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Paper RG03

Japanese submission/approval from programming perspective

Ryan Hara, Novartis, Basel, Switzerland

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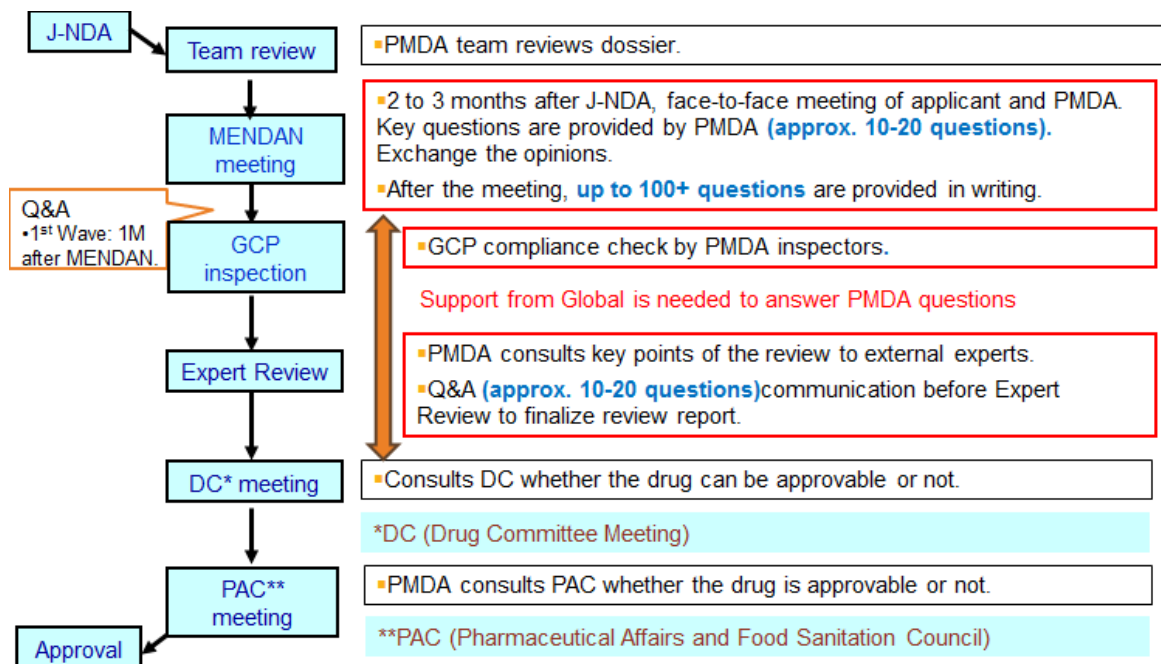
ABSTRACT

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 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, 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, safety analyses to support the creation of the "Guide for appropriate use of medication" and/or Japan risk management plan (J-RMP). Additionally, various examples of PMDA questions and answers are presented as well as my experience with Japanese submissions/approvals processes whilst working at Novartis.

OVERVIEW OF SUBMISSION AND REVIEW/APPROVAL PROCESSES



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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 from the programming perspective. 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 of multiple studies (which can be different from global pooling for Summary of Clinical Safety) and its summary tables of adverse events with suspected relationship to study drug are a requirement for medical package insert, and programming support is necessary to prepare Japanese submission.

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 waves of PMDA questions. The first one is after Mendan meeting (face to face meeting with PMDA 2-3 months after filing) and the second one which usually requires substantial programming involvement is after GCP (Good Clinical Practice) compliance check conducted by PMDA inspectors but before Expert Review meeting. PMDA may travel to the sites in other country for GCP inspection.

(Before Mendan meeting, key questions come out, but most of them are the high level (clinical related) which normally do not require statistical analyses with programming support to answer those questions.)

Below are examples of major differences from programming perspective. First of all, PMDA always asks for 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.

As of October 2014, CDISC format is not mandated by PMDA. Also, the Pharmaceutical companies do not need to provide SAS datasets to PMDA. But PMDA plans to mandate the pharmaceutical companies to provide SDTM and ADAM along with SAS programs starting in 2016.

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:

Type of documents	Language
Global CSR	English is acceptable.
J-CTD 2.5 Clinical Overview	Japanese
J-CTD 2.7.2 Summary of Clinical Pharmacology	Japanese
J-CTD 2.7.3 Summary of Clinical Efficacy	Japanese
J-CTD 2.7.4 Summary of Clinical Safety	Japanese
PMDA questions	Japanese only. Japan team translates them into English when they need support from global.
Answers for PMDA questions	Japanese only
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.

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.

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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. The most important relate to 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 the 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 EMEA.

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). 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 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 beginning, 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.

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SAFETY ANALYSES FOR “GUIDE FOR APPROPRIATE USE OF MEDICATION” AND/OR 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 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 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 EMEA. 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 EMEA:

- 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” and/or J-RMP)

VALIDATION LEVEL OF LISTINGS

In general, patient data listings are more important for Japan submission as compared to FDA and EMEA 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 requesting submission of SDTM and ADAM datasets in 2016. On the other hand, PMDA is planning to stop requesting pharmaceutical companies to provide listings once PMDA have proper systems in place to start reviewing SDTM datasets or so.

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.

CONCLUSION

The submission and review/approval processes in Japan are similar to those of FDA and EMEA with some differences as described above. The key to a successful Japan submission is to understand the specificities of a Japan submission 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 filing within the compact timelines.

ACKNOWLEDGMENTS

I would like to thank all who reviewed a paper and gave me valuable comments.

RECOMMENDED READING

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

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ACRONYMS

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
US	United States of America

CONTACT INFORMATION

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

Ryan Hara
Novartis Pahrma AG
Oncology Biometrics and Data Management
Postfach
CH-4002 Basel
Switzerland
Work Phone: +41 61 6968728
Email: ryan.hara@novartis.com
Web: www.novartis.com

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