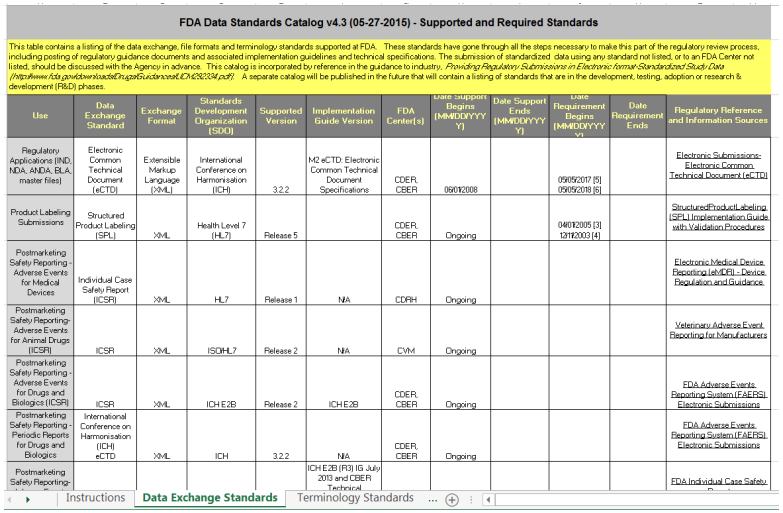
** Note: FY13, FY14, and FY15(Q1) self-identification data was not released by FDA*

Initial Timetable for Implementation of Study Data Standards Requirements



The Data Standards Catalog (DSC) defines FDA-supported standards as Exchange Format, Study Data, and Controlled Terminology Standards, as well as specific implementation timetables

1. **Exchange Format**
   - Particular way information is encoded
   - PDF, XPT, XML
2. **Study Data**
   - Describe data elements and relationships for unambiguous information exchange
   - Tabulations (CDISC/SDTM, CDISC/SEND) and Analysis (CDISC/ADaM)
3. **Controlled Terminology**
   - Vocabularies critical for achieving semantically interoperable data exchange
   - Specify key concepts represented as preferred terms, definitions, synonyms, codes, and code systems
   - Does not include custom terms, though extensible codelists are included
   - NDF, CDISC CT, MedDRA



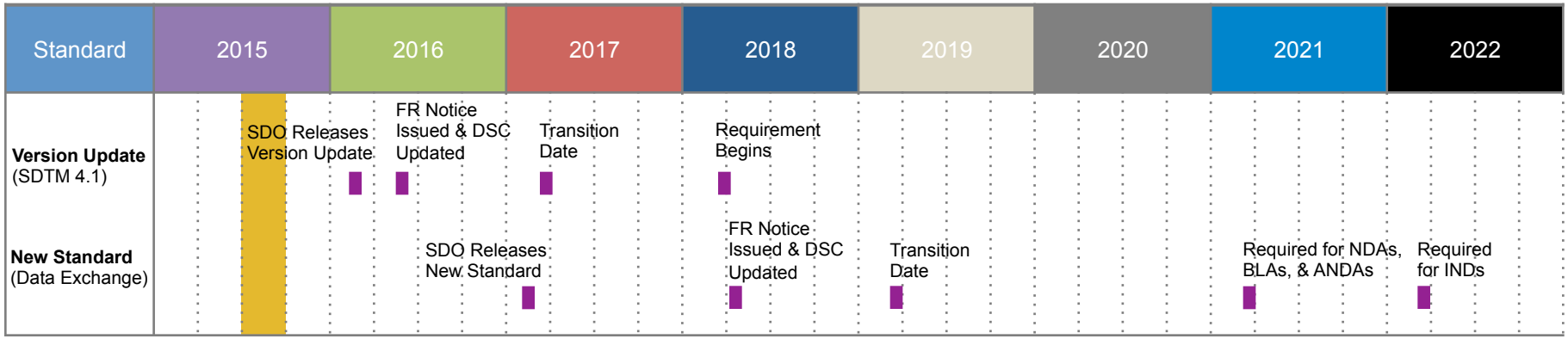
FDA Data Standards Catalog v4.3 (05-27-2015) - Supported and Required Standards

This table contains a listing of the data exchange, file formats and terminology standards supported at FDA. These standards have gone through all the steps necessary to make this part of the regulatory review process, including posting of regulatory guidance documents and associated implementation guidelines and technical specifications. The submission of standardized data using any standard not listed, or to an FDA Center not listed, should be discussed with the Agency in advance. This catalog is incorporated by reference in the guidance to industry, *Providing Regulatory Submissions in Electronic Format-Standardized Study Data (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf)*. A separate catalog will be published in the future that will contain a listing of standards that are in the development, testing, adoption or research & development (R&D) phases.

Use	Data Exchange Standard	Exchange Format	Standards Development Organization (SDO)	Supported Version	Implementation Guide Version	FDA Center(s)	Date Support Begins (MM/DD/YYYY)	Date Support Ends (MM/DD/YYYY)	Date Requirement Begins (MM/DD/YYYY)	Date Requirement Ends	Regulatory Reference and Information Sources
Regulatory Applications (IND, NDA, ANDA, BLA, master files)	Electronic Common Technical Document (eCTD)	Extensible Markup Language (XML)	International Conference on Harmonisation (ICH)	3.2.2	M2 eCTD: Electronic Common Technical Document Specifications	CDER, CBER	06/01/2008		05/05/2017 [5] 05/05/2018 [6]		Electronic Submissions-Electronic Common Technical Document (eCTD)
Product Labeling Submissions	Structured Product Labeling (SPL)	XML	Health Level 7 (HL7)	Release 5		CDER, CBER	Ongoing		04/01/2005 [3] 12/11/2003 [4]		StructuredProductLabeling (SPL) Implementation Guide with Validation Procedures
Postmarketing Safety Reporting - Adverse Events for Medical Devices	Individual Case Safety Report (ICSR)	XML	HL7	Release 1	N/A	CDRH	Ongoing				Electronic Medical Device Reporting (eMDR) - Device Regulation and Guidance
Postmarketing Safety Reporting- Adverse Events for Animal Drugs (ICSR)	ICSR	XML	ISO/HL7	Release 2	N/A	CVM	Ongoing				Veterinary Adverse Event Reporting for Manufacturers
Postmarketing Safety Reporting - Adverse Events for Drugs and Biologics (ICSR)	ICSR	XML	ICH E2B	Release 2	ICH E2B	CDER, CBER	Ongoing				FDA Adverse Events Reporting System (FAERS) Electronic Submissions
Postmarketing Safety Reporting - Periodic Reports for Drugs and Biologics	International Conference on Harmonisation (ICH) eCTD	XML	ICH	3.2.2	N/A	CDER, CBER	Ongoing				FDA Adverse Events Reporting System (FAERS) Electronic Submissions
Postmarketing Safety Reporting-					ICH E2B (R3) IG July 2013 and CBER Technical						FDA Individual Case Safety

Instructions | Data Exchange Standards | Terminology Standards

Example Implementation Timetables



http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM340684.xls

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Governance Issues

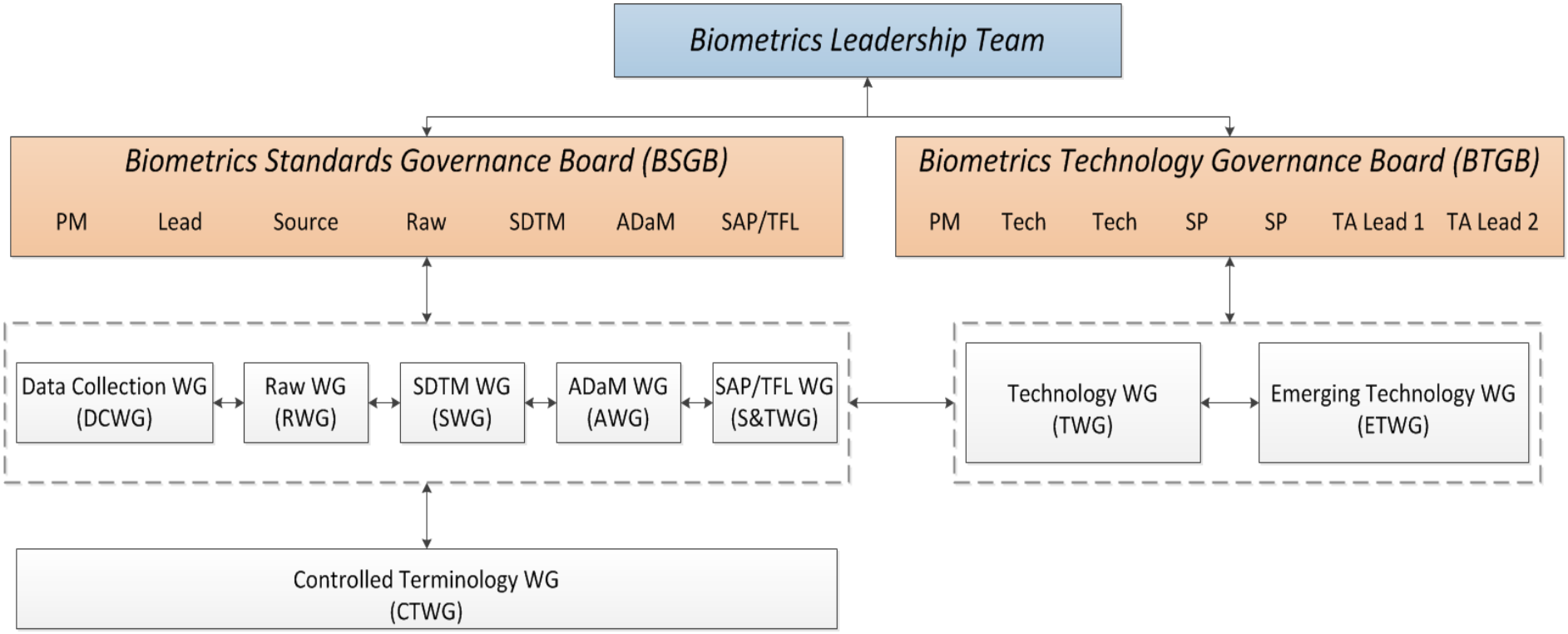
- How to create single vision for multiple data states when they are all in different stages of standards development and implementation?
- How to discern difference between technology and standards, while being mindful of technology without having it drive our company standards?
- How to identify best practices from our Data Management group (furthest along) and leverage into other data states? How much is transferrable?
- Do we start standards development from DM? SAP/TFLs?

Why standards at all? Our quality is already great…

Thoughts (for now…)

- Take what works and go with it
- Integrate technology but only for what is needed now, not what we see/think the future is
- Develop a strategy independent (for the most part) of technology to address our specific business challenge
- Lots of interviews with leaders and doers across data states
- Consider both end and beginning for our standards development
- Not just quality, but **efficiency**

Gilead needed to establish a governance structure that could encompass all data states



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Enacting standards within Gilead is dependent upon an effective change (read transformation) management strategy

- Goal is not necessarily to "improve" final product (i.e. CDISC datasets)
- Make internal processes and decision-making more efficient

Success Requires

1. Define aspiration at onset
2. Clear themes and initiatives
3. Well-thought out plan to visualize the journey
4. Exciting story (with quick wins)
   - Case for change
   - Challenges and opportunities
   - Impact of change on individuals

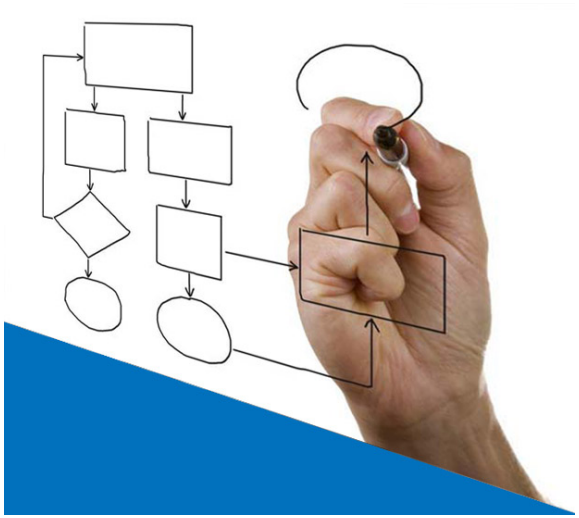
Kotter's 8-Step Change Model

Employ specific use cases to demonstrate tangible ROI for various functional groups to increase buy-in and support

- Impact of standards and automation on clinical study cycle time
  1. Study start-up
  2. Study conduct
  3. Analysis & reporting
  4. Cumulative / trial
- Identify a common function requiring significant manual efforts which could be impacted by data standards & automation activities
- Detailed step-by-step walkthrough of staff activity (how, why, when, how long)
- Tangible implementation of standards and automation procedures of same exact activity
- Demonstrate tangible benefits (e.g. time) to staff
- Illustrate at-large benefit → time savings **x** n-times/week **x** n-studies
- Grassroots movement and appreciation leading to organizational buy-in

Standardized training and knowledge transfer is critical to ensure staff understand the bigger picture of standards and their impact outside of their specific functional roles

- Staff turnover and attrition is very real, very serious risk to operational efficiency
- Knowledge transfer → training/ education are critical remedial steps
- Education also increases awareness of standards and high-level benefits and organizational ROI
- Transition & Succession Planning
- Not limited to external standards, but also internal SOPs & SWIs



Encourage organizational engagement with external associations to increase knowledge base, leverage lessons learned, and (selfishly) effect changes to standards

phuse

CDISC

HL7 INTERNATIONAL

SCDM
Society for Clinical Data Management
DATA DRIVEN

Develop a project plan with specific dates, data state deliverables, and detailed activities across company

- Develop multiple work streams that can run concurrently, given some dependencies exist
- 3 Main Areas
  - Standards Governance
  - Standards Development
  - Technology Development
- Start small and expand (DM/AE/LB)
- Get into details, assign predecessors, identify resources, and follow-up on any missed dates

Task Name
Standards Implementation
Standards Governance
Define Governance Structure
Define standards development process flow
Define experiment process flow
MDR
Standards Development
Demographics
AE
Labs
Pilots
Define v2.0
Technology Development
Emerging Technology Development
Metadata Macros
MDR POC
Preliminary Experiment
Historic Study Experiment
Current Technology
MKCDISC
Update User Guides/Documentation for Current Macros

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Investigate global metadata data management repositories for standardizing processes and maximizing efficiencies

- End-to-end data standards from protocol to submission for data life cycle
- Content?
  1. Data Collection → CRF structure/layout/design; CRF fields
  2. Data Tabulation → SDTM vX, SDTMIG vX, CT, extensions
  3. Data Analysis → Specs for derived data elements
  4. Consistent Definitions → data elements & defined concepts; versioning
- Metadata Model User Interface (UI)
  1. Conceptual data model
  2. Data standards models
  3. Value level metadata
- Run Pilots and develop Use Cases
- Metadata-driven load programs

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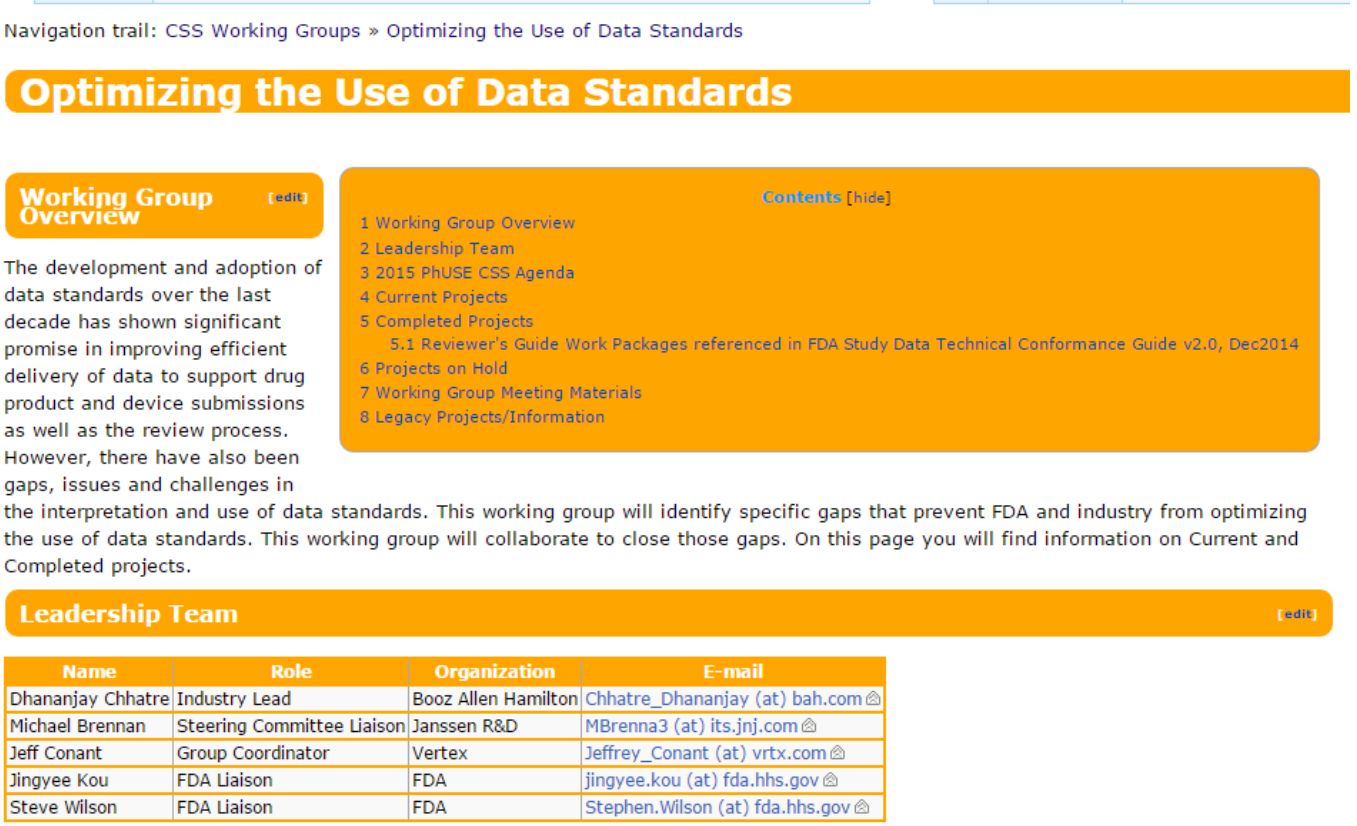
The PhUSE "Optimizing the Use of Data Standards" Working Group provides tangible deliverables which guide decisions on data standards and implementation strategies

- Best Practices
- Standardizing Data within the Inspection Site Selection Process
- Others!



Navigation trail: CSS Working Groups » Optimizing the Use of Data Standards

Optimizing the Use of Data Standards

Working Group Overview [edit]

The development and adoption of data standards over the last decade has shown significant promise in improving efficient delivery of data to support drug product and device submissions as well as the review process. However, there have also been gaps, issues and challenges in the interpretation and use of data standards. This working group will identify specific gaps that prevent FDA and industry from optimizing the use of data standards. This working group will collaborate to close those gaps. On this page you will find information on Current and Completed projects.

Contents [hide]

Leadership Team [edit]

Name	Role	Organization	E-mail
Dhananjay Chhatre	Industry Lead	Booz Allen Hamilton	Chhatre_Dhananjay (at) bah.com
Michael Brennan	Steering Committee Liaison	Janssen R&D	MBrenna3 (at) its.jnj.com
Jeff Conant	Group Coordinator	Vertex	Jeffrey_Conant (at) vrtx.com
Jingyee Kou	FDA Liaison	FDA	jingyee.kou (at) fda.hhs.gov
Steve Wilson	FDA Liaison	FDA	Stephen.Wilson (at) fda.hhs.gov

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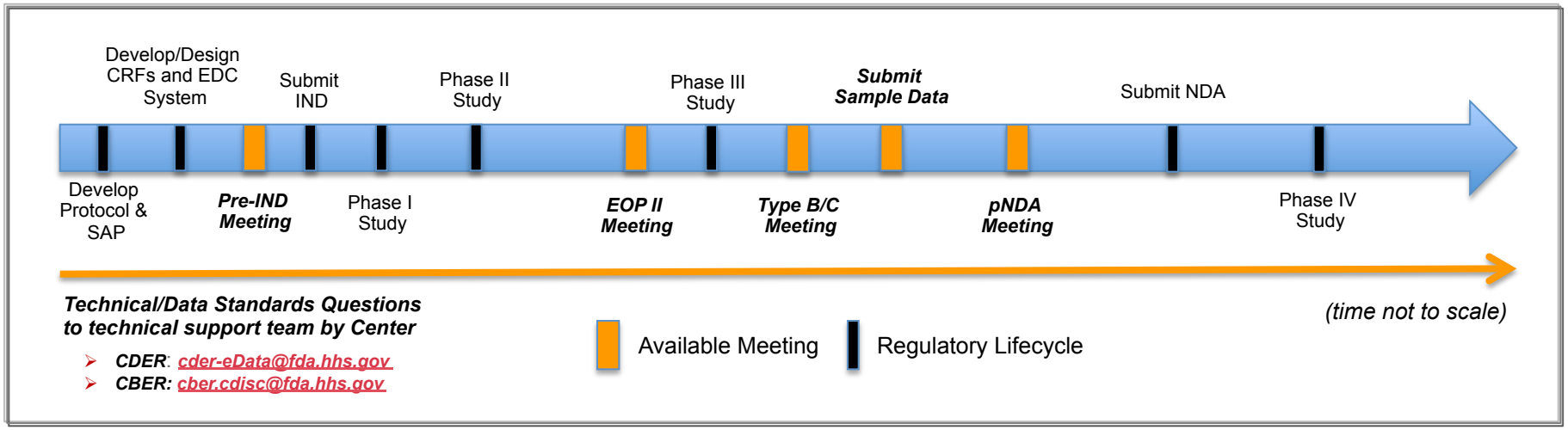
Thank you!

Appendix

The Agency has afforded sponsors with Sponsor/FDA meetings and e-mail access to FDA technical SMEs to discuss their study data standardization plan and technical issues prior to submission



- FDA has historically-available meetings in Pre-IND and EOP2 meetings to discuss study data standardization plan (SDSP) and raise data standardization issues
  - No later than EOP2, though earlier suggested
  - Pre-NDA and pre-BLA meetings are considered "too late to initiate data standardization discussions"
- ANDAs → discuss SDSP prior to initiation of bioequivalence program
- Type C meeting to discuss substantive data standardization issues for NDAs/BLAs
  - E.g. sponsor wishes to use standard not currently supported by FDA (i.e. TA standard)
- Submit sample data for pre-submission technical review → pre-cursor to FDA's JumpStart