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Consideration of R submission in Japan

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ABSTRACT

R adoption and submission are key topics in the pharmaceutical programming industry, and Japan is no exception. Although SAS users still constitute a large population in Japan, interest in R has grown significantly in recent years.

Industry communities such as Japan Pharmaceutical Manufacturers Association (JPMA) and PHUSE have conducted surveys on R adoption and initiated communication with Pharmaceuticals and Medical Devices Agency (PMDA), the Japanese health authority. PMDA has shown openness to accepting R, and sponsors need to consider the best approaches for R submissions, including understanding PMDA-specific requirements (e.g., PMDA consultations, PMDA gateway submissions following folder structure guidelines, etc.).

In this paper, we will briefly introduce the New Drug Application (NDA) process with PMDA and highlight key points for preparing PMDA communications and R submission deliverables.

INTRODUCTION

As of March 2025, PMDA has expressed its readiness to accept R for submission purposes. Notably, one global pharmaceutical company has been the sole company to submit using R in Japan so far. However, no substantial information has been shared by PMDA regarding their experiences.

Figure 1 shows the results of an R adoption survey conducted by Japan Pharmaceutical Manufacturers Association (JPMA) in 2024.

59% (32/54) of pharma companies in Japan have used R in clinical programming activity. The details of 32 responses are as follows. Sample size calculations (28/32, 87.5%), analyses of internal meetings (23/32, 71.9%), exploratory analyses (22/32, 68.8%), and clinical pharmacology analyses (17/32, 53.1%). There are fewer use cases of clinical reporting activities such as creating SDTM, ADaM and TFLs for Clinical Summary Reports.

In addition, while most cases are observed in clinical pharmacology analyses, 41% (13/32) and 37.5% (12/32) of pharma companies have submitted TLFs using R and R programs for TLFs. However, none of the pharma companies have submitted R packages to PMDA.

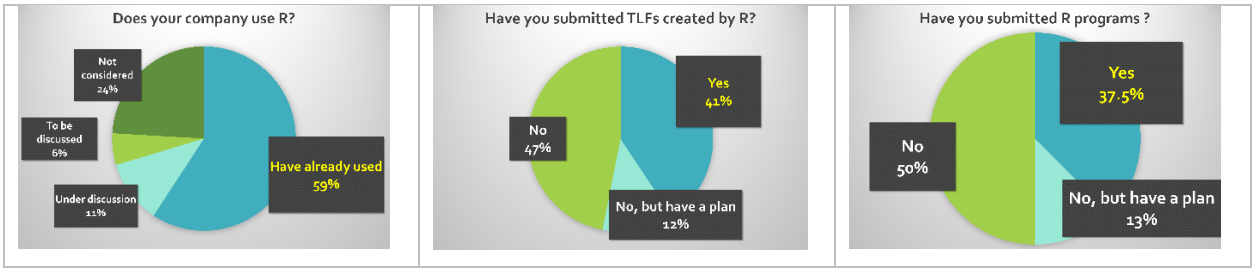

Figure 1. JPMA R adoption survey (2024)

Although R-related deliverables have been partially submitted to PMDA, the number of complete “R submissions” in Japan remains very limited.

SIX POINTS TO CONSIDER FOR PMDA R SUBMISSION

PMDA’s primary concern is the ability to execute the submitted R code. Sponsors must ensure appropriate pre-submission communication and documentation.

PMDA MEETING FOR R SUBMISSION

Table 1 summarizes PMDA meetings related to PMDA R submission.

One is “Pre-NDA meeting” which takes place in one to three months prior to NDA. The primary purpose of the pre-consultation prior to NDA is to allow sponsors to confirm the content and format of the documents they plan to submit with PMDA in advance, thereby improving the quality of the submission materials. Sponsors can also notify PMDA that they intend to conduct an R-based submission.

Another relevant meeting is the “Consultation on preparation of submission of electronic study data”. In this consultation, the sponsor and PMDA discuss the preparation of eStudy data for R-related deliverables.

We recommend that sponsors hold at least a Pre-NDA meeting to notify PMDA of their intention to conduct an R-based submission.

MEETING	WHEN	WHAT (Purpose of the meeting)
Pre-NDA meeting	1 to 3 months prior to NDA.	To notify PMDA of an R-based submission.
Consultation on preparation of submission of electronic study data	Anytime during data preparation.	To discuss how to prepare R-related deliverables with PMDA. For example, how to submit internally developed R packages, how to describe R-related information in ADRG, etc.

Table 1. Summary of PMDA meeting for R submission

ADRG DOCUMENTATION

It is well known that PMDA defines specific validation rules in Pinnacle 21 validator. There are differences in the validation rules for CDISC compliance between PMDA and FDA, and those differences must be described in ADRG. However, the descriptions related to R can remain consistent.

In Section 7 of the ADRG, sponsors must summarize the following analysis-related information regarding R:

1. The version of R and RStudio along with OS version of analysis environment.
2. R package information including version and descriptions.
3. R programs for ADaM and TLFs.

Please note that the OS version of analysis environment (e.g., Windows, Linux, …) must be specified for PMDA. PMDA has emphasized that this is an item frequently overlooked.

FOLDER STRUCTURE (M5)

No significant differences are observed in folder structure for both the FDA and PMDA; however, subfolders cannot be created for PMDA.

R-related information (Programs, Packages) can be included in “…/analysis/adam/programs”.

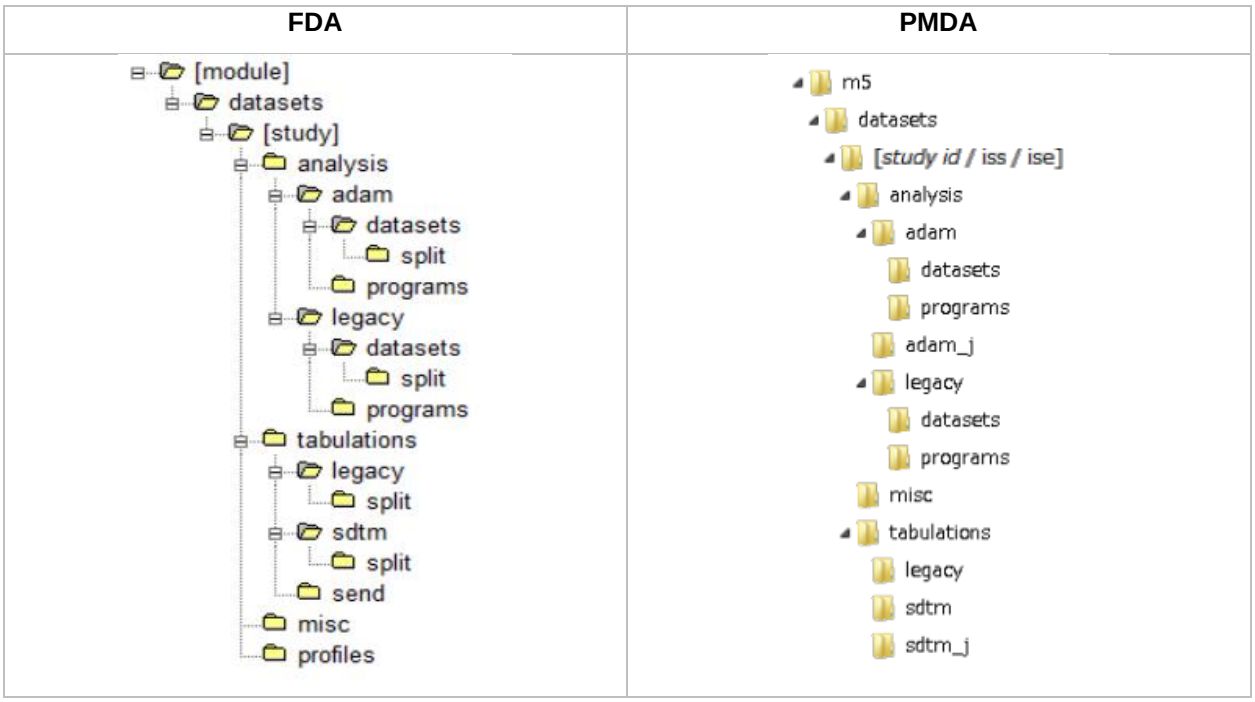

Figure 2. m5 folder structures for both FDA and PMDA

PMDA GATEWAY SYSTEM

When a sponsor submits eStudy data to PMDA, the files are submitted via the PMDA Gateway system.

This is a PMDA-specific system, but there are no notable differences regarding R submissions. The file naming convention of the PMDA Gateway is almost the same as that of the FDA Electronic Submission Gateway. File names must be within 32 characters and consist only of alphanumeric characters (lower case) and certain symbols (underscore, hyphen, and single dot).

If a single file exceeds 10GB or the total file size of one submission exceeds 100GB, the sponsor should notify PMDA in advance.

R PROGRAMS & R PACKAGES

As of March 2025, the PMDA Technical Conformance Guide on Electronic Study Data Submissions states that programs do not have to be executable. However, this requirement may be updated in the future due to the increasing acceptance of open-source software.

If submitting R packages is challenging, sponsors may submit a specification document that includes package version information and details of the packages used instead of submitting R code and packages (PMDA Technical Conformance Guide, Section 4.1.6.1).

In addition, the R Consortium Pilot 3 project provides an excellent example of submitting R code and R packages. Sponsors may follow the same approach. Further discussions can be held at a PMDA consultation.

R PACKAGE MANAGEMENT

R package management is not a specific consideration for PMDA R submissions, and the validation of R packages is the sponsor's responsibility.

Freezing the analysis environment, including R package management, is crucial for conducting analyses in response to inquiries after submission.

For PMDA inspections, it is recommended that sponsors prepare an R package management document, including a system validation report, in addition to ADaM and TFL QC report.

THE RECOMMENDED PROCESS TOWARD PMDA R SUBMISSION

Figure 3. shows the recommended process for PMDA R submission.

The first step is to list the R packages to be used. If a sponsor plans to submit an internally developed R package, a PMDA consultation should always be considered. In general, it is recommended to use publicly available R packages from CRAN to avoid unnecessary discussions, as verifying internally developed packages can be extremely time-consuming.

Secondly, the Analysis Data Reviewer's Guide (ADRG) should include key information on the R analysis environment, code, and packages. If submitting R code and packages is difficult, details of the analysis algorithms should be provided in ADRG Section 7.

Lastly, a sponsor should inform PMDA about the R submission so that PMDA can acknowledge it. The sponsor should also prepare for potential questions from PMDA and inspection to ensure the reproducibility of results.

If the eStudy data includes a new type of data related to the R submission, a consultation on the submission method should be considered. For example, this applies to analysis metadata, such as LinkML in association with the CDISC Analysis Results Standard. Sponsors can discuss the submission of such new types of data with PMDA.

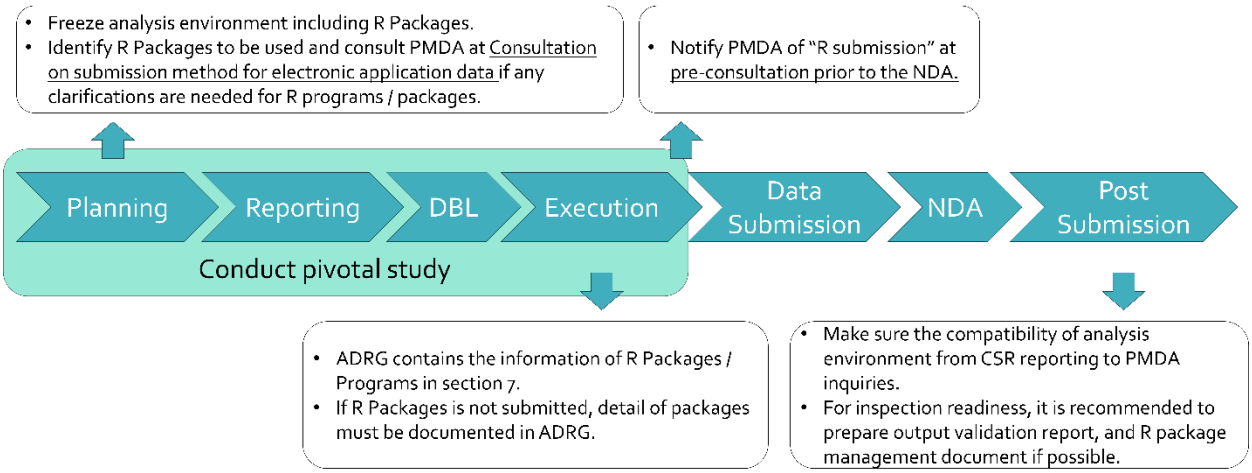

Figure 3. The recommended process of R submission in Japan

CONCLUSION

While there are some differences in eStudy data submission between FDA and PMDA, the requirements for R submission are expected to be largely the same. However, it is strongly recommended to plan a PMDA consultation, especially when submitting R packages for the first time in company R submission.

There are still many uncertainties regarding R submission to PMDA. However, if leading companies take the initiative to share information, it will enhance the overall understanding within the industry and ultimately contribute to the faster approval of new drugs.

REFERENCES

PMDA, "Revision of Technical Conformance Guide on Electronic Study Data Submissions", April 8, 2024.

PMDA, "New Drug Applications Using the Gateway System", April 1, 2022.

JPMA, 2024, “OSS surveillance in Japan” (Japanese only) Accessed March 20, 2025. https://www.jpma.or.jp/information/evaluation/results/allotment/eo4se30000002zrx-att/DS_202412_oss_questionaire.pdf

R Submission Working Group, Available at https://rconsortium.github.io/submissions-wg/

Yuichi Nakajima, PHUSE EU Connect 2021, “(You) R Programs for Health Authorities in Japan”.

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