Japan: Key considerations for successful PMDA consultation meetings

Introduction
The Pharmaceuticals and Medical Devices Agency (PMDA) is an incorporated administrative agency with non-civil service status which was established in 2004 by consolidating the services of the Pharmaceuticals and Medical Devices Evaluation Center of the National Institute of Health Sciences (PMDEC), the Organization for Pharmaceutical Safety and Research (OPSR), and part of the Japan Association for the Advancement of Medical Equipment (JAAME).

The PMDA’s three key areas of focus are relief services for adverse health effects, product reviews and safety measures. Under product reviews, the PMDA provides several types of consultations for those wishing to seek its advice and guidance based on the phase of development. In doing so, applicants can seek input to determine whether their latest development strategies and planned clinical trial designs are appropriate and in line with PMDA expectations prior to commencing the next development phase. Early consultation with the PMDA is actively encouraged. Typically the PMDA review team will be assigned from the first engagement through the pre-approval and approval stages to the launch of the product onto the Japanese market. The same product review team will take the lead from the first consultation meeting and remain in place throughout the process of product review through to marketing application dossier review and ideally, eventual product approval. This is thought to facilitate development and is key to the successful objective of streamlining the process and delivering consistent quality advice to the applicant.

Keywords
Pharmaceuticals and Medical Devices Agency (PMDA); Product review; Consultation; Pre-meeting; Briefing document; Clinical study design; Priority-track.

Abstract
The submission of clear and comprehensive information to global regulatory authorities is a cornerstone to the success of regulatory applications and subsequent approvals. Appropriate engagement with the authorities during product development is a key factor contributing to that success. Japan is a major pharmaceutical market and like other regulatory bodies, the Pharmaceuticals and Medical Devices Agency (PMDA) has the desire to engage with the pharmaceutical industry and reduce delays to market that have been a historical issue. Currently, the PMDA offers a consultation service for clinical trials, research and development strategy including pathways for priority review. This article describes how the Japanese authorities have embraced the historical challenges. It illustrates the PMDA’s willingness to engage and to open consultation with those intending to conduct clinical trials in Japan. Moreover, this article offers some key advice, useful tips and strategic considerations towards having a successful consultation meeting with the Japanese regulatory authorities.

Types of PMDA consultation
The PMDA offers a variety of consultation opportunities to those companies planning to develop and launch pharmaceuticals and medical devices onto the Japanese market. PMDA consultation is not mandatory for applicants; however, applicants can take advantage of PMDA consultations based on the development phase. Appropriateness of development/regulatory strategy can be confirmed in each PMDA consultation. Consultations concerning clinical trials and JNDA submissions are listed in Table 1.

While taking advantage of the aforementioned options for PMDA consultation is voluntary, applicants are required to consult with the PMDA on the quality and safety of advanced therapy medicinal products (ATMPs) prior to initiation of such clinical studies in Japan.

Applying for PMDA consultation
Applicants looking to take advantage of a PMDA consultation are required to submit an application, including a list of questions, for a pre-meeting (“prior-consultation meeting”) with the PMDA. The purpose of this pre-meeting is to clarify the nature and background of the applicant’s questions as well as the required information to be submitted to the PMDA for the consultation. The pre-submission meeting prior to scientific advice in Europe offers a similar clarification. If the applicant deems it necessary, information about its product should also be submitted as supplemental information together with the application, so that the PMDA can gain a complete and comprehensive understanding of the product and applicant’s related enquiries. It is important to note that the enquiries for PMDA consultation should be described as precisely as possible. Enquiries which are very “open” or “closed” will not lend themselves well to a productive communication with the agency and should be avoided.

Generally the number of attendees from the applicant at the pre-meeting (prior-consultation meeting) is limited to five people. This meeting is expected to last 30 minutes and official meeting minutes are not generated. Subsequent to this meeting, an application for request of coordination of the PMDA consultation date – which also includes the summary of the applicant’s queries – should be submitted to the PMDA. This application must be made on the first working day of each month. The applicant should list its dates of

Authors
Natsuko Hosoda, Manager, Regulatory Affairs, and Hirooki Ishiji, Associate Director, Regulatory Affairs; PPD Japan, K.K., Tokyo, Japan.
### Table 1: Types of PMDA consultation.

<table>
<thead>
<tr>
<th>Consultation category</th>
<th>Consultation contents</th>
<th>Fee (JPY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required procedures for drugs</td>
<td>Consultation re procedure related to implementation of clinical trial for new drug application (NDA). No data evaluation included.</td>
<td>143,800</td>
</tr>
<tr>
<td>Bioequivalence, etc</td>
<td>Consultation on data evaluation.</td>
<td>571,900</td>
</tr>
<tr>
<td>Pre-Phase I study</td>
<td>Consultation on rationale for conducting first trial with human subjects and study design.</td>
<td>4,360,500</td>
</tr>
<tr>
<td>Pre-Phase IIa study</td>
<td>Consultation specific to dose-finding study with small number of subjects based on result of Phase I study.</td>
<td>1,669,400</td>
</tr>
<tr>
<td>Pre-Phase IIb study</td>
<td>Consultation specific to study to be conducted after Phase I study completion and before clinically recommended dosage is determined.</td>
<td>3,114,900</td>
</tr>
<tr>
<td>End of-Phase II study</td>
<td>Consultation on design of Phase III study after clinically recommended dosage determined.</td>
<td>6,183,300</td>
</tr>
<tr>
<td>Pre-NDA</td>
<td>Consultation on contents of NDA when clinical studies end or about to end.</td>
<td>6,183,200</td>
</tr>
<tr>
<td>Additional consultation</td>
<td>1. Consultation to be conducted between pre-Phase I and pre-Phase IIa study consultation.</td>
<td>2,752,100</td>
</tr>
<tr>
<td></td>
<td>2. Consultation to be conducted between pre-Phase IIb and post-Phase II study consultation.</td>
<td>*2,067,900</td>
</tr>
<tr>
<td></td>
<td>3. Consultation to be conducted between post-Phase II and pre-NDA consultation.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Consultation to be conducted between pre-NDA and pre-submission of NDA.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Consultation to be conducted between re-examination/re-evaluation study design and post re-examination/re-evaluation consultation.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6. Consultation to be conducted between post re-examination/re-evaluation and prior-end of re-examination/re-evaluation.</td>
<td></td>
</tr>
<tr>
<td>Prior-evaluation of Phase I study</td>
<td>Consultation on Phase I study results of product under development, to be used in its NDA.</td>
<td>3,584,300</td>
</tr>
<tr>
<td>Prior-evaluation of Phase II study</td>
<td>Consultation on Phase II study results of product under development, to be used in its NDA.</td>
<td>4,625,900</td>
</tr>
<tr>
<td>Prior-evaluation of Phase II and Phase III study</td>
<td>Consultation on a part of Phase II and Phase III study results of product under development, to be used in its NDA.</td>
<td>7,185,300</td>
</tr>
<tr>
<td>Applicability of priority review for new drug</td>
<td>Consultation on applicability for priority review of new drug before filing of NDA (not for orphan drugs).</td>
<td>846,800</td>
</tr>
<tr>
<td>Applicability of priority review and prior to NDA for new drug</td>
<td>Consultation on applicability for priority review in parallel with pre-NDA consultation of new drug (not for orphan drugs).</td>
<td>173,500</td>
</tr>
<tr>
<td>Prior-consultation meeting**</td>
<td>Pre-meeting to confirm contents of enquiries from applicant for the formal consultation.</td>
<td>Free</td>
</tr>
<tr>
<td>Applicability of priority consultation product</td>
<td>Consultation on necessary studies and evaluation of data from early stage of development to product approval.</td>
<td>1,541,600</td>
</tr>
</tbody>
</table>

*For orphan drugs  **Without minutes.
available for consultation during the third month following the application (=first month). For example, if the applicant applies for the consultation on the first working day in April, the consultation would be scheduled in June, therefore the approximate lead time from submission of the application to the actual consultation/meeting date would be approximately 8–12 weeks.

Within five working days, the PMDA will contact the applicant to schedule the formal consultation date, usually in the third month from the application (=first month). After setting the formal consultation date, the applicant must submit the application form together with payment of the fee via a bank transfer within 15 working days.

The PMDA consultation begins from the date when the application form for the formal PMDA consultation is submitted. Dossiers which include a summary of enquiries (briefing document) and supplemental information (necessary information/data) for the consultation should be submitted to the PMDA five weeks prior to the consultation date. Generally, 20 copies of the dossiers, in the required format, need to be submitted to the PMDA.

The briefing document (summary of enquiries) is critical to a successful PMDA consultation. In the briefing document, each enquiry and the scientific rationale should be stated. The applicant should therefore prepare this document tactically and with key strategic thought to increase the chances of an acceptable outcome from the PMDA.

Should the PMDA have questions regarding the content of the dossiers submitted, it will contact the applicant with its questions by phone and/or by email. The applicant is required to answer the agency's questions and can discuss, negotiate, and/or consult on any matters and/or concerns related to the topics for consultation for which the applicant would like to have the PMDA's opinions, instructions, and/or advice. The PMDA will try to respond to applicants requests and currently adopts as flexible an approach as possible.

The required information for consultation can vary depending on the type of consultation needed. For consultation on clinical study design at each phase, generally, the following information should be included in the dossiers (summary of enquiries and/or supplemental information) and submitted to the PMDA five weeks prior to the scheduled consultation date:

- Comparison table with a similar drug on the market in terms of efficacy, dose and administration, precaution for use, etc, if available
- Problems/issues on the treatment already available on the market and merit of the investigational product (IP)
- Package inserts if available in the US/EU and their Japanese-translation versions
- Background information of development of the IP concerned
- Complete clinical data package
- The latest investigator brochure
- Draft protocol and informed consent form (ICF)
- List of clinical studies conducted to date
- List of toxicity studies conducted to date
- Relevant articles, if any
- Record of previous PMDA consultation, if any
- The latest periodic safety update report (PSUR), if applicable.
- The following two consultations have been established in addition to the consultation on clinical study design at each phase.

**Consultation with the PMDA**

Consultation with the PMDA begins after making the formal application for consultation and submission of the dossiers required. If the PMDA requires additional items to the summary of enquiries (briefing document), it will contact the applicant to ask these by phone or email. At this time, the applicant can also ask their questions and can discuss and consult on any concerns with the PMDA. If the content of the enquiries from the applicant, as described in the summary of enquiries (briefing document), has changed after discussion with the PMDA, the applicant is required to submit the revised application with their enquiries for the consultation as a replacement for the initial one. Summary of enquiries (briefing document) must be stated correctly.

As a result of the discussion on the phone and/or email, the PMDA will send formal enquiries in writing to the applicant by fax and/or email (usually one to two weeks after the dossier submission). The applicant should respond to the enquiries in writing within the required timeframe (approximately one week). After submitting answers to the PMDA's enquiries in writing, if the PMDA still has additional enquiries, it will contact the applicant by phone and/or email. After all answers to the enquiries have been submitted to the PMDA, the agency will provide the applicant with its interpretation and opinions for each enquiry and answer in writing by fax and/or email at least four days before the actual consultation/meeting date.

**Priority-track consultation and examination**

For orphan drugs, priority-track consultation and priority review is usually applied. However even if non-orphan drugs (eg, the Japanese patient number is more than 50,000), there is an opportunity to have a priority-track consultation and/or examination. To that end, consultation on the applicability for the priority-track consultation and/or examination is available. The necessary information/data for the consultation on the applicability of the priority-track consultation which needs to be submitted to the PMDA is as follows:

- Data by which usability of the drug concerned can be estimated (for drugs, study results from the first study through to the Phase IIb study should be submitted). For the consultation on applicability of the priority-track examination, the product will be evaluated from the following two perspectives including detailed conditions:
  - Seriousness/severity of indication (target disease)
    - Fatal disease
    - Progression of disease is irreversible and has tremendous negative impact on daily life
    - Others.
  - Usability of the drug concerned in the clinical environment
    - There is no existing treatment, preventive method, or diagnostic method
    - Clinical usability of the drug is superior to existing treatment, preventive method, or diagnostic method in terms of efficacy, safety, and the physical and mental burden borne by patients.

**Regulatory strategy consultation**

Regulatory strategy consultation has been provided since July 2011 and is targeted at innovative drugs, medical devices and ATMPs. The PMDA provides consultation, from an early stage in the development, for quality and safety of cell and gene therapy products. This consultation has replaced “Kakunin Shinsei” (submission to confirm the quality and safety of biological products) which had been conducted until June 2011. For this type of consultation, the applicant can submit an application on any date and the formal consultation can be scheduled on a date whenever the PMDA is available without having to wait for two months as per the standard process.
The applicant should submit their response (acknowledgement and/or opinions if they deem that the PMDA’s understanding is incorrect, etc) to each of the PMDA’s interpretations and opinions in writing within required timeframe before the actual consultation date.

At the formal consultation/meeting, the maximum number of people that can attend the consultation from the applicant’s side is 15 people in principle. If interpreters also need to attend (consultation meetings are conducted in Japanese) the applicant can prepare simultaneous interpreters in advance and a meeting room with a booth for simultaneous interpretation is available at the PMDA office on the applicant’s request. At the start of the formal consultation, the applicant is required to give a 20-minute presentation about their enquiries and/or product. Subsequently, the consultation will be conducted based on each of the PMDA’s interpretations and opinions and the applicant’s responses as described in the documents most recently exchanged before the consultation date. The PMDA confirms each item listed in the document with the applicant. If the applicant still has some items to discuss and/or negotiate, they can consult and/or negotiate further with the PMDA. The formal consultation takes two hours.

Within ten days after the consultation, the PMDA prepares draft minutes in writing which are sent to the applicant. These should be reviewed carefully by the applicant and confirmation provided as to whether they are in agreement with the content. Should the applicant request any revisions, then draft suggested revisions in writing should be submitted to the PMDA within the required timeframe. Finally, when both parties agree to the contents of the draft minutes, the PMDA will send the finalised minutes officially to the applicant by mail as well as on CD as a record of the consultation meeting. It will take around one month from the consultation to the finalisation of the minutes.

**Contact:**

Masami Tamura, Executive Vice President & COO
mtamura@coremed.co.jp www.coremed.co.jp
Osaka - Tokyo

---

**Focus – Japan’s regulatory environment**

The applicant should submit their response (acknowledgement and/or opinions if they deem that the PMDA’s understanding is incorrect, etc) to each of the PMDA’s interpretations and opinions in writing within required timeframe before the actual consultation date.

At the formal consultation/meeting, the maximum number of people that can attend the consultation from the applicant’s side is 15 people in principle. If interpreters also need to attend (consultation meetings are conducted in Japanese) the applicant can prepare simultaneous interpreters in advance and a meeting room with a booth for simultaneous interpretation is available at the PMDA office on the applicant’s request. At the start of the formal consultation, the applicant is required to give a 20-minute presentation about their enquiries and/or product. Subsequently, the consultation will be conducted based on each of the PMDA’s interpretations and opinions and the applicant’s responses as described in the documents most recently exchanged before the consultation date. The PMDA confirms each item listed in the document with the applicant. If the applicant still has some items to discuss and/or negotiate, they can consult and/or negotiate further with the PMDA. The formal consultation takes two hours.

Within ten days after the consultation, the PMDA prepares draft minutes in writing which are sent to the applicant. These should be reviewed carefully by the applicant and confirmation provided as to whether they are in agreement with the content. Should the applicant request any revisions, then draft suggested revisions in writing should be submitted to the PMDA within the required timeframe. Finally, when both parties agree to the contents of the draft minutes, the PMDA will send the finalised minutes officially to the applicant by mail as well as on CD as a record of the consultation meeting. It will take around one month from the consultation to the finalisation of the minutes.