Paper SA08

Key guidelines, Tricks and Experiences for PMDA and comparison with FDA and NMPA CDE submission

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ABSTRACT

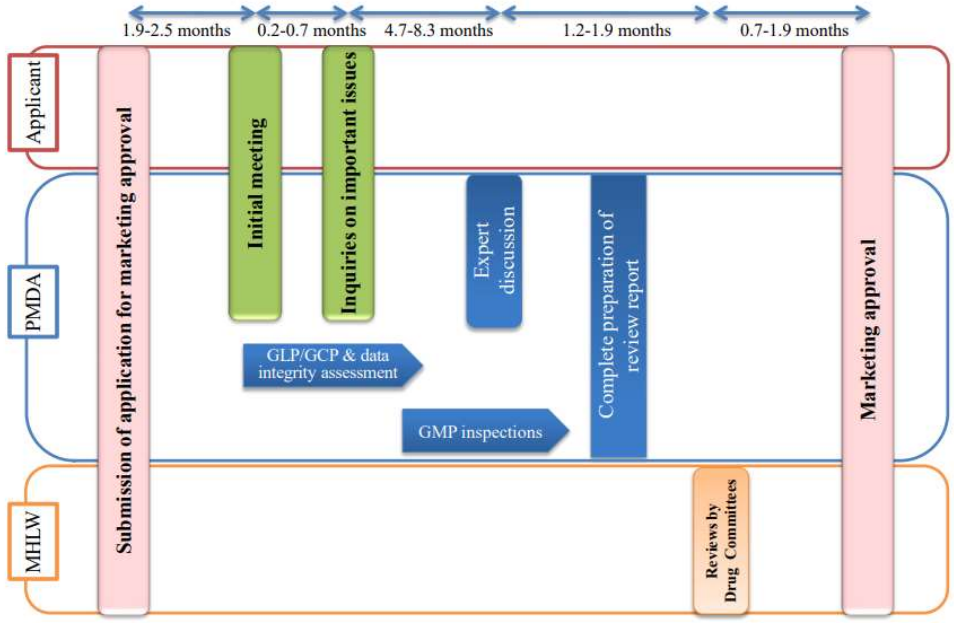
Submitting documents to regulatory authorities such as the Pharmaceuticals and Medical Devices Agency (PMDA) and the Food and Drug Administration (FDA) is a complex task requiring careful preparation and an in-depth understanding of regulatory requirements. This paper outlines key guidelines and highlights the differences between submissions to PMDA, FDA, and the Nation Medical products Administration (NMPA) Center for Drug Evaluation (CDE). Additionally, it provides practical tips and shared experiences to equip programmers and regulatory teams with the necessary knowledge for efficient PMDA submission processes and effective handling of regulatory inquiries.

COMPARISON OF PMDA, FDA AND CDE SUBMISSION REQUIREMENTS

Topic	PMDA	FDA	NMPA(CDE)
Validation rules for CDISC e-data packages	PMDA uses Pinnacle 21 Enterprise 5.1.2 tool to verify compliance with published PMDA validation rules.	The FDA does not require an P21 enterprise version or specify a particular validation tool, and P21 community version is commonly used to check compliance.	NMPA's requirements continue to evolve. For datasets not translated into Chinese, FDA/PMDA validation rules can be applied. For Chinese-translated datasets, the NMPA validation engine within the P21 tool may be utilized.
CDISC Requirement	CDISC compliance is mandatory for NDAs submitted on or after April 1, 2020. A transition period (Oct 2016–Mar 2020) allowed sponsors preparation time. Non-CDISC formatted data submissions require advance consultation with PMDA to determine the scope and content of submissions.	CDISC standards are required for studies initiated after: - Dec 17, 2016 (for NDA, BLA, ANDA) - Dec 17, 2017 (for Commercial IND) Study data must follow formats listed in FDA Data Standards Catalog.	CDE aligns with FDA and PMDA, recommending CDISC standards as the preferred standard for clinical research data submissions in China. Moving forward, CDISC is the only global standard explicitly endorsed by CDE, streamlining reviews and approvals.
Analysis Results Metadata (ARM) Requirements	ARM is highly preferable by PMDA to support primary efficacy and safety results justifying dosage and administration. PMDA's technical guidance states inclusion of ARM in the ADaM define file is 'desirable.' ARM is not required when ADaM datasets aren't used (e.g., exceptional non-CDISC analyses).	FDA currently considers ARM optional. Sponsors may include ARM metadata in define.xml to aid reviewers, but it is not mandated.	Current guidance from CDE does not explicitly require ARM. However, as alignment with FDA/PMDA increases, inclusion of ARM to assist reviewers may be encouraged in future.
Translation Requirements	No translation required for e-data packages; English is acceptable. Translation required only for queries and responses.	English is acceptable; no translation requirement.	Translation is required for e-data packages in the following areas: - Dataset labels and variable labels - Terms for adverse events, concomitant medications, and

Topic	PMDA	FDA	NMPA(CDE)
			medical history - Definition file labels, specifications, and values or codes list of efficacy indicators - Annotated CRFs (aCRFs) and Data Reviewer's Guides
Causality/ Relationship Definitions	The PMDA expects sponsors to categorize each adverse event's causality clearly, indicating whether it is related or not related. In studies, causality categories may include related/not related, probable/possible/unlikely/unrelated. Only 'unrelated' is considered 'not related'; all other categories, including 'unlikely related,' are considered 'related' by the PMDA. Any deviation from ICH guidelines must be justified.	FDA uses the 'reasonable possibility' standard and follows ICH guidelines for defining adverse events and adverse drug reactions. Considering 'Unlikely related' as 'not related' is accepted by FDA.	The CDE follows the same approach and definitions as the FDA for the causality/relationship of adverse events (AEs)

STANDARD REVIEW TIMELINE FOR NEW DRUG APPLICATION FOR PMDA SUBMISSION



MHLW- The Ministry of Health, Labour and Welfare (MHLW) is a government ministry in Japan responsible for overseeing health, labor, and welfare policies.

BEST PRACTICES AND TIPS FOR EFFICIENT PMDA SUBMISSION

- **DATA VALIDATION RULES**

The PMDA performs independent validation of your study data using their P21 Enterprise environment and reconciles their results with those of the sponsor. If the PMDA identifies any new or undisclosed error issues without explanations, they will send inquiries to the sponsors to address these discrepancies. The PMDA website (New Drug Review with Electronic Data | Pharmaceuticals and Medical Devices Agency) provides clear guidance on acceptable versions of PMDA validation rules. It is highly preferable to select the latest version of PMDA rules, considering the time of submission and potential queries related to the submission. A single set of validation rules needs to be implemented for a PMDA submission across all e-data packages that are CDISC conformant.

PMDA validation rules categorize issues as 'REJECT', 'ERROR', and 'WARNING'. If issues with a severity of 'REJECT' are found in your validation results, the PMDA's review will be suspended until these issues are fixed. For 'ERROR' and 'WARNING' issues that are not resolved, proper explanations need to be provided in the reviewer's guide, especially for 'ERROR' issues.

E-data packages submitted to the FDA must be revalidated against PMDA rules, and any validation issues must be addressed in the reviewer's guide before they can be reused.

- **UNDERSTANDING THE SCOPE OF STUDIES FOR SUBMISSION**

It is essential for the regulatory team to collaborate with PMDA to clearly define the scope of the study electronic data packages required for submission. These e-data packages may focus on clinical pharmacology studies, population analyses, or physiologically based pharmacokinetic model analyses. Specifically, data from studies or analyses that establish dosage and administration guidelines or evaluate safety, efficacy and pharmacokinetics, must be submitted electronically. Integrated safety, Integrated efficacy analysis should be included when applicable. Clearly understanding the focus and scope helps in effectively assigning and managing specific tasks among team members.

- **IDENTIFYING CDISC AND NON-CDISC STUDIES**

It is essential to classify electronic data packages as CDISC-compliant or non-CDISC since legacy non-CDISC studies might require conversion to CDISC standards. Sponsors must consult PMDA if they wish to seek an exemption from CDISC standards for specific studies. When submitting electronic data from clinical studies not formatted according to CDISC standards, sponsors should include clinical study data collected via Case Report Forms (CRFs), analysis datasets, analysis programs used to generate results, and dataset definition documents. Sponsors should utilize the “Explanation of Electronic Study Data (Form B)” during consultations to clearly explain exemption requests. Non-CDISC-compliant clinical study data should be stored in the legacy folder as outlined in Section 3.5 of the Technical Conformance Guide. For clinical pharmacology studies that are not CDISC-compliant, data should be stored in a newly created "cp" folder within the analysis level of the M5 folder.

- **PROGRAMS REQUIRED FOR SUBMISSION:**

Submitting ADaM datasets and analysis programs is crucial, as PMDA may request additional information if these programs are not included in the initial package. Programs related to ADaM datasets and analyses that support critical findings on efficacy, safety, and clinical results influencing dosage and administration must be submitted. Detailed information about the specific software, its version, and the analysis environment in which the programs were developed must be clearly documented in the Analysis Data Reviewer's Guide (ADRG). If macro programs were used, they should preferably be submitted alongside the main programs. However, if submitting macro programs or the actual programs is challenging, providing clear specifications detailing the analysis algorithms will suffice.

- **ARM PREPARATION BASED ON PRIMARY AND KEY EFFICACY ENDPOINTS**

A significant difference between PMDA and FDA submissions lies in the requirement for Analysis Results Metadata (ARM). ARM consists of metadata describing key analysis results, such as efficacy endpoints, and provides clear traceability to the corresponding data and analysis methods. ARM is typically included within the define.xml file for ADaM datasets.

The FDA currently views ARM as optional, allowing sponsors to include it in define.xml to assist FDA reviewers, but does not mandate its inclusion. Conversely, the PMDA highly prefers ARM for specific analyses, particularly those supporting pivotal efficacy and safety conclusions. For instance, the PMDA expects sponsors to submit ARM documenting primary efficacy analyses and critical safety analyses that underpin dosing and labeling decisions within e-data packages for pivotal studies.

To proactively address potential questions from the PMDA, it is recommended as best practice to provide comprehensive ARM for all pivotal analyses in a PMDA submission. Doing so enables PMDA reviewers to clearly understand how each reported result was derived and facilitates replication of the analysis if needed. For non-pivotal analyses within the submission, ARM is not required; instead, providing the relevant ADaM datasets and corresponding analysis programs is sufficient.

- **INSPECTION READINESS**

Inspection preparation should be coordinated with the quality function and focus on the documentation based on Good Clinical Practice (GCP) BIMO list. Mock interviews are highly recommended to prepare for the real inspection.

CONCLUSION

A thorough understanding of PMDA regulatory requirements, early and meticulous planning, proper identification of CDISC compliance, clear documentation of analysis datasets and programs, and detailed preparation of Analysis Results Metadata (ARM) are essential elements for an efficient submission. By following these best practices and proactively preparing for potential inquiries, regulatory and programming teams can significantly streamline the PMDA submission process, facilitating timely approvals and enhancing overall submission quality.

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