Paper DS13

Key Programmer Tasks for Japan Submission and Programmer Role Allocation

Yoko Yamaguchi, Bristol Myers Squibb, Tokyo, Japan

ABSTRACT

Pharmaceutical companies are increasingly expected to advance regulatory submissions across multiple countries within a similar timeframe to deliver medicines to patients worldwide more quickly. As strategies that minimize differences in review timelines become widespread, early filing and rapid regional expansion have emerged as key drivers of competitiveness.

At the same time, submission packages must comply with country-specific regulatory requirements, demanding tailored preparation and efficient execution. Programmers are also expected to manage these diverse tasks accurately and rapidly.

This paper summarizes key programming tasks and role allocation for Japan regulatory submissions. It outlines Japan-specific requirements and important considerations for programming work, describes how responsibilities are divided between the Global and Japan teams, and highlights the growing importance of optimized role allocation as closely aligned multi-country submissions under tight timelines become more common.

INTRODUCTION

This paper describes key programming tasks and role allocation for Japan regulatory submissions. First, it outlines Japan-specific requirements and important considerations for programming tasks. Next, it describes the division of roles between Global and Japan teams in our organization. The growing importance of optimized role allocation is emphasized to efficiently manage complex tasks, especially as multi-country submissions under tight timelines become more common.

KEY PROGRAMMER TASKS FOR JAPAN SUBMISSION

Key programmer tasks for Japan submission include generating the following deliverables:

- Tables, Figures and Listings (TFLs) for Japan submission
- eSubmission (eSub) package
- TFLs for inquiries

Programmers must carry out multiple tasks in parallel, starting after End of Phase2 (EOP2) through Japan submission and up to just prior to approval. (Figure 1)

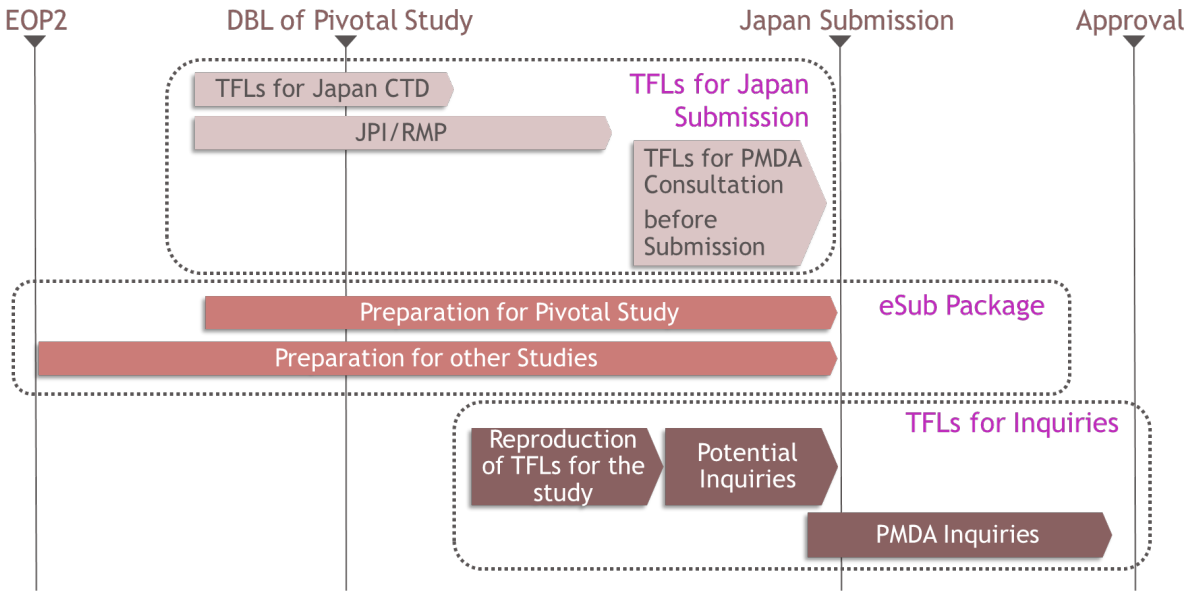

Figure 1: Illustrative Key Programmer Tasks for Japan Submission

TFLS FOR JAPAN SUBMISSION

For Japan submission, programmers generate analysis outputs that mainly meet Japan-specific regulatory requirements as follows:

- TFLs for Japan CTD
- Package Insert for Japan(JPI)/Japan-RMP outputs
- TFLs for PMDA consultation before submission

KEY POINTS OF OUTPUTS

Japan subgroup analysis is required to evaluate the consistency between the entire population and the Japanese population in pivotal global studies. PMDA's intention is to focus on primary and secondary efficacy endpoints and safety endpoints (plus others as needed).

Programmers should generate Japan subgroup analysis tables and figures in a timely manner for topline and non-topline outputs of pivotal study CSR/ISS/ISE to align with CTD preparation. For JPI and RMP, Japan subgroup analysis is also required. If data from multiple studies need to be pooled and the MedDRA versions differ, programmers must ensure that the same MedDRA version is applied across studies for pooled outputs.

In addition, MedDRA terms for adverse events must be reported in Japanese. Programmers support the conversion of English MedDRA terms into Japanese terms using tools or programs.

There are specific safety TL requirements based on PMDA notification on Japan CTD (called JIMUREN). However, they have recently become less necessary to follow every instruction.

Additionally, PMDA consultations before submission may require analyses or lead to inquiries. In such cases, programming timelines are tight and often overlap with other tasks, making workload coordination challenging.

ESUB PACKAGE

For eSub package preparation, programmers need to review and refine the outputs of ongoing pivotal global studies as well as complete the preparation work for all studies included in the submission package.

KEY POINTS OF PACKAGE PREPARATION FOR PIVOTAL STUDY

For ongoing pivotal study, it is important to perform PMDA validation during the draft stage before database lock and address any issues in advance. In particular, as REJECT issues are not acceptable in Japan submissions, all REJECTs related to data issues should be resolved prior to lock.

Furthermore, it is necessary to confirm mandatory requirements to avoid inquiries or any correction requests.

In addition, file-naming compliance should be verified not only against the eSub rules but also against the eCTD naming conventions.

By resolving key issues during the draft stage, we can avoid making data corrections during the final validation and ensure a smoother submission process.

Then, programmers need to prepare meeting materials for PMDA consultation meetings, if needed.

KEY POINTS OF PACKAGE PREPARATION FOR OTHER STUDIES

For studies other than pivotal studies, begin preparation of eSub with those studies that have already been completed. Sufficient time should be secured for this work, and all eSub preparation should be completed before submission.

First, studies that must be submitted to PMDA are identified in accordance with the Notification on Handling of Submission of Electronic Study Data for New Drug Applications. The scope of eSub should be agreed upon with PMDA at EOP2.

Next, the source materials for each study are reviewed to confirm alignment with the CSR version to be submitted and to ensure that all datasets, documents, and programs are available. If any information is missing, programmers should contact the Global team or vendors for confirmation.

If needed, hold PMDA consultations and prepare meeting materials such as BB, Form A and Form B, etc. For example, if the study qualifies for CDISC exemption, consultation with PMDA may be required. In such cases, prepare documents such as Form B to explain source data availability, and participate in the consultation meeting with PMDA to obtain agreement on the CDISC exemption.

If there are issues with the source data, additional consultation meetings may also be necessary.

After completing these checks, validation is performed for each study in accordance with the rules specified in the TCG, and the contents are finalized.

TFLS FOR INQUIRIES

KEY POINTS OF PMDA INQUIRIES

Generating analytical outputs for inquiry responses is one of the most important and challenging tasks for programmers in the submission process.

Multiple rounds of inquiries are typically received, and immediate responses are required. In addition, a large volume of TFLs must be produced within a short period. (Figure 2)

Furthermore, as the review process moves into later phases, the deadlines for responding to inquiries become even tighter, and inquiries require faster turnaround. Programmers are expected to deliver accurate outputs promptly, often completing the required programming within one to two days.
Therefore, meticulous preparation in advance is essential to ensure smooth handling of these inquiries.

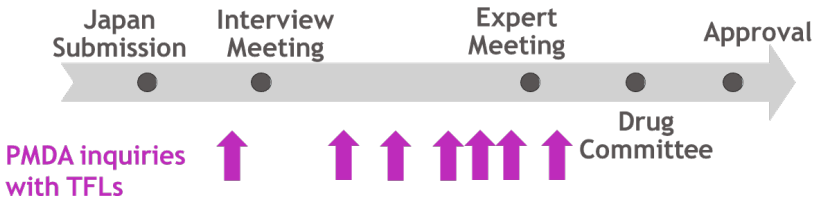

Figure 2: Image of a flow of PMDA Inquiries

KEY POINTS OF PREPARATION BEFORE JAPAN SUBMISSION

To execute a large number of analyses quickly and accurately, the following advance preparations are essential:

- Reproduce study TFLs to ensure programs are accurate and executable

  Because outsourcing arrangements may limit access to all programs—and internally the execution environment may differ—critical code may not run as is (e.g., missing macro dependencies). For high-priority programs, make them executable in the internal analysis environment ahead of time; confirm data availability, verify derivation logic, and document dependencies and versions. Where artifacts are incomplete, identify gaps early and coordinate with the vendor or Global team to obtain the missing components.
- Prepare potential inquiries

  Collaborate with the clinical team to anticipate likely inquiries and pre-generate analytical tables/listings for candidate responses. Distinguish between routine, template-driven requests and project-specific questions. For project-specific analyses, prioritize by likelihood and impact to avoid excessive pre-work while ensuring coverage for high-probability scenarios.
- Establish rules of collaboration with the Global team in advance

  When Global support is available, define roles and responsibilities, agree on a communication cadence (channels, response windows), and align program management (repository access, branching, change control, and review). Clear collaboration rules established up front are critical to sustaining rapid workflows during the inquiries window.

EXAMPLE OF PROGRAMMER TASKS FOR AN ONCOLOGY PRODUCT SUBMISSION

This is an example of a submission for an oncology product.
Volume of clinical data package

- ✓ 24 studies (Pivotal studies: 7, Reference studies: 17), ISS, ISE

Volume of eSub packages

- ✓ 18 packages

TFLs for submission

- ✓ JPI/RMP: 4 tables
- ✓ Preparation for inquiry responses
  - ➢ Potential inquiries: 22 tables, 10 listings
  - ➢ Reproduced CSR output programs: 10-15 tables per study for 23 studies, prepared more than a year in advance
  - ➢ Modified CSR programs: About 50 tables made executable for the pivotal Japan study
- ✓ First important inquiries after submission: 762 tables and listings within 4 weeks
- ✓ Four rounds of additional inquiries after the first inquiry: revised or newly created outputs within a short period

PROGRAMMER ROLE ALLOCATION

ROLE ALLOCATION FOR PROGRAMMING TASKS: GLOBAL AND JAPAN

As part of our statistical programming department's basic strategy, outputs for Japan submissions and eSub packages for Global-led studies are primarily handled by the Global team. This allocation is both accurate and efficient, as it leverages Global's familiarity with the study.
However, in recent years, US and Japan submission timelines have increasingly been aligned in parallel, resulting in significantly tighter schedules. Under these circumstances, priority projects are increasingly requiring Japanese programmers to take on tasks necessary for Japanese submission.
Table 1 describes the role allocation between Global and Japan, and shows the basic approach as well as recent possibilities for priority projects.

Table 1: Role Allocation of Global and Japan - Basic Approach and Possibilities for Priority Projects

	Basic Approach	Possibilities for Priority Projects
TFLs for Japan Submission	Almost prepared by Global	Japan prepares outputs based on Global results
eSub for PMDA	Created by Global Japan checks PMDA requirements	Same as Basic Approach
TFLs for Inquiries	Efficacy: Global Safety and Others: Japan	All analyses by Japan; Global reviews if needed

These shifts in role allocation have been driven by the recent global trend toward aligning submission timelines across regions, between the US and Japan.
Under such compressed schedules, outputs for US and Japan submissions must progress in parallel; otherwise, it would be difficult to meet the challenging timelines required for submissions to multiple regulatory agencies.
To adapt to these changes, several challenges remain for Japanese programmers (Table 2), and addressing them will be essential going forward.

Table 2: Challenges of Japanese Programmers for Primary Project's Japan submission

	Possibilities for Priority Projects	Challenges of Japanese programmers
TFLs for Japan Submission	Japan prepares outputs based on Global results	● Need Frontloaded action before lock: Share global programs and be ready to perform analysis for Japan ● Require more resources
eSub for PMDA	Created by Global Japan checks PMDA requirements	● Confirm compliance with PMDA requirements before DBL
TFLs for Inquiries	All analyses by Japan; Global reviews if needed	● Need deep SAP understanding for quick responses ● Require time to learn the study ● Require more resources for preparation

ADVANTAGES OF JAPANESE PROGRAMMERS FOR JAPAN SUBMISSION

Japanese programmers bring several advantages when taking on tasks for Japan submissions:

- Regional location
  Working in the same time zone as the submission team and being able to communicate in Japanese enables rapid, in-depth discussions of complex issues.
- Familiarity with regional submission
  Japanese programmers are familiar with PMDA expectations and can anticipate the agency's intent. This experience also enables them to proactively propose appropriate analyses to the clinical team.
- Meticulousness for analysis readiness
  Based on the understanding of typical PMDA inquiries in terms of both volume and content, Japanese programmers can anticipate potential questions and prepare programs, resource plans, and programmer training in advance.

IDEAS FOR EFFICIENT WORK MANAGEMENT

Japanese programmers have established practical approaches to manage large volumes of inquiries efficiently.
Japanese programmers have established a platform to manage diverse analysis requests from multiple departments, each arising for different purposes and at different times. This platform integrates a centralized tracking sheet for all requests, well-organized and access-controlled folders, and mechanisms that streamline collaboration between statisticians and programmers. It also allows quick look-up and easy reuse of past work, contributing to improved operational efficiency and quality.

CONCLUSION

Key deliverables for Japan submission include TFLs for Japan submission, eSub packages, and TFLs prepared in response to inquiries.
For TFLs for Japan submission, Japan subgroup analysis is needed. For eSub preparation, early issue resolution in pivotal studies and proactive checks in other studies ensure smooth submission. Efficient handling of inquiries also relies on meticulous preparation, such as anticipating potential questions, reproducing CSR outputs, performing integrated analyses, and building close collaboration with the Global team.

To maximize quality and speed, roles between the Global and Japan teams should be thoughtfully allocated and optimized as necessary. Japanese programmers also need to address challenges such as ensuring sufficient preparation for Global-led studies, and securing adequate resources.
Thoughtful role allocation and strong autonomy at regional sites are essential for efficient multi-country submissions under tight schedules.

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CONTACT INFORMATION

Author Name: Yoko Yamaguchi
Company: Bristol Myers Squibb
Email: Yoko.Yamaguchi@bms.com