



Lessons Learned for Successful e-Study Data Submission to PMDA toward the End of Transitional Period

CDISC Japan User Group (CJUG) ADaM Team

Presenter: **Takashi Kitahara** (Novartis Pharma K.K.)
Ayako Noda (Janssen Pharmaceutical K.K.)

Co-authors:

Yohei Takanami (Takeda Pharmaceutical Company, Ltd.), **Ayuko Yamamura** (Eli Lilly Japan K.K.), **Akira Kurisu** (MSD K.K.), **Yasuhiro Iijima** (Novartis Pharma K.K.), **Tomotaro Shiraishi** (A2 Healthcare Corporation), **Yoshifumi Arita** (Bayer Yakuhin, Ltd.), **Ataru Nogawa** (intellim Corporation)

PhUSE EU Connect 2018, Frankfurt Germany

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.

Outline

- **CDISC Japan User Group (CJUG)
ADaM Team Theme 1**
- **Background**
 - e-Study Data Submission to PMDA
- **Lessons Learned**
 - Identification of study data and analyses to be submitted
 - Consultation on data format of submission of electronic study data
 - Considerations on Global Development
- **Summary**



Outline

- **CDISC Japan User Group (CJUG)
ADaM Team Theme 1**



- **Background**

- e-Study Data Submission to PMDA

- **Lessons Learned**

- Identification of study data and analyses to be submitted
- Consultation on data format of submission of electronic study data
- Considerations on Global Development

- **Summary**

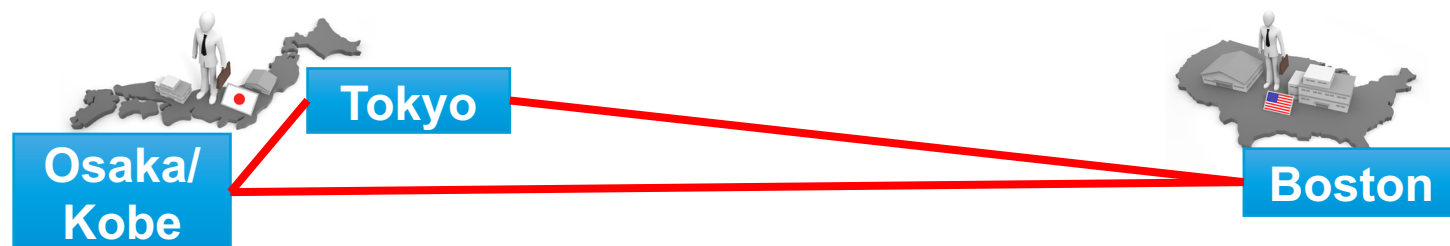
CJUG ADaM team theme 1

Members



Across regions and companies!

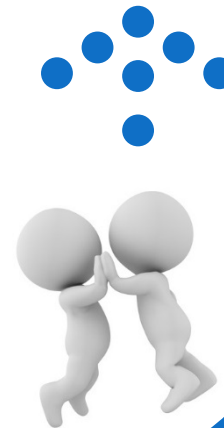
Name	Company
Ayako Noda	Janssen Pharmaceutical K.K.
Ayuko Yamamura	Eli Lilly Japan K.K.
Akira Kurisu	MSD K.K.
Ataru Nogawa	intellim Corporation
Takashi Kitahara	Novartis Pharma K.K.
Tomotaro Shiraishi	A2 Healthcare Corporation
Yasuhiro Iijima	Novartis Pharma K.K.
Yohei Takanami (Lead)	Takeda Pharmaceutical Company, Ltd.
Yoshifumi Arita	Bayer Yakuhin, Ltd.



CJUG ADaM team theme 1

Deliverable in 2018

has been discussing the best practice and creating a document to summarize useful tips of e-Study data submission to PMDA based on our practical experiences.



Successful e-Study data submission

PMDA 申請電子データ提出及び 申請後対応に関する課題

CDISC Japan User Group (CJUG) ADaM Team
Theme 1

目次

1. はじめに.....	2
2. 電子データ提出における Framework に関する議論.....	
2.1 データ作成部門 (DM, 統計, CP) の役割分担と他部門との関わり・巻き込み.....	
2.2 臨床パッケージと申請電子データ提出対象試験.....	
2.3 Global 開発・共同開発等の場合、担当者と連携して現状の整理.....	
2.4 PMDA 面談に向けた議論.....	
2.5 想定される業務フロー.....	
3. 通常の治験相談に関する課題.....	
3.1 提出対象試験の相談.....	
3.2 ADaM の提出範囲や ARM の範囲の相談をするかしないか.....	
3.3 相談資料の作成にあたっての業務との関わり方.....	
3.4 データ作成担当者の相談への出席要否.....	
3.5 CRO の担当者が関わるケース (資料の作成～相談同行まで).....	



Accumulation of know-how for each company



Collaboration across companies

Outline

- CDISC Japan User Group (CJUG)
ADaM Team Theme 1
- **Background**
 - e-Study Data Submission to PMDA
- **Lessons Learned**
 - Identification of study data and analyses to be submitted
 - Consultation on data format of submission of electronic study data
 - Considerations on Global Development
- **Summary**



Key date for e-study data submission to PMDA

Here!



Oct-2016

Start accepting
e-study data

Transitional period (3.5 years)

Apr-2020

To be
mandatory

- e-Study data submission during transitional period (as of Sep/30/2018)
 - ✓ 61 products (34 companies)
 - ✓ Characteristic for products
 - Regardless of Japanese company/foreign company, NDA/sNDA*
 - Several therapeutic area

* sNDA: Supplemental new drug application

Huge change for us...

- Sponsor has to implement streamlined process for e-Study data submission because it greatly affects timeline and cost for NDA
- Data science dept. has to lead e-Study data submission and discuss it with stakeholders (e.g. other dept. and PMDA)

Technical skill

CDISC,
Programming,
Statistics, Clinical
Pharmacology

Discussions/Collaborating
with internal and
external stakeholders

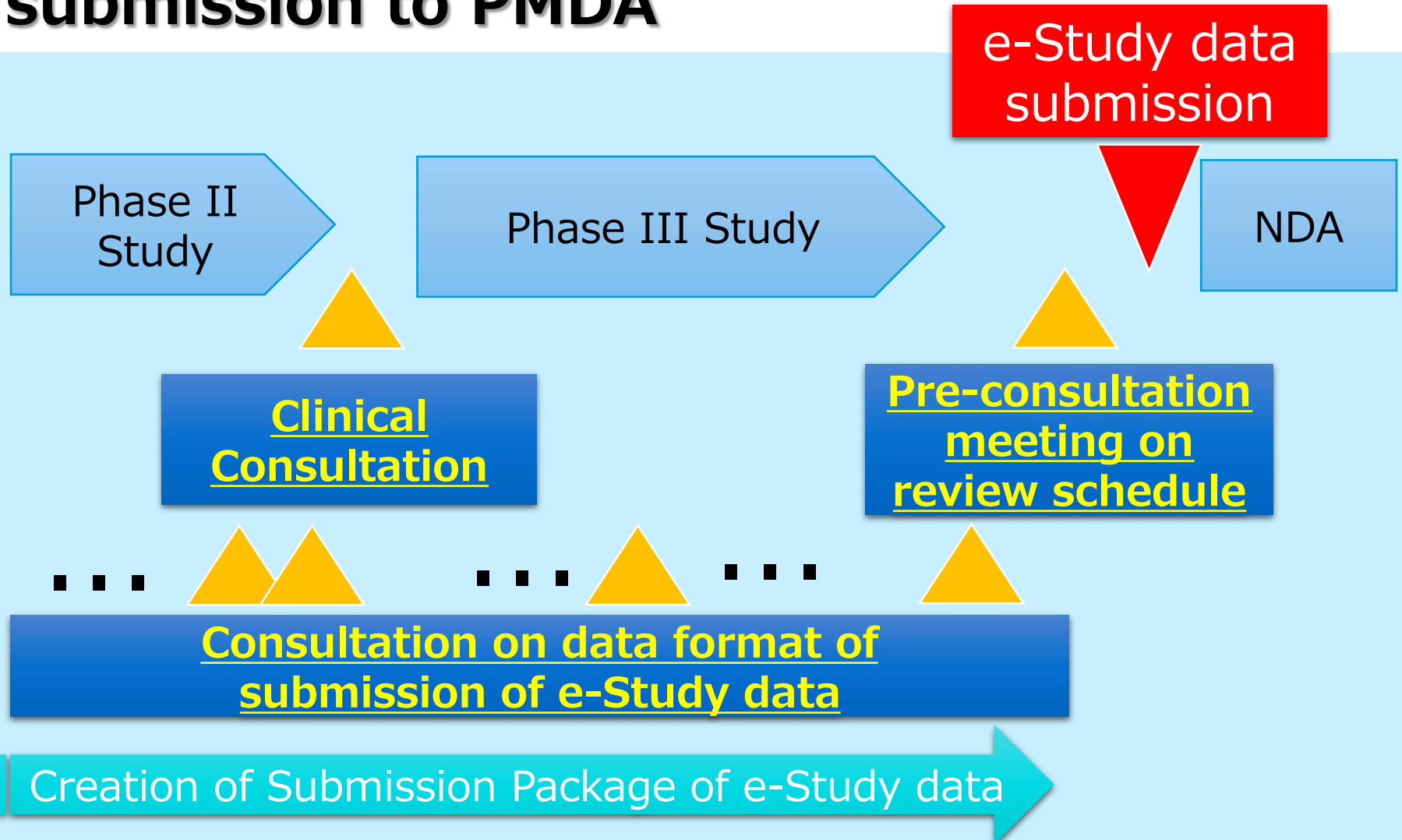
Soft skill

Outline

- CDISC Japan User Group (CJUG)
ADaM Team Theme 1
- Background
 - e-Study Data Submission to PMDA
- **Lessons Learned**
 - Identification of study data and analyses to be submitted
 - Consultation on data format of submission of electronic study data
 - Considerations on Global Development
- Summary



General milestones for e-study data submission to PMDA



Identification of data/studies and analyses

Discussions at Clinical Consultation

- Target data/studies and analyses (ADaM-related materials) should be identified and agreed with PMDA based on clinical data package at clinical consultation (e.g. End of phase II meeting)
- Data science dept. (e.g. Stat, DM, CP, Programmer) is heavily involved in the preparation of e-Study data submission section in Briefing Book as well as the discussion with PMDA at the consultation

Clinical data package

Study 001
Study 002
Study 003
Study 004
ISS
PPK

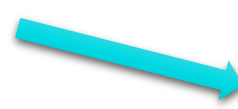
Target data/study

Study 001
~~Study 002~~
Study 003
~~Study 004~~
ISS
PPK

Target analyses

PK, LB, AE

Primary efficacy endpoint,
Key secondary efficacy end
Point, AE, LB, EG



Identification of data/studies and analyses

Target data/studies

- To identify target data/studies according to PMDA requirements (e.g. Notification, FAQ)
- To confirm the clinical data package, [evaluation or reference](#)

✓ Evaluation data/study

A data/study used for main evaluation of drug

✓ Reference data/study

A data/study which is positioned as supplement of evaluation studies



- Which data/studies should be submitted?
 - Even for reference data/studies?

Identification of data/studies and analyses

Notification on Practical Operations of Electronic Study Data Submissions

a. Data on results from all phase II and phase III studies (including long-term studies) that are generally regarded to be the major evidence for evaluation of efficacy, safety, and dose and administration

b. Study data from phase I studies and clinical pharmacology studies listed right

Special
Condition
(FAQ 5-6)

Phase I studies of oncology drugs

Phase I studies that have been conducted in both Japanese and non-Japanese subjects (e.g.; in case of a strategy of global clinical trials and bridging studies)

QT/QTc studies based on ICH E14 Guideline

Phase I and clinical pharmacology studies other than a and b, which were deemed necessary by PMDA

Special
Condition
(FAQ 4-4)

Clinical studies where standard pharmacokinetic analysis was Performed
(Standard CP study)

Population analyses (PPK)

Physiologically based pharmacokinetic sufficient model analyses (PBPK)

References other than a and b, which were deemed necessary by PMDA

Integrated summary of safety and efficacy (ISS/ISE)

Identification of data/studies and analyses

Target analyses

- It is **NOT** necessary to submit all ADaM datasets created.
- However, ADaM datasets related to more important analyses should be submitted.
 - primary efficacy analysis
 - secondary efficacy analyses
 - primary safety analyses
- Deliverables related to target analyses other than ADaM dataset (i.e. same requirement as ADaM dataset)
 - Programs used to create ADaM datasets
 - Programs used to create analyses
 - Analysis Results Metadata (ARM) → PMDA strongly recommends!!

Identification of data/studies and analyses

Target analyses for e-study data submission on clinical data package

Protocol No	Phase	Evaluation/Reference	e-Study data submission	Notes	Target analyses
001	I	Evaluation	Yes	To meet condition to be submitted e-study data for CP study on FAQ (e.g. TQT study, BE study)	PK, AE, LB
002	I	Evaluation	Yes		PK, AE, EG
003	I	Reference	Yes		PK, AE
004	I	Reference	No	NOT to meet condition to be submitted e-study data for CP study on FAQ (e.g. Within the 0.8 - 1.25 range on the geometric mean ratio in Food Effect and DDI studies)	-
005	I	Reference	No		-
006	II	Evaluation	Yes	Studies that are generally regarded to be the major evidence for evaluation of efficacy, safety, and dose and administration	Key efficacy endpoint, AE, LB, Biomarker
007	II	Evaluation	Yes		Key efficacy endpoint, AE, LB, EG
008	III	Evaluation	Yes		Key efficacy endpoint, AE, LB
009	III	Evaluation	Yes		Key efficacy endpoint, AE, LB, EG
ISS	-	Evaluation	Yes	Analyses were performed to assess rare adverse events	AE

Consultation on data format

General information

Consultation	Purpose	Timing (recommendation)
Consultation on data format	- To discuss technical issues/concerns for data format - To share validation issues on Pinnacle 21	Several months before NDA to before Pre-consultation meeting on review schedule

- Might be held **more than once**
 - Depends on the volume of clinical package, situation etc.
- **Data science dept. has to mainly lead to create a document in the "Exhibit 8" format and to discuss with PMDA at the consultation**
 - Adjust a schedule with stakeholders (e.g. Regulatory Affairs)
 - Summarize the discussion points



Consultation on data format

What kind of technical issues/concerns can we ask PMDA?

Timeline

Folder structure

Media to be submitted

Difficulty in creating CDISC-compliant e-Study data due to specific reasons

File size

How to create CDISC standard dataset

Dataset not in English

How to submit e-Study data without eCTD

Custom domain

Additional e-Study data submission after NDA

SUPPQUAL that includes variables related to primary analyses

Consultation on data format

Content of Exhibit 8

- Section 1: Basic information of compound
- Section 2: Matters to be discussed
- Section 3: Summary of clinical data package
- Section 4: **Detailed information of data to be submitted**
 - Version of CDISC standards
 - SDTM/ADaM domain to be submitted
 - Submit the followings or not
 - Analysis Result Metadata
 - Programs for creating ADaM datasets
 - Analysis programs including programs with macros
 - Results of validation on Pinnacle 21

Consultation on data format

Quality of Exhibit 8

Case1: Explanation of validation errors should be more specific



More details should be explained regarding data issues or errors

Store the data according to CRF

Store the data according to CRF. If actual amount of dose of concomitant medication was unknown, "UNK" is entered in Dose Description (CMDOSTXT) field and Dose Units (CMDOSU) is not provided.

Not modify because analyses are not affected

There are some records of which PARAMCD/PARAM are empty. Alternatively, there are equivalent variables EGTESTCD/EGTEST. Statistical analyses and data summary were performed using them.

Implemented as per company's standards.

In addition to variables of IDVAR and IDVARVAL, COGRPID and COSPID were also populated per company's standard. COGRPID provides the traceability of where the comment came from, while COSPID is the sequence order within each subject.

In case validation errors are detected in PMDA validation

In this trial, subjects were expected to receive multiple treatments. Therefore, period start date time (i.e. TRxxSDT & TRxxSDTM where xx=01, 02 ...etc.) were used in place of TRTSDT/TRTSDTM to avoid confusion.

In case validation errors are detected in PMDA validation

All records of "LBSTRESN does not equal LBSTRESC" are subjective tests. Subjective results reported in LBORRES and also in LBSTRESC values, but LBSTRESN is set to null. So LBSTRESN does not equal LBSTRESC.

Consultation on data format

Quality of Exhibit 8

Case2: Consistency between Exhibit 8 and Reviewer's Guide

- Explanation of validation errors also has to be described in RG
 - Need to keep consistency between Exhibit 8 and RG
 - PMDA points out the inconsistency (e.g. version of CDISC standards, list of CDISC-compliant data)
 - RG could be attached in Exhibit 8 to explain data issues/errors
 - To reduce the workload to copy the results of validation to Exhibit 8 and RG (and QC)



Considerations on Global Development

- Differences on requirements between FDA and PMDA
 - Target data/studies
 - **PMDA: Submission level $\Leftrightarrow$ FDA: Study level**
 - Validation Rules
 - PMDA has **"Reject" criteria**
 - **Validation has to be conducted for both FDA and PMDA**
 - The reasons of errors should be described in Reviewer's Guide

Dataset	Rule ID	Diagnostic Message	FDA Severity	PMDA Severity	Explanation
LB	SD1122	Missing value for LBSTRESN	Warning	Error	The conversion of lab value to standard value cannot be performed for those records with missing original unit (LBORRESU) or original unit cannot be converted to standard unit (LBSTRESU).

*Image of RG to describe results of validation for both FDA and PMDA

• **SI unit**

- Specific requirements to Japan NDA
- Data might be modified for submission to PMDA



Considerations on Global Development

- Timeline/Schedule for US and Japan NDA
 - To streamline the process for submission to PMDA
 - To take into consideration PMDA requirements beforehand
 - To continuously communicate with global team



Need to meet both FDA and PMDA requirements under the tight schedule especially for simultaneous NDA

Creation of e-Study Data

Validation

Test Submission

Submission to FDA

Validation

Consultation on Data Format

Pre-consultation meeting on review schedule

Submission to PMDA

Outline

- **CDISC Japan User Group (CJUG)
ADaM Team Theme 1**
- **Background**
 - e-Study Data Submission to PMDA
- **Lessons Learned**
 - Identification of study data and analyses to be submitted
 - Consultation on data format of submission of electronic study data
 - Considerations on Global Development
- **Summary**





Summary

- For successful e-Study data submission
 - Important to collaborate across companies and share the knowledge and experiences towards the fast-approaching mandatory phase
- New role for Data Science department
 - To improve technical and soft skill for e-Study data submission
 - Deeply involved in the discussions with stakeholders especially for clinical consultation and consultation on data format
- Global Development
 - To understand the differences between regions and meet both the requirements of FDA and PMDA on e-Study Data Submission

Reference

- [1] PMDA:
Basic Principles on Electronic Submission of Study Data for New Drug Applications
- [2] PMDA:
Notification on Practical Operations of Electronic Study Data Submissions
- [3] PMDA:
Question and Answer Guide Regarding “Basic Principles on Electronic Submission of Study Data for New Drug Applications
- [4] PMDA:
Question and Answer Guide Regarding “Notification on Practical Operations of Electronic Study Data Submissions”
- [5] PMDA:
Technical Conformance Guide on Electronic Study Data Submissions
- [6] PMDA:
FAQs on Electronic Study Data Submission (Excerpt)
- [7] FDA:
Providing Regulatory Submissions in Electronic Format - Standardized Study Data: Guidance for Industry

Back up

Consultations with PMDA on e-Study data submission

Consultation	Discussion topics on e-Study data submission	Timing (recommendation)
Clinical consultation (e.g. End of Phase II meeting)	To agree with PMDA about <u>target data/studies and analyses</u> of e-Study data submission	A couple of years to 6 months before NDA
Consultation on data format of submission of e-Study data (Consultation on data format)	- To discuss <u>technical issues/concerns</u> for data format - To share <u>validation issues</u> on Pinnacle 21	Several months before NDA to before Pre-consultation meeting on review schedule
Pre-consultation meeting on review schedule	- To confirm finalized submission package and application date - To submit <u>finalized Exhibit 8</u> to PMDA beforehand	6 weeks before NDA

Identification of data/studies and analyses

Condition to be submitted e-study data for CP study (FAQ)

Q5-6: When a sponsor conducts clinical trials to evaluate the effect of intrinsic or extrinsic factors such as age, sex, weight, genetic factors, severity of disease, disease complications, or dietary, alcohol or smoking habits on the pharmacokinetics of an investigational drug, are these study data subject to submission even if the study result indicates **negative effect** of these factors on the pharmacokinetics of the drug?

A: It is not necessary to submit study data in that case. **The 0.8 - 1.25 range on the geometric mean ratio of pharmacokinetic parameters (when pharmacokinetic parameters are log-normally distributed) can be used as one of the criteria for assessing a “negative effect” in deciding whether the study data need to be submitted.** In some cases, study data might not need to be submitted even though the ratio is not within the range of 0.8 - 1.25. To ensure the necessity of submission of study data evaluating the effect of intrinsic or extrinsic factors, we recommend using a clinical trial consultation if necessary.

Identification of data/studies and analyses

Condition to be submitted e-study data for ISE/ISS (FAQ)

Q4-4: When is it necessary to submit electronic datasets of integrated analyses (ISS/ISE)? What is the scope of electronic data on ISS/ISE that must be submitted?

A: ..., submission of electronic data for ISS/ISE will be requested when integrated analyses of multiple clinical studies were performed for the assessment of specific efficacy or safety, such as assessments in special populations or of rare adverse events, and when the results are considered to be relevant to the assessment of efficacy, safety, and dosage and administration of the product. In order to confer with the PMDA on the scope of the submission of electronic data of integrated analyses, applicants must use the clinical trial consultation, not the “consultation on data format of submission of electronic study data,” because a decision on the scope of the submission accompanies scientific evaluations.

At the submission of data, ...

Identification of data/studies and analyses

Target analyses

<https://www.pmda.go.jp/files/000215100.pdf>

It is not necessary to submit ADaM datasets for all analyses described in the statistical analysis plan. However, ADaM datasets should be submitted for analyses performed to obtain important results on efficacy and safety and clinical study results that provide the rationales for setting of the dosage and administration, such as **primary efficacy analysis and secondary efficacy analyses (secondary analyses of primary variable and analyses of key secondary variables), primary safety analyses and basic analyses of adverse events, and analyses to investigate the effect of major factors on efficacy and safety.** The applicant should preferably consult the PMDA **beforehand** on the sufficiency of the datasets to be submitted.

With respect to the programs related to the electronic study data conforming to the CDISC standards, the programs used to create the **ADaM datasets and programs used for analyses** must be submitted for **analyses performed to obtain important results on efficacy and safety and clinical study results that provide the rationales for setting of the dosage and administration**



- **To identify the important ADaM datasets/programs and programs used for analyses that should be submitted.**
- **To agree them with PMDA at clinical consultation.**