

Challenges of Submitting Electronic Study Data to Two Authorities: PMDA and FDA

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ABSTRACT

The clinical development of pharmaceutical drugs aims to demonstrate safety and efficacy for new compounds and to gain regulatory approval to bring it to the market in various countries. In the ideal world, a submission package would be created once and could be reused for all submissions across countries. Due to requirements still differing this is not yet possible and depending on the country, updates to the initial submission package may be needed.

In particular, when electronic datasets (e-data) have to be included this can be cumbersome and may have an impact on workload and timelines. The situation has improved since the introduction of CDISC standards and making it a requirement or recommendation for submission of e-data.

The purpose of this presentation is to share experience on challenges, points to consider and solutions implemented when the sponsor had submitted electronic study data of the same compound to two authorities: The U.S. Food and Drug Administration (FDA) and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA). Both agencies are currently expecting (FDA) or strongly recommending (PMDA) that sponsors submit standardized e-data.

INTRODUCTION

Since October 2016, the PMDA started with a transitional period of 3.5 year where they initiated the submissions of e-data before it will become a requirement in 2020. The FDA started accepting standardized data years ago and with the FDA Guidance 'Providing Regulatory Submissions in Electronic Format' (December 2014) the requirements for an electronic submission of standardized clinical and nonclinical study data became binding for all NDAs, certain BLAs and certain INDs.

The requirements defined by both agencies are similar. However, there are some differing rules that need to be taken into account to have an accepted similar e-data package for the same substance by the PMDA and FDA. The hands-on experience described in this paper is coming from converting e-data by Business & Decision Life Sciences (BDLS) to the CDISC standard for Boehringer Ingelheim (BI) and subsequent submissions.

It is assumed that the reader has a basic understanding of CDISC standards and requirements for submissions to FDA and PMDA. References to critical specifications published by both agencies are enclosed. [2] [3]

SUBMISSION BACKGROUND

The first submission of study e-data for this particular compound to the FDA was in 2014. Data of two studies of the same compound were submitted to the PMDA in 2017. All studies had been conducted and reported based on a legacy data structure. Conversion to CDISC standards was performed afterwards for submission purposes and was outsourced to a CRO. Legacy data conversion requires special considerations. It has to be planned for early on to fit the context of a submission and to ensure compliance with regulatory and sponsor standards. [1]

The maintenance of a project database containing all the involved studies at BI was with a global team, which had to oversee and manage the preparation of the e-data. A Submission Manager supported the coordination of activities. The role of a Submission Manager was set-up at BI a few years ago in order to build in-house expertise on all the current and developing needs for eCTD submissions as published by agencies. In addition, this includes lessons learned from previous submissions and implications for the future. A Submission Manager supports the operational teams with respect to the submission planning, preparation and implementation.

For the submission to the PMDA a local Japanese team became involved to drive the interaction with the PMDA and to provide the global team with input on the PMDA requirements and eventually submit the package. The PMDA submission required two waves of submitting e-data:

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- Wave 1 contained interim data of one study and final data of another one. It was submitted a first time on 28-Aug-2017. Three cycles of review by PMDA and updates by the sponsor took place until the package was accepted on 20-Sep-2017.
- In wave 2 the final data of the first study was submitted on 06-Nov-2017 and accepted on 09-Nov-2017.

SUBMISSION REQUIREMENTS

Both the PMDA and the FDA have published guidance documents regarding eCTD for submissions and the recommended and required use of e-data therein. Main references for e-data are the Data Standards Catalogs and the Technical Conformance Guides. [2] [3]

It has to be noted that the requirements for eCTD submissions follow the same principles and in general, reusability of packages is possible. A detailed review of the published specifications also revealed that there are a number of differences with a potential impact on the reusability and possibly required updates in particular to the e-data.

COMPARISON OF REQUIREMENTS BETWEEN PMDA AND FDA

In the following section the major differences between PMDA and FDA specifications are described which were identified when preparing for this submission.

INCLUSION OF STUDY DATA IN CDISC STANDARD IN E-DATA SUBMISSIONS

The PMDA is in a transition period, CDISC standards for e-data will become mandatory for submissions with planned submission date after 31st of March 2020.

Submissions to the FDA have to follow eCTD specifications including e-data since several years.

Studies that start after 17th of December 2016 must use the data standards listed in **FDA Data Standards Catalog** [3].

GUIDANCES AND NOTIFICATIONS

General guidance documents and detailed specifications are available on the internet homepages of the FDA and the PMDA. [2] [3]

For the PMDA please be aware of the “Notification on Practical Operations” which among other details also describe specific requirements for Phase I / Clinical Pharmacology studies, the inclusion of SAS programs used for analysis and ADaM creation and SI unit as standard unit in SDTM.

PATIENT DATA REPORTS (E-CRF)

A common question for eCTD packages is which e-crfs to include. For the PMDA it is not part of the eCDT package and may be needed after the application as submission documentation. The FDA requests e-crf files to be included in module 5.

ADAM: ANALYSIS RESULTS METADATA (ARM)

The PMDA strongly recommends providing analysis results metadata along with the initial submission whereas the FDA did not at the time of this submission.

STUDY DATA STANDARDIZATION PLAN

The Study Data Standardization Plan (SDSP) goes back to an initiative of the FDA. It is a document to describe the details of standards used in the studies of a development project. All types of studies - planned, running and finalized studies – shall be included. It can be used for communication with regulatory bodies so that questions and concerns regarding the implementation of standards can be addressed as early as possible. An SDSP template and guidance for implementation in an organization are available at the PhUSE homepage. [5]

The PMDA does not have it in use. The FDA expects it to be used as early as possible as an element in the ongoing communication with a sponsor. It should be created for INDs and located in the general investigational plan.

CDISC SDTM/ ADAM VALIDATION RULES

The FDA and the PMDA have published validation rules that have to be used to demonstrate the level of compliance with the standards. More details along with issues seen are discussed in the section on Lessons Learned.

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MEETINGS FOR DISCUSSION OF QUESTIONS AROUND E-DATA STANDARDS

The FDA offers three types of formal meetings (Type A, Type B, Type C) are possible [4]. We typically use a Type C meeting to discuss technical questions. Instead, it could also be part of Type B meetings such as Pre-IND, Pre-NDA and others.

The PMDA has developed a variety of consultations tailored for a range of needs. When the PMDA started to accept e-data a new type of meeting became available: eData Consultation. It allows addressing technical questions around the e-data. Questions are restricted to topics directly related to the submission under discussion and a special focus is on reviewing remaining issues from compliance checks against the validation rules. At least one eData Consultation meeting is needed to explain the delivery package. Initiation and set-up are following a formal process, which may take up to one month until the actual meeting.

The first step is to apply for a consultation and provide general information about the sponsor, the list of the participants and describe the questions ("Appendix form 14").

別紙様式 14

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	() —			
	Fax/Fax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		
<table border="1"> <tr> <td>表 題</td> <td>title of consultation</td> </tr> </table>				表 題	title of consultation
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				

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In a second step, information is submitted about the studies involved, details of the questions to discuss, CDISC conformance and more ("Appendix form 8").

付録

申請電子データ

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)	

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

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

分類	試験番号 (又は報告書番号)

Overview of clinical data package and clinical trial

・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

The meeting can be held face-to-face or as a telephone conference.

The main purpose is to discuss open questions and to get agreement for remaining data deviating from validation rules. Typically, all interactions are in Japanese.

LESSONS LEARNED

OVERVIEW ON VALIDATION RULES

Identifier of the checks are different but can be matched

PMDA: Pinnacle 21 Enterprise edition (PMDA ID = P21 ID)

FDA: Pinnacle 21 Enterprise edition (FDA ID specific, starting with FDA...)

	PMDA	FDA
Number of rules	326	314
Severity		
Reject	9	4*
Error	128	201
Warning	189	113

*No rejection in P21, but according to the Technical Rejection Criteria for Study Data [3]

The number of rules in place is similar but the categorization of severity is different. More important, the expected handling of findings differs between PMDA and FDA. The FDA expects sponsors to either correct any discrepancies between study data and the standard or the business rules or explain meaningful discrepancies in the Reviewer Guide.

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The PMDA has specified the impact of violations according to severity. For example if a rule categorized as “Reject” is violated it will cause the review to be suspended until corrections have been made. [2]

In consequence, it is recommended to resolve as many violations as possible and to agree in e-data consultation what is acceptable if anything is left.

For the interim data submitted to PMDA, some hard coding in SDTM became necessary to omit a Pinnacle 21 rejection error (missing stop dates due to patients still in the study).

There are options how and to which extent to apply the validation rules and which versions to use.

For crosschecking ADaM with SDTM, it was found that at least the SDTM domains AE, DM and EX should be included to confirm traceability between ADaM and SDTM datasets.

At the time of submission, the PMDA was using the Pinnacle 21 Enterprise edition (v3.0.5). BI and BDLS have the free version of Pinnacle 21 Community tool in use and started the validation process with version 2.2.0, but then changed to version 2.1.3 in order to match findings at PMDA and the sponsor end as good as possible.

HANDLING OF UNITS IN FINDINGS DOMAINS (LABORATORY / VITAL SIGNS)

Units used for standardization and reporting by the sponsor but partially deviating units expected by PMDA and FDA added complexity and required additions to submission packages. In general, the PMDA expected SI units to be used for standardization of test results. The FDA expected a mixture of SI units and/or US conventional units.

For example:

	PMDA	FDA	Sponsor
Systolic Blood Pressure	Pa	mmHg	mmHg
Haemoglobin	kg/L	g/dL	g/L

For the VS dataset systolic blood pressure had been standardized into VSSTRESC based on the unit mmHg but was updated to Pa for the submission package.

For the FDA two different versions of the LB dataset were created:

- Version one was included to the initial submission. The standardization of values into LBSTRESC was based on the units actually used for the clinical trial report.
- For version two, the values were standardized based on US conventional units. This dataset was planned to be submitted on request only, which did not take place.

For the PMDA the combination of LB / SUPPLB dataset was created. The values were standardized into LBSTRESC based on SI units. The values in the units used for the clinical trial report were included to the SUPPLB dataset as separate QNAMs (Units, results, lower range, higher range).

CONCLUSION

There are many similarities and overlaps between specifications and requirements outlined by PMDA and FDA. Nevertheless, there are also some differences that may have an impact on resource and timeline planning. If the same package shall be used for submission to both agencies, it is recommended to plan for it early on.

With the implementation of standards as an integral part of the submission process FDA and PMDA have established additional options to communicate on technical aspects of submission eCTD packages.

Opening the dialog with the authorities as early as possible is highly recommended.

A subject matter expert for submissions supporting the submission teams can be very helpful.

A high level of harmonization across regulatory agencies is already in place. Further harmonization would be helpful.

There is an increasing need for the industry to see how the authorities drive the e-data within eCTD submissions in the future. The better it is understood how e-data are processed the better submission packages can be prepared to allow for a smooth review process.

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REFERENCES

- [1] A. Tinazzi, C. Marchand, An FDA Submission Experience Using CDISC Standards. PhUSE 2017

Available at the PMDA homepage:

<http://www.pmda.go.jp/english/review-services/reviews/advanced-efforts/0002.html>

- [2] Basic Principles on Electronic Submission of Study Data for New Drug Applications
Notification on Practical Operations of Electronic Study Data Submissions
Technical Conformance Guide on Electronic Study Data Submissions
Data Standards Catalog (2017-03-03)
Study Data Validation Rules (2015-11-18)

Available at the FDA Study Data Standards Resources webpage

<https://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>

- [3] FDA Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Submissions Under Section 745A(a) of the Federal Food, Drug and Cosmetic Act
FDA Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Standardized Study Data
FDA Data Standards Catalog – FDA
FDA Data Technical Conformance Guide
FDA Technical Rejection Criteria for Study Data
- [4] Formal Meetings Between the FDA and Sponsors or Applicants
<https://www.fda.gov/downloads/drugs/guidances/ucm153222.pdf>
- [5] Study Data Standardization Plan – SDSP Template and further guidance
<https://www.phuse.eu/css-deliverables>

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