Disclaimer

- The views and opinions presented here represent those of the speaker and should not be considered to represent advice or guidance on behalf of the Food and Drug Administration.

Presenter – Dhananjay (DJ) Chhatre

- FDA Data Standards Lead, Booz Allen Hamilton (2013 – Present)
- Operations Research Analyst at FDA/CDER/OBI/eData (2009 – 2013)
- PhUSE “Optimizing the Use of Data Standards” Working Group Industry Lead (2014 – present)
- PhUSE “Data Validation and Quality Assessment” Working Group FDA Lead (2012-2013)
- RAPS Annual Conference Planning Committee Member and Track Chair (2012 – 2013)
- Speaker, Panelist, and Session Chairman at various international conferences and webinars

Discussion Summary

- FDA Guidance Documents
  - Background (FDASIA and FD&C Act)
  - Guidance Overview
  - Technical Specification Documents (DSC & SDTCG)
  - Impact on Industry
- Planning and Providing Standardized Study Data to FDA
  - Meeting with FDA
  - Data Documents (SDSP, SDRG, ADRG)

Discussion Summary

- FDA Guidance Documents
  - Background (FDASIA and FD&C Act)
  - Guidance Overview
  - Technical Specification Documents (DSC & SDTCG)
  - Impact on Industry
- Planning and Providing Standardized Study Data to FDA
  - Meeting with FDA
  - Data Documents (SDSP, SDRG, ADRG)

Section 745A of the Food, Drug, and Cosmetic (FD&C) Act [1], amended by the Food and Drug Administration Safety and Innovation Act (FDASIA) requires applications be submitted electronically 24 months after publication of final guidance

- 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): NDAs, ANDAs, BLAs, and INDs
    - Requires electronic submissions **24 months** following issuance of final guidance
  - 745A(a)(2): Guidance Contents
    - Timetable of further standards
    - Criteria for waivers and exemptions

1. 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

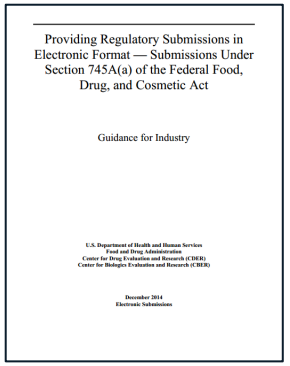
- FDA published 2 guidance and 4 technical specification documents on 12/17/2014

1. *Providing Regulatory Submissions in Electronic Format – Submissions Under Section 745(a) of the Federal Food, Drug, and Cosmetic Act* [1]

2. *Providing Regulatory Submissions in Electronic Format – Standardized Study Data* [2]
   - Data Standards Catalog
   - Study Data Technical Conformance Guide: Technical Specifications Document
   - 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."* [3]

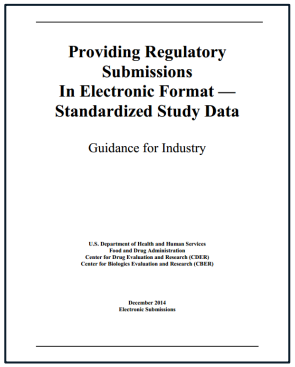
*"FDA **does not** foresee the **replacement** of CDISC standards for study data."* [3]


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)

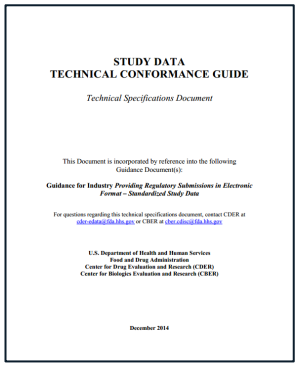
December 2014
Electronic Submissions


Providing Regulatory Submissions In Electronic Format — Standardized Study Data

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


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 oder-edata@fda.hhs.gov or CBER at cber.cdisc@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)

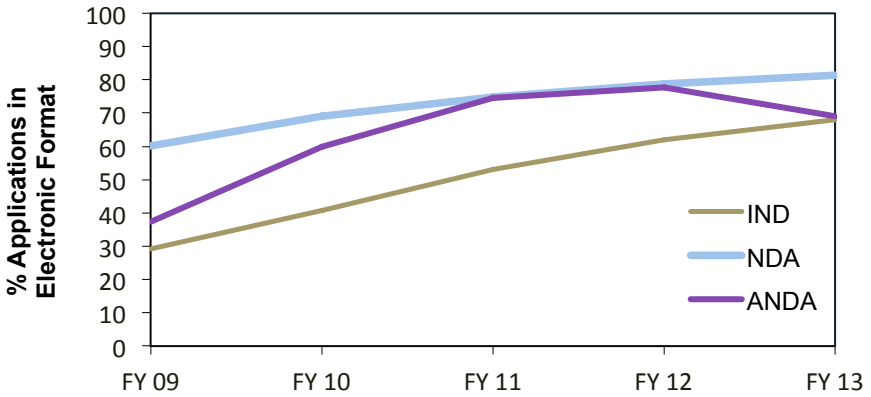
December 2014

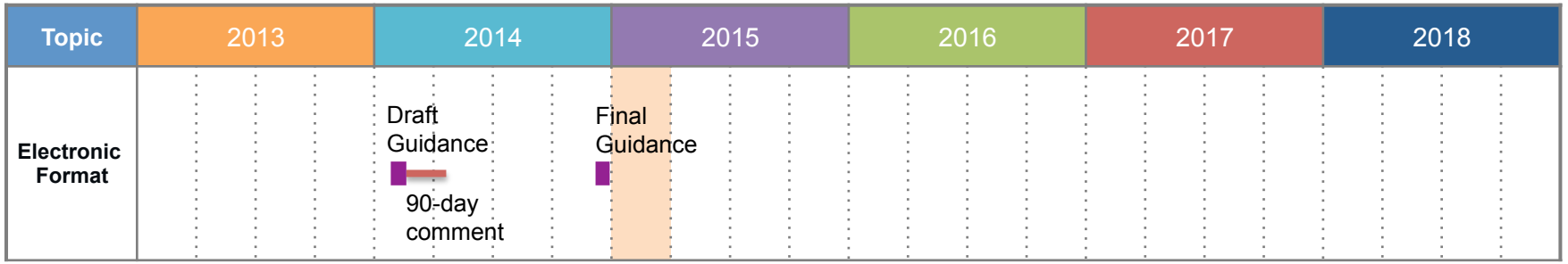
1. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM384686.pdf
2. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf
3. FDA "Study Data Standards for Regulatory Submissions Position Statement", 09/13/2013

The Agency issued final guidance [1] describing how FDA interprets and plans to implement section 745A(a), describing which submission types must be submitted electronically and the timetable and process for implementing these requirements

- "Providing Regulatory Submissions in Electronic Format – Standardized Study Data" → **BINDING**
  - Applies to all **NDAs, ANDAs, BLAs, and INDs**
- FDA will issue **individual guidance** documents to specify **formats** for specific submissions and **corresponding timetables** for implementation
  - Study Data
  - Submission Format
- Submissions not in electronic format(s) will not be filed (RTF) or received (unless exempt/waived) if study data do not conform to required standards, formats, and/or terminologies

% Applications in Electronic Format by FY [2]



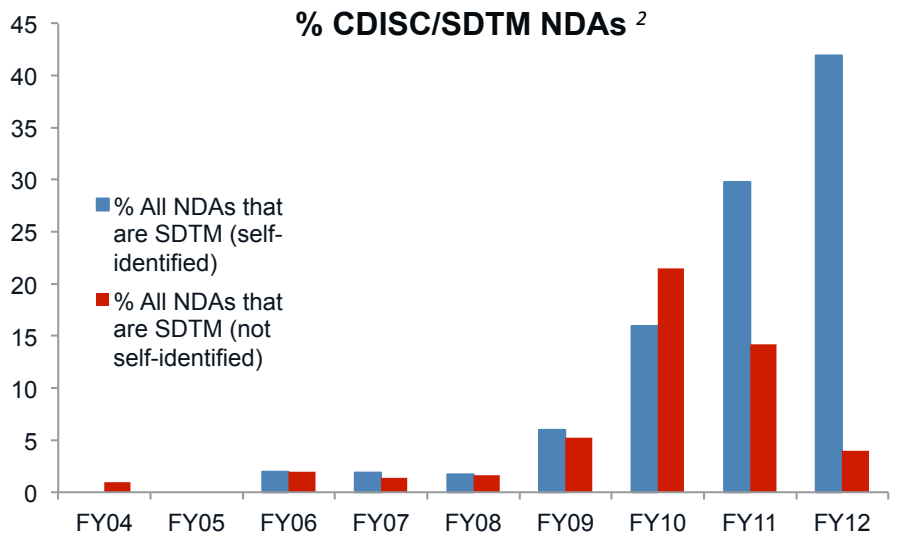


1. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM384686.pdf
2. *"eCTD Update", Mark Gray, DIA EDM Webinar 12/2013*

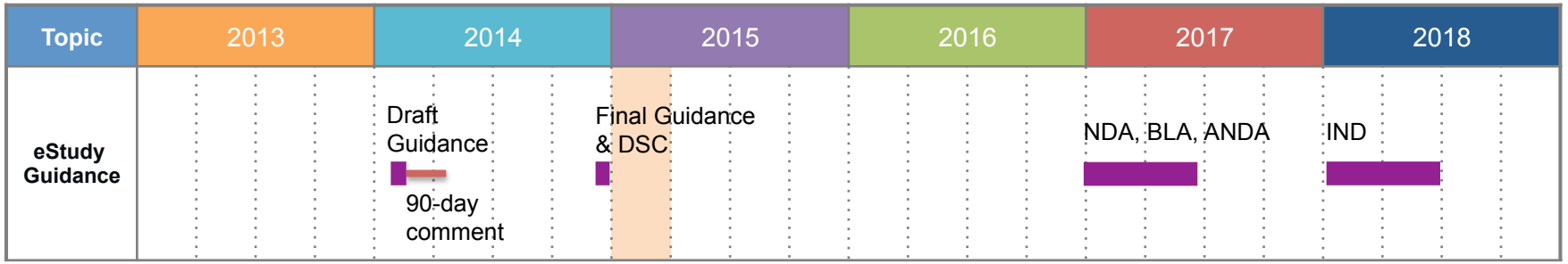
Booz | Allen | Hamilton

FDA issued individual guidance describing requirements for electronic submission of standardized clinical and non-clinical study data under section 745A(a) of the FD&C Act [1]

- "Providing Regulatory Submissions in Electronic Format – Standardized Study Data" → **BINDING**
  - Applies to all **NDAs, ANDAs, BLAs, and INDs**
- **Data Standards Catalog** (**DSC**) lists **formats** for study data that FDA can process, review, and archive,
  - Includes **required** and/or **supported** versions
  - **Key dates** for each standard → Requirement and Support begins/ends
- No waivers for eStudy requirement, though possible for data standard versions in DSC



Initial Timetable for Implementation

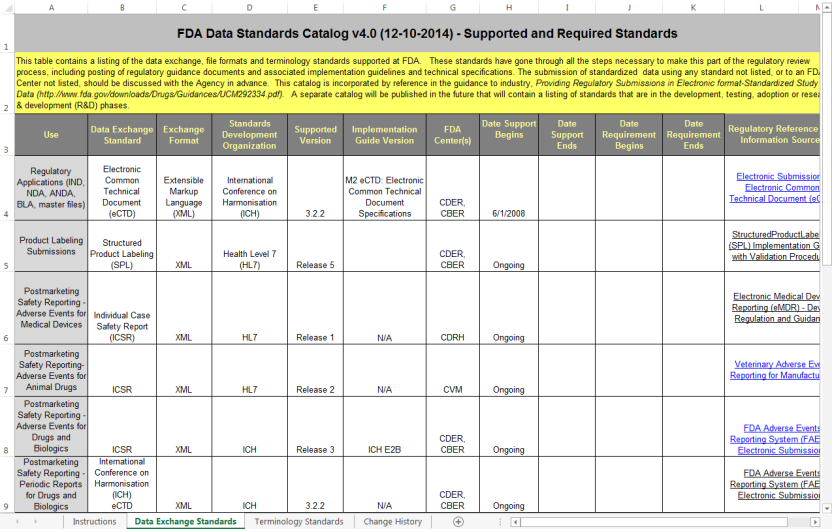


1. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf
2. *"The State of Electronic Submissions", Virginia Hussong, DIA 06/2012*

Booz | Allen | Hamilton

The Data Standards Catalog (DSC) [1] defines FDA-supported standards as Exchange Format, Study Data, and Controlled Terminology Standards

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



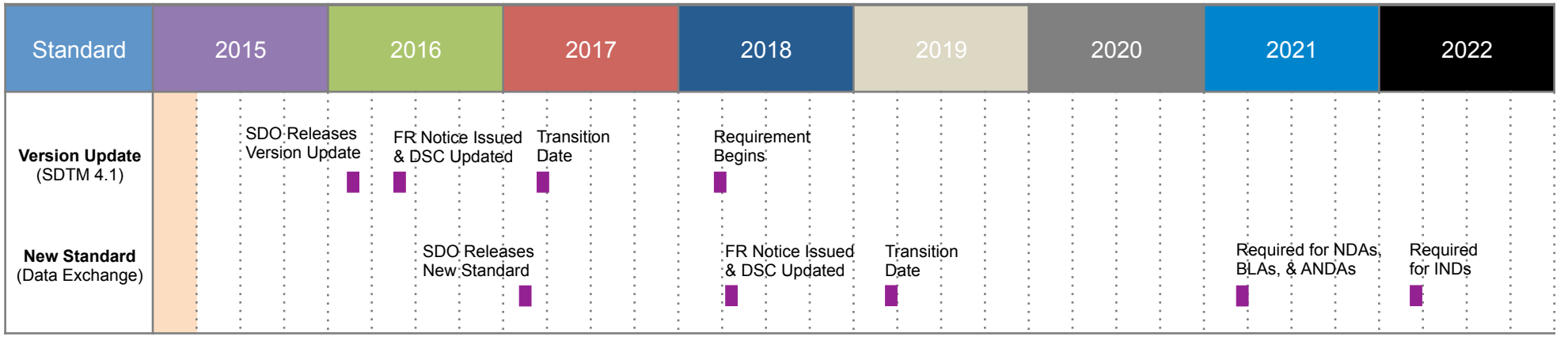
FDA Data Standards Catalog v4.0 (12-10-2014) - Supported and Required Standards

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/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 rese & development (R&D) phases.

Use	Data Exchange Standard	Exchange Format	Standards Development Organization	Supported Version	Implementation Guide Version	FDA Center(s)	Date Support Begins	Date Support Ends	Date Requirement Begins	Date Requirement Ends	Regulatory Reference Information Source
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	6/1/2008				Electronic Submissions Electronic Common Technical Document (eC
Product Labeling Submissions	Structured Product Labeling (SPL)	XML	Health Level 7 (HL7)	Release 5		CDER, CBER	Ongoing				StructuredProductLabe (SPL) Implementation G with Validation Procedu
Postmarketing Safety Reporting - Adverse Events for Medical Devices	Individual Case Safety Report (ICSR)	XML	HL7	Release 1	N/A	CDRH	Ongoing				Electronic Medical Dev Reporting (eMDR) - Dev Regulation and Guidan
Postmarketing Safety Reporting- Adverse Events for Animal Drugs	ICSR	XML	HL7	Release 2	N/A	CVM	Ongoing				Veterinary Adverse Eve Reporting for Manufactu
Postmarketing Safety Reporting - Adverse Events for Drugs and Biologics	ICSR	XML	ICH	Release 3	ICH E2B	CDER, CBER	Ongoing				FDA Adverse Events Reporting System (FAE Electronic Submissio
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 (FAE Electronic Submissio

Instructions | Data Exchange Standards | Terminology Standards | Change History

Example Implementation Timetables



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

The non-binding Study Data Technical Conformance Guide (SDTCG) [1] provides specifications, recommendations, and general considerations on how to submit standardized study data using data standards listed in the DSC (1 of 2)

Format	Type	Use Case	Key Takeaway(s)		
Exchange	XML	CDISC define.xml	• Uncompressed • Submit both define.xml and define.pdf to FDA (unless define.xml v2.0 being used)		
	PDF	Blankcrf, aCRF	• FDA eCTD website for specs • aCRF should be submitted regardless of legacy or SDTM datasets		
	XPORT	AE.xpt	• Single, uncompressed dataset per transport file • FDA cannot process CPORT • 1 gb size limit / dataset file • Submit split and whole datasets • Column length = max variable length across all datasets in study • ASCII names with no special characters		
Study Data (Clinical & Non-clinical)	CDISC (SDTM, SEND, & ADaM)	Clinical, Non-Clinical, & Analysis Data	**<u>All CDISC</u>** • Discuss uncertainty or questions about data standardization with FDA • SUBJID is specific to a trial • USUBJID is same across studies (no leading or trailing 0's) • Use custom domains wisely! • Submit ***<u>all</u>*** required, expected, and permissible variables collected, ***<u>plus</u>*** any variables needed to compute derivations • EPOCH for clinical subject-level observations • Dates in ISO 8601	**<u>SDTM/SEND</u>** • Utilize CDASH to "simplify creation process of SDTM domains" • Variables supporting key analyses should be in parent, not supp domains • Screen failures in DM with ARM blank • Split LB domain by LBCAT and LBSCAT to reduce dataset size • All data should be traceable back to CRFs	**<u>ADaM</u>** • Imputed data should be submitted in analysis datasets (ADaM) • Analysis datasets used to support CSRs, ISS, and ISE • Include core variables in each analysis dataset • Provide software programs used to create ADaM datasets • Data should be traceable back to SDTM, and then to CRFs

1. http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf

The non-binding Study Data Technical Conformance Guide (SDTCG) [1] provides specifications, recommendations, and general considerations on how to submit standardized study data using data standards listed in the DSC (2 of 2)

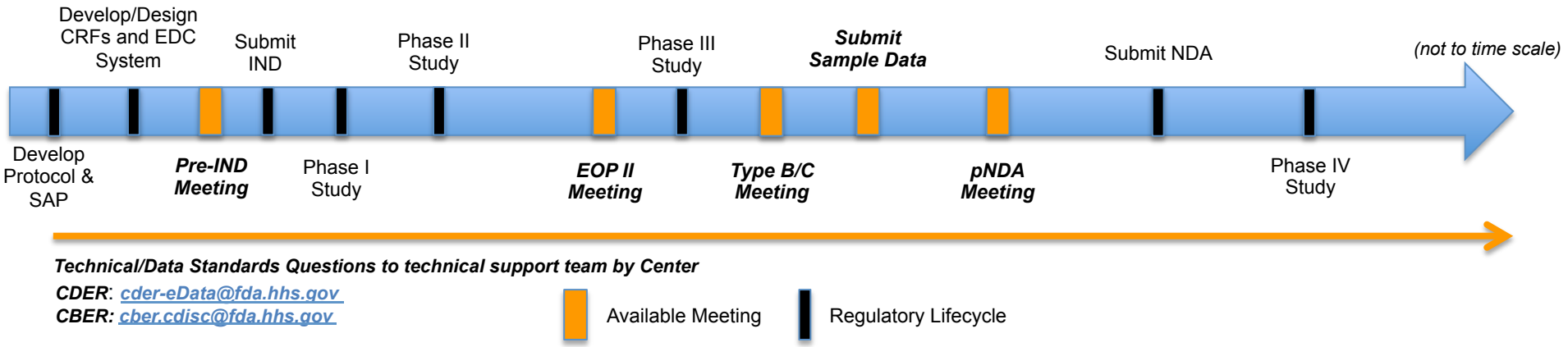
Format	Type	Use Case	Key Takeaway(s)
TA Standards	CDISC	Asthma	• TBD
Terminology	All	n/a	• Provide actual verbatim terms collected on CRF as well as coded term • ISS/ISE should contain single version of terminology used • Extensible codelists are discouraged
	CDISC CT	NCI EVS	• If custom terminology used, provide information in define.xml and SDRG
	Adverse Events	MedDRA	• Spelling and case should match MedDRA dictionary • ISS should include MedDRA Preferred Terms from single version of MedDRA
	Medications	UNII, WHODrug	• UNII provided in TS (TSPARM=TRT or TRTUNII; TSPARM=COMPTRT; TSPARM=CURTRT) • One record for each active moiety • UNII and preferred substance names found in FDA's Substance Registration System
	Pharmacologic	NDF	• NDF-RT to identify all pharmacologic class(es) of active investigational substances (in TS domain where TSPARM=PCLAS)
	Indication	SNOMED	• In TS domain where TSPARM=INDIC and TSPARM=TDIGRP • Should improve harmonization with SPL
Electronic Submission	Folder Structure	eCTD	• Follow specified file directory structure which is distinct from eCTD headings and hierarchy • Define.xml and style sheet should be in same folder as associated dataset(s) • Original datasets in data folder and split datasets in "split" sub-folder • Reference all datasets in eCTD XML backbone and accurately tag datasets with STF
Data Validation & Traceability	OpenCDISC Checks	SDTM Validation Rules	• Conformance Validation → Compliant Data (conforms to applicable data standard) • Quality Checks → Useful Data (supports intended use

1. http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf

Discussion Summary

- FDA Guidance Documents
  - Background (FDASIA and FD&C Act)
  - Guidance Overview
  - Technical Specification Documents (DSC & SDTCG)
  - Impact on Industry
- Planning and Providing Standardized Study Data to FDA
  - Meeting with FDA
  - Data Documents (SDSP, SDRG, ADRG)

The Agency has provided sponsors with Sponsor/FDA meetings and e-mail access to FDA technical SMEs for discussion of their data standardization plan prior to application 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 (e.g. TA standard)
- Submit sample data for pre-submission technical review → pre-cursor to FDA’s JumpStart

FDA recommends submission of supplemental documents which describe submission of standardized study data and any special considerations or directions in order to facilitate regulatory review

Document	Summary	Contents	Key Points
Study Data Standardization Plan (SDSP)	Plan (in IND) describing submission of standardized study data to FDA (pre-IND) to assist FDA in identifying potential data standardization issues	1. List of planned studies 2. Type of studies (phase I, II, III) 3. Study designs (parallel, cross-over, open-label) 4. Planned data standards, formats, and terminologies with versions 5. Justification of studies that my not conform to currently supported standards in DSC	• PhUSE Working Group (Optimizing the Use of Data Standards) has team working on draft SDSP template as collaboration between industry groups with oversight by FDA
Study Data Reviewer's Guide (SDRG)	Describes, for each study, special considerations or directions to facilitate FDA reviewer's use of data and relationships between study report and data	1. Study protocol title, number, and version 2. Study design 3. Standards, formats, and terminologies and their versions 4. Description of study datasets 5. Data standards validation rules, versions, and issues 6. Description of all sponsor decisions related to data standard implementations	• Legacy Data Conversion Plan and Report should be included within SDRG • PhUSE Working Group has developed SDRG Template (v1.1) which includes SDRG completion guidelines, template, and example SDRGs
Analysis Data Reviewer's Guide (ADRG)	Provides context for analysis datasets and terminology in addition to information presented in define.xml. Also provides summary of ADaM conformance findings.	1. Duplicate limited information in other documentation is purposely requested (e.g., protocol, SAP, CSR, define.xml) so FDA reviewers have a single point of orientation	• PhUSE Working Group has developed ADRG Template (v1.01) which includes ADRG completion guidelines, template, and example ADRGs

Questions?

- Interested in discussing FDA requirements further?
- Want to join the PhUSE “Optimizing the Use of Data Standards” working group?
- Want to learn how to communicate best with FDA and/or CROs about data standards?

Dhananjay (DJ) Chhatre

chhatre_dhananjay@bah.com