

## Japanese submission/approval processes from programming perspective

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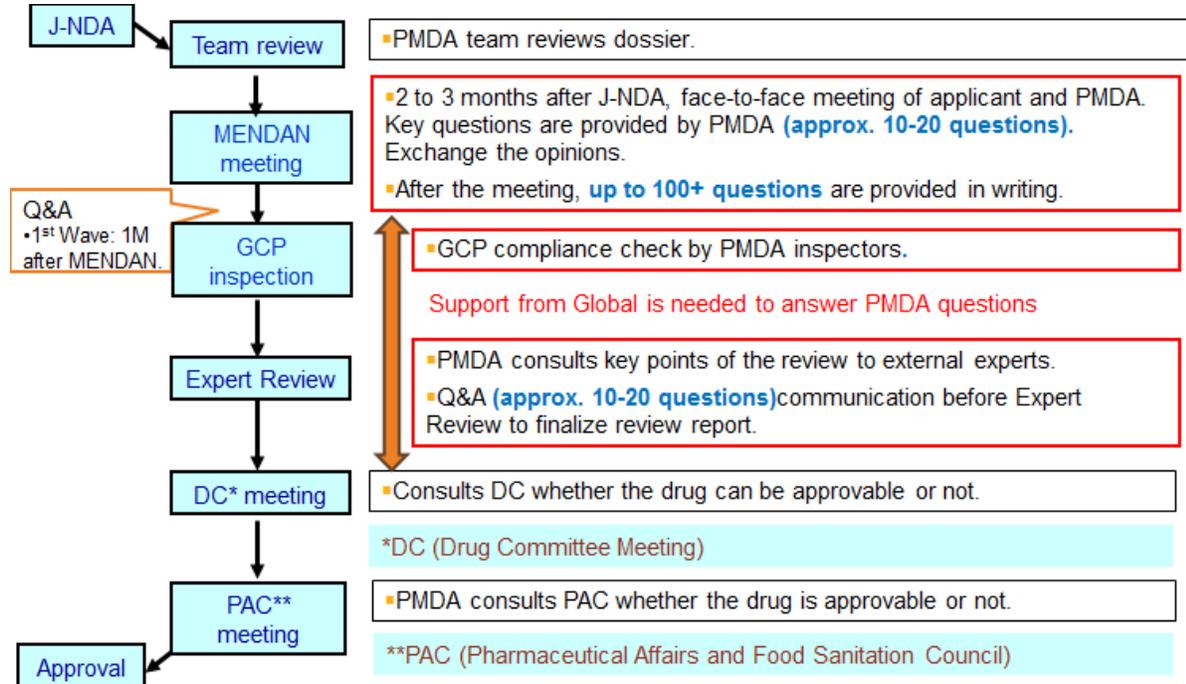
### ABSTRACT

Japan is one of the world's biggest pharmaceutical markets and as such, development and approval of new drugs in Japan is one of the top priorities for pharmaceutical companies. The intent of this paper is to present Japan-specific submission requirements and also the review/approval process of the Japanese health authority PMDA (Pharmaceuticals and Medical Devices Agency) to a non-Japanese audience, especially programmers. Thus, the main focus of this paper is the specific programming requirements for a submission/approval in Japan that may differ from global processes. This knowledge may help global teams to better understand the specificities of Japanese pharmaceutical market and in turn, strengthen collaboration of global groups with Japanese teams and colleagues.

### INTRODUCTION

This paper focuses on programming related topics that include overall submission and PMDA review guidelines (including electronic data submission in CDISC standard format requirement in October, 2016). It also discusses specific requirements for subgroup analyses of Japanese patients, simultaneous submission with US and EU, Japan CTD (common technical document), pooling of studies for medical package inserts in Japan, and safety analyses to support the creation of "Guide for appropriate use of medication" and Japan risk management plan (J-RMP). Additionally, various examples of PMDA questions and answers as well as my experience with Japanese submissions/approvals processes at Novartis are presented in this paper.

### OVERVIEW OF SUBMISSION AND REVIEW/APPROVAL PROCESSES



**Figure 1. Over view of Submission, review, and approval process**

**JAPAN NEW DRUG APPLICATION (J-NDA)**

J-NDA submission and review/approval processes and their requirements are similar to those of FDA (Food and Drug Administration) and/or EMA (European Medicines Agency), but there are some important differences that should be noted. For example, there is a mandatory submission of key results of the Japanese population if Japan participates in global studies (or regional studies e.g. Asian studies). This is the most important thing to be understood because substantial programming support is needed.

Similar to FDA and EMA, the CSR (clinical study report) and CTD are key documents which need programming involvement for a Japan submission. However, the pooling of adverse events from multiple studies may require inclusion of different indications and thus, may require additional programming support from those who are familiar with PMDA's requirements.

The review time after filing J-NDA is similar to US and EU (European Union) and is 12 months for standard filing and 9 months for the "Orphan Drug Designation". During this review, there are two big periods of PMDA questions. The first one is after Mendan meeting (face to face meeting with PMDA approximately 2-3 months after filing) and the second one is after GCP (Good Clinical Practice) compliance check conducted by PMDA inspectors but before the Expert Review meeting. PMDA may travel to the sites in other country for GCP inspection. The question received during the first period are mostly of general nature (e.g. clinical) but the questions received during the second period require a substantial programming involvement which should be planned ahead.

**GLOBAL STUDY AND ITS PLAN/REPORTS**

Many phase 3 studies, especially for oncology compounds, include Japanese sites and a Japanese submission is part of the global submission package. It is not easy to recruit several hundreds of Japanese patients to conduct Japanese phase 3 studies especially in oncology and rare disease indications.

In a statistical analysis plan, the key safety/efficacy tables/figures of sub analyses for Japanese patients must be included in the global statistical analysis plan describing statistical analyses for Japan submission. J-CTD (Japan Common Technical Document) summarizes and discusses key results of the Japanese population in addition to global data. Global CSR focuses on a summary and discussion of whole population and subgroup analyses of important factors of the study and the tables/figures of Japanese patients are included in the appendix of global CSR or J-CTD. The Japan submission team (mainly medical writers and clinicians) writes a J-CTD by using tables/figures of all patients and Japanese patients. Japanese team will attach the global CSR in the J-CTD because PMDA accepts CSR written in English.

This table summarizes which documents need to be submitted to PMDA and language requirements:

<b>Type of documents</b>	<b>Language</b>
Global CSR	English is acceptable.
J-CTD 2.5 Clinical Overview	Summary in Japanese. Tables can be in English.
J-CTD 2.7.2 Summary of Clinical Pharmacology	Summary in Japanese. Tables can be in English.
J-CTD 2.7.3 Summary of Clinical Efficacy	Summary in Japanese. Tables can be in English.
J-CTD 2.7.4 Summary of Clinical Safety	Summary in Japanese. Tables can be in English.
PMDA questions	Japanese only. Japan team translates them into English when they need support from global.
Answers for PMDA questions	Answers have to be written in Japanese. However summary tables can be in English. Translation of AE tables/listings from English into Japanese is time consuming, so AE tables/listings in Japanese are often requested by clinical team/medical writers.
Mendan meeting (face to face meeting with PMDA)	Japanese in the meeting. An interpreter is needed if global team joins.
GCP inspection	Japanese during the inspection. An interpreter is needed if global team joins.

## **Table 1. Summary Table of Which Documents Have to Be Written in Japanese**

The collaboration between global and Japan teams is crucial in order to incorporate specific requirements of Japan submission in a statistical analysis plan and in selection of key tables/figures of Japanese population. Therefore, a Japanese patient flag should be populated in the analysis datasets, and global programs/macros should be adjusted to produce tables/figures of Japanese only patients.

### **SIMULTANEOUS SUBMISSION**

Historically PMDA submissions were after global approval, but the drive for simultaneous submission in Japan with the US and the EU due to a strong need for shortened drug approval time from a patient/doctor perspective is now extremely important in Japan. This is why PMDA tries to review all new drug applications within the standard timelines.

Global studies can facilitate this if a statistical analysis plan includes requirements for Japanese submission and results of studies (both data for all and Japanese patients) are available at almost the same time as the global CSR. However, time is needed to translate global documents to Japanese and this can lead to a Japan submission one month after Global. Despite this, some global pharmaceutical companies in Japan have already filed some of their studies only 1 month after the US/EU filing.

### **JAPAN CTD**

The contents and structure are similar to the global document. The main difference is that for the key results, Japanese data are summarized and discussed regardless of whether the results for Japanese patients were consistent with global results. If results are inconsistent between the whole and Japanese populations, the inconsistencies must be discussed. The tables/figures of all/Japanese patients are used in J-CTD 2.5 (Clinical Overview), J-CTD 2.7.2 (Summary of Clinical Pharmacology), J-CTD2.7.3 (Summary of Clinical Efficacy), and J-CTD2.7.4 (Summary of Clinical Safety). Key messages/conclusion of J-CTD should be aligned with the global CTD, so medical writers in the Japanese submission team need to collaborate with global medical writers to prepare J-CTD in parallel with global CTD.

### **JAPAN-SPECIFIC PROGRAMMING REQUIREMENTS**

Below are details for specific programming requirements for a Japanese submission. Some of them are mentioned in CTD format guideline issued by PMDA (written in Japanese). The most important things are key summary tables/figures of Japanese patients which will be used in J-CTD. These outputs can be standardized and included in the global SAS programs/macros. If the number of Japanese patients enrolled in the study is less than 10-15, many tables/figures of Japanese population are not needed because medical writers and clinicians can mainly use listings to write a J-CTD to discuss on Japanese data. Only a few tables of adverse event and key efficacy tables/figures are requested by medical writers and clinicians.

### **SUB ANALYSES OF JAPANESE PATIENTS**

To write a Japan CTD for a Japan submission, sub analyses of Japanese patients of key safety/efficacy tables/figures are always required unless the number of Japanese patients is very small in a study. The tables/figures of Japanese patients can follow the shell in global statistical analysis plan, but only include Japanese subpopulation. Regarding PK outputs, Japanese and non-Japanese tables are usually requested to verify the ethnic sensitivity. These are the main requirements for a Japan submission and should be prepared in advance prior to database lock if the team aims to simultaneously submit to PMDA, FDA and EMA.

For submission of oncology studies and studies for which safety profiles are of concern, PMDA requests box plots of lab values during study treatment (mainly phase 2/3 studies) and spaghetti plots (mainly phase 1 studies). Also, minor adjustment of programs/macros may be needed (e.g. unstratified rather than stratified method for p-value and/or Hazard Ratio) due to a small number of Japanese patients.

The key for successful simultaneous Japan/US/EU submission is a timely finalization of the statistical analysis plans and adjustment of SAS programs/macros in the early stage, so the programmers can easily produce tables/figures of Japanese patients using the same global programs/macros with minor adjustments. Such an approach does not only shorten the timelines but also allows programmers to avoid inconsistency. If there are separate SAS programs or macros to produce outputs for the whole population and Japanese patients, programmers may forget to update the Japanese tables/figures and only fix the programs for the whole population based on the review comments or changes to shells or statistical analysis plans. Implementation of programs/macros in the late stage is not

recommended from a quality perspective as it may jeopardize a timely delivery of outputs for Japanese patients and subsequently result in a delayed Japan submission.

## **POOLING SAFETY ANALYSES FOR MEDICAL PACKAGE INSERT**

Adverse events pooling activity for medical package insert is a specific local requirement for Japan submission. The summary tables of adverse events with suspected study drug need to be produced. However, the shells can be standardized among compounds since normally the same summary tables are requested from the safety evaluation group/function. PMDA prefers the latest MedDRA version for all adverse event outputs. The difference between Japan and global is global SCS normally pool all studies in the same indication, but PMDA requests to pool multiple studies of all indications in the same compound.

## **SAFETY ANALYSES FOR “GUIDE FOR APPROPRIATE USE OF MEDICATION” AND J-RMP**

Additional safety analyses might be needed to get approval from PMDA. These additional safety analyses can be requested by PMDA depending on the results and needs after the database lock. The timing to produce and submit these documents depends on PMDA's request but it usually occurs after the submission. It is not easy to standardize these analyses because they depend on the safety profile of the study/compound. It is good, however, to be aware that this is one of requirements for the approval and extensive programming support is essential.

The first draft of the J-RMP is almost the same as the global RMP for the submission, but after the submission PMDA may consider additional risks (e.g. Interstitial Lung Disease) which are not considered a risk in the global document. Such requests usually come before the Drug Committee meetings and additional safety analyses may be needed. For J-RMP, sub analyses of Japanese patients are not required.

## **ANALYSES FOR PMDA QUESTIONS**

There is a standard timeline for J-NDA review and also certain PMDA meeting dates can be set in advance, so the programming teams can secure sufficient programming resources for additional analyses to answer PMDA questions. PMDA may ask questions that are different from those asked by FDA or EMA. One of the tips for efficient work on the analyses for PMDA questions is to create and regularly update a database of the past HAQ questions/analyses and of SAS programs for all compounds because similar questions might have come up in the past.

Here are three examples asked by PMDA which are not regularly asked by FDA and EMA:

- a. Ethnic sensitivity related questions. e.g. summary of safety data in non-Japanese /Japanese patients
- b. Detailed questions regarding listings
- c. AE tables by time period (this may be requested for “Guide for appropriate use of medication” or J-RMP)

## **VALIDATION LEVEL OF LISTINGS**

In general, patient data listings are more important for Japan submission as compared to FDA and EMA submission because pharmaceutical companies or CROs do not provide source/derived SAS datasets to PMDA. Thus, PMDA reviewers can rely only on the data presented as listings. During the GCP inspection before PMDA approves the drug, PMDA inspectors crosscheck the data presented in the CSR listings and source data in CRF or eCRF. If data in the listings and source data are inconsistent, PMDA may ask the company (and programmers) to document whether these are due to data collection issues or programming errors. Therefore, the tables/figures for key results may be more important than the listings, but the listings should be of a good quality to facilitate proper review and approval by PMDA.

*Note: The listings PMDA inspectors review are same as the ones included in the CSR, they are usually based on derived datasets and only include data up to the cut-off date for analysis (which is then the data used on summary tables/figures).*

Recently, PMDA has been shifting their focus to process review, and this will be the major trend for years to come after PMDA starts accepting electronic data submission in CDISC standard format in 2016.

Listings of only Japanese patients are not required if data in the listings are sorted by country so medical writers, clinicians, or PMDA reviewers can easily find out the patients' data in the specific sites or countries.

## **ELECTRONIC DATA SUBMISSION IN CDISC STANDARD FORMAT IN JAPAN**

As of May 2015, pharmaceutical companies in Japan do not need to provide submission data in electronic format including SAS datasets or programs to PMDA, however PMDA plans to request pharmaceutical companies to provide electronic data in CDISC (Clinical Data Interchange Standards Consortium) standard format along with relevant documents and SAS programs starting in October, 2016.

From October 1<sup>st</sup> 2016, in principle all pharmaceutical companies will be asked to submit SDTM/ADaM dataset along with relevant documents including define.xml to PMDA. This process will be quite similar to that for FDA submission, and final submission packages for PMDA and FDA look almost same. There will be also a transition period until March 31<sup>st</sup>, 2021, therefore if pharmaceutical companies will not be able to provide electronic data in CDISC standard format, they could petition with explanation why it is not possible for them to submit them. Like FDA, PMDA also recommends sponsors to convert legacy pooled data (e.g. adverse events of several studies) to CDISC standard format as much as possible.

According to PMDA's plan, a review period of drugs can be shortened in Japan in the future. PMDA has started hiring and training SAS programmers and Biostatisticians. In the near future, PMDA will be able to analyze data by themselves instead of asking questions to sponsors for additional analyses during a review period. Also, the listings will be less important in the future once PMDA has a proper system and professional data reviewers in place to start reviewing SDTM data.

There are two points that should be considered for electronic data submission in CDISC standard format in Japan. First of all, PMDA recommends pharmaceutical companies to submit all data and related documents in English, but it will still accept data containing Japanese language (as mirror data) in addition to data in English language because of requests from some Japanese pharmaceutical companies. However in such case, mirror data (in Japanese) and additional document (Data Reviewer's Guide) explain how both data are related needs to be created and provided to PMDA. Data (in Japanese) is 2 bytes, but Open CDISC validator supports only single byte data. Therefore data which will be submitted has to be English (single byte). The second point to remember is that like FDA, PMDA will have original study data validation rules which are based on open CDISC Enterprise. It is important to understand PMDA's original data validation rules before submission and clean up those critical errors/warnings in advance by programmers for Japan submission to avoid delays in review of J-NDA by PMDA because based on their rules, PMDA will assess the quality of SDTM/ADaM provided by sponsors if they are acceptable or not. Fortunately, PMDA will accept all CDISC related data/documents in English. Therefore, if the submitted data and relevant documents will be submitted in English only, and also data deemed good, no additional deliverable will be needed except "Analysis result metadata" for CDISC related submission packages.

Below is a list of CDISC related deliverables to be submitted to PMDA from October 1st, 2016.

Deliverables	Notes
SDTM/ADaM dataset	Only single byte data is accepted. Therefore, data should be in English. Data in Japanese is two bytes.
Define.xml for SDTM/ADaM dataset	English is acceptable.
Study Data Reviewer's guide	English is acceptable.
Analysis Data Reviewer's guide	English is acceptable.
Annotated CRF	English is acceptable.
SAS programs/macros for ADaM/Statistical analyses	Primary, key secondary related dataset/analyses. Consult with PMDA to decide which programs/macros to be submitted prior to submission. The programs/macros are not necessarily to be runnable in the environment at PMDA. The main purpose for PMDA is to check algorithm of datasets creation and analyses. If providing programs/macros is not possible, the documents explaining algorithm of analyses is also acceptable.
<b>Mirror data (in Japanese) and its data reviewer's guide.</b>  <i>E.g. AETERM in AE domain or Japanese specific questionnaire in QS domain.</i>	<b>This is Japan specific, but this is not required.</b> If all SDTM/ADaM dataset are in English, this mirror data is not required. A mirror data (in Japanese) must be relevant to data in English.  Data reviewer's guide that explains how data in English and mirror data (in Japanese) are relevant has to be provided to PMDA. This document can be defined xml or defined pdf.

<p><b>Analysis result metadata</b></p>	<p><b>This is Japan specific requirement which is not requested by FDA as of May 2015.</b> This document explains which ADaM datasets/variables are used for each analyses of primary and key secondary (which analyses to be included must be discussed). This document can be written in English.</p> <p>If it is difficult to submit analysis result metadata in xml format, an applicant is able to document required specification in another format e.g. PDF.</p>
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**Table 2. A List of CDISC Related Deliverables.**

## CONCLUSION

The submission and review/approval processes in Japan are similar to those of FDA and EMA with some differences as described above. The key to a successful Japan submission is to understand the specificities of a Japan submission/approval processes from global colleagues. This can be achieved by close collaboration between Japanese and global teams, early planning to incorporate the requirements for Japan submission in the statistical analysis plan and early adjustment of global SAS programs/macros to produce key tables/figures of Japanese patients which will be used in J-CTD for Japan submission. If the simultaneous submission is the key objective, these are the most crucial steps required for a high quality and successful filling within the compact timelines.

## ACKNOWLEDGMENTS

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## RECOMMENDED READING

- PMDA official web site (in English) <http://www.pmda.go.jp/english/index.html>

## ACRONYMS

ADaM	Analysis Data Model
CDISC	Clinical Data Interchange Standards Consortium
CRO	Contract Research Organization
CSR	Clinical Study Report
CTD	Common Technical Document
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAQ	Health Authority Question
J-CTD	Japan Common Technical Document
J-NDA	Japan New Drug Application
J-RMP	Japan Risk Management Plan
NDA	New Drug Application
PMDA	Pharmaceuticals and Medical Devices Agency
RMP	Risk Management Plan
SAS	Statistical Analysis System
SCS	Summary of Clinical Safety
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SDTM	Study Data Tabulation Model
US	United States of America

## CONTACT INFORMATION

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<Japanese submission/approval processes from programming perspective >, continued

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