



Preparing for a PMDA and FDA submission simultaneously

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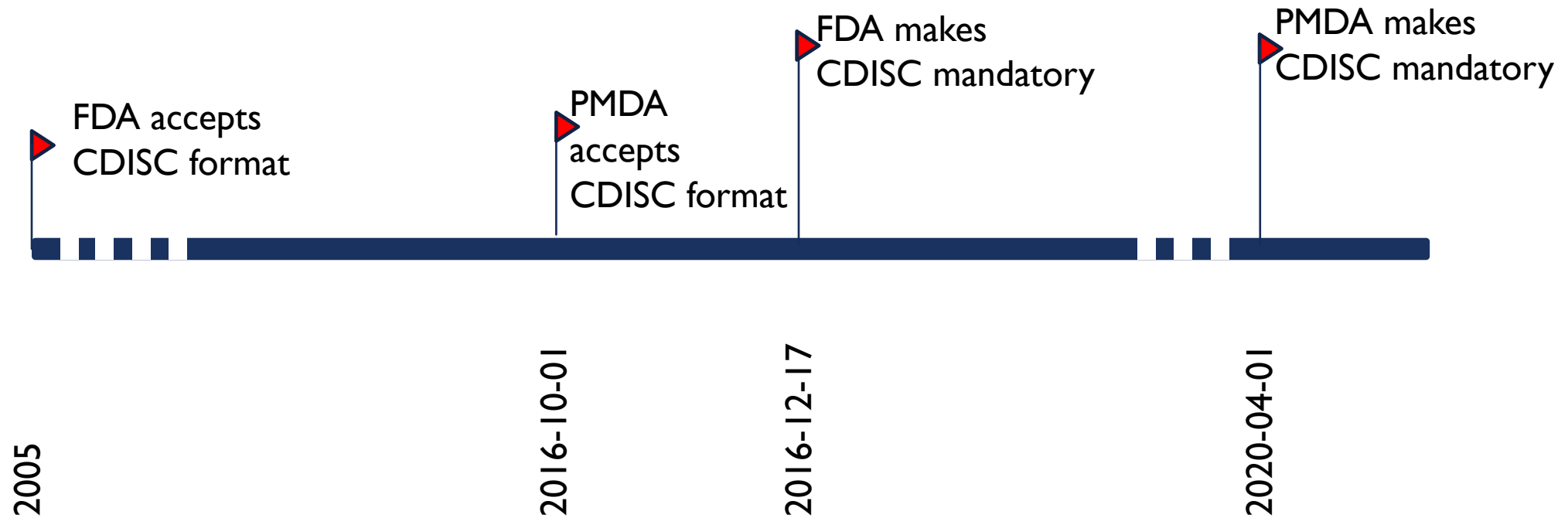
Data Consultant

PHUSE EU Connect Conference – November 2020

Agenda

- *Alignment of PMDA and FDA*
- *Alignment of the Agencies and CDISC*
- *Dealing with differences in a Submission*

The alignment



Submitting simultaneously was going to be easy, right?



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PMDA

Data Exchange Standard	Supported Version	Supported Implementation Guide version	Date Support Begins (MM/DD/YYYY)	Date Support Ends (MM/DD/YYYY)
Analysis Data Model (ADaM)	2.1	1.0	Ongoing	03/15/2019 [1] 03/15/2020 [2]
ADaM	2.1	1.1	03-15-2018	
Define	1.0	N/A	Ongoing	03-15-2018
Define	2.0	N/A	08-07-2013	

	Data Exchange Standard	Supported Version(s)	Implementation Guide Version	Exchange Format	Date Support Begins (YYYY-MM-DD)	Date Support Ends (YYYY-MM-DD)
	SDTM	1.4	3.2	XPT	2016-10-01	
	SDTM	1.3	3.1.3	XPT	2016-10-01	
Clinical study datasets	SDTM	1.2	3.1.2 Amendment1	XPT	2016-10-01	
Clinical study datasets	SDTM	1.2	3.1.2	XPT	2016-10-01	
Clinical study datasets	ADaM	2.1	1.0	XPT	2016-10-01	
Clinical study data definition files	Define	2.0	-	XML	2016-10-01	
Clinical study data definition files	Define	1.0	-	XML	2016-10-01	

Analysis Results Metadata

Study Data Tabulation Model Metadata Submission Guidelines (SDTM-MSC)

Prepared by the CDISC SDTM Metadata Team

Notes to Readers

This is a non-official CDISC Submission Guidelines created by the CDISC Submission Data Standards.

Revision History

Rev	Version	Summary of Changes
2016-05-14	1.0 Draft	Original draft document
2017-12-31	1.0 Final	Final version 1.0 released

Display	Table 14-5.02 Incidence of Treatment Emergent Serious Adverse Events by Treatment Group
Analysis Result	Incidence of Treatment Emergent Serious Adverse Events by Treatment Group
Analysis Parameter(s)	
Analysis Variable(s)	AEODSYS (Body System or Organ Class) AEDECOD (Dictionary-Derived Term)
Analysis Reason	SPECIFIED IN SAP
Analysis Purpose	PRIMARY OUTCOME MEASURE
Data References (incl. Selection Criteria)	ADAE [TRTEPL = "Y" and AESER = "Y"] ADSL [SAFEL = "Y"] Get denominators for percentages from ADSL and counts and numerators from ADAE. Join ADAE with ADSL based on the unique subject identifier (USUBJID) keeping only records in ADAE for the numerator.
Documentation	Unique count of subjects that experienced an Adverse Event by Preferred Term, System Organ Class, and Treatment Group and percentages based on the number of subjects in the safety population within each treatment group. The total number of times an event occurred was recorded by Preferred Term, System Organ Class, and Treatment Group. Fisher's exact test was used for treatment comparison of event rates. SAP Section 11.2
Programming Statements	[SAS version 9.2] at14-5-02.sas

Validating against PMDA ADaM IG v1.0

FDA ADaM v1.1

Source	Pinnacle 21 ID	Publisher ID	Message	Issue Summary	Severity	Found
AD AE	CT2001		AECN value not found in 'Action Taken with Study Treatment' non-extensible codelist		Error	3
	SD0087		Value for AECN not found in (Action Taken with Study Trt. (Concrt)) user-defined codelist		Error	3
	SD0087		Value for AECOUT not found in (Outcome of Adverse Event) user-defined codelist		Error	1
AD CM	AD0099		ASTDY is greater than AENDY		Error	1
	AD0361		Value of ASTDT is greater than value of AENDT		Error	1
AD EG	AD0018		Variable label mismatch between dataset and ADaM standard		Warning	3
	CT2002		DTYPE value not found in 'Derivation Type' extensible codelist		Warning	1640
AD EX	AD0018		Variable label mismatch between dataset and ADaM standard		Warning	1
AD LB	AD0018		Variable label mismatch between dataset and ADaM standard		Warning	16
AD MBLE	AD0018		Variable label mismatch between dataset and ADaM standard		Warning	19
	CT2002		DTYPE value not found in 'Derivation Type' extensible codelist		Warning	17901
AD MBLS	CT2002		DTYPE value not found in 'Derivation Type' extensible codelist		Warning	2044
AD MBLU	AD0018		Variable label mismatch between dataset and ADaM standard		Warning	3
	CT2002		DTYPE value not found in 'Derivation Type' extensible codelist		Warning	38570
AD MH	AD0102		Secondary custom variable is present but its primary variable is not present		Warning	3
	AD0125		Inconsistent value for PARCAT2		Error	844
AD MI	AD0018		Variable label mismatch between dataset and ADaM standard		Warning	3
AD MK	AD0018		Variable label mismatch between dataset and ADaM standard		Warning	7
	CT2002		DTYPE value not found in 'Derivation Type' extensible codelist		Warning	2336
AD MKF	AD0018		Variable label mismatch between dataset and ADaM standard		Warning	5
	CT2002		DTYPE value not found in 'Derivation Type' extensible codelist		Warning	2336
AD MKL	AD0018		Variable label mismatch between dataset and ADaM standard		Warning	5
	CT2002		DTYPE value not found in 'Derivation Type' extensible codelist		Warning	2336
AD MO	AD0018		Variable label mismatch between dataset and ADaM standard		Warning	3
	CT2002		DTYPE value not found in 'Derivation Type' extensible codelist		Warning	11980
AD PC	AD0018		Variable label mismatch between dataset and ADaM standard		Warning	4
AD PE	AD0018		Variable label mismatch between dataset and ADaM standard		Warning	3
AD OS	AD0193		Illegal variable name: y is not in [1-9] for CRITY(PURN)		Error	6
	AD0018		Variable label mismatch between dataset and ADaM standard		Warning	3
	CT2002		DTYPE value not found in 'Derivation Type' extensible codelist		Warning	17438
AD SL	AD0196		Required ARM value is null		Error	4641
	AD0196		Required SEX value is null		Error	1
	CT2002		RACE value not found in 'Race' extensible codelist		Warning	75
AD TTE	AD0018		Variable label mismatch between dataset and ADaM standard		Warning	2
	AD0018		Variable label mismatch between dataset and ADaM standard		Warning	3

Source	Pinnacle 21 ID	Publisher ID	Message	Issue Summary	Severity	Found
AD CM	AD0361	361	Value of ASTDT is greater than value of AENDT		Error	1
	CT2002		RACE value not found in 'Race' extensible codelist		Warning	85
AD DV	CT2002		RACE value not found in 'Race' extensible codelist		Warning	27
AD EG	AD0102	*	Secondary custom variable is present but its primary variable is not present		Warning	1
	CT2002		DTYPE value not found in 'Derivation Type' extensible codelist		Warning	1640
	CT2002		RACE value not found in 'Race' extensible codelist		Warning	80
AD EX	CT2002		RACE value not found in 'Race' extensible codelist		Warning	480
AD LB	CT2002		RACE value not found in 'Race' extensible codelist		Warning	4453
AD MBLE	CT2002		DTYPE value not found in 'Derivation Type' extensible codelist		Warning	17901
	CT2002		RACE value not found in 'Race' extensible codelist		Warning	483
AD MBLS	CT2002		DTYPE value not found in 'Derivation Type' extensible codelist		Warning	2044
	CT2002		RACE value not found in 'Race' extensible codelist		Warning	32
AD MBLU	CT2002		DTYPE value not found in 'Derivation Type' extensible codelist		Warning	38570
	CT2002		RACE value not found in 'Race' extensible codelist		Warning	504
AD MH	AD0102	*	Secondary custom variable is present but its primary variable is not present		Warning	3
	CT2002		RACE value not found in 'Race' extensible codelist		Warning	98
AD MI	AD0102	*	Secondary custom variable is present but its primary variable is not present		Warning	4
	CT2002		RACE value not found in 'Race' extensible codelist		Warning	288
AD MK	AD0102	*	Secondary custom variable is present but its primary variable is not present		Warning	1
	CT2002		DTYPE value not found in 'Derivation Type' extensible codelist		Warning	2336
	CT2002		RACE value not found in 'Race' extensible codelist		Warning	416
AD MKF	AD0102	*	Secondary custom variable is present but its primary variable is not present		Warning	1
	CT2002		DTYPE value not found in 'Derivation Type' extensible codelist		Warning	2336
	CT2002		RACE value not found in 'Race' extensible codelist		Warning	416
AD MKL	AD0102	*	Secondary custom variable is present but its primary variable is not present		Warning	1
	CT2002		DTYPE value not found in 'Derivation Type' extensible codelist		Warning	2336
	CT2002		RACE value not found in 'Race' extensible codelist		Warning	416
AD MO	AD0102	*	Secondary custom variable is present but its primary variable is not present		Warning	2
	CT2002		DTYPE value not found in 'Derivation Type' extensible codelist		Warning	11980
	CT2002		RACE value not found in 'Race' extensible codelist		Warning	804
AD PC	CT2002		RACE value not found in 'Race' extensible codelist		Warning	30
AD PE	AD0102	*	Secondary custom variable is present but its primary variable is not present		Warning	2
	CT2002		RACE value not found in 'Race' extensible codelist		Warning	90
AD PR	CT2002		RACE value not found in 'Race' extensible codelist		Warning	4
AD OS	CT2002		DTYPE value not found in 'Derivation Type' extensible codelist		Warning	17438
	CT2002		RACE value not found in 'Race' extensible codelist		Warning	1342
AD SL	AD0196	196, 197	Required ARM value is null		Error	4641
	AD0196	196, 197	Required SEX value is null		Error	1
	AD0102	*	Secondary custom variable is present but its primary variable is not present		Warning	3
	CT2002		RACE value not found in 'Race' extensible codelist		Warning	75
AD TTE	CT2002		RACE value not found in 'Race' extensible codelist		Warning	24
AD VS	AD0102	*	Secondary custom variable is present but its primary variable is not present		Warning	1
	CT2002		RACE value not found in 'Race' extensible codelist		Warning	206

✓ = consistent output

Not only the versions differ

Conformance Checks by agency

	FDA	PMDA	FDA + PMDA
SDTM	17	1	436
ADaM	90		251
Define	1		136

*This table does not take into account differences in Severity
– Except for REJECTION criteria,
no longer published by FDA, still present in Pinnacle21*

Differences in “REJECTION” Criteria

 PRODUCTS SERVICES COMMUNITY About Us 												
SDTM SEND ADAM DEFINE-XML												
Search ALL FDA PMDA 1511.6 PMDA 1810.3												
Rule ID	Publisher ID	Message	Description	Domains	FDA	PMDA 1511.6	PMDA 1810.3	FDA Severity	PMDA Severity	3.1.2	3.1.3	3.2
SD1020	eCTD 1736	Missing DM dataset	Demographics (DM) dataset must be included in every submission.	DM	X	X	X	Reject	Reject	X	X	X
SD1115	eCTD 1734	Missing TS dataset	Trial Summary (TS) dataset must be included in every submission.	TS	X	X	X	Reject	Error	X	X	X
SD2232	eCTD 1734, FDAB011, CG0287	Missing SSTDC Trial Summary Parameter	'Study Start Date' (SSTDTC) record must be populated in Trial Summary (TS) domain. It is expected for SDTM IG v3.1.2 data and required for data in all more recent SDTM versions.	TS	X	X	X	Reject	Warning	X	X	X
SD2247	eCTD 1734, CG0285	Invalid TSVAL value for SSTDC	TSVAL variable value must be in ISO 8601 format, when TSPARMCD='SSTDTC'.	TS	X	X	X	Reject	Error	X	X	X
SD0002	FDAB027, CG0014	NULL value in variable marked as Required	Required variables (where Core attribute is 'Req') cannot be NULL for any records.	ALL	X	X	X		Reject	X	X	X

Where difference in rejection criteria lead to conflict

Dataset	Rule ID	Publisher ID	Message	FDA	PMDA
DM	SD0002	FDAB027, CG0014	NULL value in SEX variable marked as Required	Error	Reject

- *Issue : Collected Screened Subject withdrew consent prior to data entry:*
 1. *Remove screen failures? No, FDA review division requested that screen failures are included.*
 2. *Discuss with PMDA? Sure, but when?*
 3. *Create 2 different DM datasets?*

It get's worse



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Technical conformance guides deviating from CDISC

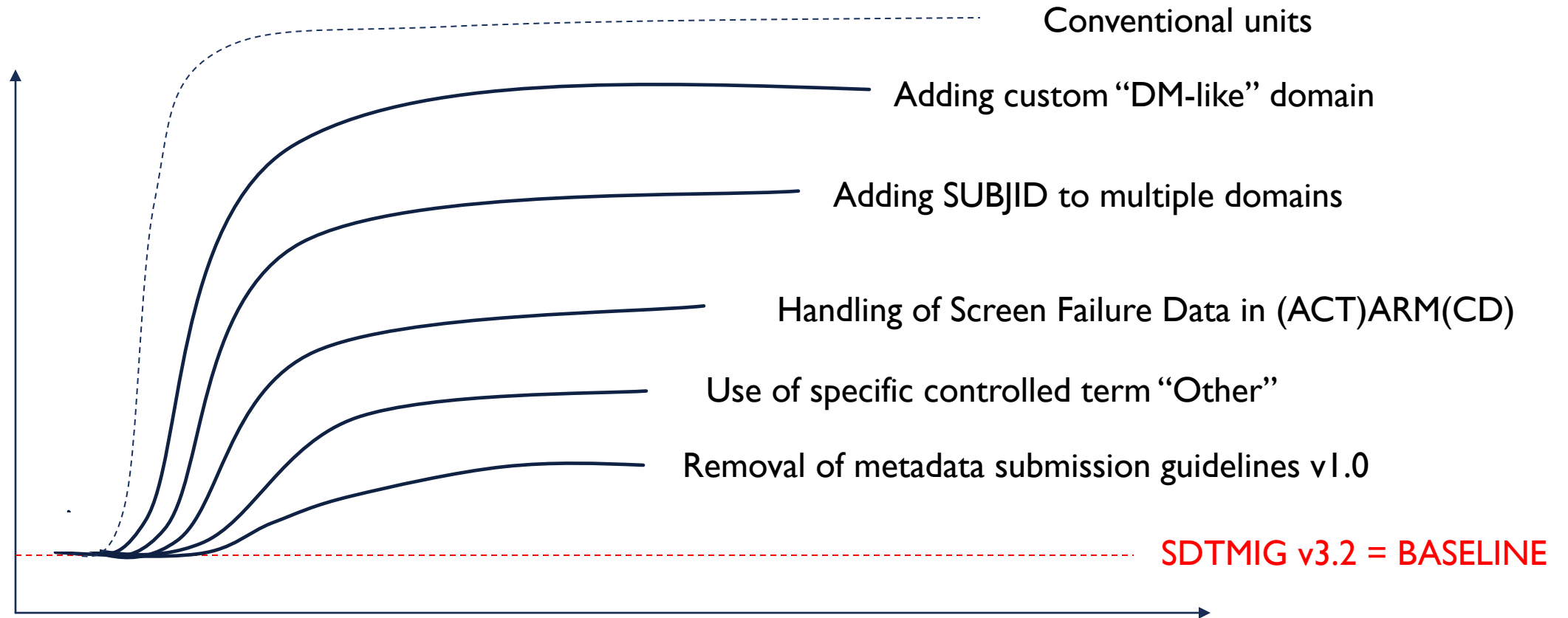
“The SDTMIG should be followed unless otherwise indicated in this Guide or in the Catalog.”

(pg 18 FDA SDTCG July 2020)



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FDA TCG moving away from SDTM IG, ... and from PMDA TCG



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Discrepancies 'Conformance checks' – CDISC IG

Rule ID	Publisher ID	Message	FDA	PMDA
CT2001	CG0020, CG0085, CG0131, CG0232-CG0235, CG0387-CG0396	AEACN value not found in 'Action Taken with Study Treatment' non-extensible codelist	Error	Error

AE Dataset

AETERM	AEREL	AEACN
RASH	MULTIPLE	MULTIPLE

SUPPAE Dataset

QNAM	QLABEL	QVAL
AERELABC	Causality of Abcicim	POSSIBLY RELATED
AERELXYZ	Causality of Xyzamin	UNLIKELY RELATED
AEACNABC	Action Taken with Abcicim	DOSE REDUCED
AEACNXYZ	Action Taken with Xyzamin	DOSE NOT CHANGED

Term	Submission Value
C150826	DOSE RATE REDUCED
C17998	UNKNOWN
C48660	NOT APPLICABLE
C49501	DRUG INTERRUPTED
C49502	DRUG WITHDRAWN
C49503	DOSE INCREASED
C49504	DOSE NOT CHANGED
C49505	DOSE REDUCED

And sometimes the SDTM IG lags on regulations

Rule ID	Publisher ID	Message	FDA	PMDA 1810.3
SD1097	FDAB001	No Treatment Emergent info for Adverse Event	X	X

AE Domain (Adverse Events (AE))

Currently, there is no variable in the AE domain that indicates if an AE was ‘treatment-emergent.’ The AE domain should include all adverse events that were recorded in the subjects’ case report forms, regardless of whether the sponsor determined that particular events were or were not treatment-emergent.

QNAM	QLABEL	Applicable Domains
AESOSP	Other Medically Important SAE	AE
AETRTEM	Treatment Emergent Flag	AE
--CLSIG	Clinically Significant	Findings
--REAS	Reason	All general observation classes

Not everything is terrible



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Analysis Results Metadata (PMDA) vs FDA request

Display	Table 14-5.02 Incidence of Treatment Emergent Serious Adverse Events by Treatment Group
Analysis Result	Incidence of Treatment Emergent Serious Adverse Events by Treatment Group
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Analysis Variable(s)	AEBODSYS (Body System or Organ Class) AEDECOD (Dictionary-Derived Term)
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Programming Statements	[SAS version 9.2] at14-5-02.sas

5 Submit a table detailing all of the tables and figures featured in the clinical efficacy and safety sections of the application. The table should contain the following:

- Title of the table or figure in the application
- A hyperlink to the location of the table or figure with page number
- A hyperlink to the SAS code used to create the table or figure (including information regarding the datasets that were used)



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And some differences are expected

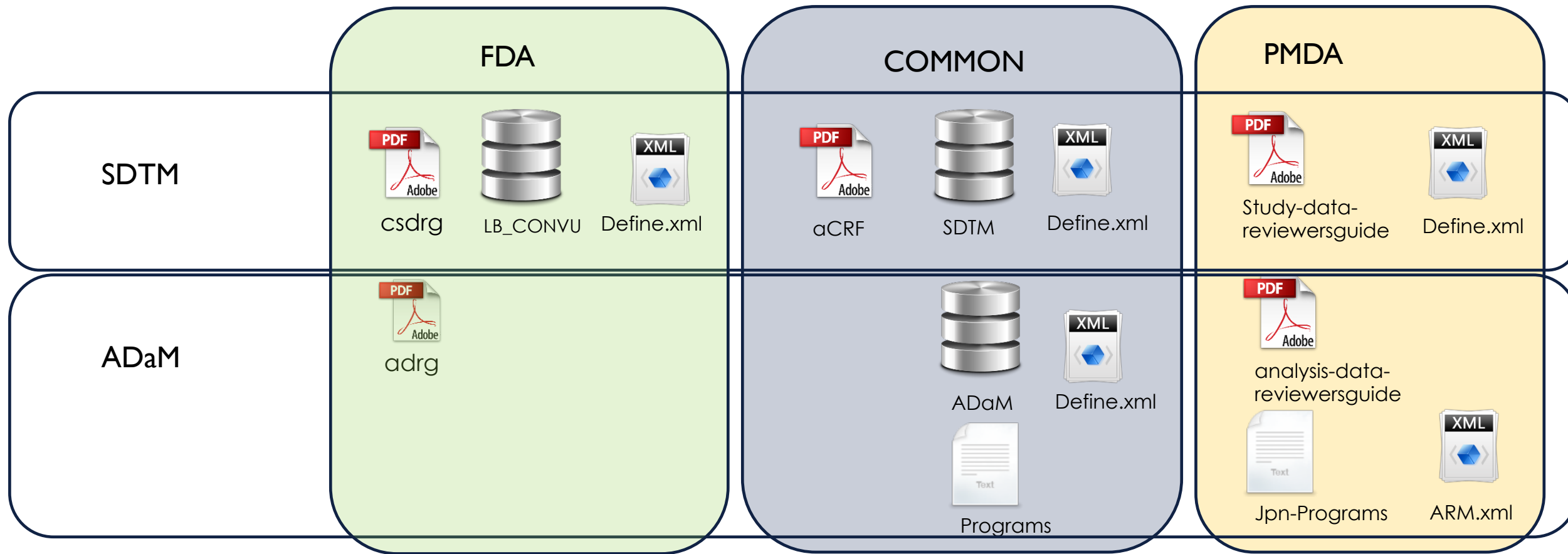


Impact on Submissions

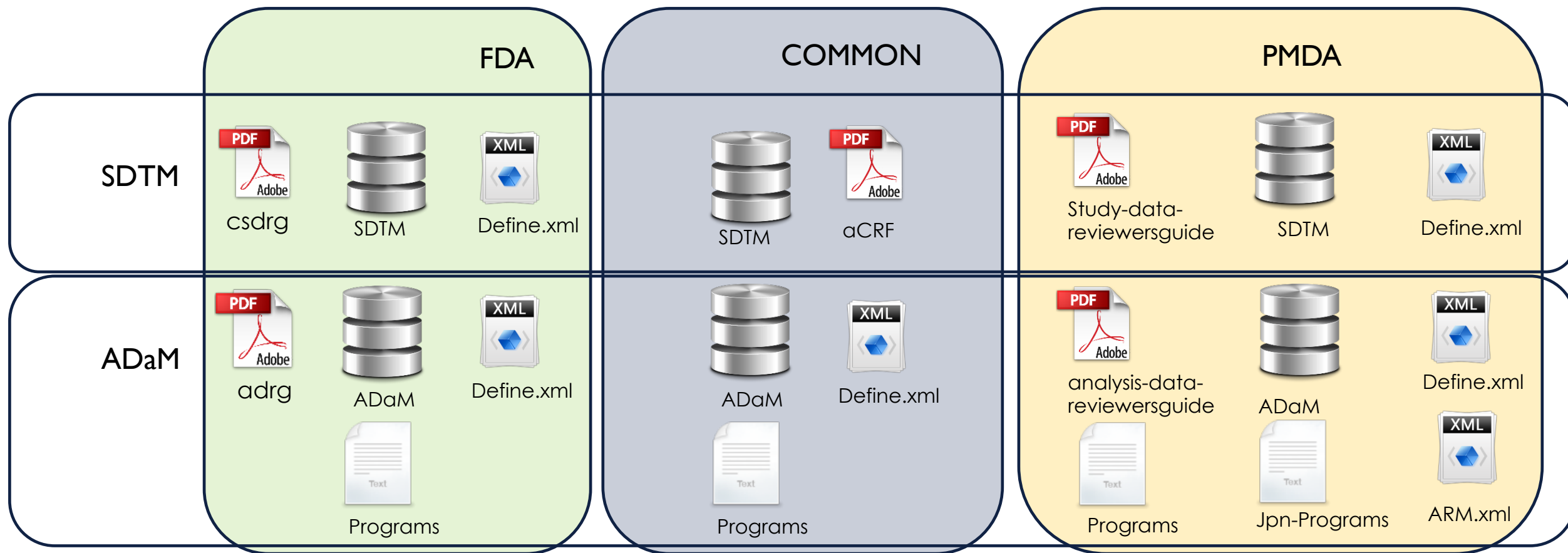


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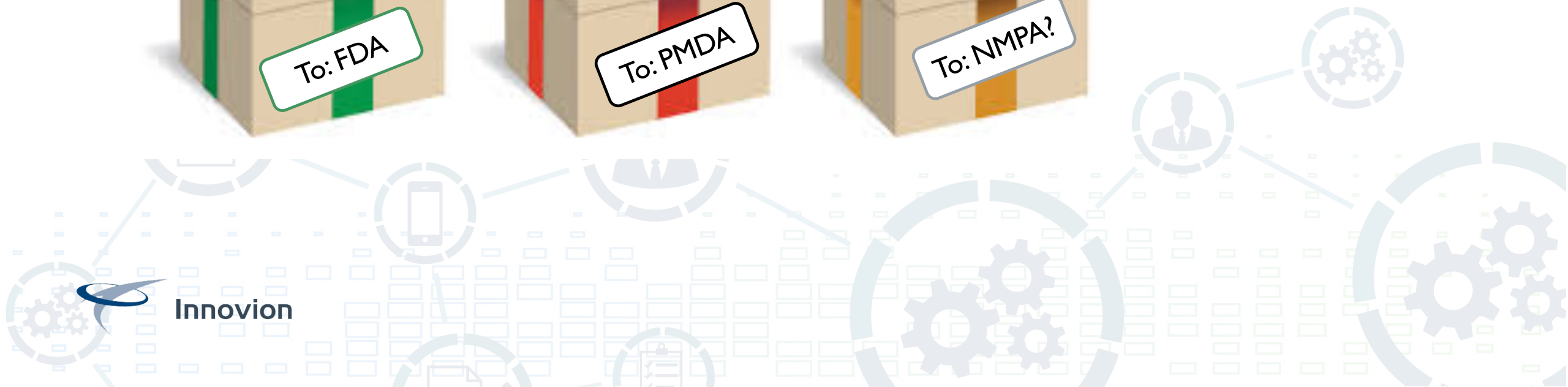
What did we do?



Being Fully Compliant Means:



CDISC gave structure, we should focus on content





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Thank you for your attention