

10 things you need to know about PMDA eSubmission

Yuichi Nakajima, Novartis Pharma K.K.

ABSTRACT

From April 2020, Pharmaceuticals and Medical Devices Agency (PMDA), health authority in Japan, mandates electronic submission (eSubmission) in new drug application (NDA). PMDA has published Basic Principals, Notification on Practical Operations, Technical Conformance Guide and FAQs of electronic submission for applicants. Although those guidance documents cover general and practical topics, there are many operational and technical challenges found in the transitional period from October 2016 to March 2020. Submission requirements of Food and Drug Administration (FDA), health authority in United States, and PMDA are different. Needless to say, electronic Case Report Tabulation (eCRT) package accepted by FDA is not always accepted by PMDA. It is difficult to define “golden standard” of electronic submission due to its various submission requirements.

This poster will provide challenges, tips and awareness of potential pitfalls which was obtained from actual submission experiences during transitional period, that will support your smooth PMDA submission

INTRODUCTION

After 3.5 years transitional period, PMDA has started to accept eCRT as mandatory requirements. According to PMDA announcement, more than 90 NDAs were submitted with eCRT and about 300 PMDA consultations regarding eSubmission were held during transitional period. This brought several insights to both PMDA and pharmaceutical companies and those are reflected in guidance, several workshops and conferences.

Novartis has attempted various type of eSubmission during PMDA transitional period. In fact, there were many obscure points in guidance and these could not have been clarified without hands on experiences and engagement with the PMDA.

10 THINGS YOU NEED TO KNOW ABOUT PMDA ESUBMISSION

Figure 1 shows summary of 10 important things from our experiences, in relation to timeline, cost and resource, two important factors to eCRT preparation plan. It is recommended that legacy data conversion should be prioritized and need concrete preparation plan at the early phase of clinical drug development.

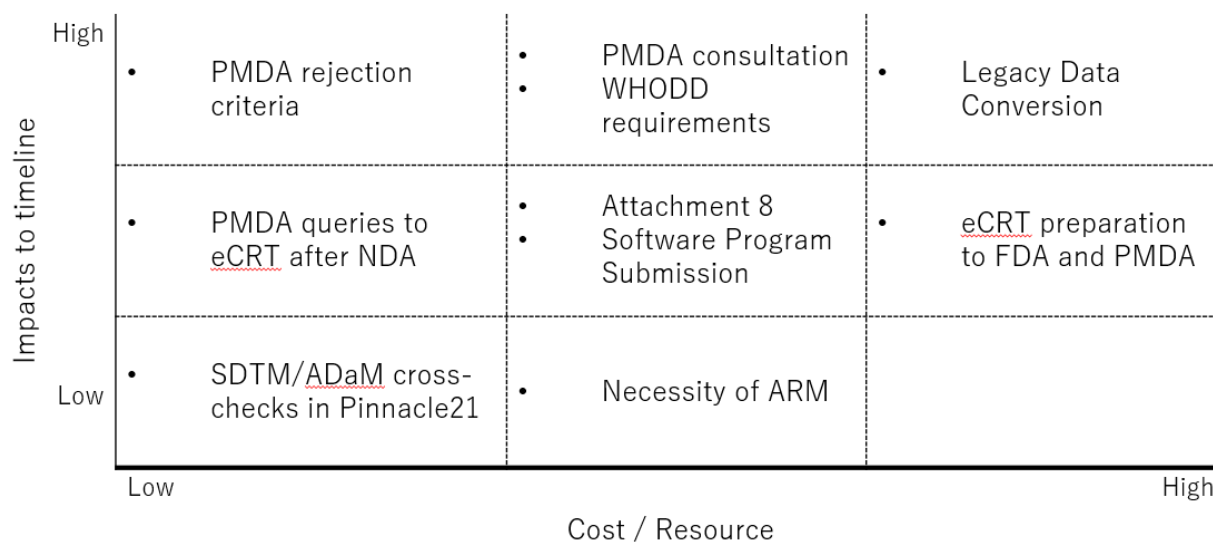


Figure 1. 10 important things learned from hands on experiences

LEGACY DATA CONVERSION

Legacy data conversion is one of big challenge for PMDA eSubmission. Whereas FDA could accept legacy format submission whose study started before December 16, 2016, PMDA will require CDISC compliant data for NDA after April 1, 2020. This means, PMDA will request more legacy data conversion than FDA. There were a few cases in our experiences that more than 10 legacy data conversions prepared for only one PMDA eSubmission. Usually clinical package for eSubmission is discussed in clinical trial consultation so it is important to have an agreement of legacy data conversion target before this stage, so early planning will be the key to success.

During legacy data conversion, data point traceability must be taken care of in SDRG. Sponsors have responsibility to explain how converted data was created from legacy format. As of March 2020, Legacy data conversion plan and report in SDRG is not mandated to use in PMDA eSubmission but it will be helpful for summarizing legacy data conversion.

PMDA CONSULTATION

PMDA provides two type of consultations to support eCRT preparation.

- **Consultation on data format of submission of electronic study data:** Most important and difficult to skip unless there were no Pinnacle 21 validation error. Error issue must be consulted and shared at this meeting. Otherwise, drug review will not be initiated. This consultation is free but costs 99,300 JPY if minutes are needed.
- **Consultation on preparation of submission of electronic study data:** To discuss topics on eCRT preparation. For example, handling data with reject issue, data conversion strategy, and so on. This consultation will cost 249,000 JPY.

It is significantly important that sponsors should plan the timing of these consultations according to eCRT preparation plan and NDA timeline. For example, error explanation at consultation on data format must be done before SDRG/ADRG finalization because error explanation should be documented in conformance section. Generally speaking, last consultation on data format should occur 3 months prior to NDA. Therefore eCRT completion should be completed before consultation on data format.

Note that discussion regarding which study/analysis data should be included in eSubmission must take place at clinical trial consultations such as end of Phase 2 meeting.

ATTACHMENT 8

Attachment 8 is the official document of PMDA consultation for eSubmission. It has to be written in Japanese. Contents in attachment 8 are similar to Study Data Standardization Plan (SDSP) for FDA and it will need to be finalized before pre-NDA meeting that takes place in 2-3 months before NDA.

Main purposes of attachment 8 are

- Inform PMDA about entire eSubmission package, data standards and contents of eCRT.
- Track discussion items for PMDA consultation
- Summarize Pinnacle 21 validation error issues and share them with PMDA.

Especially attachment 8 is an important tool to reach agreement on error explanation to be described in SDRG/ADRG. Based on our experiences, PMDA will request more detail in explaining Pinnacle 21 error than FDA. In other words, explanation accepted by FDA may not be always accepted by PMDA. Table 1 shows some examples.

Pinnacle 21 ID	Pinnacle 21 Message	Not acceptable	Acceptable	Issues
AD0124	Inconsistent value for PARCAT1 within a unique PARAMCD	As per the data collected in SDTM (source dataset)	<i>PARCAT1 is based on QSCAT to differentiate on time frame the questionnaire was collected</i> as per the data collected in SDTM (source dataset).	<ul style="list-style-type: none"> Variables that cause issue should be clearly documented. Describe impacts of data issue to analysis.
SD0040	Inconsistent value for LBTEST within LBTESTCD	This is a data issue for LBTESTCD=HCG that was not resolved.	This is a data issue for LBTESTCD=HCG that was not resolved. <i>It can be differentiated by either SERUM or URINE in LBSPEC.</i>	<ul style="list-style-type: none"> Need to specify how to distinguish LBTEST parameters.
AD0047	Required variable is not present	Datasets ADCM and ADCMNDT follow ADAE-like structure, not BDS.	<i>These datasets don't need PARAM, PARAMCD.</i> Datasets ADCM and ADCMNDT follow ADAE-like structure, not BDS.	<ul style="list-style-type: none"> Variables that cause issue should be clearly documented.
AD0162	ANRLO is greater than ANRHI	ANRLO is greater than ANRHI. This is due to an issue with the source data coming from local lab.	ANRLO is greater than ANRHI. This is due to an issue with the source data coming from local lab <i>for 11 patients for PARAMCD=ALPSI (7 records) where the same issue exists for the LB Lower Limit and the LB Upper Limit, respectively. This is a data issue that could not be resolved. However, these data was not used for any analysis and therefore no impact.</i>	<ul style="list-style-type: none"> Variables that cause issue should be clearly documented. Describe impacts of data issue to analysis.

Table 1. Actual example of acceptable error explanation

In error explanation, sponsor must be careful to specify,

- reason(s) why the error occurred
- Domain and variable associated with the error
- Impacts on the analysis

Of course, sponsor must check the consistency between attachment 8 and eCRT especially SDRG and ADRG. For example, version of CDISC standards and dictionary, list of SDTM/ADaM to be submitted.

ECRT PREPARATION TO FDA AND PMDA

There are 2 important points in eCRT preparation to both FDA and PMDA.

First, eCRT creation is always time-consuming activity and appropriate planning should be considered. One common CRT is ideal approach to submitting eCRT to both FDA and PMDA. If the two submissions are planned simultaneously, it will not be a problem. However, when FDA submission is planned first, creation of one common CRT is more difficult because sponsor needs to consider PMDA consultation to share Pinnacle 21 errors. . It means having confirmation to error explanation by PMDA will be a bottleneck to finalize SDRG/ADRG for FDA. Otherwise, sponsor has to update SDRG/ADRG again after FDA submission. Therefore, if there will be the time gap between FDA and PMDA NDA, having separate eCRTs might be more efficient and reduce overall workload.

Second, in simultaneous NDA sponsors should be more careful of PMDA eSubmission timeline. Usually as described in previous section, PMDA consultation always needs consider finalizing the eCRT package because PMDA feedback to Pinnacle 21 error explanation affects SDRG/ADRG finalization timing. Whereas eCRT completion for FDA can be planned a few weeks before NDA, PMDA will take a few months because of PMDA consultation. Figure 2 is general steps and timeline toward NDA for PMDA

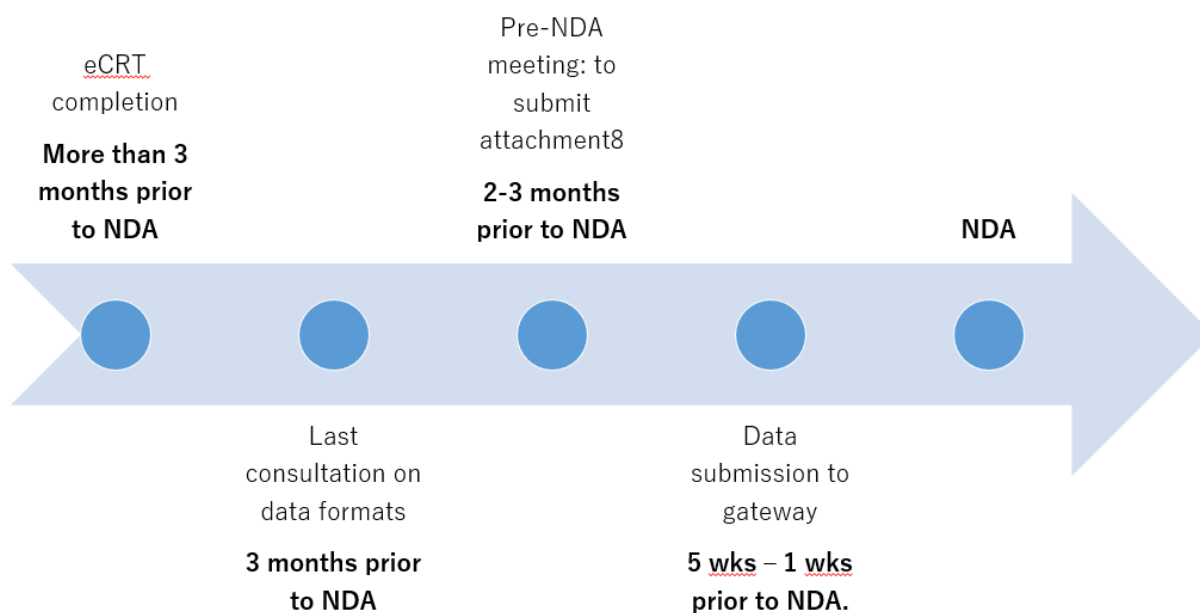


Figure 2. General timeline toward PMDA eSubmission

WHODD REQUIREMENTS

Sponsors must be careful to check WHO Drug Dictionary version in CM domain. According to PMDA data standard catalog, PMDA only accepts the version of April 2008 or later. During legacy data conversion, if WHODD version doesn't meet this PMDA requirement, drug terms have to be recoded.

PMDA REJECTION CRITERIA

Reject issue must be eliminated. No exception.

It is well known that PMDA defines the rejection criteria in their validation rules for SDTM, ADaM and corresponding Define.xml. According to PMDA guidance, rejection criteria is defined as "Rules which, if violated, will cause the review to be suspended until corrections. Very basic rules such as the presence/absence of necessary datasets for each clinical study". This is also challenge in NDA for both PMDA and FDA when FDA comes first. Some of Errors for FDA are Reject for PMDA. Hence, sponsor needs to run Pinnacle 21 validation with PMDA validation criteria if FDA submission followed by PMDA submission at later date.

When sponsors see rejection issues, all things sponsors need to do is to try hard to address the rejection issues. No matter how sponsors ask PMDA for exception with explanation, PMDA will request us to fix it. PMDA consultation on data preparation may be helpful to have an agreement on how to fix it.

SDTM/ADAM CROSS-CHECKS IN PINNACLE 21

During Pinnacle validation checks, do not forget below 2 points.

1. ADaM validation must be run along with SDTM AE, DM and EX.
2. Define-xml must be included as reference when SDTM and ADaM are being processed.

NECESSITY OF ANALYSIS RESULTS METADATA (ARM)

It is often discussed that “Is ARM mandatory requirement?” The answer is NO.

Although it is highly recommended to submit, sponsors have a choice of not submitting of ARM. However, PMDA may ask sponsor for ARM submission even if sponsors decide not to submit. As PMDA will accept ARM with PDF format, ARM should be submitted for reviewers.

SOFTWARE PROGRAM SUBMISSION

Both FDA and PMDA will request software programs used to create ADaM and generate tables and figures. Whereas both Health authority requests primary and secondary efficacy analyses, PMDA additionally requests programs of primary safety analyses and basic analyses of adverse events, and analyses to investigate the effect of major factors on efficacy and safety. Thus, sponsor should consult which programs are submitted with PMDA at clinical trial consultation (e.g. End of Phase 2 meeting) in along with submission package discussion.

If a sponsor is not able to submit software programs due to systemic reason, PMDA will request us to submit program specification to show the analysis algorithm.

PMDA QUERIES AFTER NDA

Awareness of quality issues and subsequent impact needs to be interested for PMDA eSubmissions. Here is an actual case that PMDA pointed out minor typo in SDRG. Figure 3 is a screen capture of SDRG.

Dataset – Dataset Label	Efficacy	Safety	Other	SUPP.-	Custom	Related Using RELREC	Observation Class
AE - Adverse Events		X		X			Events
B1 - Biomarkers	X			X	X		Findings
CM - Concomitant Medications		X		X			Interventions
CO - Comments			X				Special Purpose
DM - Demographics			X	X			Special Purpose
DS - Disposition			X	X			Events
DV - Protocol Deviations			X				Events
EG - ECG Test Results		X		X			Findings
EX - Exposure		X		X			Interventions

Figure 3. PMDA points out typo in SDRG

Tick in red square was not specified at the timing of NDA. 10 days after NDA, PMDA contacted Novartis to update SDRG. As this study was a global study, Japanese team had to reach out to global team and ask vendor who is responsible for define-xml creation if there is impact on define-xml generation. Fortunately, it was resolved by only replacing updated SDRG.

If eCRT creation was conducted in one place, one organization, this will not take much time to respond. When several sites and teams were involved in a PMDA eSubmission that includes global studies, there might be critical impact on the approval timeline.

Key message here is improvement of quality checks for submitted documents. This submission included only 2 studies so it did not have a significant impact to timeline. However imagine more than 10 studies are included in your submission package, how quickly could a sponsor respond to PMDA inquires?

CONCLUSION

Here is the summary of this paper.

- Always consider additional activities onto FDA eSubmission.
- PMDA may have severe review criteria to eCRT not only to data but also documents.
- For simultaneous NDA, it is recommended to set up timeline based on PMDA eSubmission.

It is not that PMDA eSubmission is more difficult than FDA. However, the requirements between FDA and PMDA are clearly different. If NDA is planned for both FDA and PMDA, it is not enough to only follow FDA's requirements. After eSubmission mandatory period, there will be more things that sponsors need to know.

It is important for sponsors to monitor PMDA updates carefully and work closely with your Japanese representatives.

REFERENCES <HEADING 1>

PMDA, "Revision of Basic Principles on Electronic Submission of Study Data for New Drug Applications." . January 24, 2019. Available at <https://www.pmda.go.jp/files/000229464.pdf>

PMDA, "Revision of Notification on Practical Operations of Electronic Study Data Submissions". January 24, 2019. Available at <https://www.pmda.go.jp/files/000229465.pdf>

PMDA, "Revision of Technical Conformance Guide on Electronic Study Data Submissions". January 24, 2019. Available at <https://www.pmda.go.jp/files/000229468.pdf>

PMDA, "FAQs on Electronic Study Data Submission (Excerpt)". April 10, 2019. Available at <https://www.pmda.go.jp/english/review-services/reviews/0007.html>

ACKNOWLEDGMENTS

Authors would like to thank my colleagues, particularly Vincent Guo, Steve Fitzpatrick and Mayumi Kominami for you valuable comments.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Yuichi Nakajima
Novartis Pharma K.K
yuichi.nakajima@novartis.com