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Ingelheim

Business & Decision
Life Sciences

SA02 - Challenges of submitting electronic study data to 2 authorities – PMDA and FDA

Torsten Petsching – 6th November 2018



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Agenda



Submission Background



Submission Requirements



Lessons Learned



Conclusions



Q&A





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Submission background



 *Data of two studies were submitted to the PMDA in 2017*

 *The first submission of study data of the same compound to the FDA was in 2014*

Submission setting for PMDA

 *Interim and final data for two studies were submitted in two waves*

- **Wave 1:** *interim data of one study AND final data of the second study*

→ *submitted 28-AUG-2017*

→ *accepted 20-SEP-2017*

- **Wave 2:** *final data of the first study*

→ *submitted 06-NOV-2017*

→ *accepted 09-NOV-2017*

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Submission Requirements: PMDA versus FDA (1)

Item	PMDA	FDA
Inclusion of study data in CDISC standard in eData Submissions	Transition period Mandatory for submissions with planned submission date after 31-MAR-2020 based on the PMDA Data Standards Catalog .	eCTD submissions required, with eData sets included for several years. Studies that start after 17-DEC-2016 must use the data standards listed in FDA Data Standards Catalog .
Guidance/Notification	• Basic Principles • Notification on Practical Operations ▪ Specific requirements for Ph-I/CP studies ▪ Analysis / ADaM creation SAS programs ▪ SI unit as standard unit in SDTM	Providing Regulatory Submission In Electronic Format - Standardized Study Data
Technical Guide	• Technical Conformance Guide ▪ Specific requirements for Ph-I/CP studies ▪ Analysis Results Metadata (ARM) • PMDA Data Standard Catalog	• Technical Conformance Guide ▪ E.g. includes considerations on the Legacy Data Conversion • FDA Data Standard Catalog

Submission Requirements: PMDA versus FDA (2)

Item	PMDA	FDA
Data File Size Limitations	5 GB is the current size limit	5 GB is the current size limit. Bigger files must be split, but the big file should also be included.
Study Data Standardization Plan	NA	For INDs, it should be created and located in the general investigational plan
Patient Data Reports (eCRFs)	After the application (not part of the eData package, rather as submission documentation after the application)	In the eCTD submission (required as part of the eData package and included in module 5)
ADaM: Analysis Results Metadata (ARM)	Strongly recommend to be submitted	Not required
Meetings	Consultation meeting specific to eData submission	pre-NDA meeting , Type C Meeting
Validation Rules	SDTM, ADaM, Define.xml	SDTM, ADaM, Define.xml, SEND

Meetings for discussion of eData Standards (1)

FDA:

 **3 different types of formal meetings (Type A, Type B, Type C)***

- *Technical questions as part of Type C meeting*
- *but could also be part of Type B meetings
(e.g. Pre-IND, End of Phase 2, Pre-NDA/Pre-BLA meeting)*

*<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.pdf>

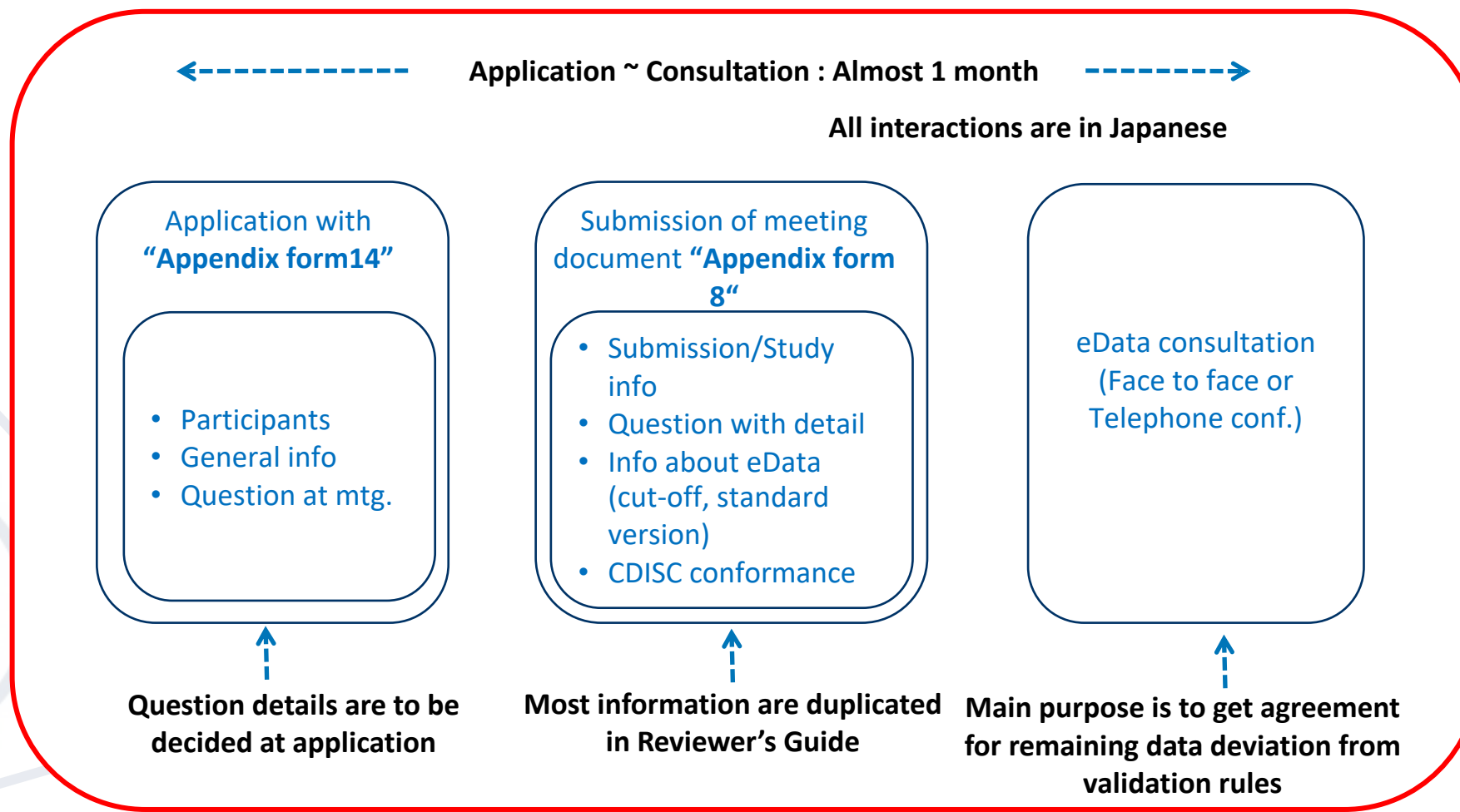
Meetings for discussion of eData Standards (2)

PMDA

eData consultation meetings

- *At least one eData consultation meeting to explain the delivery package*
- *eData submission topics only*
- *For this project, BI had 6 meetings (at the request of the local Japanese team in Japanese)*

PMDA process- eData consultation



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Validation Rules for SDTM (1)

Item	PMDA	FDA
Identifier of the check	Pinnacle 21 Enterprise edition (PMDA ID = P21 ID)	Pinnacle 21 Enterprise edition (FDA ID specific, starting with FDA...)
Number of rules	326	314
Severity	• Reject: 9 • Error: 128 • Warning: 189	• Reject: 4* • Error: 201 • Warning: 113

* No rejection in P21, but according the „Technical Rejection Criteria for Study Data“

Validation Rules for SDTM (2)

Different handling of source data issues

- *PMDA: resolve P21 rejection*
- *FDA: describe issue in Clinical Study Data Reviewers Guide (csdrg)*

Example

- *For the interim data, hard-coding in SDTM was done to omit a Pinnacle 21 rejection error*
→ ***Hard-coding does not fit to the CDISC philosophy***

Validation Rules for SDTM (3)

Options to run the validation rules

- *SDTM – ADaM cross-check:
AE, DM and EX should be included for traceability checks between ADaM and SDTM*

Version

- *PMDA: Pinnacle 21 Enterprise edition (v3.0.5)*
- *BI/BDLS: Free version of Pinnacle 21 Community tool
(started with version 2.2.0, but then changed to version 2.1.3)*

Findings domain (Laboratory / Vital signs) concept (1)

BI Standard units <> SI units <> US conventional units

- *PMDA: SI units*
- *FDA: SI units and/or US conventional units*
- *Examples:*

SYSBP:

BI unit = FDA US conventional unit: mmHg

PMDA SI unit: Pa

Haemoglobin:

BI unit: g/L

PMDA SI unit: kg/L

US conventional unit: g/dL

Findings domain (Laboratory / Vital signs) concept (2)

Solution for the FDA → 2 different LB datasets created:

LB dataset submitted:

- The values in the unit used for the clinical trial report included in the Result/Finding in standard format (LBSTRESC)

Second LB dataset:

- The values in US conventional unit included in the Result/Finding in standard format (LBSTRESC)
- Prepared, but submitted only on request

Findings domain (Laboratory / Vital signs) concept (3)

Solution for the PMDA → One LB / SUPPLB dataset created:

LB dataset:

- *The values in SI units included in the Result/Finding in standard format (LBSTRESC)*

SUPPLB dataset:

- *The values in the units used for the clinical trial report as separate QNAMs (Units, results, lower range, higher range)*

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Conclusions (1/2)

- ① *If the same package is to be submitted to both authorities → **plan for it** (Many similarities, but also some differences which need considerations and resource planning upfront)*
- ① *As better you have the **data under control**, the better for the submission → as for all Data Management processes 😊*
- ① *Consider to develop a submission subject matter expert for PMDA/FDA*

Conclusions (2/2)

① *Industry need to see how the authorities drive the eData within the eCTD submissions in the future (i.e. development in the same direction of rather more differences)*

① *Open the **dialog with the authorities** as early as possible!!*

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Questions...

Thank You



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Back-up Slides

PMDA rejection rules (SDTM)

RULE ID	MESSAGE	DESCRIPTION	DOMAINS
CT2001	<Variable Name> value not found in '<Codelist Name>' non-extensible codelist	Variable must be populated with terms from its CDISC controlled terminology codelist. New terms cannot be added into non-extensible codelists.	ALL
CT2004	<Variable Name> value not found in '<Codelist Name>' non-extensible codelist	Variable must be populated with terms from its CDISC controlled terminology codelist, when its value level condition is met. New terms cannot be added into non-extensible codelists.	QS, TS
SD0002	NULL value in variable marked as Required	Required variables (where Core attribute is 'Req') cannot be NULL for any records.	ALL
SD0056	SDTM Required variable not found	Variables described in SDTM IG as Required must be included in the dataset.	ALL
SD0062	Incompatible data source	Domain table must have a valid format (e.g., SAS transport (XPORT) v.5 or text-delimited).	ALL
SD0064	Subject is not present in DM domain	All Subjects (USUBJID) must be present in Demographics (DM) domain.	ALL
SD1020	Missing DM dataset	Demographics (DM) dataset must be included in every submission.	DM
SD1073	Variable prohibited for use in SDTM	Variables described in IG as inappropriate for usage must be not included in the dataset.	ALL
SD1074	Variable which can be used only in SEND	Variables designed only for SEND pre-clinical studies must be not included in the SDTM dataset.	ALL

Link to the FDA Technical Rejection Criteria (SDTM):

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM523539.pdf>

- ⌚ A “Trial Summary (**TS**)” dataset must be present for each study in module 4/5
- ⌚ The correct **STF file-tags** must be used for all standardized datasets in module 4/5
- ⌚ **DM** dataset and define.xml must be submitted in module 4 /5
- ⌚ For each study in module 4 and in module 5 **no more than one dataset of the same name** should be submitted as new

PMDA process- eData consultation (Appendix form 14)

別紙様式14 治験質問申込書

Sponsor information

Attendees with department name

申込者名			他の面談出席者と所属部署名	
連絡先	申込責任者名			
	所属部署名			
	電話番号	() —		
	ファクシミリ番号	() —		
治験成分記号		治験薬の一般名（販売名）	担当分野	
Code of active ingredient		Name of active ingredient	section in PMDA	
		表 題	title of consultation	
[質問事項]				
1.		planned question at consultation - 1		
2.		planned question at consultation - 2 ...		
同一治験薬についての過去の対面助言		Consultation history in this project		
相談資料		consultation document in previous		

PMDA process- eData consultation (Appendix form 8)

付録

申請電子データ

General information

Code of active ingredient
Name of finished product
Name of active ingredient
Pharmaceutical form and Unit Strength
Indication in the submission plan
Dose and administration in the submission plan
Planned submission year and month
Sponsor

1. 基本情報

治験成分記号
販売名 (予定)
一般名
剤形・含量
申請予定効能・効果
申請予定用法・用量
申請予定年月
相談者名
担当者連絡先 (担当者名、所属、連絡先)

2. 相談事項

Outline of Consultation (Question / discussion topics at consultation with detail)

3. 臨床データパッケージと臨床試験の概要

(1) 予定される臨床データパッケージ

Overview of clinical data package and clinical trial

分類	試験番号 (又は報告書番号)

・電子データの提出の有無にかかわらず、臨床データパッケージに含まれる予定の全ての臨床試験を記載する。
・「分類」には、第Ⅰ相、第Ⅱ相、第Ⅲ相、臨床薬理試験、安全性併合解析、有効性併合解析、PPK 解析等を記載する。

(2) 電子データを提出する予定の臨床試験又は解析

① 個々の臨床試験

試験番号 (又は報告書 番号)	実施 地域	対象	試験デザイン	投与群 (用法・用量) 投与期間	投与群毎の 被験者数	有効性評価項目 安全性評価項目	実施 状況