PharmaSUG China 2025 - Paper LS-145

Strategy Development of NMPA Submission Package

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ABSTRACT

Developing an effective NMPA submission package demands comprehensive strategic planning that carefully considers submission timelines, content requirements, and resource availability. The strategic framework encompasses various approaches, ranging from FDA-based submissions utilizing complete or partial package adaptation, to PMDA-based submissions, or independent submissions leveraging global studies and China local studies.

Through detailed case studies and analysis of cross-departmental collaboration methods, this paper explores the unique advantages and challenges of each approach, ultimately providing guidance for optimal strategy selection while addressing potential risk mitigation measures.

INTRODUCTION

The National Medical Products Administration (NMPA) mandates that all submissions must be made electronically. This requirement was formalized when the NMPA issued the "Guiding Principles for Clinical Trial Data Submission" (药物临床实验数据递交指导原则) in July 2020, which became effective on October 1st, 2020. Under this guideline, the NMPA recommends the use of Clinical Data Interchange Standards Consortium (CDISC) standards for data submission, aligning China's requirements with international standards.

The NMPA submission packages typically include SDTM, ADaM, Define-XML, Clinical Study Data Reviewer's Guide (cSDRG), Analysis Data Reviewer's Guide (ADRG), programs and annotated Case Report Forms (aCRF).

E-DATA SUBMISSION OF OTHER HEALTH AUTHORITY

FOOD AND DRUG ADMINISTRATION (FDA)

FDA has been at the forefront of electronic data submission, having begun accepting electronic data since the 1990s. In a significant move to standardize clinical trial data submissions, the FDA mandated compliance with CDISC standards for all clinical studies starting December 17, 2016. This requirement marked a crucial milestone in the standardization of clinical trial data submissions and has since become a cornerstone of the FDA's electronic submission framework.

PHARMACEUTICALS AND MEDICAL DEVICES AGENCY (PMDA)

PMDA initiated electronic data submission on October 1st, 2016. Following a transition period to allow industry adaptation, the PMDA made electronic data submission mandatory for all applicable submissions starting April 1st, 2020. This phased implementation approach allowed pharmaceutical companies and sponsors to gradually adapt their systems and processes to meet the new electronic submission requirements.

THE EUROPEAN MEDICINES AGENCY (EMA)

EMA currently does not mandate the submission of electronic data packages. However, the agency is actively exploring this area through pilot programs to assess the feasibility and benefits of standardized electronic data submissions. These pilot initiatives are part of the EMA's ongoing efforts to modernize its regulatory processes and align with global trends toward data standardization, while gathering valuable insights before potentially implementing formal requirements in the future.

NMPA SUBMISSION PACKAGE STRATEGY

Upon receiving notification to prepare a submission package for NMPA, programmers need to establish a comprehensive strategy for the NMPA submission package. The following strategies can be considered when preparing an NMPA submission package:

- FDA-based submission package
    - Complete FDA package
    - Partial FDA package
- PMDA-based submission package
- Independent submission package
    - Global study
        - EMA submission
        - Study never submitted
    - China local study (include PAC study)

The strategy for the NMPA submission package should be determined by considering multiple factors, including but not limited to the NMPA submission timeline, required submission contents, and available resources.

Let us conduct a comparation of the submission package requirements across the FDA, PMDA, and NMPA regulatory authorities (Table 1).

	FDA	**PMDA**	**NMPA**
Mandates	FDA Data Standard Catalog	PMDA Data Standard Catalog	Not Applicable
Study Data Standards	CDISC SDTM, ADaM and TAUGS	CDISC SDTM, ADaM and TAUGS (optional)	Recommend CDISC standards
Validation rule	FDA Validation and Business Rules	PMDA Study Data Validation Rules	Not Applicable
CDISC compliance check	SDTM, ADaM, Define-XML	SDTM, ADaM, Define-XML with specific “Reject” criteria	No requirement for validation
Planning	SDSP	Not Applicable[a]	Not Applicable
Tabulation	aCRF, xpt, Define-XML, cSDRG	aCRF, xpt, Define-XML, cSDRG	Recommend CDISC standards
Analysis	xpt, Define-XML, ADRG, programs, ARM (optional)	xpt, Define-XML, ADRG, programs, ARM (strongly recommended)	xpt, Define-XML, ADRG[b], programs
BIMO	listings, clinsite.xpt, Define-XML	Not Applicable	Not Applicable
Programs	ASCII text format	The file name should include the extension attached by the analysis software.	TXT file
Dataset size	Required to split if > 5GB	Optional, but need to inform	Required to split if >4GB
Language	English	PMDA recommends submitting data written in English as much as possible, but also allows to submit data in Japanese.	Some Chinese labels and texts are required. (e.g. dataset/variable labels, derivation rules, coding terms, efficacy related CTs, RGs, etc.)
File type accept[c]	XPT, PDF, TXT, XML, XSL, XLS, XLSX, etc.	XPT, PDF, TXT, XML, XSL, XLS, XLSX, etc.	XPT, PDF, TXT, XML, XSL

Table 1. Comparison of FDA/PMDA/NMPA

[a] From October 1, 2023 (application date), PMDA does not require to submit "Explanation of Electronic Study Data (Form A)".

[b] Recommend sponsor to submit the Reviewer’s Guide.

[c] FDA: Specification for Transmitting Electronic Submissions using eCTD Backbone Specifications; PMDA: 000267935.pdf; NMPA: eCTD 技术规范 V1.0

The comparison presented in Table 1 indicates that the main difference between preparing FDA-based and PMDA-based submission packages lies in the requirement for Chinese versions of Define-XML, Reviewer's Guides (RGs), and aCRF. In terms of overall resource requirements and effort, there is no substantial difference between the two submission types.

When submission packages for the same study have been prepared for both FDA and PMDA, and scheduling allows, programmers strategically choose to reference the more recent submission package. This approach leverages potential improvements and refinements that may have been implemented based on issues identified during the earlier submission process.

Another factor affecting resources is translation. For China local studies, programmers have two processes to choose from. One is to prepare English Metadata, have the translation department translate the dataset labels, variable labels, and derive rules, then programmers generate the Define-XML. Another approach is for the programmers to translate, directly writing Chinese dataset labels, variable labels, and derive rules in the Metadata, then generating a Chinese Define-XML. Programmers typically choose the second process.

The advantages of the second process are particularly evident in two scenarios. First, when derive rules are very complex, such as in Phase III pivotal studies. The translation department's translations might be inaccurate, and when programmers review and find issues, it requires updates, causing delays. The second scenario is when time is extremely tight. Although writing Chinese Metadata directly takes longer than writing English Metadata, it still takes less time than writing English Metadata plus waiting for the translation department's work. Similarly, when preparing Chinese RGs, to save resources, there's a preference for directly preparing the Chinese RGs.

It should be noted that choosing different NMPA submission package strategies will affect the resources of collaborating departments, requiring notification to the relevant departments to prepare resources in advance. Especially if translation department support is needed, they should be notified ahead of time.

USE CASES

Let us consider some common NMPA submission scenarios to illustrate the selection of submission strategies.

1. Complete FDA-based submission package

Compound A only prepares an FDA submission package, including one study. NMPA submission includes this study. The translation department translates all dataset labels, variable labels, derive rules, etc. in the SDTM and ADaM Metadata. After programmers confirm the translations are correct, they generate the Chinese version of Define-XML. The RGs are also translated by the translation department, with programmers confirming the accuracy of the translation.

2. Partial FDA-based submission package

Compound B prepares an FDA submission package, which includes three studies, ISS and ISE. The NMPA submission content includes two studies, ISS, and ISE with East Asian patients. The packages for the two studies and ISS can be submitted directly to NMPA. The process of preparing Define-XML and RGs is the same as in case 1. Support from the translation department is needed. For the ISE, programmers prepare Chinese ADaM Metadata and generate a Chinese version of ADaM Define-XML. The ISE ADRG is also prepared directly in Chinese. Programmers should explain to RA that there is a potential risk, as the ISS contains data from one study not submitted in China. Currently, CDE does not request submission of the study because it has no Chinese patients. There are two options to address this risk. If programmers have sufficient resources, they can prepare the submission package for this study after completing the NMPA submission. The other option is to prepare the package for this study when CDE requests to submit it, but programmers would need some time for preparation.

3. PMDA-based submission package

Compound C assumes a scenario where submissions are made to both FDA and PMDA. FDA submission is before PMDA submission. Compound C's FDA submission package has one US study. The PMDA submission package has one US study and one Japanese study. Japanese programmers update the US study submission package according to PMDA submission requirements. If the completion time for the Japanese submission package is earlier than NMPA submission time, then Chinese programmers can prepare the NMPA submission package based on the Japanese package. Due to the tight preparation schedule, Chinese programmers do not need support from the translation department. As soon as Japanese programmers complete a document, like Metadata or RGs, Chinese programmers can begin translating and preparing the Chinese submission package.

4. EMA submission

Compound D is only submitted to EMA, so no submission package is prepared. The English Metadata is available. Like Case 1, a Chinese version of Define-XML is prepared. Content in the Metadata requires support from the translation department, while RGs do not need translation department support. Programmers directly prepare Chinese version of the RGs.

5. Global study never submitted

For Compound E, assume a special type of study submission. Compound E is approved for marketing in China and requires a labeling update. A Natural History Study that is not previously submitted is used for the China submission package.

a) Introduction of A Natural History Study

A Natural History Study is a systematic research approach used to document and track the complete progression of a disease from its onset through its various stages. These studies are particularly crucial in rare disease research, as they help doctors and researchers better understand disease patterns and develop more effective treatment strategies.

Researchers observe and collect data from patients over time without intervening with specific treatments. This may involve regular medical examinations, tests, and patient-reported outcomes.

b) Points to note when preparing packages using Natural History Study

When reviewing Natural History Study datasets, programmers typically find that SDTM and ADaM datasets are not CDISC standard and lack Pinnacle21 validation. Therefore, these datasets should be placed in the legacy section for regulatory submission. Because the data is not standardized, programmers choose to do the translation themselves. No support from the translation department is needed. Programmers enhance the Chinese derive rules on the English version of the Metadata. Following CDISC standards, they translate dataset labels and variable labels into Chinese standard labels as much as possible and generate a Chinese version of Define-XML. Programmers rewrite the ADaM programs into a submittable program format. After rewriting, they run the datasets and compare them with the original ADaM to ensure consistency. TLF programs undergo the same updates. This requires more resources than a standard study.

6. China local study

For Compound F, assume a common type of study submission. Compound F is approved for marketing in China and requires a China Post-Approval Commitment (PAC) study submission.

a) Introduction of A PAC study

A PAC Study is a clinical research study conducted after a drug has received regulatory approval. It is also known as Post-Marketing Commitment studies or Phase IV studies.

b) Points to note when preparing packages using PAC Study

Programmers write Chinese dataset labels, variable labels, and derivation rules in the Metadata, and then generate Chinese version of Define-XML. RGs are also directly prepared in Chinese. No translation department support is needed.

CONCLUSION

Based on the previous analysis and examples, the following conclusions can be drawn：

- Given the same content, there is no significant difference in workload when preparing Chinese packages based on FDA or PMDA submission packages. It is recommended to use the later prepared submission package since issues discovered would have been corrected.
- If preparing based on non-standardized datasets, more resources might be needed, including standardizing programs, rewriting derivation rules, etc.
- During submission package preparation, all departments work as one unit. It's necessary to consider overall resources and reduce the total package preparation time, rather than just focusing on reducing programmer resources. Choose to prepare Define-XML and RGs directly in

Chinese, when possible, as this eliminates translation and review time.

- Potential risks need to be clarified with RA, and strategies should be prepared in advance.

Due to the differences in China submission package content, following the basic principles summarized above, selecting an appropriate NMPA submission strategy can greatly reduce resource usage, shorten preparation time, and ensure the accuracy of the submission package.

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