CJUG ADaM Team

Efficient preparation of eData submission to both PMDA and FDA

CDISC Japan User Group (CJUG) ADaM Team

PharmaSUG Single Day Event, Japan

October 24, 2019

Disclaimer

- The opinions expressed in this presentation and on the following slides are solely those of the presenter and not necessarily those of our organizations and companies.

- Our organization and company does not guarantee the accuracy or reliability of the information provided herein.

CJUG ADaM Team

Abstract

- Electronic study data submission (eData submission) to Pharmaceuticals and Medical Devices Agency began in 1st October 2016 with a 3.5-year transitional period, and will be mandatory starting in 1st April 2020. On the other hand, eData submission to Food and Drug Administration became effective as of 17th December 2016 for all studies that start after this date for New Drug Application. **Although both Heath authorities (HAs) require to submit eData, there are some differences in their requirements.** Under the circumstance, industries would like to file NDA to both HAs as simultaneous as possible to maximize value of its product. Thus, it is important for us to know and manage these differences.
- Therefore, CDISC Japan User Group ADaM team has been creating a document **to summarize differences in the requirements between both HAs and suggestion on streamlined process to achieve simultaneous submission**. In this presentation, major important differences in the requirements and the timeline, tips of streamlined process and the internal team organization to prepare eData submission will be provided.

Outline

- CDISC Japan User Group (CJUG) ADaM Team Theme 5&6
- Background
- Efficient preparation of eData submission which meets requirements for both FDA and PMDA
- Summary

Outline

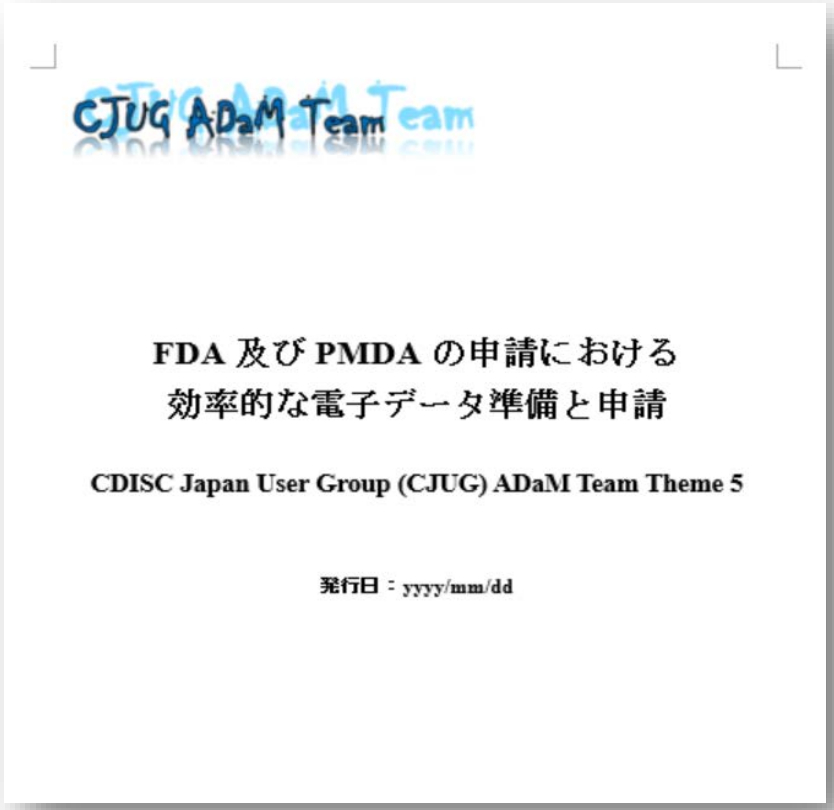
- **CDISC Japan User Group (CJUG) ADaM Team Theme 5&6**
- **Background**
- **Efficient preparation of eData submission which meets requirements for both FDA and PMDA**
- **Summary**

CJUG ADaM team theme 5&6 Members

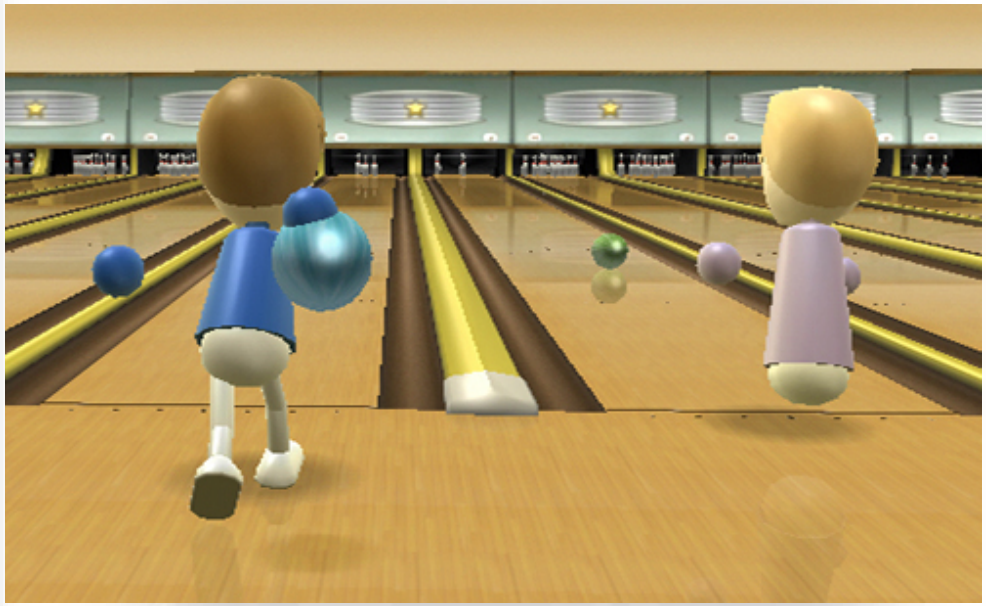
Akira Kurisu	MSD K.K.	Yasuhiro Hashimoto	Sanofi K.K.
Ataru Nogawa	intellim Corporation	Yasuhiro Iijima	Novartis Pharma K.K.
Ayako Noda	Janssen Pharmaceutical K.K.	Luo Zhengyan	Celgene K.K.
Fumiya Shimamura	Kissei Pharmaceutical Co., Ltd.	Hiroki Akashi	PPD-SNBL K.K.
Ikuko Yasuda	Abbvie GK	Chikako Miyaura	AstraZeneca K.K.
Kumiko Kimura	Amgen Astellas BioPharma K.K.	Eri Sakai	Novartis Pharma K.K.
Misaki Kato	TIS Inc.	Madoka Torimoto	Senju Pharmaceutical co.,Ltd.
Shizuka Kamiya	IQVIA Services Japan K.K.	Yoshifumi Arita	Bayer Yakuhin, Ltd.
Shunsuke Emori	ASAHI KASEI PHARMA CORPORATION	Yuji Ohta	Maruho Co., Ltd.
Takashi Kitahara	Novartis Pharma K.K.	Hiroyuki Iwabuchi	CMIC CO., Ltd.
Tomotaro Shiraishi	A2 Healthcare Corporation	Yoshiyuki Kuriya	TAIHO PHARMACEUTICAL CO., LTD.

CJUG ADaM team theme 5&6 Activities

Deliverable in Japanese



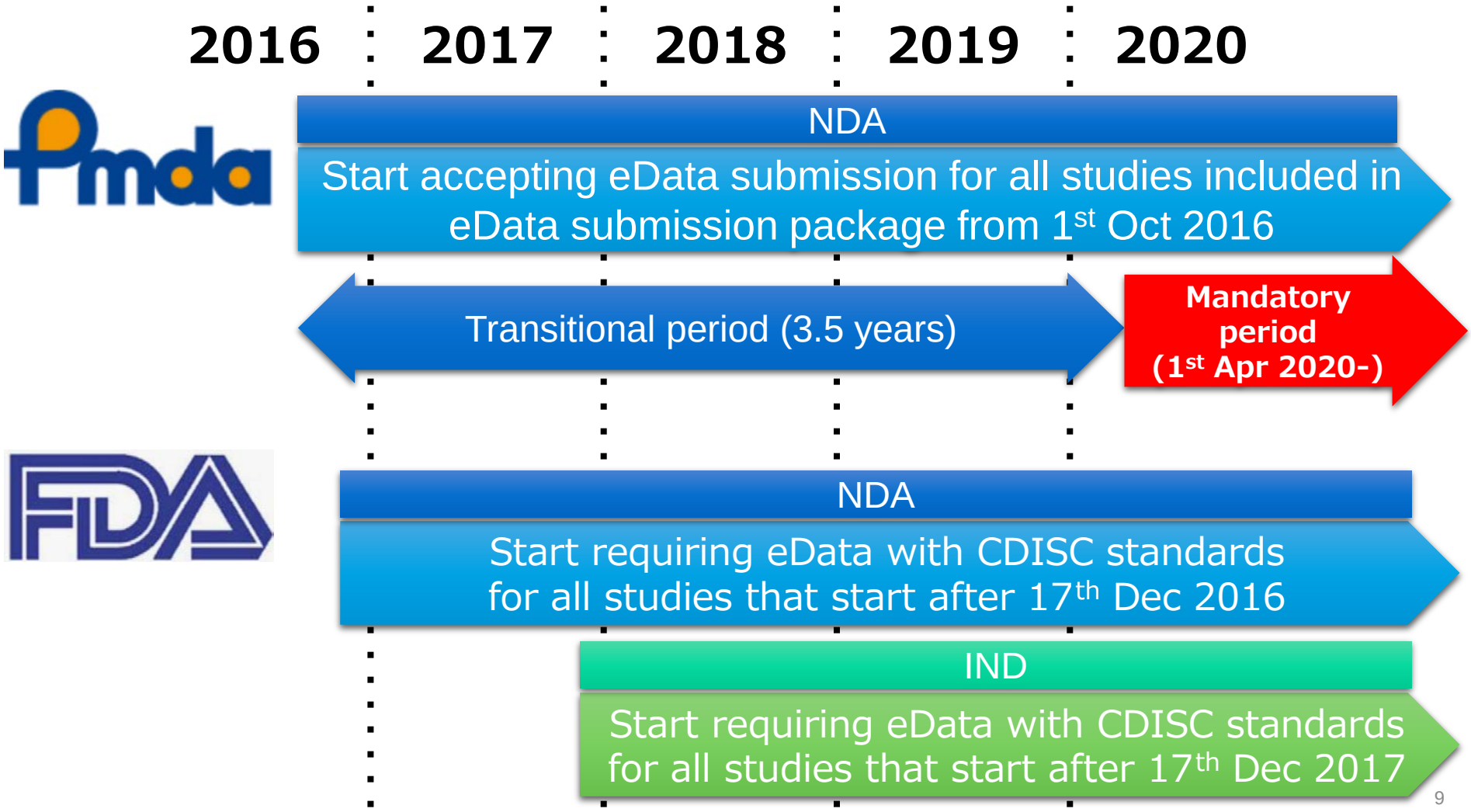
Team building



Outline

- CDISC Japan User Group (CJUG) ADaM Team Theme 5&6
- **Background**
- Efficient preparation of eData submission which meets requirements for both FDA and PMDA
- Summary

Key date for eData submission to both PMDA and FDA



Aim to streamlined process

Validation rule

Timeline

Data package

Deliverables

Pmda + FDA =

Consultation

Waiver/ Exemption

SDSP/ Attachment 8

Internal communication

One common deliverables which meet the requirements for both FDA/PMDA should be created for simultaneous submission

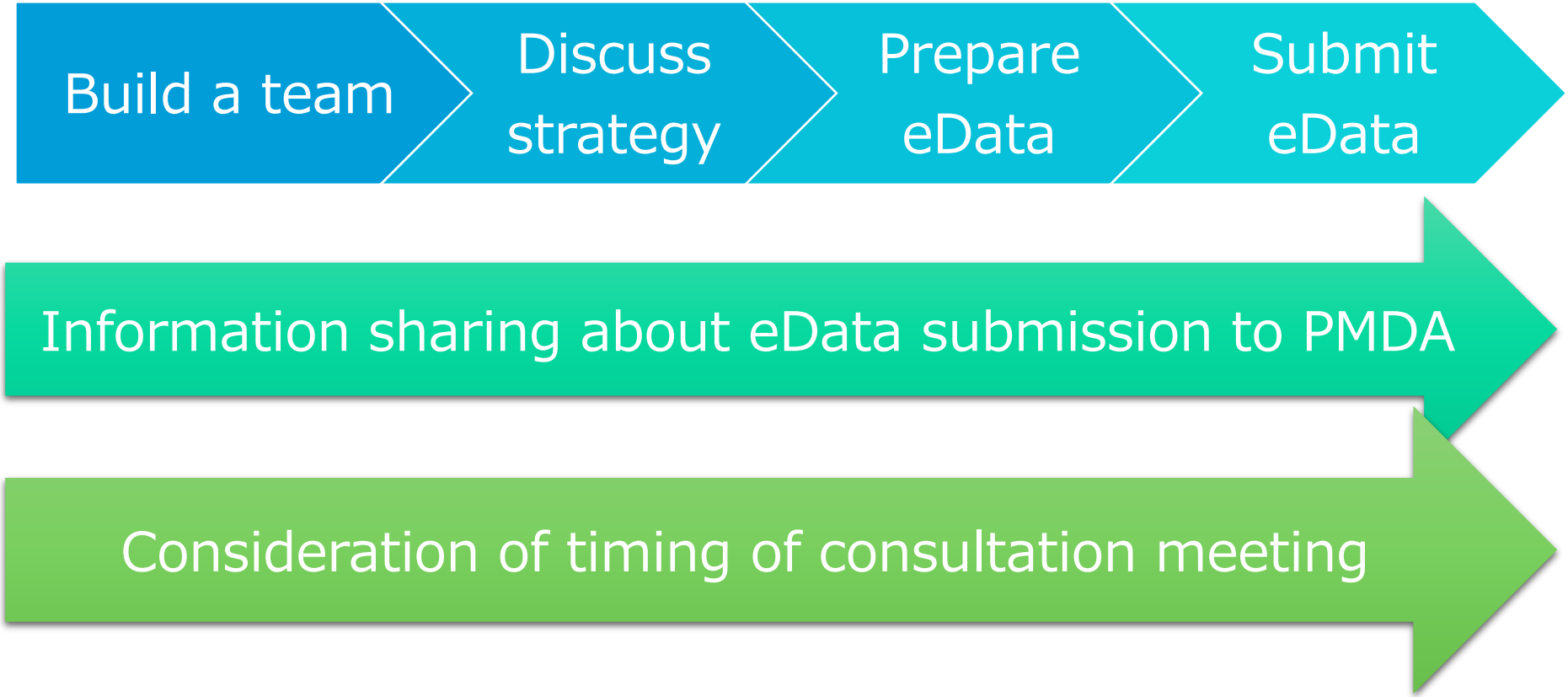
Outline

- CDISC Japan User Group (CJUG) ADaM Team Theme 5&6
- Background
- **Efficient preparation of eData submission which meets requirements for both FDA and PMDA**
- Summary

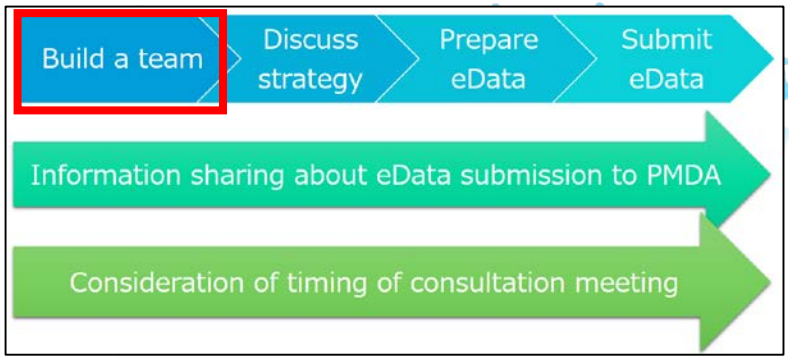
Summary of differences/common points between FDA and PMDA in the requirement

Item	FDA	PMDA	Note
*** **ADaM** ***			
ADaM IG	V1.1	V1.0	FDA accepts v1.0 for IND until 03/15/2020
Dataset	XPT	XPT	
Analysis data reviewer's guide	Filename: adrg.pdf	Filename: adrg.pdf / analysis-data-reviewers-guide.pdf	PMDA: file should be named so that the contents are identifiable
Define.XML	V2.0	V1.0/V2.0	Have to submit stylesheet FDA: Define.pdf should be submitted if Define.XML cannot be printed
…….			

Flow on this presentation



Build a team
Example



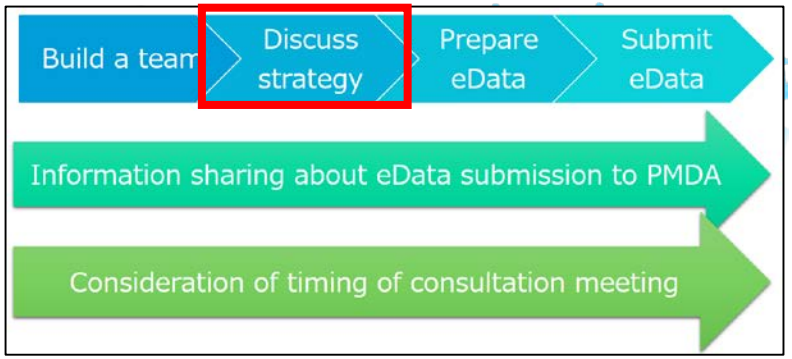
Submission team in Japan

Working contents	Main person
Identification of target study/analysis	RA, DM, CP, Stat, Prog
SDTM	DM, (Stat, Prog)
ADaM	Stat, Prog
Clinical Pharmacology	CP
Operations to submit eData	RA-ops
Overall timeline	RA
Communication with PMDA	RA
…	…

Global counterpart

Clarification of Role & Responsibility!
Information sharing, especially PMDA requirements

Confirmation with team
important point



- NDA timeline
- eData submission package
- Policy of creating deliverables
- Resource management
- Current situation per study (next slide)
- Budget
- Overall timeline of eData submission preparation

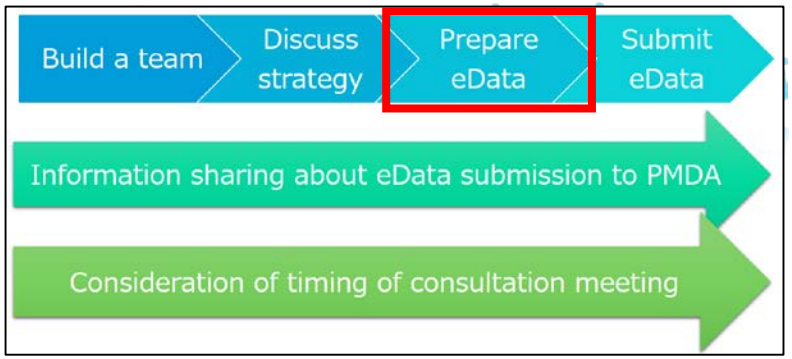
Confirmation of current situation of eData per study

important point

- **Still ongoing ?**
- **Possibility of Waiver/Exemption**
  - Are there enough electronic datasets
  - When did the study start ?
  - Is the product “Orphan drug” ?

- **Necessity of Legacy data conversion**
- **Has eData for the study already been submitted to either HAs?**
- **Are there any issues in datasets?**

Preparation of eData
Validation rule



FDA	PMDA
Conformance rule (CDISC standards) (Pinnacle 21) ***Reject*/Error/ Warning*** * Based on Rejection criteria for study data	Conformance rule (Pinnacle 21) based on PMDA validation rule ***Reject/Error/Warning***

Preparation of eData
Validation rule

CJUG ADaM Team

FDA	PMDA
Conformance rule (CDISC standards) (Pinnacle 21) ***Reject*/Error/ Warning*** * Based on Rejection criteria for study data	Conformance rule (Pinnacle 21) based on PMDA validation rule ***Reject/Error/Warning***

Rule ID	Publisher ID	Message	Description	FDA Severity	PMDA Severity	1.0	1.1	Notes
AD0001	1	Missing ADSL dataset	ADaM Subject level (ADSL) dataset should be included in every submission.	Reject	Reject	X	X	
AD0005	5	*FL value is not Y, N or null	A variable with a suffix of FL must have value that is Y, N or null (exception 1: RFL, PFL , ABLFL, ANLzzFL. Exception 2: Population flags COMPLFL,FASFL,ITTFL,PPROTFL,SAFFL,RANDFL,ENRLFL cannot be null and at least 1 must be included in ADSL).	Error	Reject	X	X	
AD0006	6	*FN value is not 0, 1 or null	A variable with a suffix of FN has a value that is not 0, 1 or null (exception: RFN, PFN, ABLFN, ANLzzFN and population flags Numeric COMPLFN,FASFN,ITTFN,PPROTFN,SAFFN,RANDFN,ENRLFN cannot be null and at least 1 must be included in ADSL).	Error	Reject	X	X	
AD0033	33	*RFL value is not Y or null	A variable with a suffix of RFL must have a value that is Y or null (R = record level flag variable)	Error	Reject	X	X	

Preparation of eData
Validation rule (Cont'd)

FDA	PMDA
Conformance rule (CDISC standards) (Pinnacle 21)	Conformance rule (Pinnacle 21) based on PMDA validation rule

Rejection criteria for study data

1. **A dataset named ts.xpt with information on SSD must be present** for each study.
2. The correct STF file-tags must be used for all XPT file.
3. **For SEND/SDTM data, a DM dataset and define.xml must be submitted Module 5. For ADaM data, an ADSL dataset and define.xml must be submitted.**
4. In a new submission include an STF and use the "Replace" operator to replace previously submitted documents which were not referenced in an STF

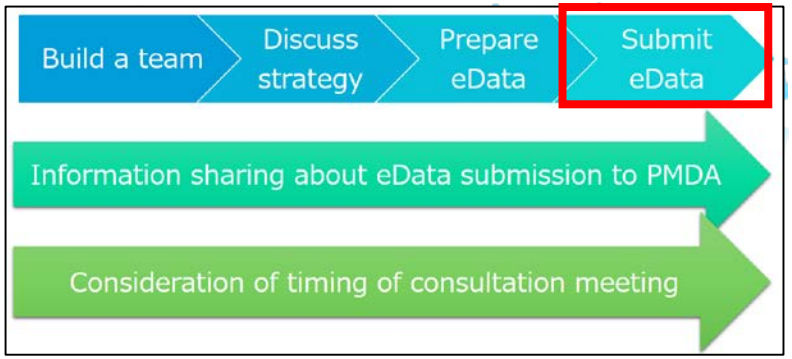
Preparation of eData
Legacy data conversion (LDC)

	FDA	PMDA
Target study	NDA: non-CDISC standard **study starting after** Dec17 2016	A: non-CDISC standard study included in eData submission package for product applied for **after** 1st Apr 2020
Non-target study	NDA: non-CDISC standard **study starting before** Dec17 2016	**Exemption** such as orphan drug plication, anti-HIV drug
Key point	Create **Legacy data conversion plan & Report (LDCP) in RG as Appendix** (PhUSE has recently released ADRG version 1.2 including LDCP)	Consult with PMDA and describe Reviewer's guide if there are any issues

Create internal template for Reviewer's guide including LDCP

Submission of eData

Timeline of around NDA (Example: very tight timeline)



FDA

Preparation completion of eData

Test loading

Pre-submission encounter meeting

eData submission

NDA

Pmda

Preparation of Attachment 8

Consultation on data format

Pre-NDA meeting

eData submission

NDA

NDA -9Wks

NDA -6Wks

NDA -5Wks

NDA -1Wk

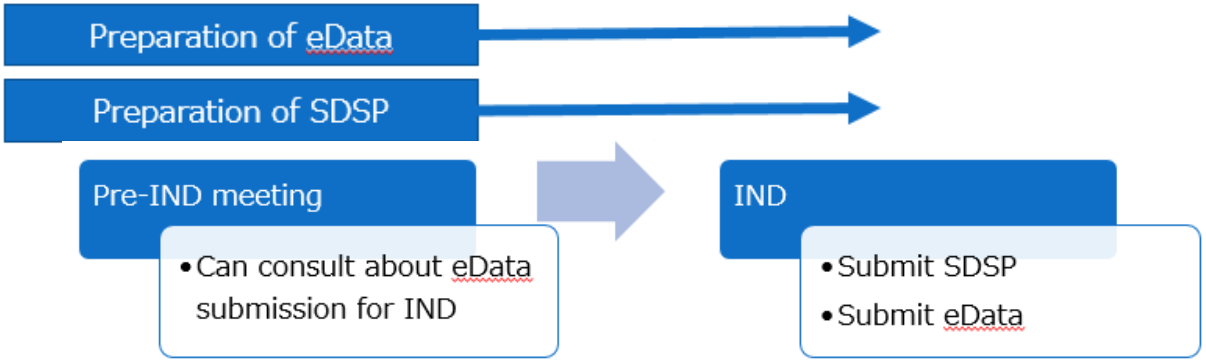
- **FDA: timeline varies from project to project in real life**
- **PMDA: there are some key consultations and dates based on the guidance**

Submission of eData

eData submission except for NDA

- Post-marketing clinical trials
- Products for which the evaluation of study results is practically carried out before NDA
  - Sakigake designation system
  - Anti-HIV drug

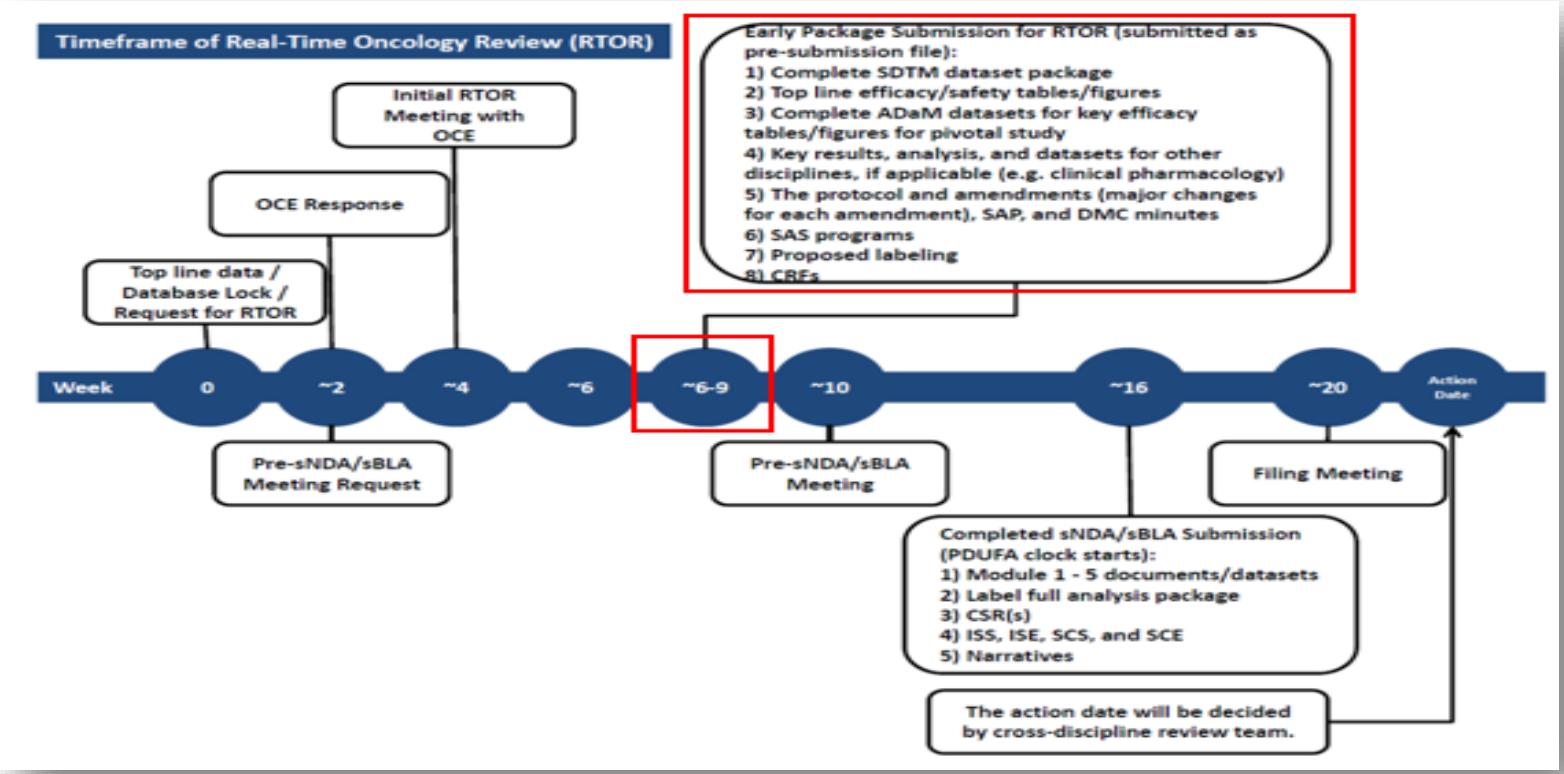
- Commercial IND
  - Submit eData for a study which starts after 17Dec2017



Submission of eData

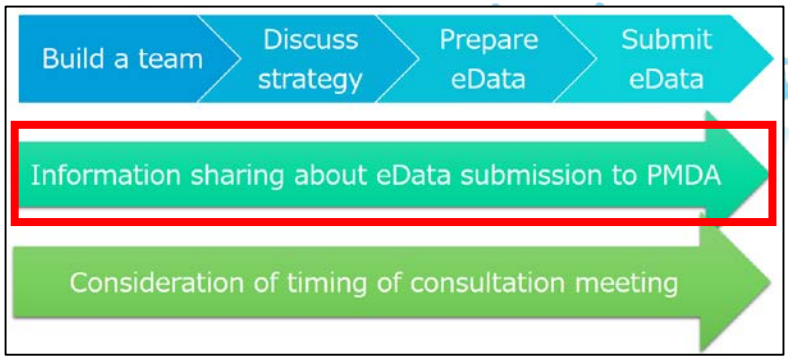
eData submission except for NDA (cont'd)

- Real-Time Oncology Review
  - ➢ Pilot-project



https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program

Information sharing about eData submission to PMDA



Japan team/Organization level

Global team

Japan team/Project level

Information sharing about eData submission to PMDA

CJUG ADaM Team

Japan team/Organization level

Provide Training/Build Task force team
Important information
- Overall of requirements for eData submission to PMDA
- Differences between FDA and PMDA
- Role & Responsibility
- Standard timeline
- Several consultation with PMDA

Global team

Share information at project level ?
- Can share more project specific contents
- Might be different from the contents between projects

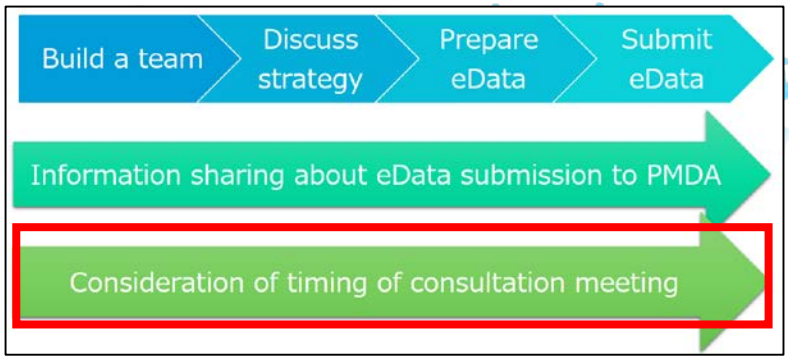
Share information at governance level ?
- Can share without variability

Japan team/Project level

- eData submission package
- Overall milestone*/timeline

* Milestone: Consultation with PMDA/start date of preparation/date of submission of eData

Consideration of timing of consultation meeting



	P2 study		P3 study		NDA
FDA		EOP II meeting		Type C meeting	pNDA (Type B) meeting
	← SDSP/ Briefing Book →				
PMDA		Clinical consultation (EOP II meeting)	Consultation on exemption	Consultation on data format/ preparation	Pre NDA meeting
	← Attachment 8/ Attachment 8-2/ Briefing Book →				

- **Timeline of FDA meeting is unclear…**
- **Timeline should be shared common file which can be confirmed timely and mutually**

Study Data Standardization Plan (SDSP) vs Attachment 8

SDSP

Attachment 8

The content of SDSP is not same as that of Attachment 8

Pick up the common term

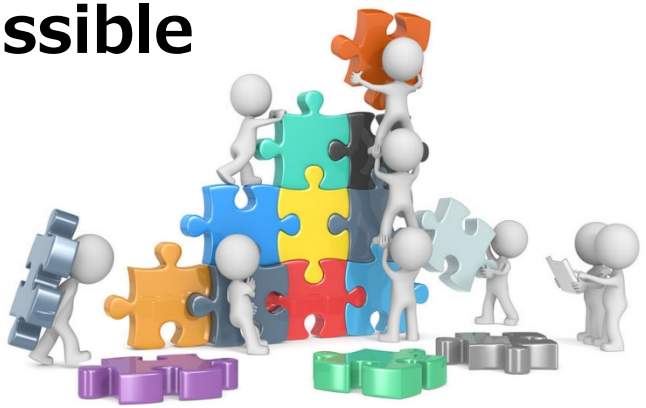
Creation of internal summary sheet including the following information to manage whole eData submission package in the product
[Study information/ CDISC standards Version/ Dictionary version/ Data standard (CDISC or legacy)/ Waiver/ Exemption/ Person in change/ Contents of consultation]

Outline

- CDISC Japan User Group (CJUG) ADaM Team Theme 5&6
- Background
- Efficient preparation of eData submission which meets requirements for both FDA and PMDA
- **Summary**

Summary

- Clarify the differences in regulatory Requirements between FDA and PMDA
- Communicate with related function and global closely
- Aim to create one common deliverables which meets the requirements for both FDA and PMDA as much as possible



CJUG ADaM Team