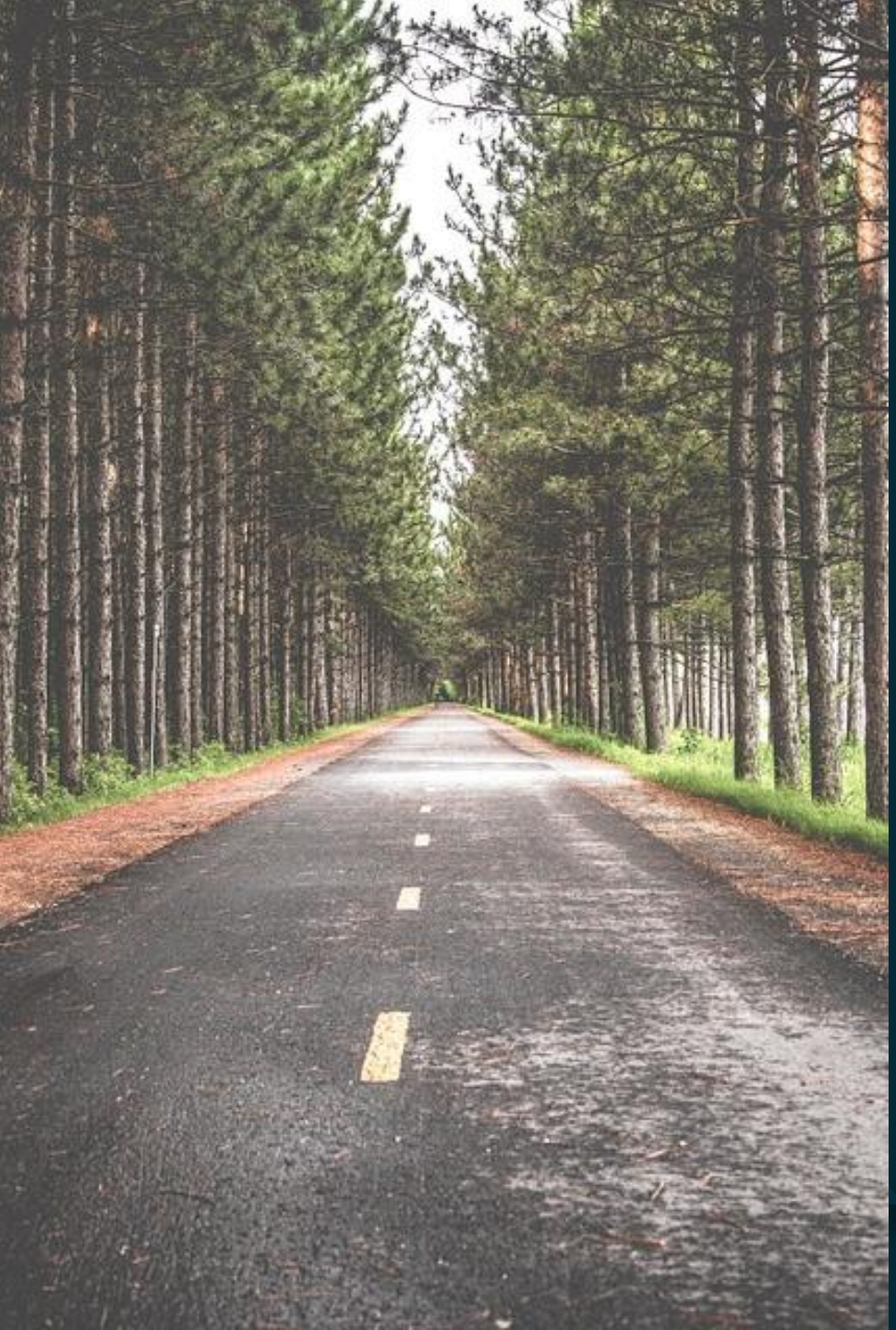
Are you ready for Dec 17th, 2016 – CDISC compliant data submission?

Kevin Lee, Director of Data Science



The Agenda

- What will happen on Dec 17th, 2016?
- Why important?
- How to prepare
- What to prepare
- FDA support
- Final thoughts

So, what will happen on Dec 17th, 2016?

According to FDA Data Standards Catalog, all clinical trial studies starting after December 17th, 2016 with the exception of certain INDs will be **required** to have CDISC compliant data.

FDA Data Standards Catalog v4.4 (08-17-2015) - Supported and Required Standards

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	SDTM	XPT	CDISC	1.3	3.1.3	CDER, CBER	12/01/2012		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - SDTM
Clinical study datasets	SDTM	XPT	CDISC	1.2	Version 3.1.2 Amendment 1	CDER, CBER	08/07/2013		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - SDTM
Clinical study datasets	SDTM	XPT	CDISC	1.2	3.1.2	CDER, CBER	10/30/2009		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - SDTM
Clinical study datasets	SDTM	XPT	CDISC	1.1	3.1.1	CDER, CBER	Ongoing	01/28/2015			CDISC.org - SDTM
Clinical study datasets	Analysis Data Model (ADaM)	XPT	CDISC	2.1	1.0	CDER, CBER	Ongoing		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - ADaM
Animal study datasets	Standard for Exchange of Nonclinical Data (SEND)	XPT	CDISC	1.2	3.0	CDER	06/13/2011		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - SEND
Clinical study data definition	Define	XML	CDISC	1.0	N/A	CDER, CBER, CDRH	Ongoing		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - Define-XML
Clinical study data definition	Define	XML	CDISC	2.0	N/A	CDER, CBER, CDRH	08/07/2013		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - Define-XML

Why important?

Can FDA “Refuse to File/Receive” if submission data does not follow FDA requirements?

YES

History of FDA Standards eSubmission

eSubmission Progress in CDER FDA

CDER Investigational New Drugs

	FY2008	FY2009	FY2010	FY2011	FY2012	FY2013*
IND Research	11,833	12,863	14,816	16,039	14,767	9,841
IND Commercial	73,784	74,163	77,402	77,013	76,419	51,040
IND Total	85,617	87,026	92,218	93,052	91,186	60,881
IND Research Electronic	307	456	721	1,185	1,477	1,251
IND Commercial Electronic	13,006	24,913	36,794	48,116	55,108	39,975
IND Electronic Total	13,313	25,369	37,515	49,301	56,585	41,226
IND Electronic %	15.55%	29.15%	40.68%	52.98%	62.05%	67.72%
IND Research eCTD	217	326	595	1,008	1,324	1,088
IND Commercial eCTD	12,338	24,448	36,219	47,564	54,677	39,661
IND eCTD	12,555	24,774	36,814	48,572	56,001	40,749
eCTD % of Total	14.66%	28.47%	39.92%	52.20%	61.41%	66.93%
eCTD % of Electronic	94.31%	97.66%	98.13%	98.52%	98.97%	98.84%

* As of May 31, 2013

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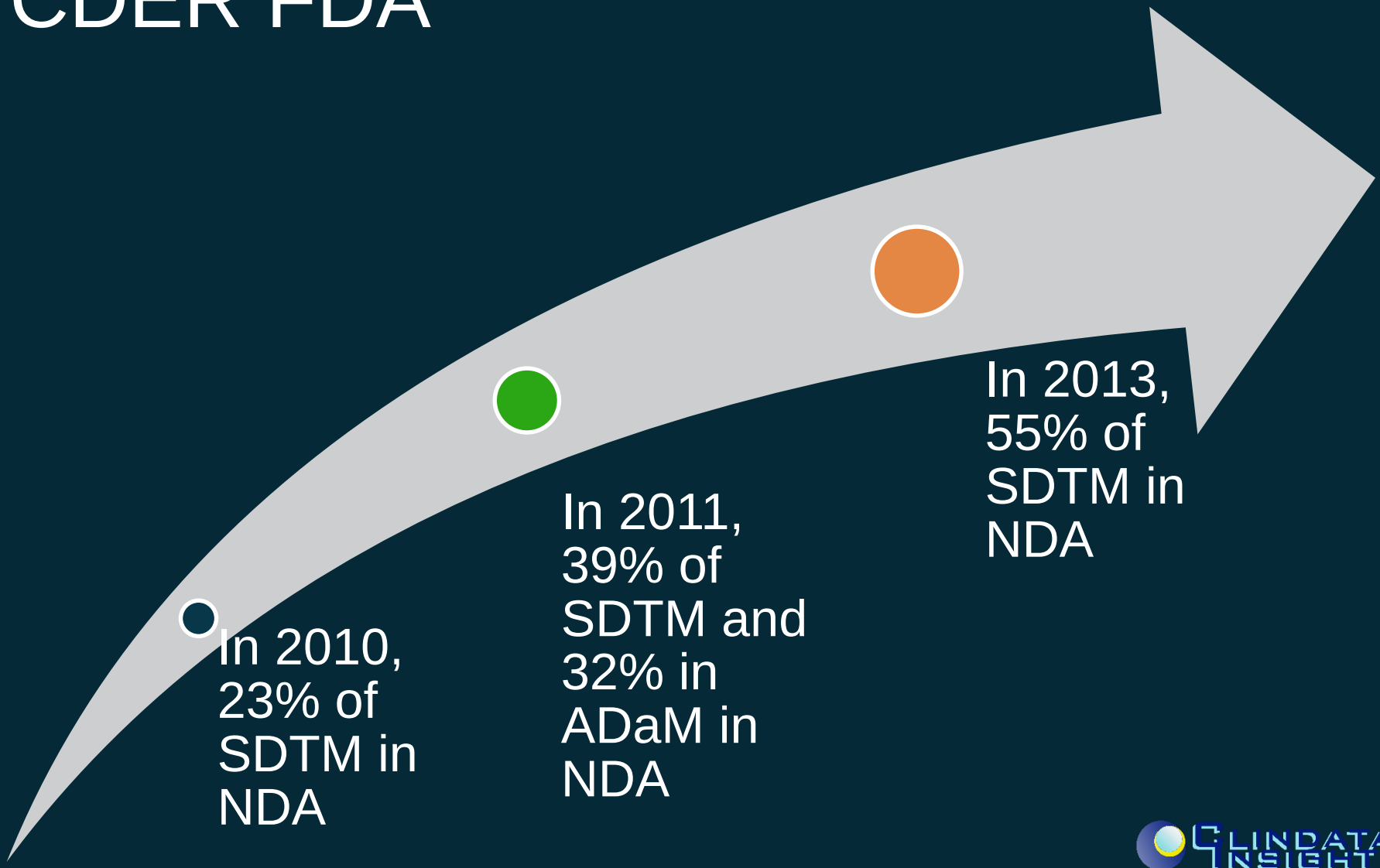
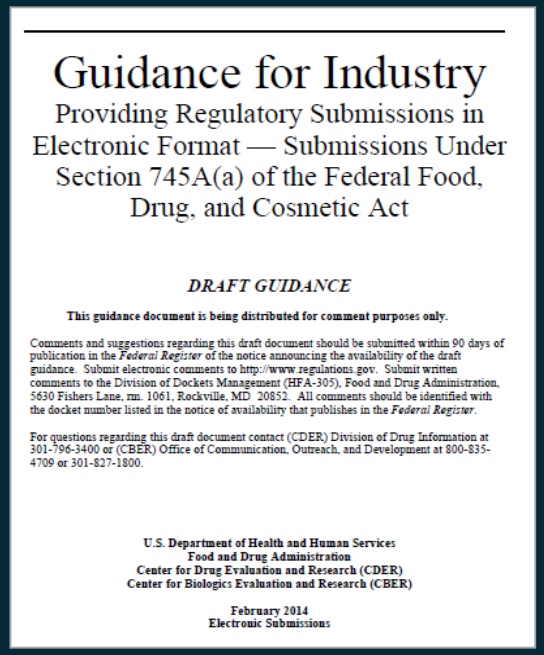
CDISC Submission Progress in CDER FDA



Section 745A(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)

- Enhanced by Food and Drug Administration Safety and Innovation Act (FDASIA) on July 9, 2012.
- Requires that data be submitted in electronic format.

New FDA Guidance on CDISC eSubmission



Guidance for Industry

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

DRAFT GUIDANCE

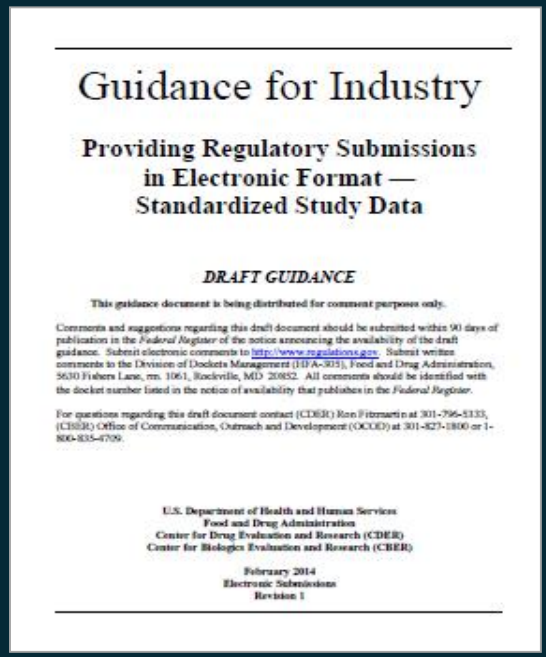
This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Division of Drug Information at 301-796-3400 or (CBER) Office of Communication, Outreach, and Development at 800-835-4709 or 301-827-1800.

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)

February 2014
Electronic Submissions



Guidance for Industry

Providing Regulatory Submissions in Electronic Format — Standardized Study Data

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Ron Fitzmartin at 301-796-5133, (CBER) Office of Communication, Outreach and Development (OCOD) at 301-827-1800 or 1-800-835-4709.

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)

February 2014
Electronic Submissions
Revision 1

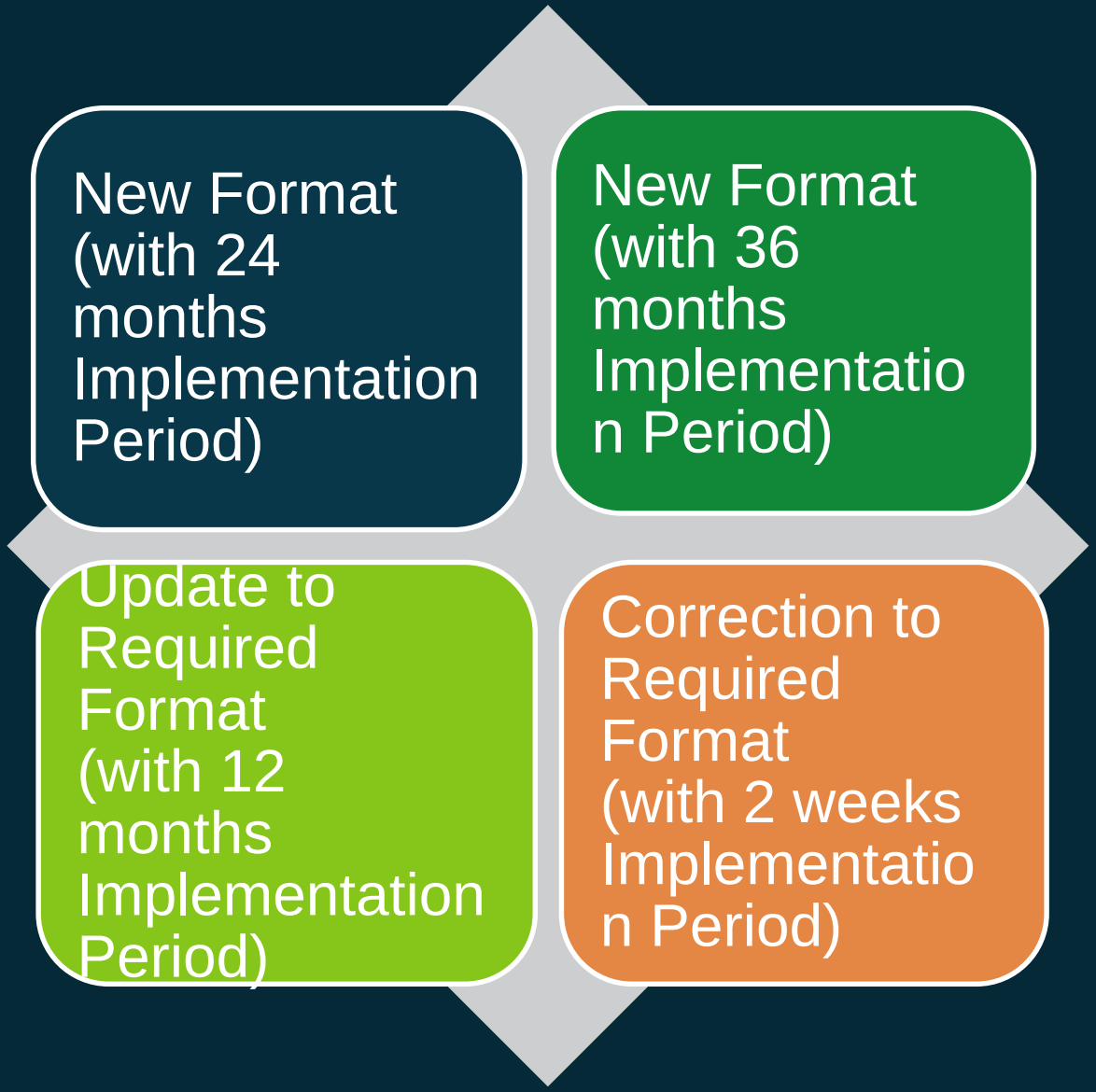
Standards mandate.

Introduction of Standards implementation process.

Guidance for Industry:
Providing Regulatory Submissions in Electronic Format – Submissions Under Section 745A (a) of the Federal Food Drug, and Cosmetic Act

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

FDA Standards Implementation Process - Timetables for Standards



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FDA Standards Implementation Process Example (Update – 12 months Implementation)

2016-02-15
- CDISC Version Update of SDTM from 4.0 to 4.1

2016-05-06
- FDA Date Support on SDTM 4.1 on Federal Register notice and DSC

2017-03-15
- FDA Effective Implementation Date of SDTM 4.1 on Federal Register notice

2018-03-15
- FDA Requirement Date of SDTM 4.1

Data Standards Catalog

Standard	Exchange Format	Supported Version	Implementation Guide Reference	FDA Center	Date Support Begins (yyyy-mm-dd)	Date Support Ends (yyyy-mm-dd)	Date Requirement Begins	Date Requirements Ends
SDTM	XPT	4.1		CBER, CDER	2016-05-06		2018-03-15	

How to prepare?

Data Standard Catalog

eCTD(Electronic Common Technical Document)

CDISC Standards

Study Data Technical Conformance Guide

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Data Standards Catalog

- Standards Type and Version (i.e., eCTD, xml, SDTM 1.3, ADaM 2.1, Define.xml 2)
- FDA Center (i.e., CBER, CDER, CDRH)
- FDA Support start and end date
- FDA Requirement start and end date

Standard	Exchange Format	Supported Version	Implementation Guide Reference	FDA Center	Date Support Begins (MM/DD/YYYY)	Date Support Ends (MM/DD/YYYY)	Date Requirement Begins	Date Requirements Ends
SDTM	XPT	1.4	3.2	CBER, CDER	08/17/2015		03/15/2018 [1] 03/15/2019 [2]	
SDTM	XPT	1.3	3.1.3	CBER, CDER	12/01/2015		12/17/2016 [1] 12/17/2017 [2]	
SDTM	XPT	1.1	3.1.1	CBER, CDER	Ongoing	01/08/2015		
ADaM	XPT	2.1	1.0	CBER, CDER	Ongoing		12/17/2016 [1] 12/17/2017 [2]	
SEND	XPT	1.2	3.0	CDER	06/13/2011		12/17/2016 [1] 12/17/2017 [2]	
Define	XML	2.0	N/A	CBER, CDER, CDRH	08/07/2013		12/17/2016 [1] 12/17/2017 [2]	
eCTD	XML	3.2.2	M2 eCTD	CBER, CDER	06/01/2008		05/05/2017 [1] 05/05/2018 [2]	

Electronic Common Technical Document

Introduction of eCTD

- FDA guidance on how sponsors prepare regulatory submission on electronic files.

File formats (i.e., pdf, txt, xml and xpt)

Submission folder - modules and their contents

- Module 1 – Administrative information
- Module 2 – Summary document
- Module 3 – Quality
- Module 4 – Non-clinical Study Reports
- **Module 5 – Clinical Study Information**

Naming Conventions of Electronic Files according to eCTD

- Lower case of letter from “a” to “z” (i.e., ae.xpt)
- Number from “0” to “9”
- “-” hypen (i.e., c-adae-sas.txt)
- No special character (#, %, $ and etc)
- File name should be less than or equal to 64 characters including the appropriate file extension
- The length of entire path of the file should not exceed 230 characters. (m5/datasets/study001/tabulations/sdtm/ae.xpt)

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pdf File Guidance according to eCTD

Version – 1.4 thru 1.7 are acceptable

Fonts

- Standard : Arial, Courier New, Times Roman
- Sizes : range from 9 to 12 point (Times New Roman 12-point font is recommended for narrative text)

Page

- Print area : 8.5 inches by 11 inches
- Margin : at least ¾ inch

xpt File Formats Guidelines

Length

- Variable length is less than or equal to 8
- Variable label is less than or equal to 40
- Dataset length is less than or equal to 8
- Dataset label is less than or equal to 40

Dataset Size

- less than 5 GB (LB1, LB2, and so on)

The length of character variables

- should be minimized – i.e, if the maximum length of USUBJID is 20 character long, keep the length as 20, not 200.

CDISC Standards

SDTM

ADaM

SEND

Define-xml

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Study Data Technical Conformance Guide

Background

- Provides specifications, recommendations and general consideration on Standardized data.
- Non-binding documents

Purpose

- Provides technical recommendation on standard data in IND, NDA, ANDA and BLA.
- Complements and promotes interactions between sponsors and FDA.

What are new in Study Data Technical Conformance Guide version 3 and 3.1?

- FDA strongly recommended Define.xml and Reviewer's Guide for ADaM, SDTM and SEND.
- FDA encouraged to include data flow diagrams in Reviewer's Guide to show traceability.
- FDA emphasized the importance of Trial Design models including Trial Arms, Elements, Visits, IE Criteria and Summary for SDTM and SEND and even for legacy study.

What to prepare for Data Submission?

CDISC compliant data according to Data Standard Catalog (DSC)

Submission supporting documents

Electronic formats of submission package according to eCTD

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CDISC compliant data according to DSC

CDSIC Standards	Model version	Implementation Guide version
SDTM	1.4	3.2
SDTM	1.3	3.1.3
SDTM	1.2	Version 3.1.2 Amendment 1
SDTM	1.2	3.1.2
~~SDTM~~	~~1.1~~	~~3.1.1~~
ADaM	2.1	1.0
SEND	1.2	3.0
Define	1.0	
Define	2.0	

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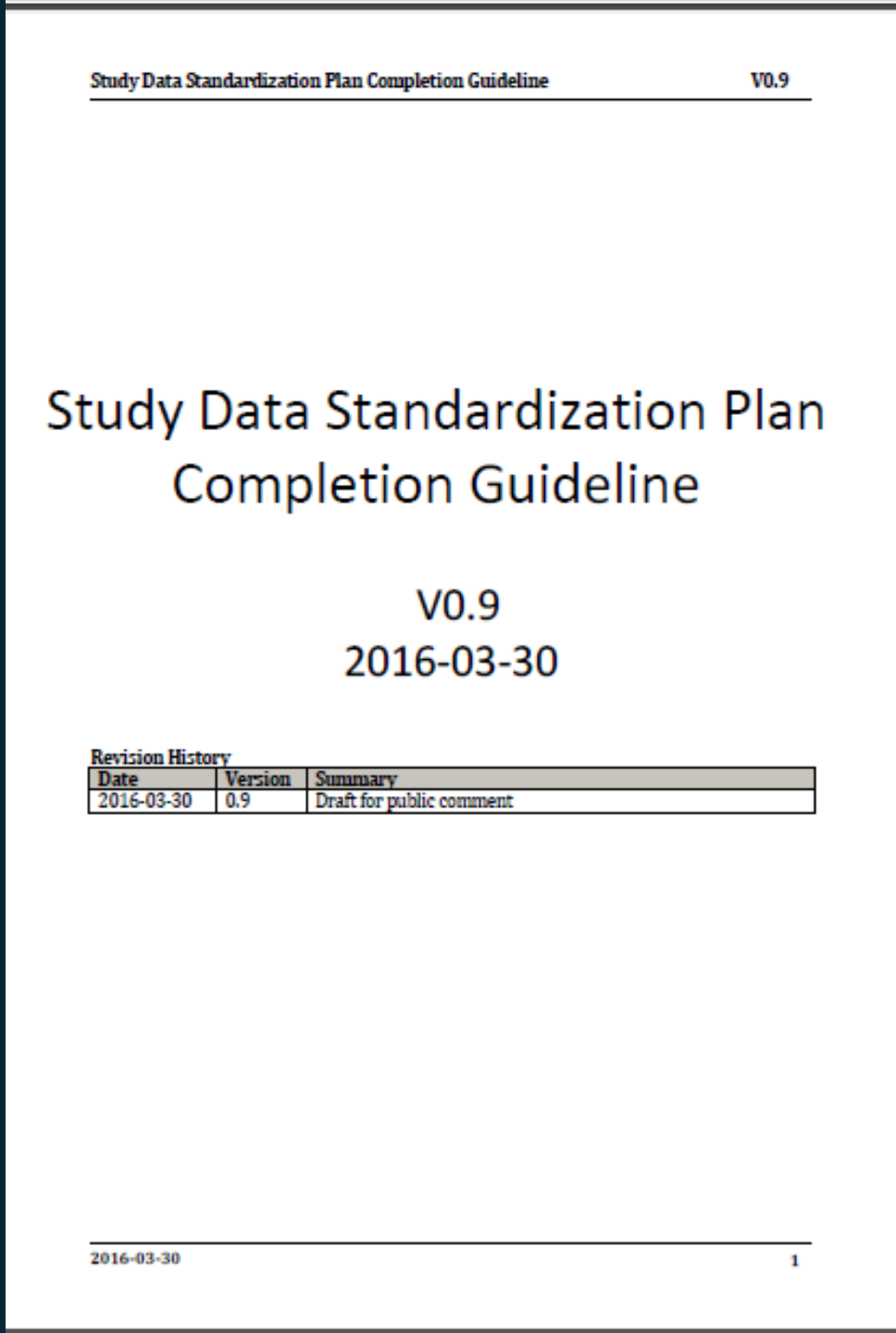
Submission supporting documents

- Study Data Standardization Plan
- Study Data Reviewer's Guide
- Analysis Data Reviewer's Guide
- Non Clinical Study Data Reviewer's Guide



Study Data Standardization Plan Completion Guideline

V0.9
2016-03-30

Revision History

Date	Version	Summary
2016-03-30	0.9	Draft for public comment

Study Data Standardization Plan (SDSP)

- SDSP describes the submission of standardized study data to FDA – will help FDA to find potential data standardization issues.
- It can be discussed with FDA at pre-IND stage.
- In a IND submission, SDSP is located in module 1.13.9 general investigational plan.
- List of the planned studies
- Type of Studies
- Study Design
- Planned Data Standards, formats and terminologies and their versions
- List of and justification for studies that may not conform to the standards

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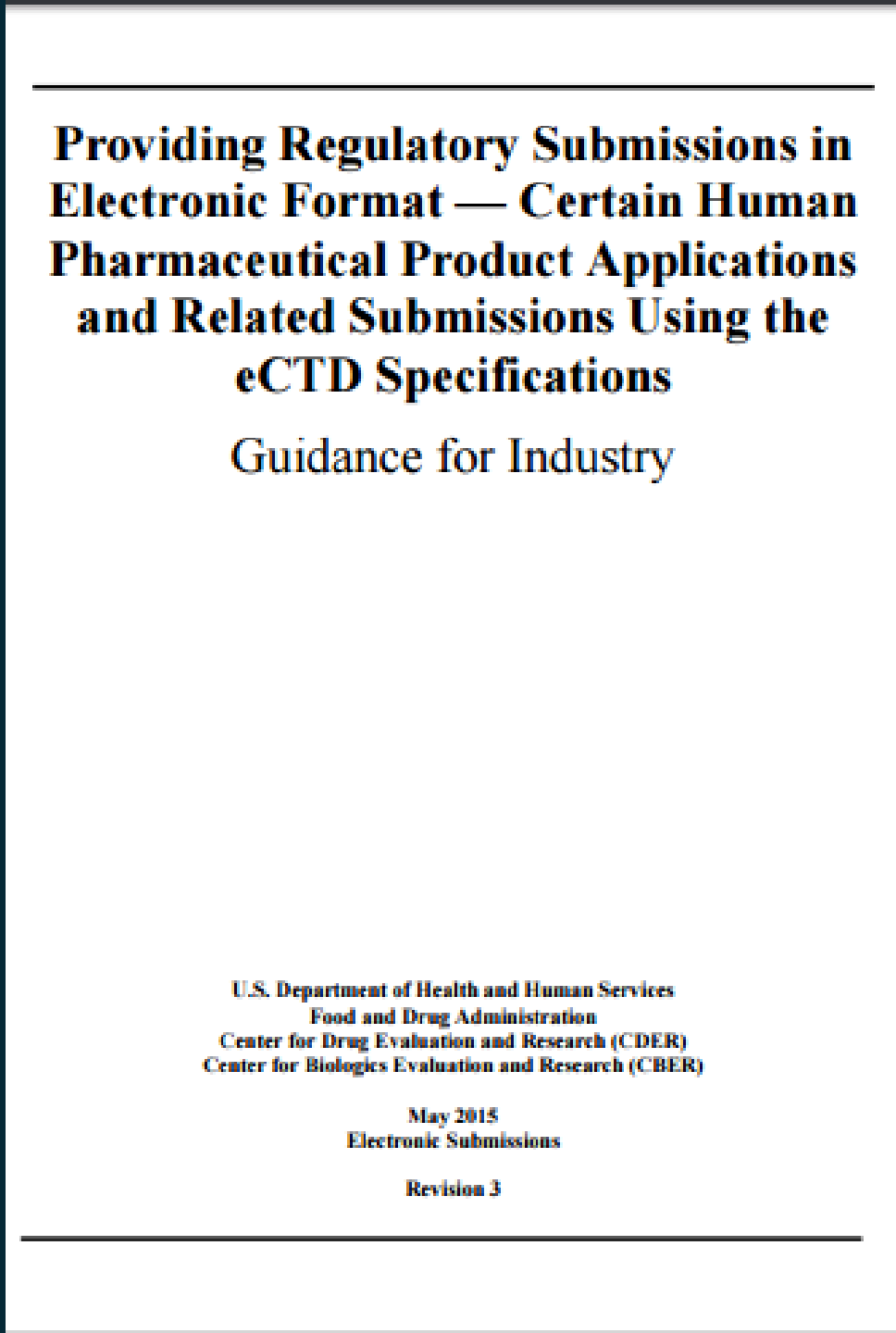
Study Data Reviewer's Guide (SDRG)

- **Study Protocol title, number and version**
- **Study Design**
- **Standards, formats and terminologies and their versions**
- **Description of study datasets**
- **Data Standards conformance validation rules, versions and issues**

Electronic Formats of submission package according to eCTD



Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

Guidance for Industry

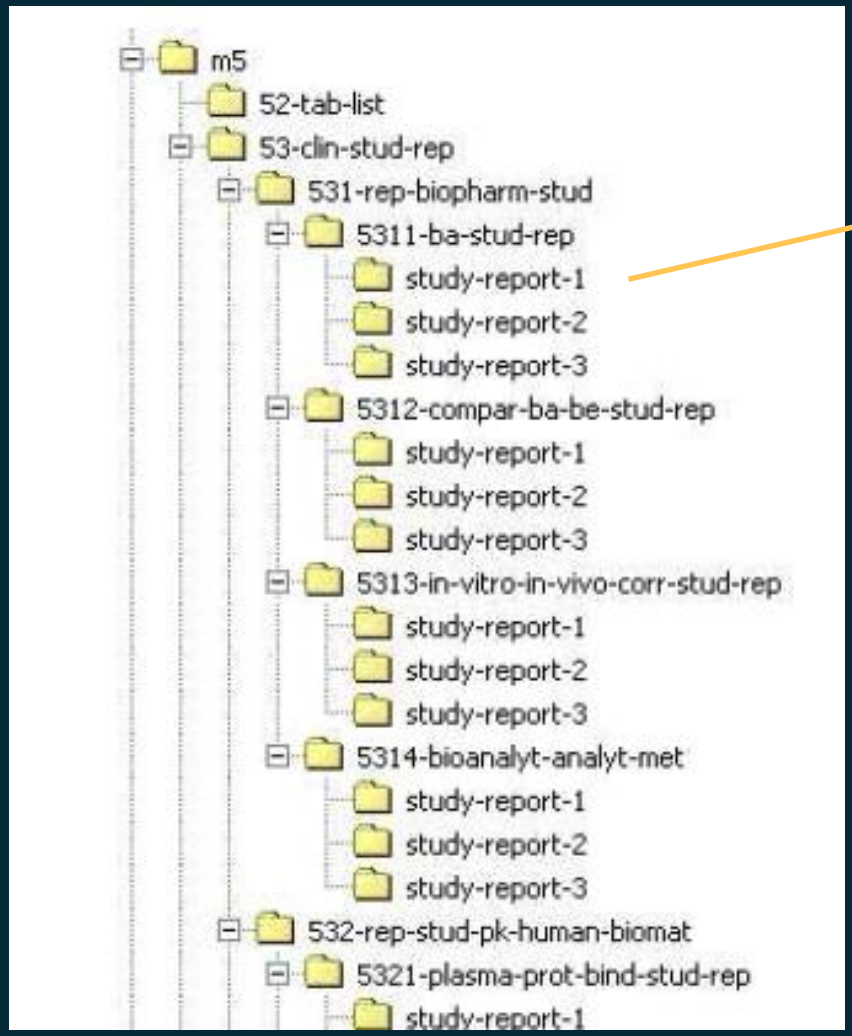
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2015
Electronic Submissions

Revision 3

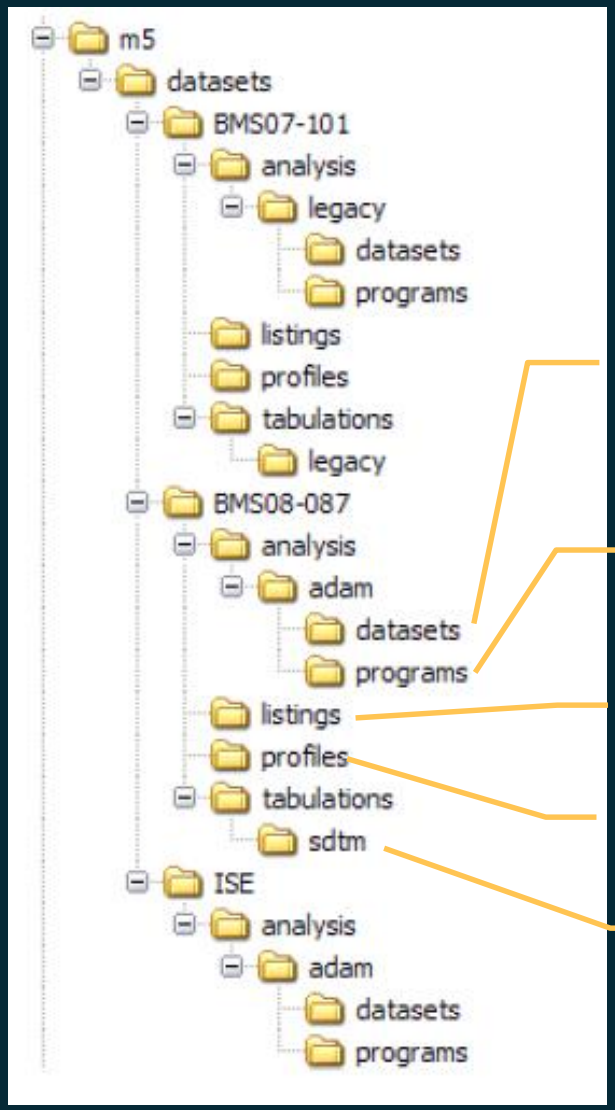
Format of Electronic Files according to eCTD

Documents in module 5.3.1.1



CSR, SAP, Protocol, CRF

CDISC Datasets in module 5.datasets



ADaM xpt datasets, Define.xml, ADRG

ADaM SAS programs, TFL SAS programs

Any xpt datasets

Patient profile

SDTM xpt datasets, Define.xml, SDTM annotated blank CRF, SDRG

Help!!!!

- Waiver
- FDA Support

Waiver Criteria for FDA Standards

No Waivers, but sponsors may apply for it

A written waiver request

- The specific requirements that sponsors seek for waivers
- A necessary reason
- A description of the alternatives

Discuss the waiver request with FDA prior to or at the pre-IND meeting and submit the request in writing prior to submission.

FDA Support

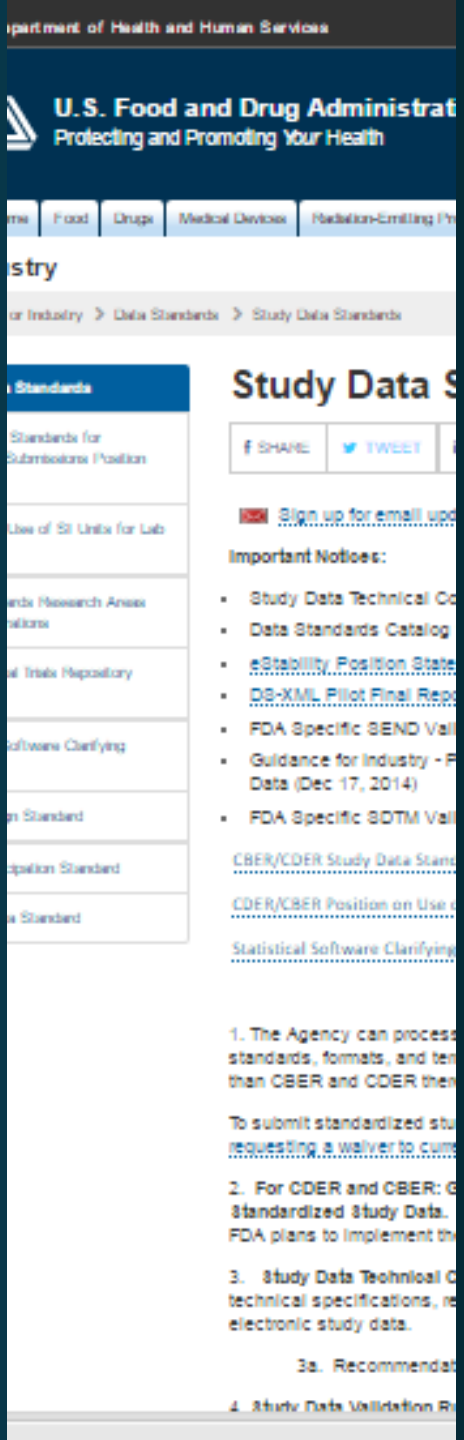
Meeting with FDA on pre-IND or prior to end-of-phase 2

- Study Data Standardization Plan
- Data Standardization Issues

Implementation Support

- Study Data Technical Conformance Guide: non-binding
- Sponsor can arrange pre-submission technical review on sample data
- cber.cdisc@fda.hhs.gov
- cder-edata@fda.hhs.gov

Final Thoughts



- Before: Recommendation
- After: Requirement
- It is better to start early with standards compliant data and document preparation.

Contact Us!

Contact Clindata Insight to learn more about CDISC electronic submission.

Email us at
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consulting@clindatainsight.com

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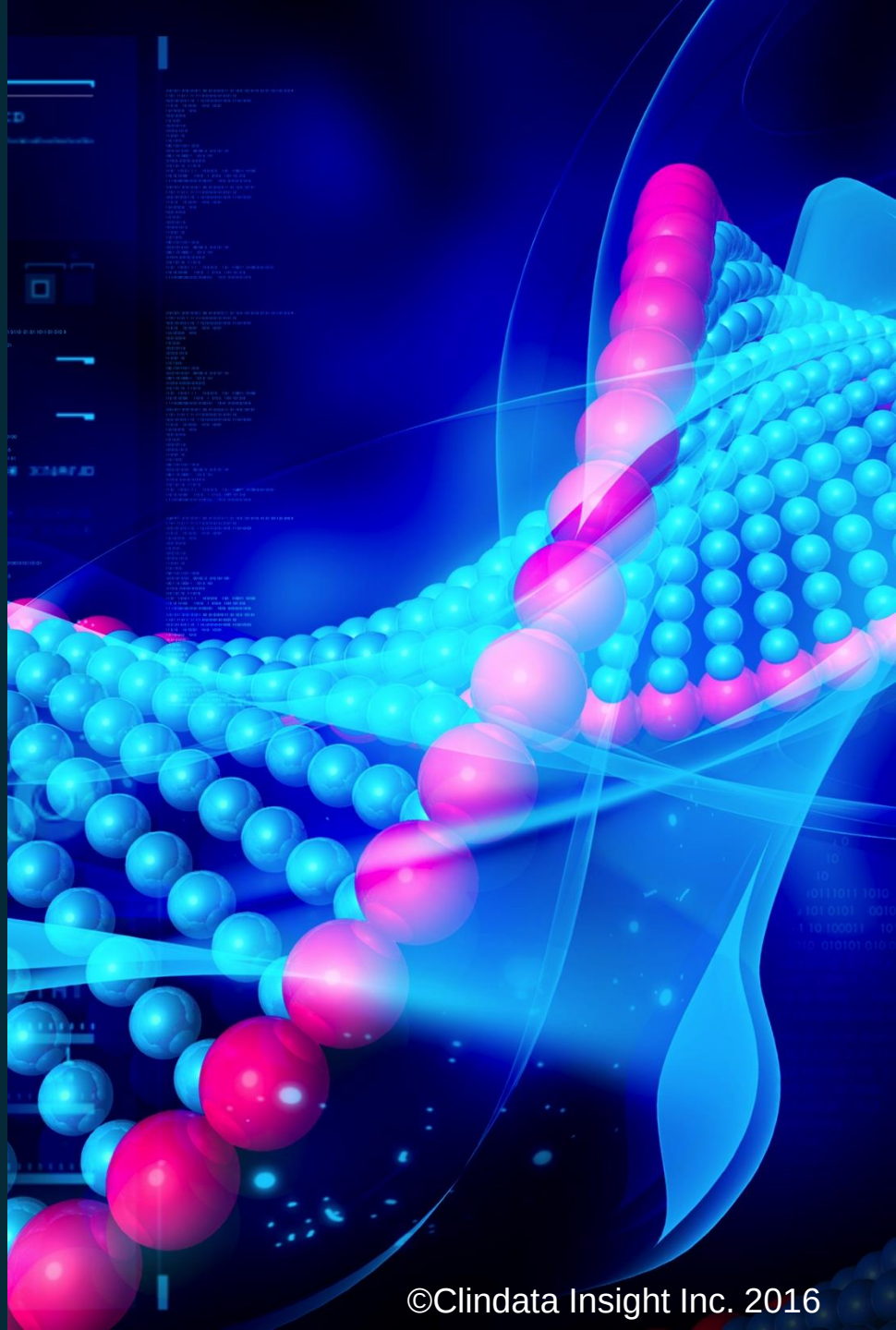

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THAT'S ALL

Questions and Discussion