



Regulatory Stream

Japanese Electronic Study Data Submission in CDISC Formats

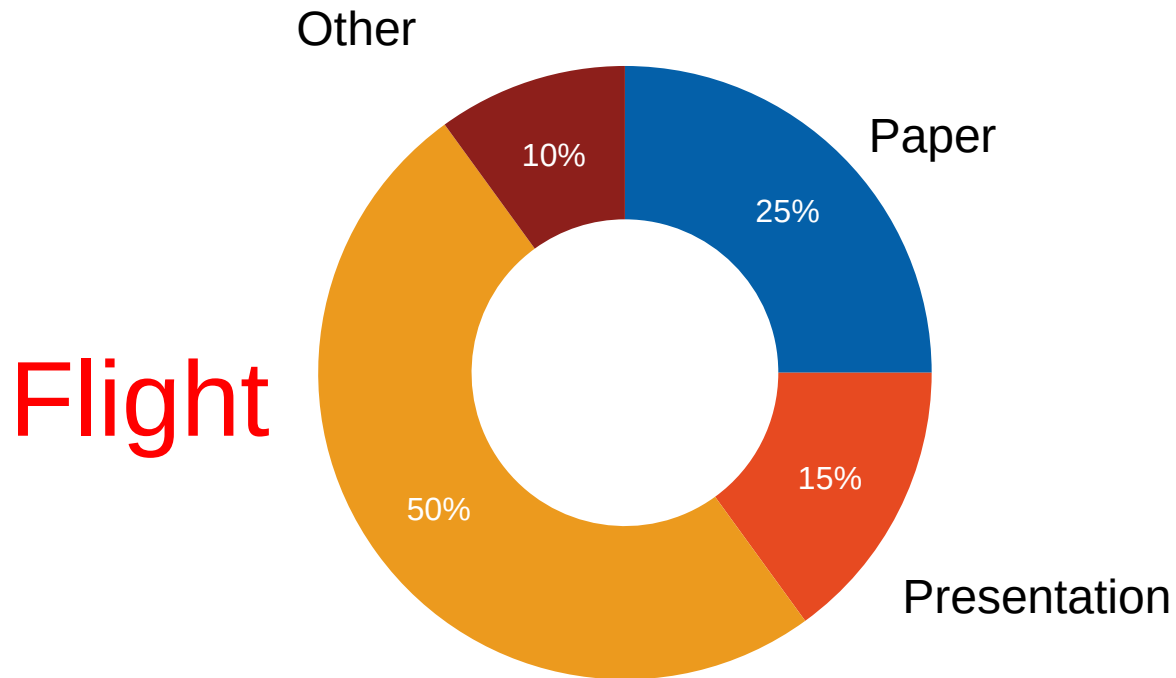
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PhUSE annual conference, Barcelona
October 11, 2016

Disclaimer

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Ice Breaker

About 160 hours used for PhUSE preparation.



Hope “80 hours flights” will help your understanding...

Agenda

1. Introduction
2. Overview
3. Key differences between PMDA and FDA
4. Suggestions for successful Japanese e-study data submission
5. Conclusion



Introduction

- Goals of this presentation are
 - To comprehend new requirements of PMDA e-study data submission.
 - To provide tips based on actual experiences and recent updates from PMDA.

Key words:

e-study data submission, PMDA, FDA, Data validation, Consultation, ARM, Legacy data conversion, One global process



Overview

Key date for electronic study data (e-study data) submission for PMDA

2016

2017

2018

2019

2020

Oct-2016~

Start accepting
e-study data

Transitional period (3.5 years)

Partial e-study data submission
can be accepted

Apr-2020~

To be mandatory

- E-study data submission is required,
 - PMDA: **Applications** after Oct 01, 2016
 - FDA: **Studies that start** after Dec17, 2016
- PMDA Transitional period (3.5 years)
 - Partial e-study data submission can be accepted.
 - NOTE: In case of partial e-study data submission, the application will be reviewed using the **conventional review process**.

Overview

Scope of e-study data submission

Mandatory	• Evaluation data that provide the major basis for the efficacy, safety, dose and administration (i.e. results of Phase 2 and 3 studies in most cases, including long-term studies) • Specific Phase 1 studies • oncology drugs • that have been conducted on both Japanese and non-Japanese subjects for ethnic sensitivity assessment • QT/QTc studies based on ICH E14 guideline
Case by Case, if requested by PMDA	• Other Phase 1 studies • Clinical pharmacology (CP) studies and analyses • Integrated analysis (ISS/ISE)

Overview

Guidance provided by MHLW/PMDA

Guidance	Published by	Language	
		Japanese	English
Basic Principles on Electronic Submission of Study Data for New Drug Applications, with Q&A document	MHLW	Yes	Yes
Notification on Practical Operations of Electronic Study Data Submissions, with Q&A document	MHLW	Yes	Yes
Technical Conformance Guide on Electronic Study Data Submissions”	PMDA	Yes	Yes
Data Standard Catalog	PMDA	Yes	Yes
Validation rule	PMDA	Yes	Yes
FAQ web site	PMDA	Yes	No
Guidance for consultation on data format	PMDA	Yes	No

MHLW: Ministry of Health, Labor and Welfare

Overview

Required Case report tabulation (CRT)

CRT	PMDA*	FDA
Datasets	SDTM, ADaM	SDTM, ADaM
Data guide	SDRG, ADRG	SDRG, ADRG
Definition file	Define-XML for SDTM Define-XML for ADaM including ARM**	Define-XML for SDTM Define-XML for ADaM
CRF	aCRF	aCRF
SAS programs	Creation of ADaM datasets and TFLs	Creation of ADaM datasets and TFLs

* Specific e-study data requirements for CP studies will be requested.

** differences between PMDA and FDA

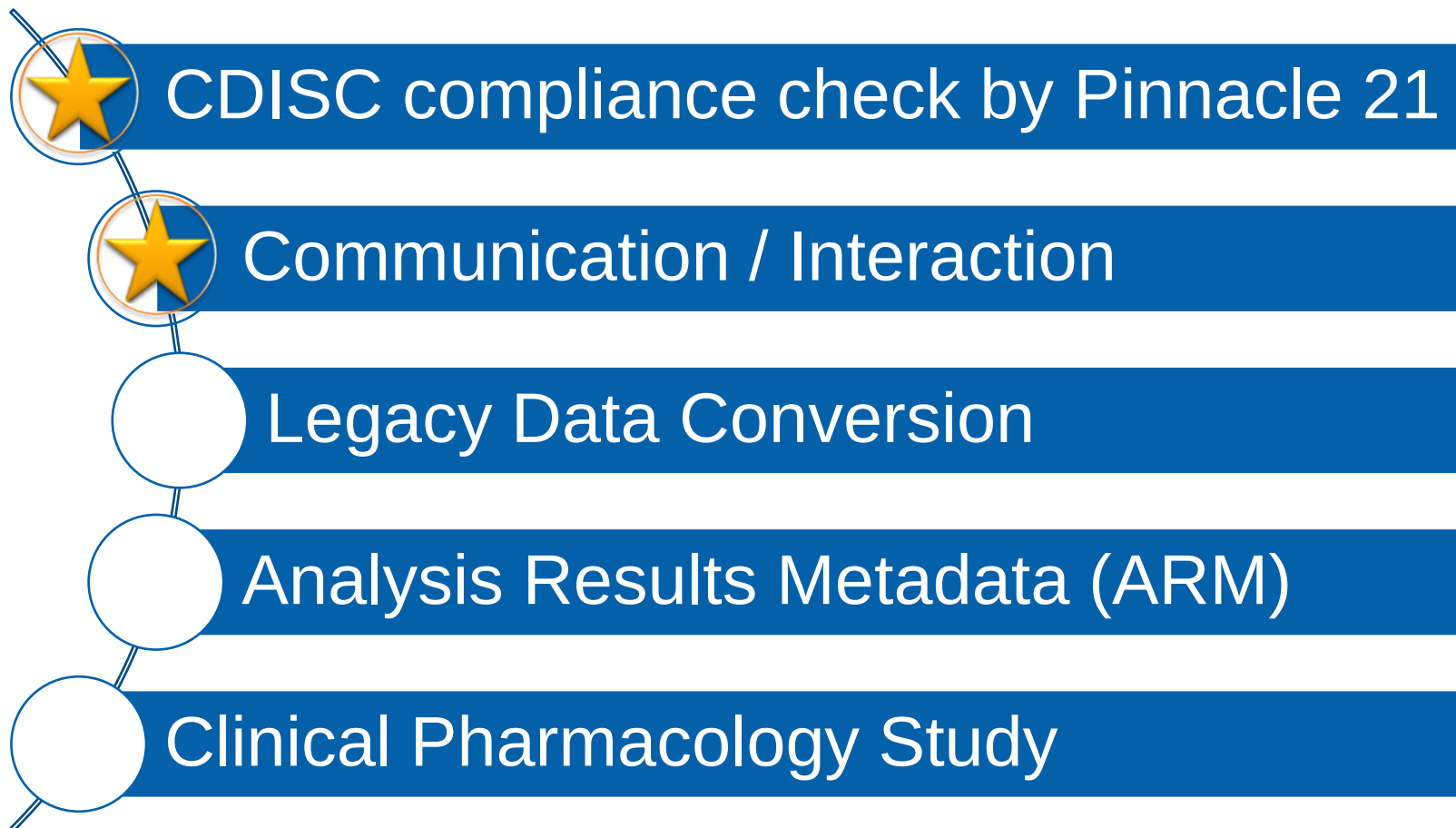
SDRG: Study Data Reviewer's Guide

ADRG: Analysis Data Reviewer's Guide

ARM: Analysis Results Metadata

TFL: Table, Figure and Listing

Key differences between PMDA and FDA



Key Differences

CDISC compliance check by Pinnacle 21

フォルダー/ファイル一覧	Study ID	試験データID	Operation	試験データ種別	Analysis Type	Description	Terminology (Tabulation)	Terminology (Analysis)	日本語文字コード
m5									
datasets									
study-01	study-01			CDISC形式のデータを	Non-CP		2014-12-19	2014-09-26	UTF-8
analysis									
adam								2014-09-26	
datasets					Non-CP			2014-09-26	UTF-8
adsl.xpt		809d0081-a979-40a	new		Non-CP			2014-09-26	UTF-8
define.xml		5e5801b4-4b35-4e0	new		Non-CP			2014-09-26	UTF-8
dm.xpt		f7e9e90f-89ad-4438	new		Non-CP			2014-09-26	UTF-8
tabulations									

- eCTD
- Other...

Notify to PMDA

- Planned application date
- Contents of deliverables
- Other...

Enter the information about e-study data



Gateway



PMDA receive the e-study data

- Pinnacle 21 enterprise version (v3.0.5)
- Specific validation criteria



CDISC compliance check by Pinnacle 21

PMDA	FDA
SDTM, ADaM and Define-XML	SDTM, SEND

Key considerations

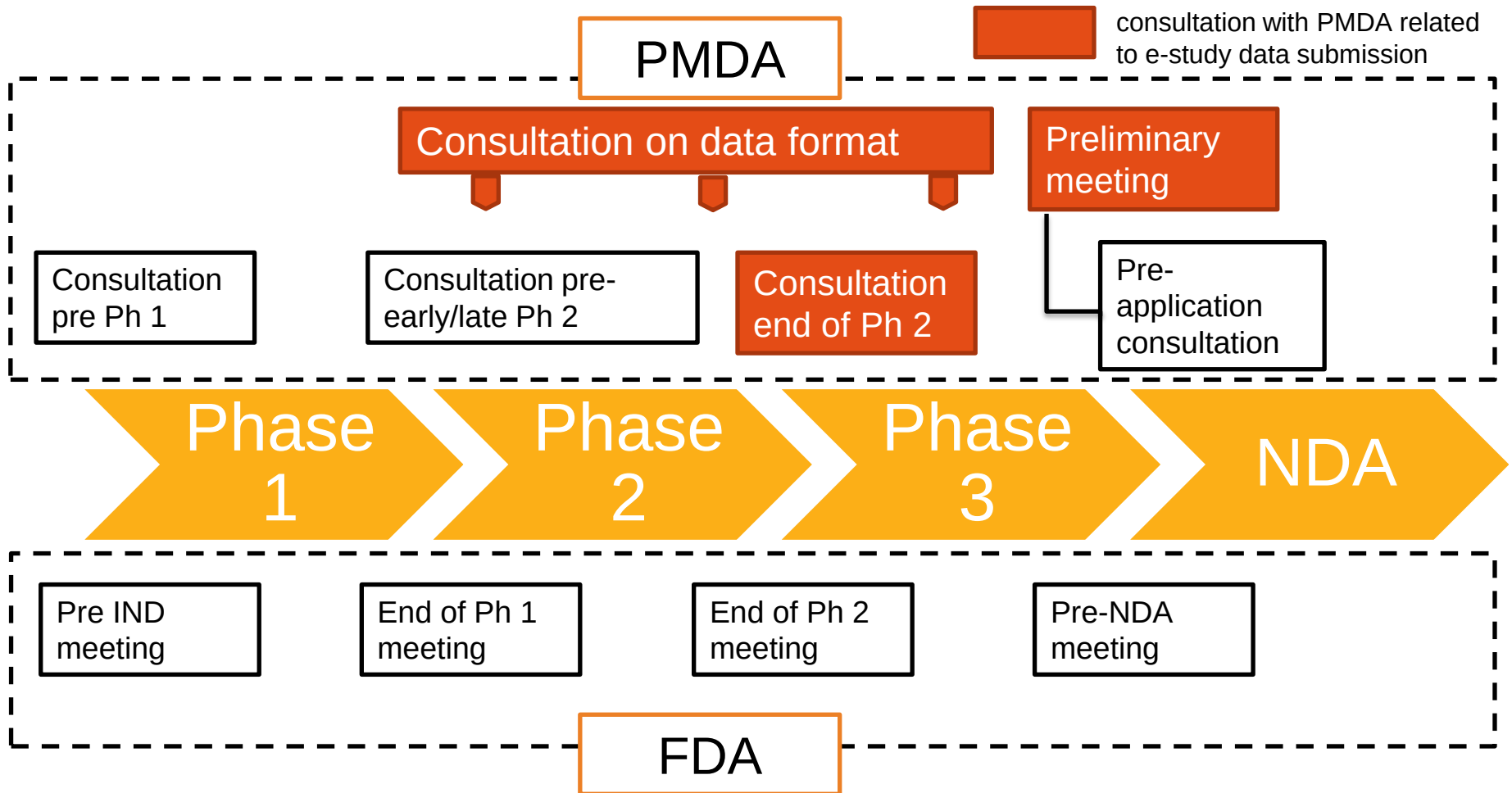
- ✓ Three PMDA specific validation criteria which are different from FDA.

Validation Criteria	Rule
Reject	<i>PMDA will not start reviewing an application if any of 'Reject' errors are detected.</i>
Error	<i>Have to explain and agree with PMDA at consultation on data format prior to e-study data submission.</i>
Warning	To be described in SDRG/ADRG as needed.

Tips

1. Executing PMDA validation at the same time as FDA validation.
2. Compatibility between validation results from Community v2.1.3 and Enterprise 3.0.5 (refer to Pinnacle 21 website).
3. No test loading environment.

Communication / Interaction



Communication / Interaction

PMDA

Consultation on data format of e-study data submission

FDA

Communicate by using Study data standardization plan (SDSP)

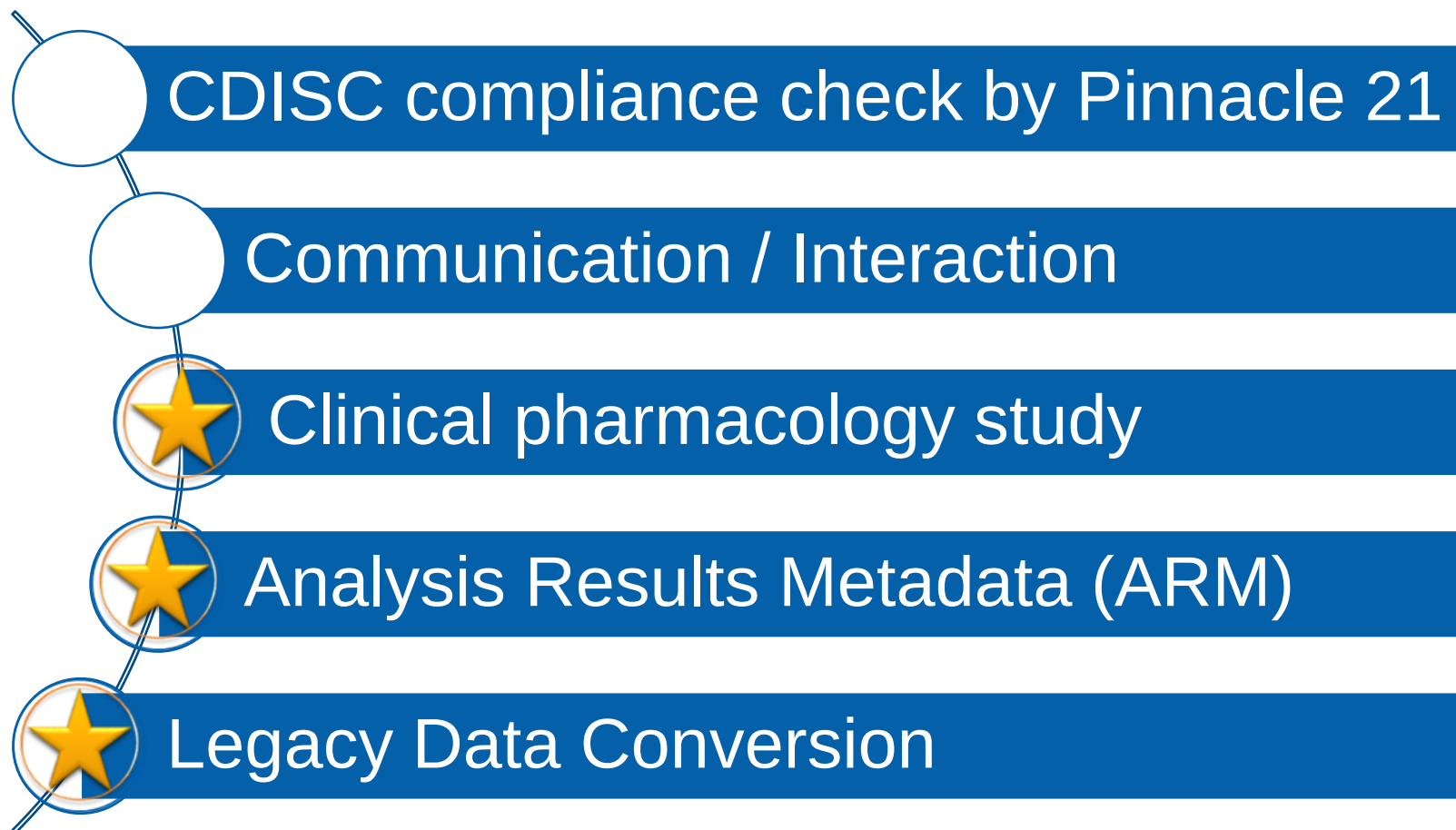
Key considerations

- ✓ Not for data assessment but for **confirmation of e-study data submission contents**.
- ✓ Explain all validation issues categorized in “Error” on e-study data.
- ✓ Form 8 is required to submit to PMDA prior to consultation to inform a summary of e-study data.
- ✓ Final version of Form 8 has to be submitted at NDA preliminary meeting.

Tips

1. Sorting out discussion points corresponding consultation.
2. Preparation of process guidance, roles and responsibility.
3. Consolidating feedback from each health authority.

Key differences between PMDA and FDA



Key Differences

Clinical Pharmacology(CP) Study and Analysis

PMDA	FDA
Specific data, documents are required.	Not specifically described in Study Data Technical Conformance Guide.

Key considerations

✓ CP studies and analysis for e-study data submission:

- 1) Standard PK analysis
- 2) Population PK (PPK) analysis,
- 3) Physiologically-based pharmacokinetic model (PBPK) analysis

CDISC compliant	Non CDISC compliant	For
ADaM	System dependent data	1), 2), 3)
Define-XML	Dataset definition document (PDF)	1), 2), 3)
Programs	Programming specification or/and procedure documents	1), 2)

Tips

- 1. Not all of CP studies will be required for e-study data submission.**
2. Communication with clinical pharmacologist.

Analysis Results Metadata (ARM)

PMDA

Define-XML for ADaM should preferably include ARM.

FDA

Not required (as of September, 2016).

Key considerations

- ✓ For targeted TFLs are
 - 1) Primary and key secondary analyses,
 - 2) Key safety analyses and
 - 3) Dose response analyses for dose finding study.
- ✓ **ARM in PDF format can be acceptable.**

Tips

1. Discussion on targeted analyses for ARM at clinical consultation (e.g. end of Phase 2)
2. ARM can be considered as a part of programming activities.

Legacy Data Conversion

PMDA	FDA
Closed / Completed study is possibly to be converted after 01Oct2016 (To be mandatory after 01Apr2020)	Non-CDISC compliant study which starts after 17Dec2016 must be followed in CDISC standards.

Key considerations

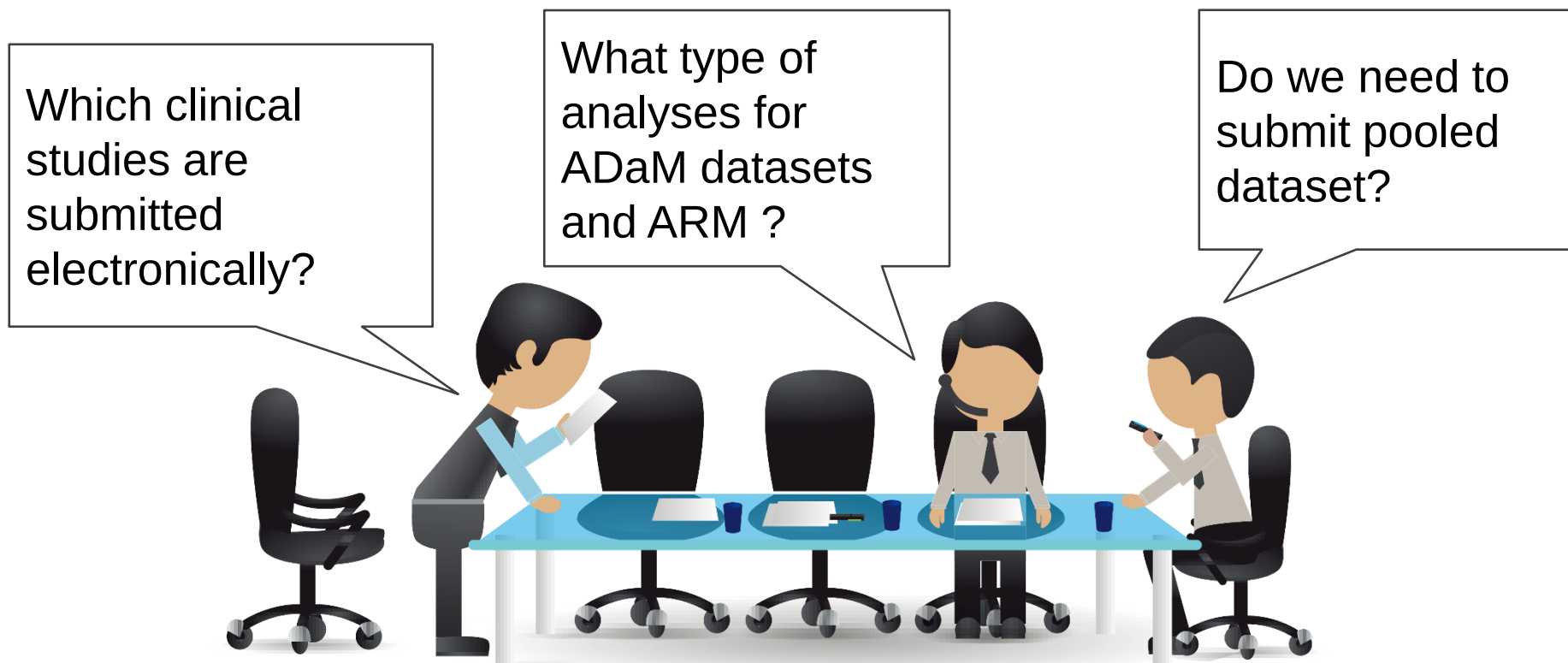
- ✓ For PMDA,
 - ✓ Same e-study data will be required as well as CDISC compliant studies.
 - ✓ Possibly SAS programs might be required to **“reproduce”** primary, secondary and key safety results in CSR.

Tips

1. Keep traceability from converted SDTM to ADaM and traceability issues need to be explained in SDRG/ADRG.
2. **Preliminary consultation with PMDA** for a reduction of workload.

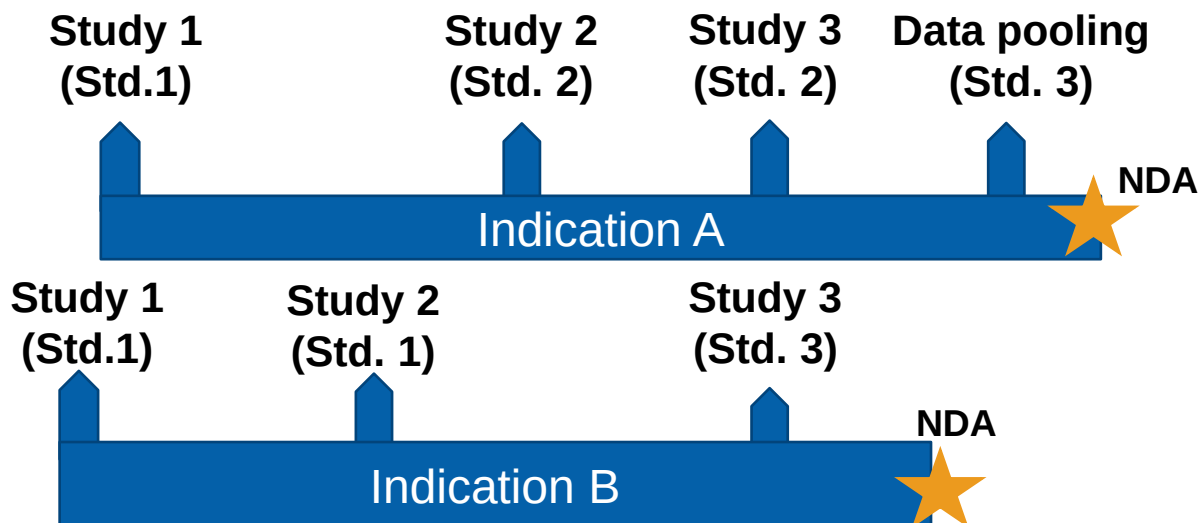
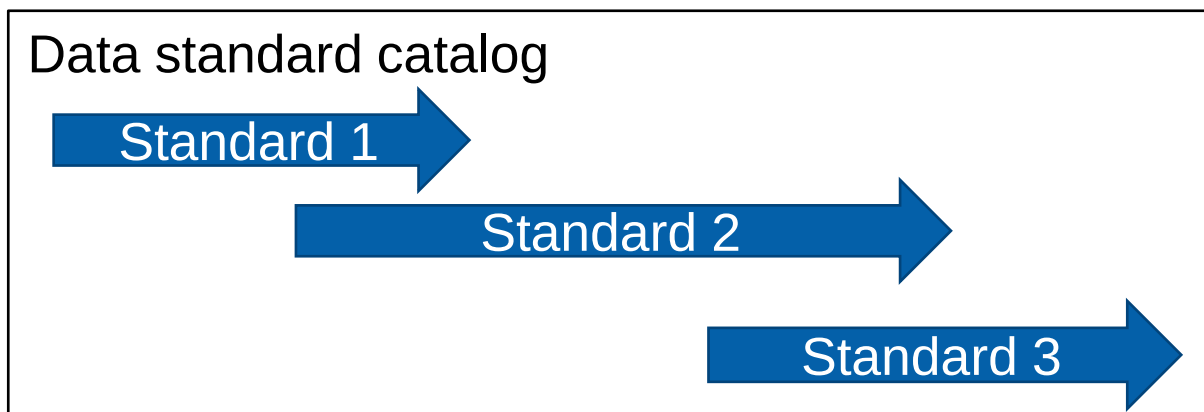
Suggestions for successful Japanese e-study data submission

- Decision of clinical data package is a key.
 - In order to estimate resources for data preparation, it is recommended to decide at an end of Phase 2 consultation.



Suggestions for successful Japanese e-study data submission

- Consolidate data standards within a compound.



- One compound can have multiple studies with different indication and timing.
- Accurate information should be tracked as data standard catalog keeps updating.

Suggestions for successful Japanese e-study data submission

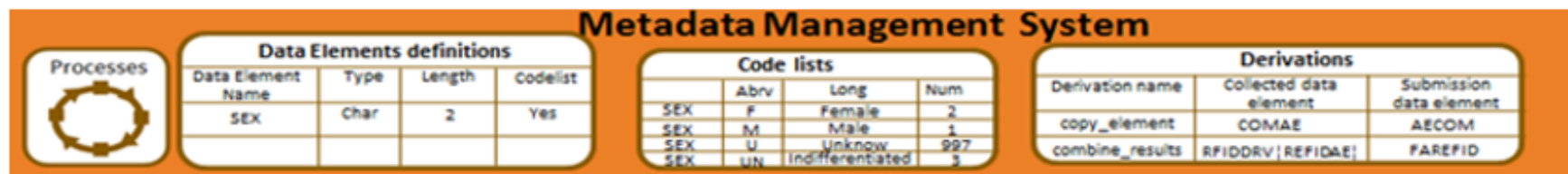
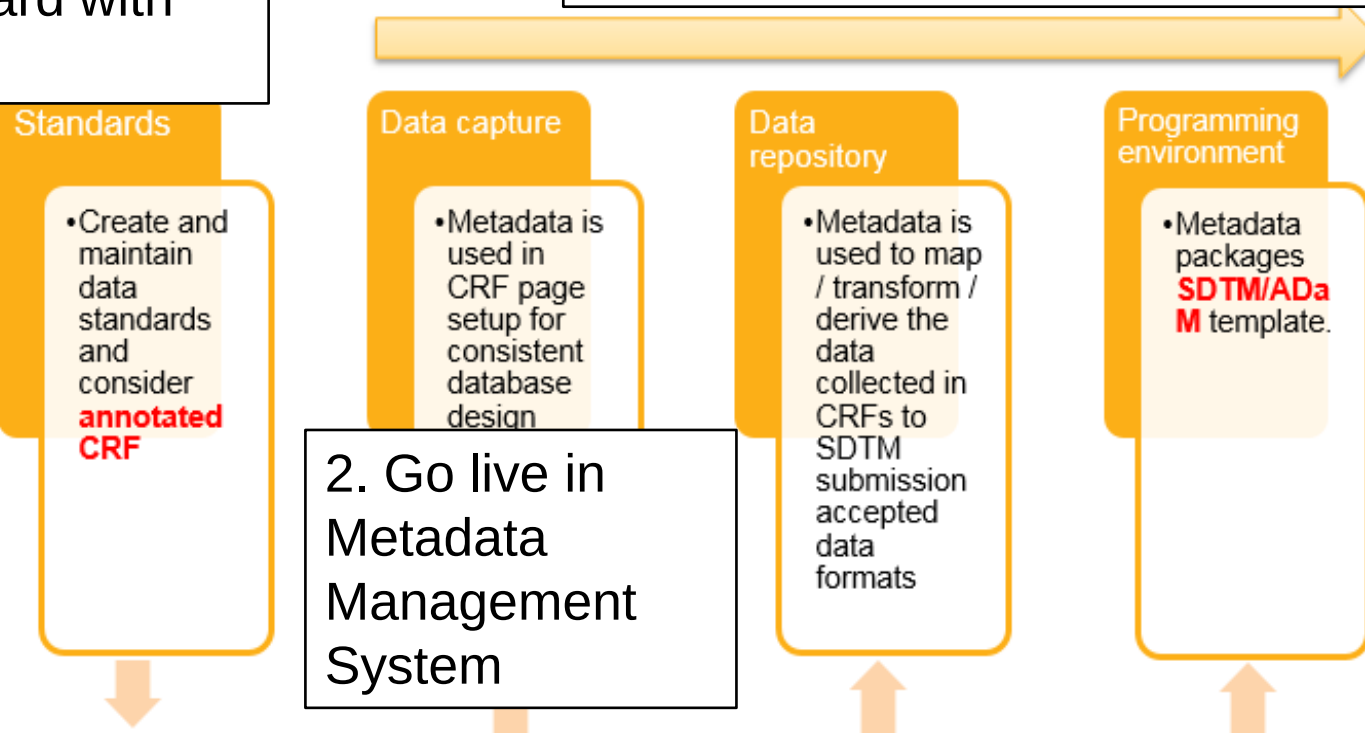
- Consolidate data standards within a compound.

Project	Study ID	Phase / Type of study	Study Status	Exchange Standards	Terminology Standards
Indication A	A101	Ph 1 / Food effect	COMPLETED	Legacy format	MedDRA v8 WHO-DD 2009Mar01
	A201	Ph 2 / Dose finding	ONGOING	SDTM v3.1.1 ADaM v1.0	MedDRA v14.1 WHO-DD 2010Jun01
	A301	Ph 3 / Confirmatory	ONGOING	SDTM v3.1.3 ADaM v1.0 Define v1.0	...
	A302	Ph 3 / long safety	PLANNED	SDTM v3.2 ADaM v1.1 Define v2.0	...
Indication B	B101	...	...	...	...
	B201	...	...	...	...
Indication C	...	...	...	...	...

Suggestions for successful Japanese e-study data submission

- Creating one CRT for PM
1. Set up data standard with aCRF

3. Provide metadata into each data phase (Data capture / Data repository / Programming) and submission (define-XML)



Suggestions for successful Japanese e-study data submission

Novartis CRT creation process

- aCRF
 - Semi-automated process for combining each standard aCRF page.
- SDTM / ADaM
 - Metadata provides template programs for general domain.
- SDRG / ADRG
 - A template document, authoring guideline, example and training package to keep high quality and consistency.
 - Validation results for both PMDA and FDA in same section.
- Define-XML
 - Currently outsourcing to vendors. New internal process under investigation.
 - ARM template and training package are available.

Suggestions for successful Japanese e-study data submission

- Collaboration between Japanese and global teams

1. Understand Japan specific requirements

- What are required for PMDA.
- One set of CRT can be prepared for both PMDA and FDA.

2. Discuss on roles and responsibility

3. Define consistent policy in advance

- To avoid big discussion for decision making and not to spend much time for discussion.



Conclusion

- To work effectively, global and Japan team need to work together, share knowledge of both FDA and PMDA requirements each other.
- E-study data submission can be beneficial not only for us for reduction of HA inquiries, but also for patients in terms of future drug accessibility.



Acronyms

aCRF	annotated CRF
ADaM	Analysis Data Model
ADRG	Analysis Data Reviewer's Guide
CDASH	Clinical Data Acquisition Standards Harmonization
CDISC	Clinical Data Interchange Standards Consortium
CP	Clinical Pharmacology
CRF	Case Report Form
CSR	Clinical Summary Report
FDA	Food and Drug Administration
IND	Investigational New Drug
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
MHLW	Ministry of Health, Labor and Welfare

Acronyms

NDA	New Drug Application
PBPK	Physiologically Pharmacokinetic Model Analysis
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PD	Pharmacodynamics
PPK	Population Analysis
SAS	Statistical Analysis System
SDRG	Study Data Reviewer's Guide
SDSP	Study Data Standardization Plan
SDTM	Study Data Tabulation Model
SEND	Standard for Exchange of Nonclinical Data
STS	Standard Two Stage approach
TFL	Table, Figure and Listing
XML	Extensible Markup Language

References

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Acknowledgments

- Ryan Hara (Co-Author), Principal Statistical Programmer, BDM Statistical Programming, Novartis
- Patricia A. Majcher, Sr. Assoc. Director, Reporting Data Stds, IQS SR Resp & EM, Novartis
- My fellow professionals who inspire us everyday.



Thank you