[Original Article]

A Proposed Process for Implementing Statistical Analyses for Global Clinical Trials

Including Japan-specific Analyses and Regulatory Responses for Submissions to PMDA

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ABSTRACT

Background　While conducting statistical analyses in global drug development, statisticians and programmers across regions may face challenges due to the differences in regulation, language, and geographic region. This article proposes a process that facilitates appropriate and timely implementation of statistical analyses and regulatory responses.

Methods　Based on the experience of US and Japanese pharmaceutical companies in conducting global clinical trials and submitting new drug applications, we propose a process for implementing statistical analyses and regulatory responses irrespective of the locations of study team members. The process is based on gap analyses of regulations and practices regarding statistical analyses between regions, including consideration of different requirements for tables, listings, and figures between the Pharmaceuticals and Medical Device Agency（PMDA）and Food and Drug Administration（FDA）.

Results　Through efficient resource utilization and early planning, Japanese and US teams were able to successfully deliver datasets and analyses for both PMDA and FDA submissions in a timely manner with high quality based on the proposed process.

Conclusions　A well-defined process improves the efficiency and quality of PMDA submissions using global clinical trials. The current proposal facilitates the appropriate and timely conduct of statistical analyses using the Clinical Data Interchange Standards Consortium standards for global clinical trials and new drug applications.

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KEY WORDS　Pharmaceuticals and Medical Devices Agency（PMDA）, Food and Drug Administration（FDA）, global drug development and new drug application（NDA）, Japan-specific analyses, Clinical Data Interchange Standards Consortium（CDISC）

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国際共同試験の統計解析プロセスの提案（PMDA 申請用解析帳票と照会事項回答プロセスを含む）

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Introduction

The Ministry of Health, Labor, and Welfare（MHLW）issued "Basic Principles on Global Clinical Trials" in 2007,[1] which has encouraged Japanese participation in international phase three clinical trials, increased the number of Japanese pharmaceutical companies conducting global clinical trials, and helped to avoid stand-alone trials in Japanese patients that are often underpowered. In the current era of globalization of drug development, multiple sponsors（industry and/or institutional）and/or geographical regions［e.g., Japan, the United States（US）, and the European Union（EU）］might be involved in development and global submissions. Data from multiregional clinical trials（MRCTs）are often submitted to multiple regulatory authorities and can be accepted by regulatory authorities across regions and countries as the primary source of evidence to support marketing approval of drugs.[2] According to the aforementioned guidance, the planning and design of global clinical trials necessitate abundant and robust discussions. Few investigations, however, examine how differences in regulatory authority, language, and region can impact operations, processes, and implementation of statistical analyses for MRCTs.

We propose a process for implementing statistical analyses and regulatory responses, based on our experience with new drug application（NDA）submission in a global drug development program by a joint development team consisting of Japan and US sponsors, which aims to provide a solution that will facilitate the conduct of statistical analyses and regulatory responses globally irrespective of region, regulatory authorities, or location of the study team members. In addition, Japan-specific preparations for PMDA consultation meetings on electronic data（e-Data）submission with Clinical Data Interchange Standards Consortium（CDISC）standards are mentioned herein. Multiple sponsors（industry and/or institutional）may be involved in the joint development process and the principles are applicable regardless of the type of companies involved（e. g., Japan headquarters and US/EU subsidiaries）.

Issues and Challenges

1　Potential differences in clinical data standards and specifications

Sponsors need to conduct statistical analyses to generate clinical study reports（CSRs）on individual studies as well as perform integrated analyses used for the Common Technical Document（CTD）for regulatory authorities such as the Food and Drug Administration（FDA）and the PMDA. Standardization of analysis datasets across clinical studies is critical for the integrated analyses. The FDA has recommended that sponsors should submit electronic clinical study data using the CDISC standards since 2004, while the PMDA did not request electronic datasets（regardless of data standard）until 2016.

The FDA has mandated that sponsors must submit electronic datasets with CDISC standards for studies starting after December 17, 2016.[3] The PMDA started accepting electronic datasets for new NDAs from October 2016, with a transition period lasting until March 2020.[4] Both regulatory authorities require sponsors to use the CDISC standards, Study Data Tabulation Model（SDTM）and Analysis Data Model（ADaM）; however, they accept different SDTM and ADaM versions.[5],[6]

2　Decisions on clinical data package and NDA timeline

Sponsors should decide studies to be included in NDA submissions based on consultation meeting(s) with each regulatory authority. Studies conducted by partner companies and/or in other geographical regions may be included. Decisions on clinical data packages have an impact on the studies to be identified as integrated summary of safety（ISS）and/or effectiveness（ISE）and electronic datasets to be submitted. In terms of efficiency for sponsors, the PMDA, FDA and other health regulatory authorities would ideally require electronic datasets of the same studies to be submitted, but a certain authority might require electronic datasets for additional studies according to its local regulations and/or scientific reasons.

Differences in clinical data packages, integrated analyses and/or electronic datasets to be submitted, and additional analyses such as Japan-specific analyses may impact the timeline for each NDA submission.

3　Other differences and communication

Due to the regional and time zone differences between the US and Japan, it is necessary to consider the time spent on translation in addition to the time spent on strategy discussions and analyses. These considerations become critical when conducting additional analyses is required based on the queries from regulatory agencies and the clinical study team members are located in the US and Japan. Communication may become more complicated since the pathway involves various functions within each participating entity.

Methods

1　Japan-specific analyses to PMDA

We identified the Japan-specific analyses required by PMDA in advance. While FDA has developed guidelines

Table 1　Tables, listings, and figures（TLFs）specifically required for PMDA submission（as of November 15, 2018）

#	TLF	Remarks
1-1	Subject listings （For major studies that became the basis for dose-setting and major confirmatory studies on efficacy）	There is no clear guidance regarding which variables should be presented in the listings, but they would include demographics, major efficacy/safety endpoints and analysis population flags. The listing(s) can be omitted if electronic datasets are submitted.[4]
1-2	Subject listings of adverse events（AEs）related to the investigational product(s)	See #2-1
1-3	Subject listings of serious AEs	
1-4	Subject listings of abnormal changes in laboratory tests	
1-5	Figures that appropriately display changes in laboratory values	Spaghetti plots or scatter plots can be created. The figure(s) can be omitted if electronic datasets are submitted.[4]
2-1	Subject listings of AEs	All AE terms（MedDRA terms）in listings/tables of CTD module 2 should preferably be written in Japanese.
2-2	Summary tables of AEs by causality	The specific shell described in the guidance should be used. Tables should be presented in CTD section 2.7.4.
2-3	Summary tables of AEs by grade （For oncology projects）	The specific shell described in the guidance should be used. Tables should be presented in CTD section 2.7.4.
2-4	Summaries of AEs by time period （For long-term studies of non-life-threatening diseases）	Tables should be included in CTD section 2.7.4.
3-1	Subject listings for discontinued subjects, protocol deviations, subjects excluded from efficacy analyses, demographics, AEs, other safety endpoints, abnormal values of laboratory tests, concomitant medications	The listings will be used for PMDA document-based assessment and GCP on-site inspection. If included in CSR section 16.2, these listings can be reused for the inspection.

Note: This table is based on Guidance A（#1-X）, B（#2-X）and C（#3-X）. Other TLFs may be required for a PMDA submission according to PMDA consultation meeting（s）

for the submission of electronic investigational new drug application（IND）in the CTD format, it does not require specific analyses across clinical trials like PMDA. Some specific analyses may be required by the FDA depending on specific protocols, products, or indications after consultation with them. The three guidance documents listed below explain the tables, listings, and figures（TLFs）required for submissions to the PMDA.

A）Organization of Application Dossier Appended to New Drug Application（NDA）for Approval[7]

B）Format for Preparing the Common Technical Document for Submission of NDAs to Reduce Total Review Time[8]

C）Procedures for Implementation of Document-based Assessment and GCP On-site Inspection for Drug Application[9]

Certain TLFs are required for PMDA submission based on the guidance A, B, and C（**Table 1**）. In addition, sponsors are expected to conduct several sub-group analyses using the Japanese population in a global trial.[1] Apart from the guidance documents, each agency might require different statistical analyses for the primary analysis or other important analyses, such as methods or metrics for multiplicity adjustments, non-inferiority or equivalence designs, even for an identical global trial.[10),11]

2　Development of a statistical analysis process for global submission and Japan-specific preparations for e-Data submission to the PMDA

We developed a three-step statistical analysis process for global NDA submission as described in **Table 2**. The steps include: A）developing a global NDA submission plan for a clinical data package, planning for consulting meetings with various regulatory agencies, and creating timelines for CTD preparation for each regulatory authority; B）specifying clinical studies to be included in the ISS/ISE and submitted as electronic data for each regulatory authority; and C）planning and implementing statistical analyses including（1）setting up the expectations and

Table 2　Statistical analysis process steps for global NDA submission

Step	Action
A　Global NDA submission plan	-Make decisions on clinical data package(s) -Develop timelines for consultation meetings with each regulatory agency -Develop timelines for CTD preparation and NDAs to each regulatory agency
B　Specification of clinical studies	-Specify clinical studies to be included in ISS/ISE -Specify clinical studies and analyses to be submitted as electronic data（SDTM, ADaM）to each regulatory agency
C　Statistical analyses 1　Project management planning	-Clarify RACI（Responsible, Accountable, Consulted, Informed）for Japan and US sponsors' statisticians, programmers and project team members -Establish communication plan -Set milestones and timeline
2　Creating Statistical Analysis Plan（SAP）	-Document SAP(s) considering the results of gap analyses regarding regulations or practices regarding statistical analysis between Japan PMDA and FDA -Finalize SAP(s) ➢ If multiple SAPs are created(e. g., Global SAP and supplemental SAP for each regulatory agency), each CSR/CTD needs to clarify which SAP(s) and version(s) are used.
3　Preparing other statistical specifications	-Create specifications for SDTM/ADaM datasets -Create TLF shells with related information such as analysis variables and fragments of statistical programs ➢ TLF shells for several Japan-specific analyses should be compliant with definitions or specifications described in the Japan guidance documents（example shown in **Fig. 1**）
4　Creating SDTM/ADaM datasets	-Run programs to create SDTM/ADaM datasets ➢ If SDTM/ADaM datasets are submitted to Japan PMDA, validation program with PMDA's validation rules should be run.
5　Generating TLFs	-Run programs to create TLFs

responsibilities for the statisticians, programmers, and team members of Japan and US sponsors,(2) creating the supplemental Statistical Analysis Plans(SAPs)for regional filing（such as Japan）based on the global SAP and country-specific requirements,(3) preparing statistical specifications for data derivation and TLFs,(4) creating CDISC datasets（SDTM/ADaM), and (5) generating TLFs with **Figure 1** serving as an example of TLF shells required by the PMDA guidance documents.

CDISC datasets should be validated by both PMDA and FDA guidelines if both submissions are planned. For a PMDA submission, if any validation issue categorized as "Error" has not been resolved, the sponsor must explain it in a briefing document with a specific format called "Attachment 8",[12] and receive agreement on them from the PMDA at e-Data consultation meeting(s) prior to an NDA submission. **Figure 2** explains the types of PMDA consultation meeting for e-Data submission and actions on CDISC datasets with metadata needed prior to NDA submission with appropriate timing and order of the meetings or actions. The sponsor could revise "Attachment 8" when an e-Data consultation meeting occurs, if there are any updates, and then submit the final version of "Attachment 8" at a pre-application meeting on procedures ("Shin-Iyakuhin Shonin Shinsa Yotei Jizen Mendan"), which should be held 1-3 months before NDA submission.

3　Development of a regulatory response process to PMDA

In addition, we developed a response process for the queries from PMDA in the case where the clinical database is located within a US company, considering efficient use of the time difference between Japan and the US. **Figure 3** shows the regulatory response process including the assignment of roles and responsibilities in handling and triage of queries based on the necessities of additional analyses.

Results

We applied the process for implementing statistical analyses and regulatory responses, as described above, to four

Table X.X. Adverse events by system organ class and preferred term（“All Grade” and “Grade 3 or higher” for treatment-emergent adverse events occurring with ≧X% frequency in either arm）（Safety Analysis Set）

System Organ Class Preferred Term	Treatment Group X N=xx		Treatment Group Y N=xx	
	All Grade n（%）	Grade 3 or higher n（%）	All Grade n（%）	Grade 3 or higher n（%）
Number of subjects reporting at least one adverse event	x（x.d）	x（x.d）	x（x.d）	x（x.d）
SOC 1（in Japanese）	x（x.d）	x（x.d）	x（x.d）	x（x.d）
PT1-1（in Japanese）	x（x.d）	x（x.d）	x（x.d）	x（x.d）
PT1-2（in Japanese）	x（x.d）	x（x.d）	x（x.d）	x（x.d）
<...>	x（x.d）	x（x.d）	x（x.d）	x（x.d）
<...>				

Figure 1　An example of TLF shells required by the PMDA guidance documents

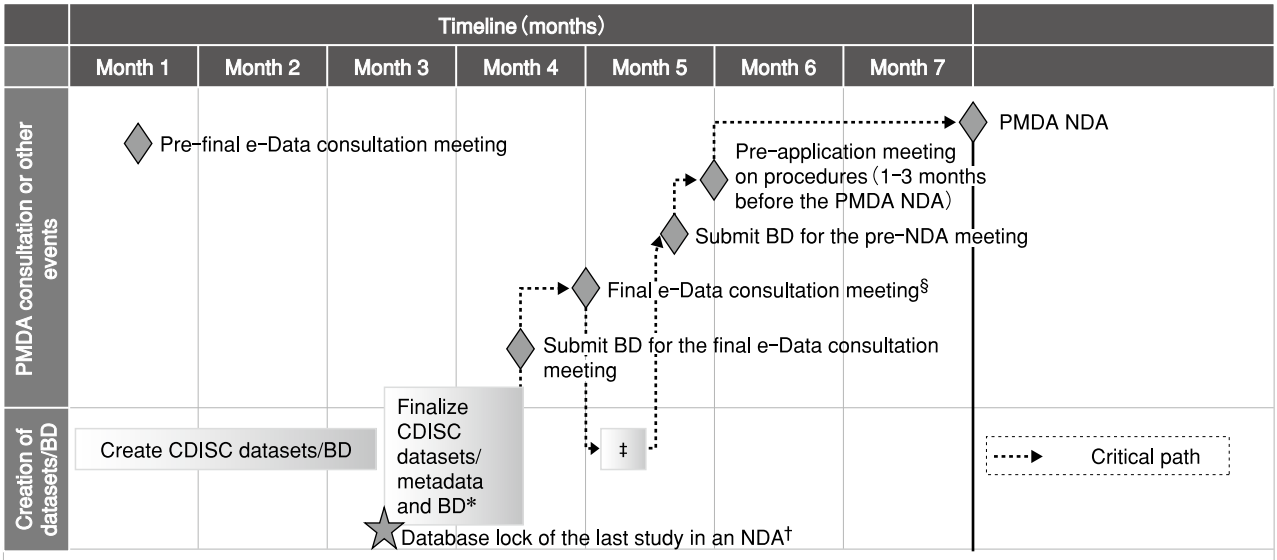

Figure 2　Types of PMDA consultation meeting for e-Data submission and actions on CDISC datasets with metadata needed prior to NDA submission

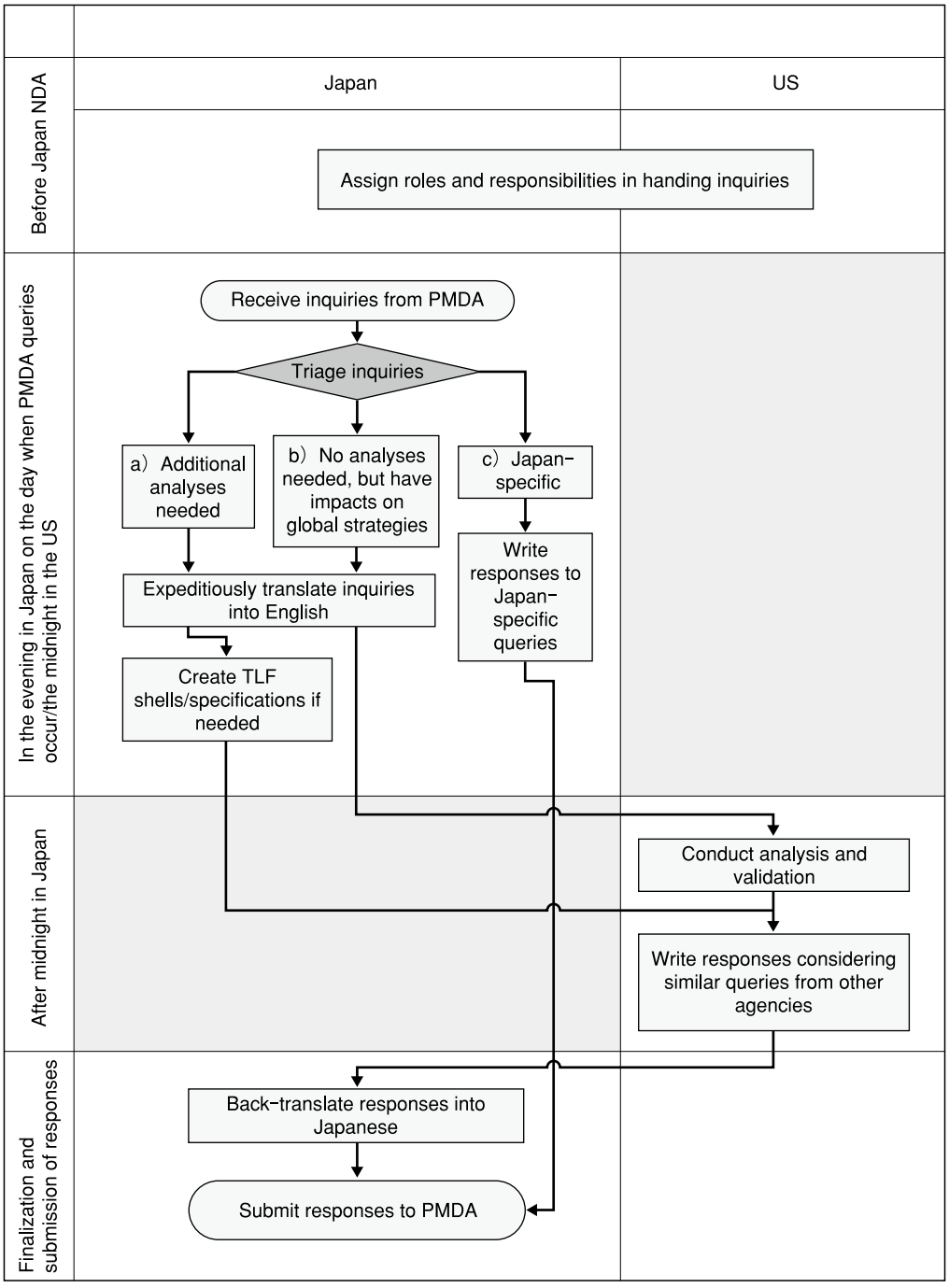

Figure 3　Regulatory response process for queries from the PMDA for global drug development

global drug development projects in the therapeutics of oncology and bone. Each project included more than two global trials including Japan, and 1–2 Japan local studies. Although each project was slightly different in terms of number of clinical studies, the following benefits were gained for all submissions:

—We were able to plan and prepare all TLFs required by the PMDA.

—We were able to use resources efficiently between Japanese and US project members.

—We were able to use datasets and analyses for both PMDA and FDA submissions, thus minimizing the need for PMDA-specific additional analyses.

—Statistical analysis and related tasks were prepared early as planned and did not become a road-block on the NDA timeline.

—We were able to prepare TLFs and responses in a timely manner for queries from the PMDA.

The full-time equivalent（FTE）for statisticians in Japan was reduced by approximately 50% in the four projects using the proposed process compared to other global projects not using it. It is difficult to compare these accurately to other NDAs since some conditions, such as the number of clinical trials included in an NDA package, were different; however, the average FTEs were 12 while using the proposed process compared to 24 while using the standard process in terms of statistical works including creating SAPs, TFL shells and other related specifications.

Discussion

1　Japan-specific analyses and CDISC submission

As described above, the PMDA requires Japan-specific TLFs（**Table 1**）that would necessitate additional resources and impact an NDA timeline. Lack of awareness about the Japan-specific TLFs and documentation required by the PMDA may be one of the reasons for the sponsors not filing the Japan NDA included in global simultaneous NDA filings.[13] In addition, the two types of PMDA consultation meetings should be held and briefing document "Attachment 8" should be finalized accordingly prior to NDA submission（**Figure 3**）, which may cause a delay in the NDA submission of global drug development projects. We believe that the submitted electronic CDISC SDTM and/or ADaM datasets can be used to substitute several PMDA-required TLFs listed in **Table 1** such as various listings of Adverse Events（AEs）（#1-2, #1-3, and #2-1）, subject listings of abnormal changes in laboratory tests（#1-5）, and other subject listings（#3-1）. These listings are redundant with the SDTM and/or ADaM datasets since the datasets contain all the information present in these listings and the reviewers can find the information in the datasets directly. We encourage an active discussion between the industry and PMDA to consider the CDISC datasets as sufficient for submission, without requiring Japan-specific TLFs. We expect that Japan-specific listings will no longer be required in the future.

2　Proposed regulatory response process and differences in geographic locations and languages

Any delay in responses to queries during review period would cause delay in marketing approval by the regulatory agencies. If we prepare responses with additional analyses in a global drug development project, additional analyses might require more time than that for a local Japan project due to differences in geographic locations and languages. Thus, we have proposed the regulatory response process（**Figure 3**）to reduce the negative impacts and utilize the differences, which has accelerated the regulatory responses of global drug development.

Conclusions

The proposed process for implementing statistical analyses and regulatory responses for NDAs aims to understand the differences in regulatory authority, geographic region, and time zone between Japan and the US to conduct statistical analyses for global clinical trials in an appropriate manner. The pre-existing process required double FTEs of statisticians in Japan for additional and duplicative work for a Japan NDA. Our well-defined proposed process improved efficiency by enabling early preparation of Japan-specific TLFs and CDISC datasets required by the PMDA and defining clear roles and responsibilities in handling and triage of PMDA queries. It has also enhanced the quality of global submissions by allowing the team to plan any quality management work required before PMDA submission.

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