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e-Submission with CDISC Standard

PhUSE SDE Shanghai
13 Nov 2015

Question #1

Required in Submission?	US FDA	EU EMA	Japan PMDA	China CFDA
Patient Data	?	?	?	?

Question #1

Required in Submission?	US FDA	EU EMA	Japan PMDA	China CFDA
Patient Data	X	X	X	X

Question #2

Required in Submission?	US FDA	EU EMA	Japan PMDA	China CFDA
Patient Data	X	X	X	X
Electronic Patient Data	?	?	?	?

Question #2

Required in Submission?	US FDA	EU EMA	Japan PMDA	China CFDA
Patient Data	X	X	X	X
Electronic Patient Data	X?	?	?	X

Question #3

Required in Submission?	US FDA	EU EMA	Japan PMDA	China CFDA
Patient Data	X	X	X	X
Electronic Patient Data	X?	?	?	X
Electronic Patient Data In Standard Format	?	?	?	?

Question #3

Required in Submission?	US FDA	EU EMA	Japan PMDA	China CFDA
Patient Data	X	X	X	X
Electronic Patient Data	X?	?	?	X
Electronic Patient Data In Standard Format	?	?	?	?

"e-Submission with CDISC Standard"

Outline

- Background (Questions #1 and #2)
- **E-Sub: current (Question #3)**
- What's the e-Sub future? (Question #4)
- Opportunities and challenges? (Question #5)

Background - CSR

- Clinical Study Report: required as part of NDA submission
- ICH E3 Guideline (adopted by listed agencies)

16.2. PATIENT DATA LISTINGS

16.2.1 Discontinued patients

16.2.2 Protocol deviations

16.2.3 Patients excluded from the efficacy analysis

16.2.4 Demographic data

16.2.5 Compliance and/or drug concentration data (if available)

16.2.6 Individual efficacy response data

16.2.7 Adverse event listings (each patient)

16.2.8. Listing of individual laboratory measurements by patient, when required by regulatory authorities

16.3 CASE REPORT FORMS

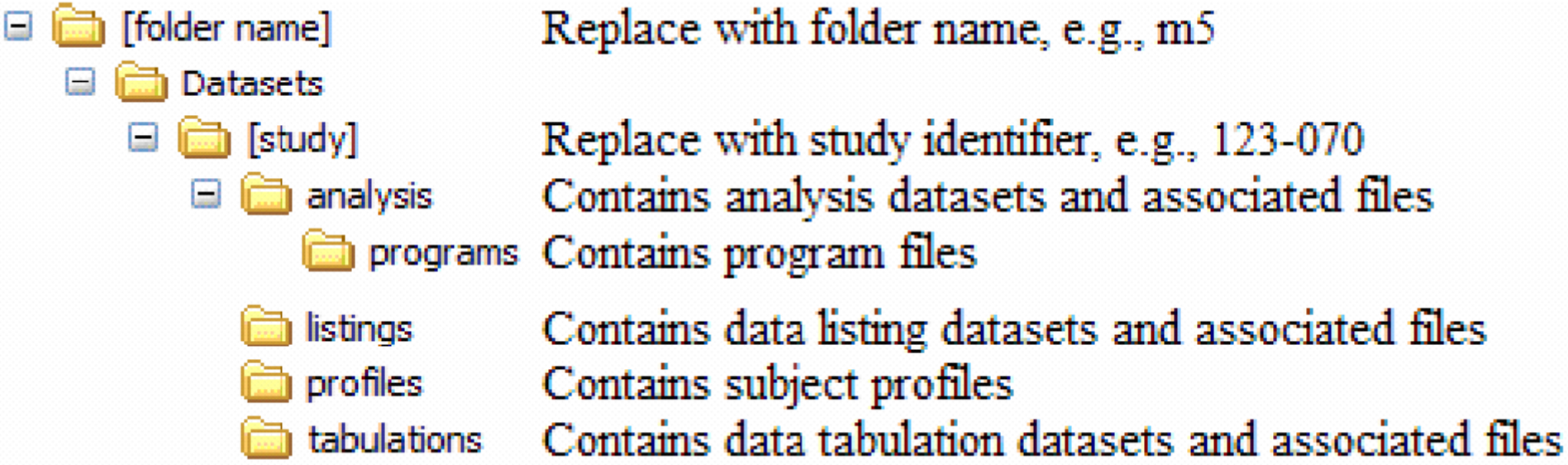
16.3.1 CRFs for deaths, other serious adverse events and withdrawals for AE

16.3.2 Other CRFs submitted

16.4. INDIVIDUAL PATIENT DATA LISTINGS (US ARCHIVAL LISTINGS)

Background – CRT / eCRT

- Case Report Tabulations used in US FDA



Background – History of US FDA Submission

- Presented at C3C 2015 Q3 Seminar by Henry Wu

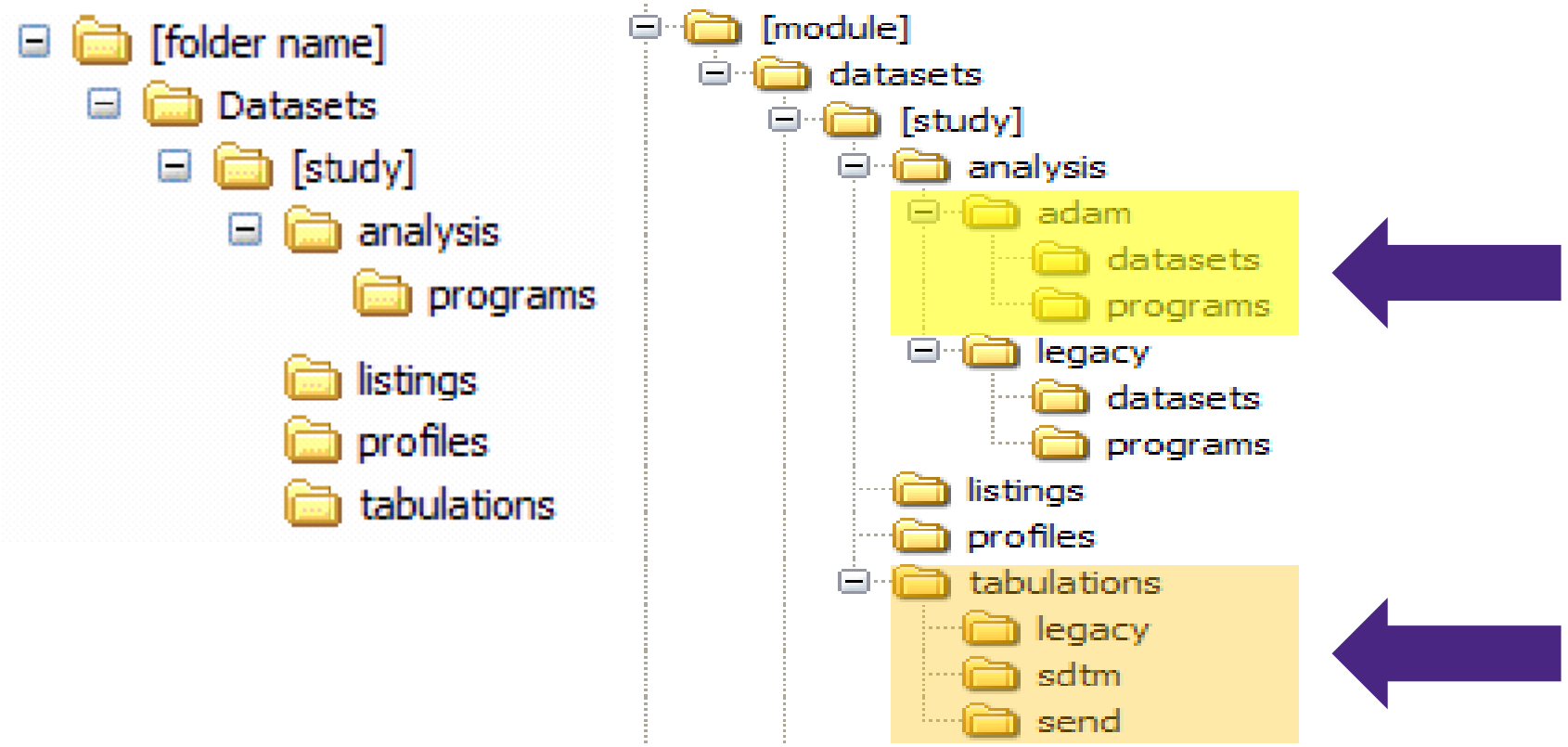
- The Paper Process (1962 –1992)
- The CANDA* Age (Roughly 1992-1999)
- E-Sub Era (Roughly 1999-2016?)
- E-Sub Era -Enhanced (Roughly 2016-?)

- Slides available at www.cdiscchina.org

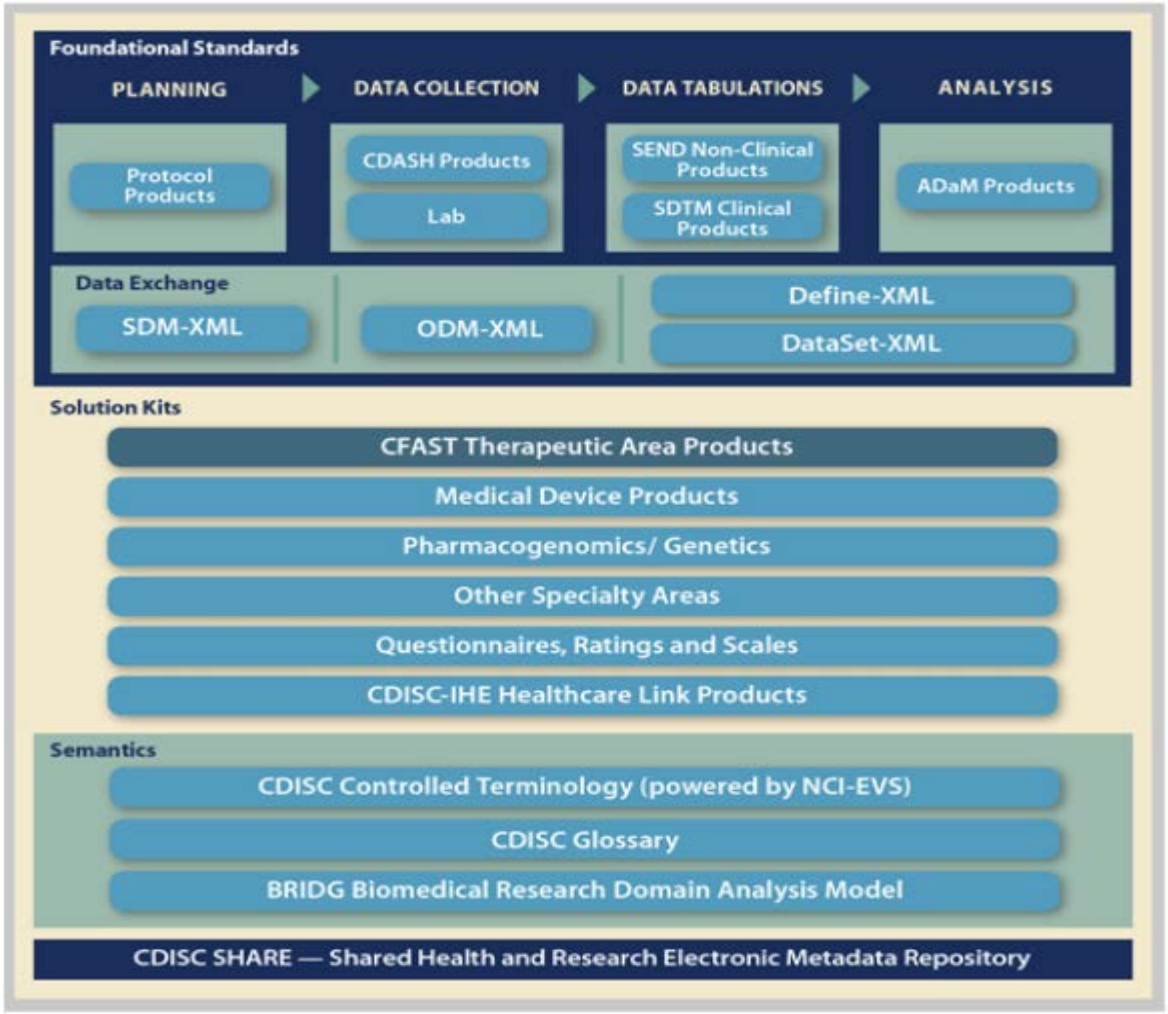
- *CANDA – Computer Assisted New Drug Application

Background – CRT / eCRT (2)

- Case Report Tabulations used in US FDA

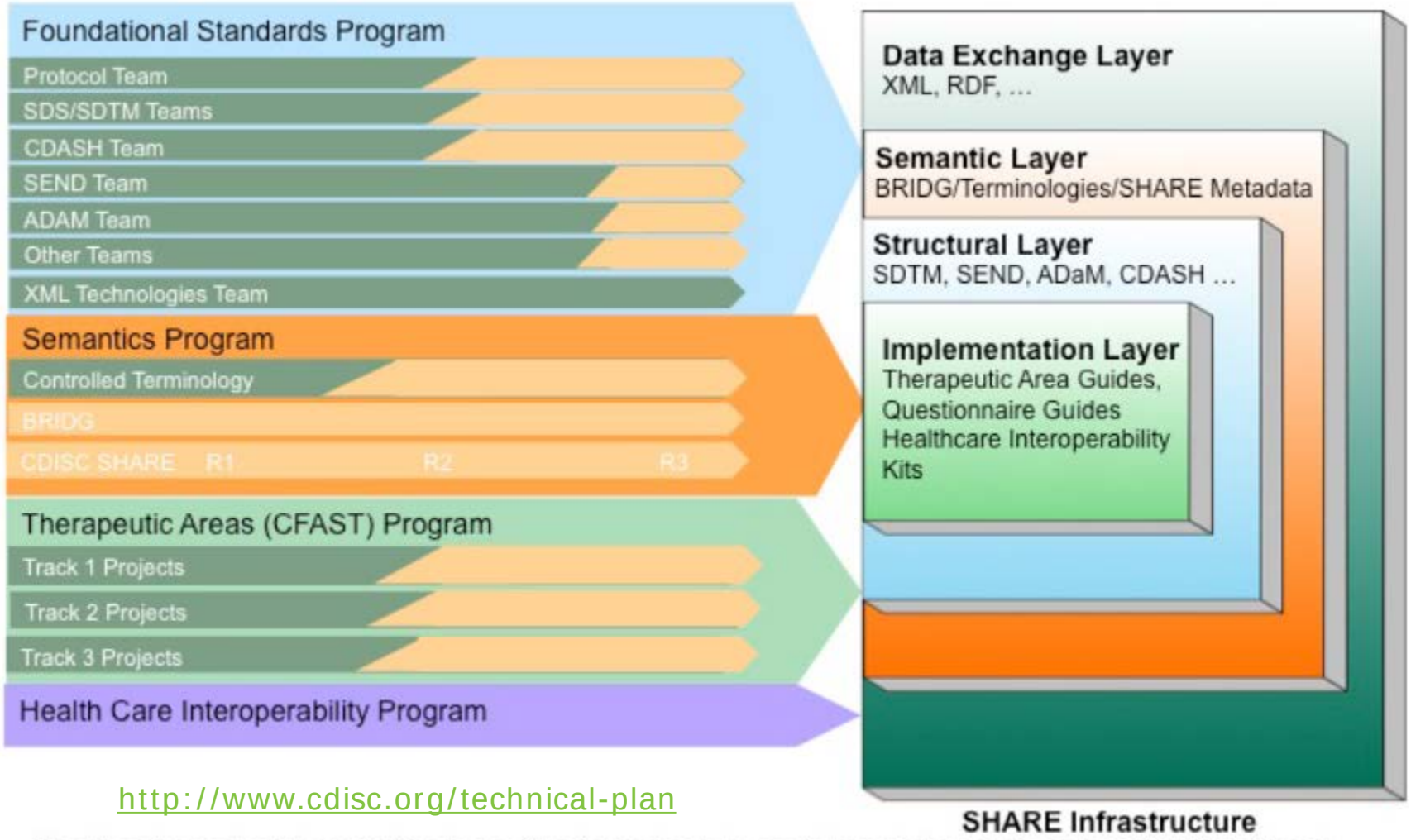


CDISC Standard (1): End to End



www.cdisc.org

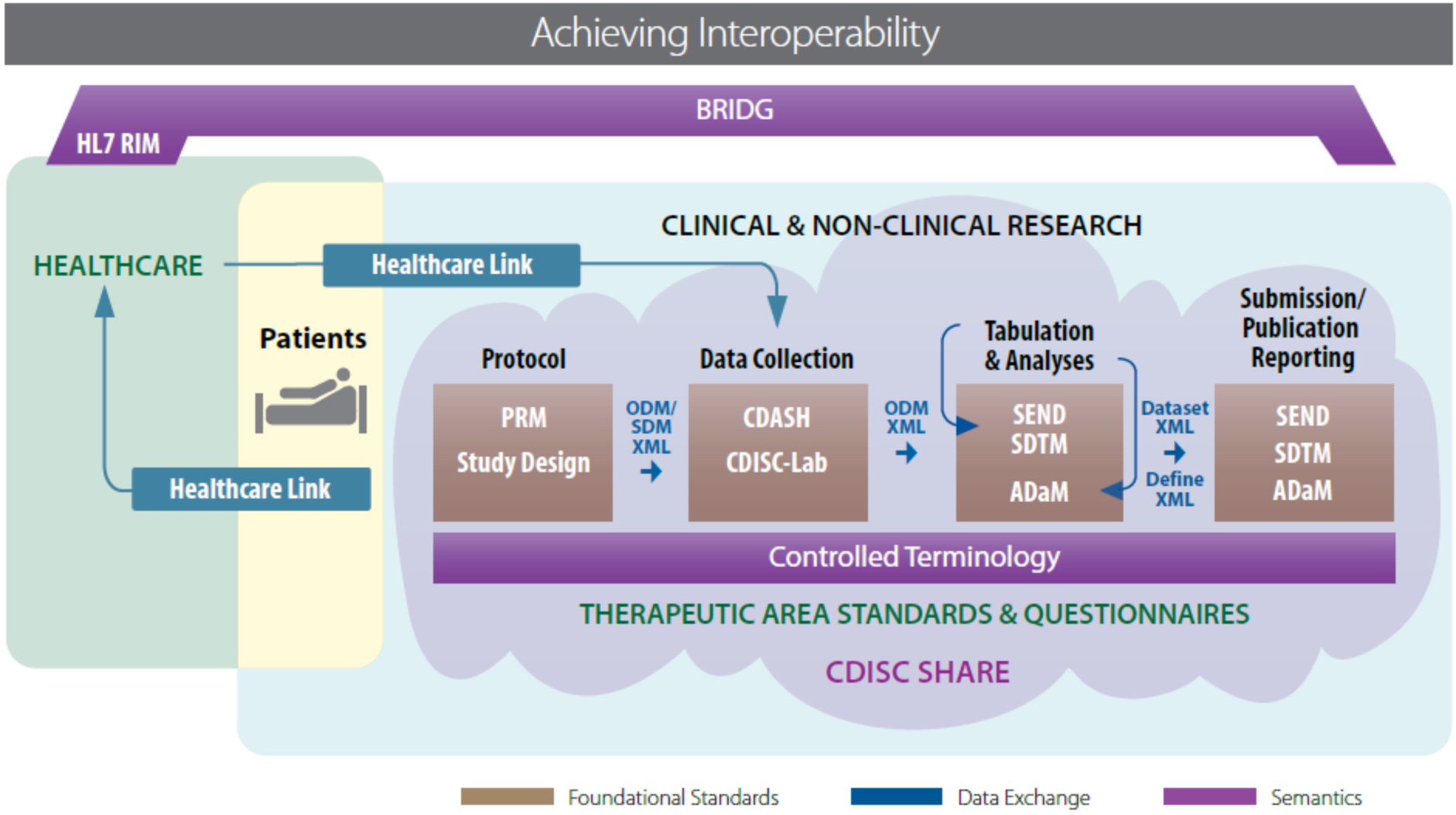
CDISC Standard (2): Integrated



http://www.cdisc.org/technical-plan

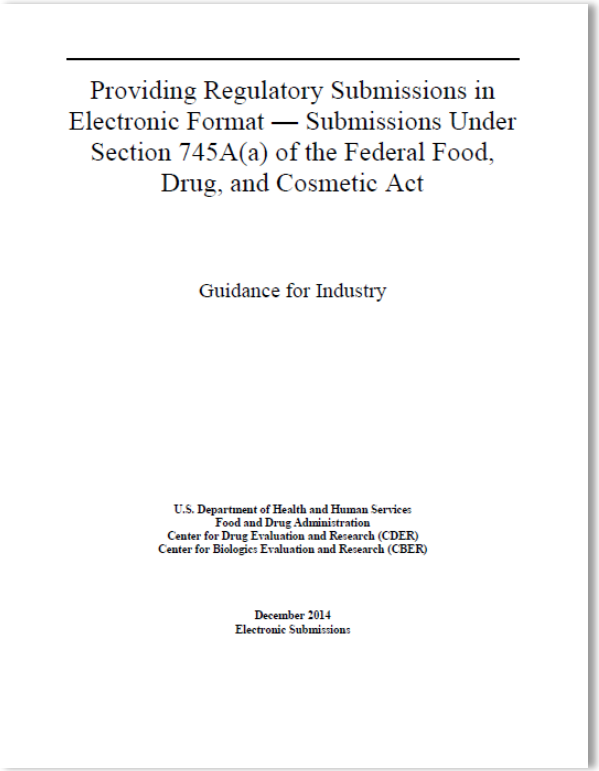
The Roadmap depicts evolution from siloed standards to an integrated stack based on BRIDG-aligned concepts and SHARE

CDISC Standard (3): Interoperability



http://www.cdisc.org/cdisc-brochure

E-Sub in US FDA: Regulatory Documents

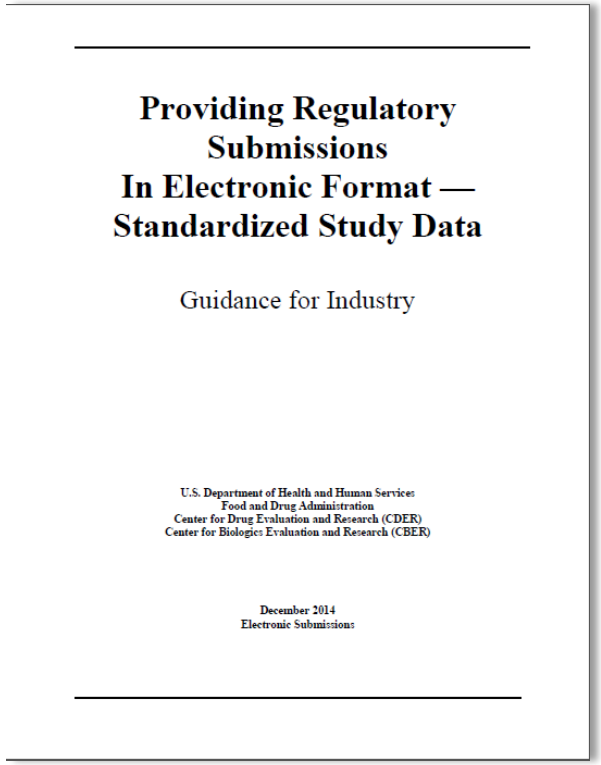


Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act

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

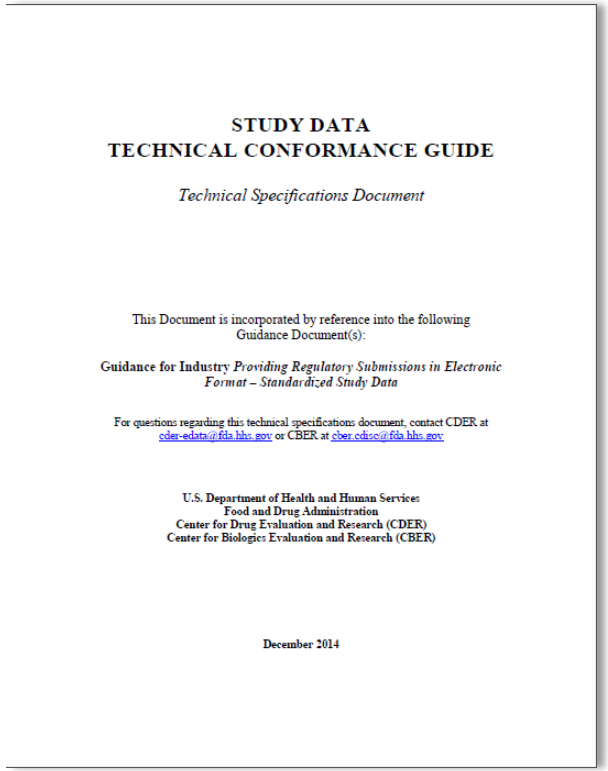


Providing Regulatory Submissions In Electronic Format — Standardized Study Data

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 cder-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

BINDING DOCUMENTS

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

Requirement of Study Data Standards

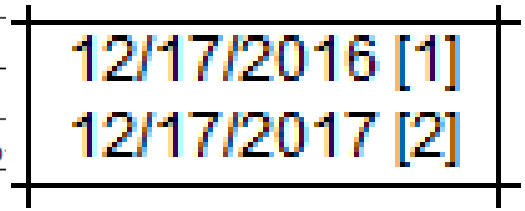
FDA Data Standards Catalogue v4.4

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

FDA Data Standards Catalog v4.4 (08-17-2015) - 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/Guidances/UCM292334.pdf).*

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
Clinical study datasets	Study Data Tabulation Model (SDTM)	XPT	Interchange Standards Consortium (CDISC)	1.4	3.2	CDER, CBER	17/08/2015		03/15/2018 [1] 03/15/2019 [2]		CDISC.org - SDTM
Clinical study datasets	SDTM	XPT	CDISC	1.3	3.1.3	CDER, CBER	12/01/2012		12/17/2016 [1]		CDISC.org - SDTM
Clinical study datasets	SDTM	XPT	CDISC	1.2	Version 3.1.2 Amendment 1	CDER, CBER	08/07/2013				
Clinical study datasets	SDTM	XPT	CDISC	1.2	3.1.2	CDER, CBER	30/10/2009				
Clinical study datasets	SDTM	XPT	CDISC	1.1	3.1.1	CDER, CBER	Ongoing	01/28/20			
Clinical study datasets	Analysis Data Model (ADaM)	XPT	CDISC	2.1	1.0	CDER, CBER	Ongoing				
Animal study datasets	Standard for Exchange of Nonclinical Data	XPT	CDISC	1.2	3.0	CDER	06/13/2011		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - SEND



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CDISC standards included are SDTM, ADaM, SEND, define.xml, TA and terminology

FDA

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FDA Submissions using CDISC Standard

FY2013, FY2014, FY2015(Q1-Q2)
Number (%) of NDAs with
Study Data Submissions in CDISC STDM*

Fiscal Year	# of Submissions	% with CDISC SDTM
2013	223	55 %
2014	233	64 %
2015 (Q1-Q2)	112	71 %

***Source: Office of Business Informatics, CDER – One or more explicitly stated SDTM studies (or study data structure that resembled SDTM).**

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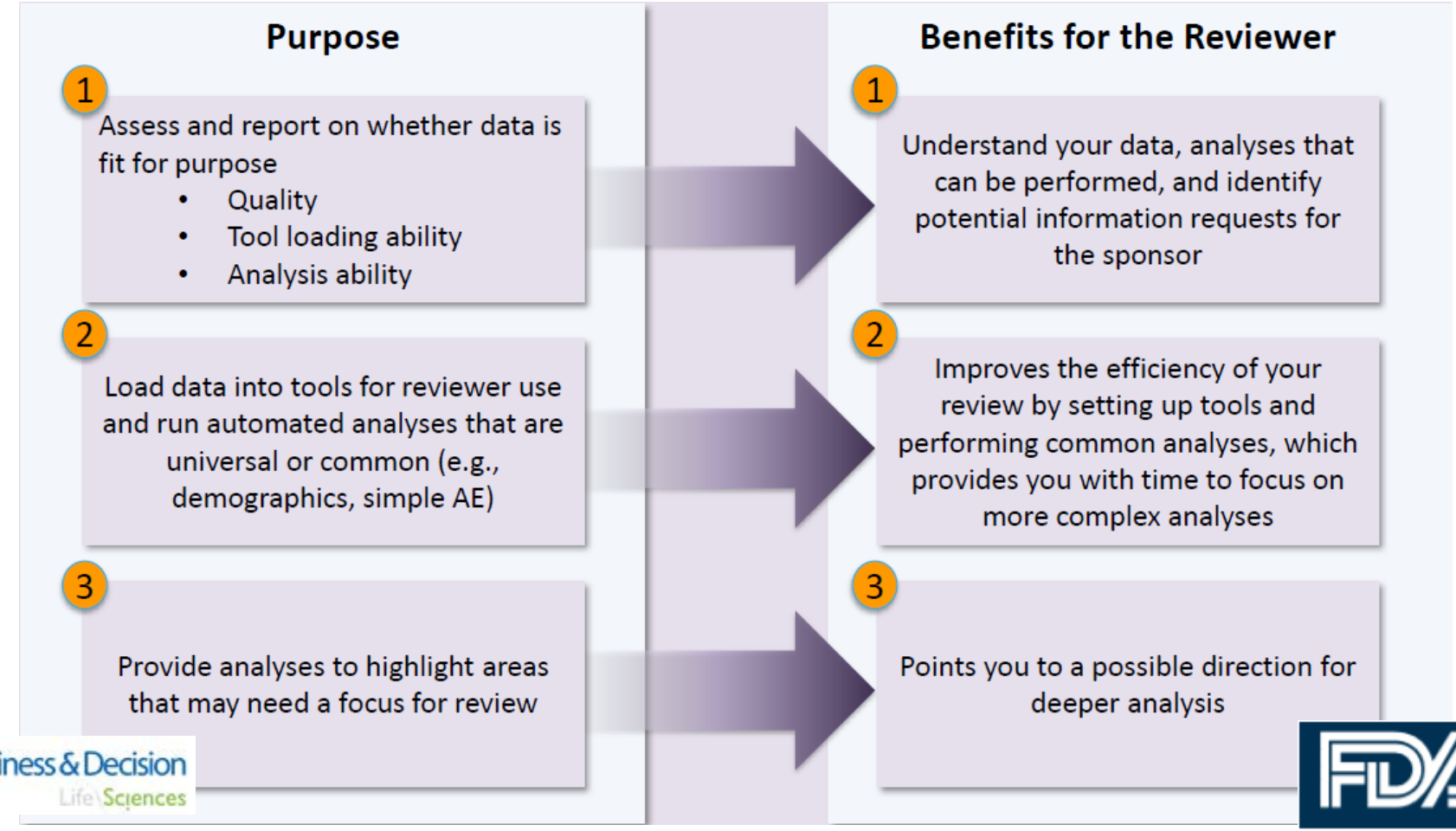
Benefits of JumpStart

http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm397921.htm



E-Submission in EU EMA

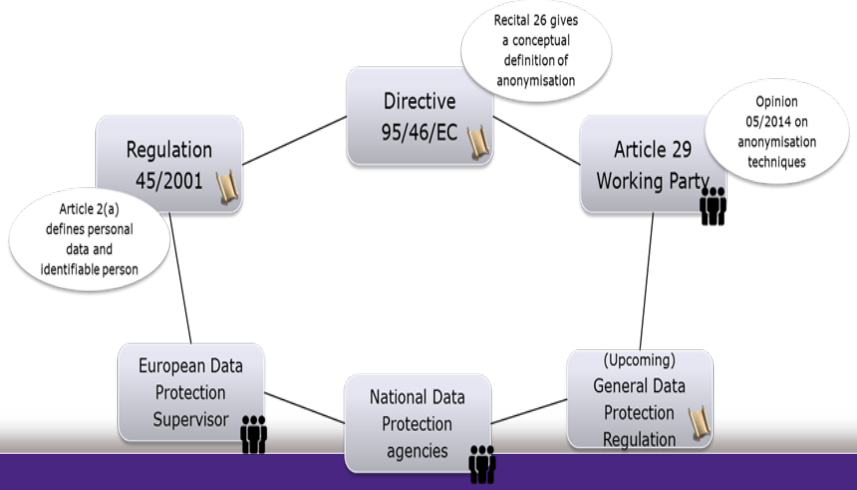
- **Publication and access to clinical-trial data**, 24 June 2013
  - CDISC standard to be used for IPD (individual patient data)

- **Publication of clinical data for medicinal products for human use**, 2 October 2014
  - **first phase**, the publication of **clinical data will relate to clinical reports only**
  - **second phase**, the Agency will review **various aspects in relation to IPD**, including finding the most appropriate way to **make IPD available** the latter in compliance with privacy and data protection laws.

- **Sharing clinical trial data / data protection / de-identification / Transparency / Independent Analysis**

Legal framework and available standards

- EU data protection legislation
- Article 29 Data Protection Working Party opinion of anonymization techniques (Opinion 05/2014)
- Information Commissioner's Office (ICO) Code of Practice. Anonymization: managing data protection risk
- Sharing clinical trial data: Maximizing benefits, minimizing risk. Institute of Medicine (IOM)
- Pharmaceutical Users Software Exchange (PhUSE) de-identification standards for CDISC SDTM 3.2
- Transcelerate BioPharma Inc., Clinical Study Reports Approach to Protection of Personal Data and Data De-identification and Anonymization of Individual Patient Data in Clinical Studies – A Model Approach



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Japan PMDA: Method of Submission

- Data standards for submission: CDISC standards
- Format of electronic data required for submission
  - Individual study data
    - Using SDTM with define.xml
    - Using ADaM with define.xml and programs for creating the ADaM datasets
  - Electronic data on ISS and ISE
    - Using ADaM with define.xml and programs for creating the ADaM datasets
    - Recommended that the applicants individually consult with PMDA regarding what to submit

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Source: CDISC Interchange Japan – Yasunori Yoshida (PMDA)

pmda

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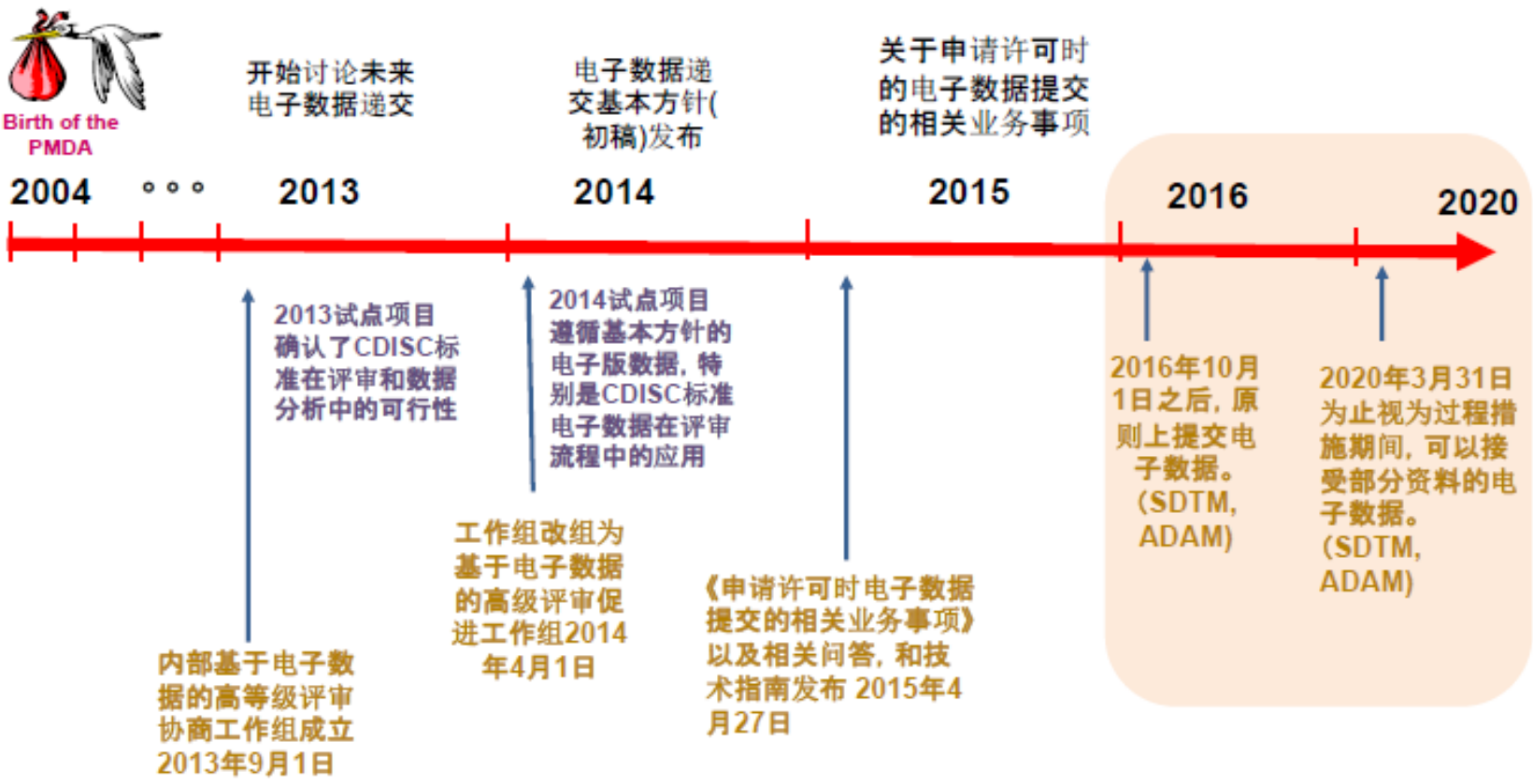
Japan PMDA Implementation Plan



Source: C3C 2015 Q3 seminar - Dehong Cao

China CFDA
中国临床试验数据注册要求 – 历史回顾 (1)*

- 1999年之前:
  - **没有明确的注册**规范（没有GCP）
- 1999-2003
  - **中国GCP**颁布，要求临床试验
- 2003-2005
  - **中国GCP修订**
- 2005-2007
  - 颁布**多个技术指南**，**如**统计指导原则，临床研究报告（CSR）
- 2007-？:
  - 新药申请（NDA）**要求递交数据库，但没有公布要求**细节
- 2010年
  - 颁布《临床试验数据管理指南（草案）》

** 参考黄钦博士幻灯片 2013*

中国临床试验数据注册要求 – 历史回顾 (2)

- 2011年
  - 药审中心成立**生物统计部**
- 2012年
  - 1月：**召开数据管理和数据**标准专家研讨会
  - 5月：发布《**临床试验数据管理指南**》 *(关于数据标准有10页)*
- 2013年
  - **6月：成立中国临床试验数据标准指导组***
  - **7月：发布《规范药物临床试验数据管理工作的实施方案》***
  - **8月：成立5个中国临床试验数据标准专题工作组（SDTM等）***
  - 10月：**召开中医**药临床试验数据标准研讨会
- 2014年
  - **召开4次季度专题工作组研讨会**
    - 专题工作组目标：发布数据递交技术推荐

*www.cde.org.cn

中国临床试验数据注册要求 - 现状和未来

- 遵照计划，C3C/工作组继续标准中文化
- 发布数据递交草案
- 发布征求意见稿
- 期待大家的参与！
- 时间表：1+2+3

Question #3

Required in Submission?	US FDA	EU EMA	Japan PMDA	China CFDA
Patient Data	X	X	X	X
Electronic Patient Data	X?	?	?	X
Electronic Patient Data In Standard Format	2004-Dec 2016	CSR 2015? IPD??	2016-Mar 2020	2016-2021?

"e-Submission with CDISC Standard"

Question #4: e-Sub Future - Globalized??

Required in Submission?	US FDA	EU EMA	Japan PMDA	China CFDA
Patient Data	X	X	X	X
Electronic Patient Data	X?	?	?	X
Electronic Patient Data In Standard Format	Globalized e-Submission Standard??			

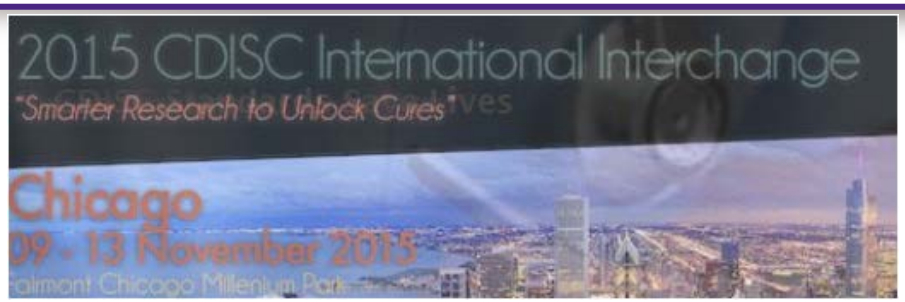
"Globalized e-Submission with CDISC Standard"

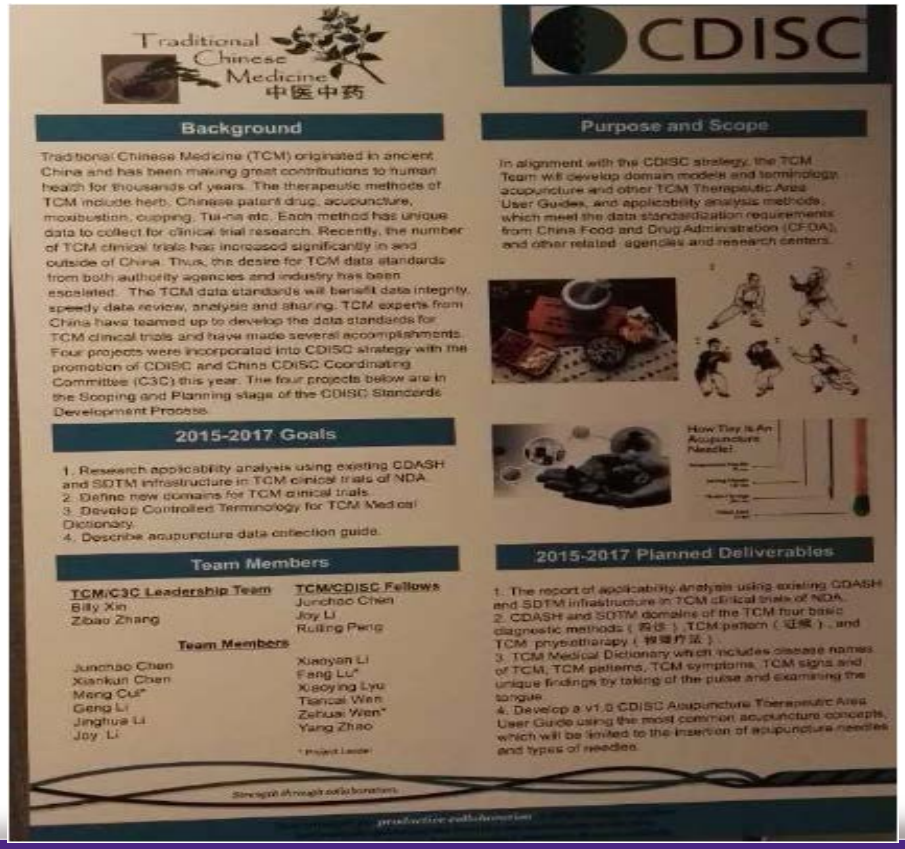
Question #5: Opportunities and Challenges

- Challenges
  - Chinese 中文
  - Traditional Chinese Medicine (TCM)
  - Talents
  - Standard Eco including Tools
    欢迎和使用数据标准的生态包括工具

- Opportunities
  - Late-development advantage 后发优势
  - From e-Source to e-Submission??

C3C/CDISC TCM Project Started





- Value Added
  - CDISC Gap Analysis in TCM trials
  - Herb/Chinese patent drugs/Acupuncture
  - CDASH/SDTM
  - TCM CT
- 2015-2017
- C3C/CDISC Fellow Program

Acknowledgement and References

- PhUSE annual meeting 2015 slides by **Peter Van Reusel** (*Business & Decision Life Sciences* for **slides 17-21, 23**)

- C3C 2015 Q3 seminar slides by **Henry Wu, Dehong Cao, John Wang** et al

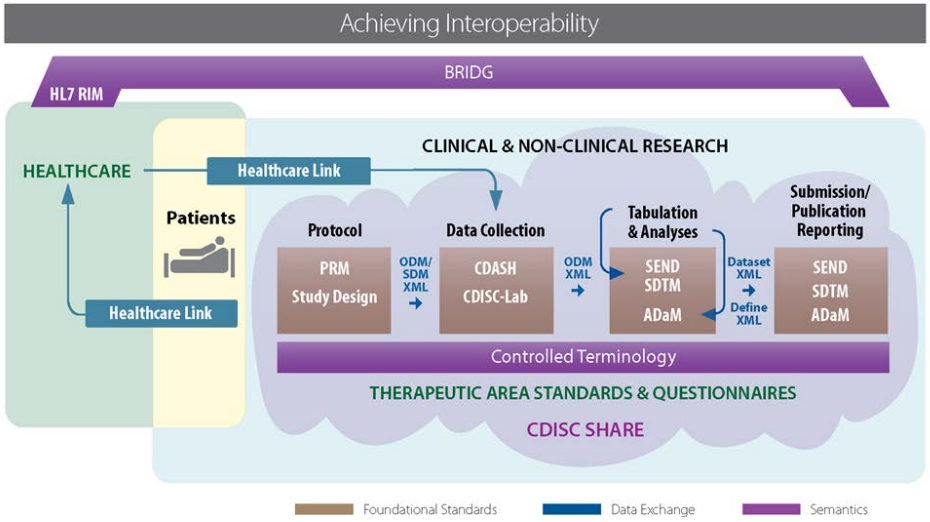
- Reference slides from **US FDA, EMA, PMDA and CFDA**

Thank You!

- Backup slides

C3C 2015/16《临床试验数据流端到端系列研讨会》

- 互联互通及电子源数据应用 Q2 *DONE*
- 数据递交标准 CDASH to e-Sub Q3 *DONE*
- **语义标准 Semantics* Q4 Dec 11, 2015**
- 临床研究方案标准 Protocol* 2016 Q1
- ……



- 敬请关注和支持（赞助、演讲等）cdiscchina@cdisc.org

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  - 微信号：CDISC-China
  - 二维码：

- 腾讯微博：
  - t.qq.com/cdiscchina

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