

# The clinical trial consultation system in Japan



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## Abstract

The Japanese regulatory agency, the Pharmaceuticals and Medical Devices Agency (PMDA), provides guidance and advice on the conduct of clinical trials of new drugs and medical devices, as well as on OTC drugs, generics and quasi-drugs, in face-to-face consultation meetings. This service was introduced in 1997 by the Organization for Pharmaceutical Safety and Research (OPSR), the predecessor of the PMDA. The PMDA has subsequently improved on the process, promoting development and speeding up approval reviews through detailed advice that meets the varied needs of sponsors at each development stage. A priority consultation system, in which face-to-face advice is provided for certain products on a priority basis, was introduced in 2004. A new category of consultation meeting, on document preparation for cell/tissue-derived drugs, was established in 2007. In addition, a paper-based consultation process was introduced in 2008 to meet the increasing demands for consultation meetings.

This article offers a detailed picture of Japan's current clinical trial consultation system for new drugs.

## Types of clinical trial consultation services

Consultation services are available for clinical trials on new drugs and *in vitro* diagnostic agents; marketing approval applications for new OTC drugs; and for document preparation of cell/tissue-derived drugs and medical devices. The latter category was established in 2007 to meet the extremely high demand for advice on the development and marketing approval applications for cell/tissue-derived medical products and drugs developed using state-of-the-art technology, such as pharmacogenomics or regenerative medicine.

## Consultations on new drugs

During a clinical trial consultation on an investigational new drug, the PMDA ensures the proposed trial meets the requirements for a marketing approval application, taking into account the ethical

and scientific acceptability of the proposed trial, its reliability, and the safety of clinical trial subjects. In addition, the agency provides guidance and advice on improving the quality of clinical and nonclinical studies. Such advice and suggestions are provided by internal and external experts, based on the documents submitted by the applicant in advance, as well as information collected independently by the PMDA. The experts' opinions are taken into account in line with the level of international scientific knowledge at the time of receipt of the application for a consultation meeting. The PMDA prepares the consultation minutes after the face-to-face meeting with the applicant. During the preparation of these minutes, the agency may, if deemed necessary, submit queries to the Council on Drugs and Food Sanitation (CDFS) within the Ministry of Health, Labor and Welfare (MHLW). Responses from the CDFS are then incorporated into the minutes, before the PMDA finalises the contents based on internal consensus. The minutes of the consultation must be attached to the marketing approval application as an addendum.

## Classification of consultations

Clinical trial consultations are classified according to the drug's development stage and its therapeutic category. Five types of consultation meeting are offered at different stages of development (numbers one to five listed below), followed by another five types of consultation offered as supplementary meetings to cover any shortfalls in the initial consultations (numbers six to ten below). For cell/tissue-derived drugs, a new classification on document preparation has been established (shown as number 11 below).

**1 Pre-Phase I consultation.** The rationale for the first administration of an investigational drug in humans and Phase I trial design is evaluated, based on available data such as quality, safety, pharmacology, pharmacokinetics, overseas clinical data, regulatory status in foreign countries and any available information on similar products.

**2 Pre-Early Phase II consultation.** Suggestions and advice are provided specifically on early Phase II trials, based on the available data such as the results of Phase I trials.

**3 Pre-Late Phase II consultation.** The design of the late Phase II clinical trial is considered before a suitable clinical dose is chosen following the Phase I trial. If a consultation meeting is sought on the design or other facets relating to a late Phase II trial, it is classified under this category, even if the early Phase II trial has not yet started.

**4 End-of-Phase II consultation.** The design and other facets of the planned Phase III trial are considered, based on available data after an appropriate clinical dose for the Phase III study has been determined.

**5 Pre-J-NDA consultation.** Suggestions and advice are given on the compilation of the Japanese New Drug Approval (J-NDA) dossier, and

**Figure 1: Step-by-step process from application of request for a consultation meeting**

Timing	Action	By
-3 months (6th working day of the month)	Submission of an initial request for a consultation meeting	Applicant
-3 months (15th of the month)	Notification of available consultation slots in the month of the requested consultation meeting are published on the PMDA website	PMDA
-2 months (1st working day of the month)	Request for choice of consultation meeting date to be submitted	Applicant
	Notification of acceptance of consultation meeting date (within 5 days of the request)	PMDA
	Transfer of fee and submission of official request for the consultation meeting	Applicant
-5 weeks (Monday of that week)	Submission of briefing documents	Applicant
	Q&A dialogue in writing, and request for submission of additional documents, if these are required	PMDA/Applicant
-7 to -2 days	Provision of the PMDA's view of consultation in writing	PMDA
Day 0	Face-to-face consultation meeting	PMDA/Applicant
	Preparation of draft minutes/Confirmation of draft minutes	
+1 month	Finalisation of official minutes	PMDA

**Figure 2: Number of clinical trial consultations by therapeutic category in FY 2007**

Therapeutic category	No of consultations*
Category 1 (Gastrointestinal drugs, dermatological medicines)	27
Category 2 (Cardiovascular drugs, antiparkinsonian drugs, antithrombotics, anti-Alzheimer's drugs)	46
<i>In vivo</i> diagnostics	3
Radiopharmaceuticals	2
Category 3 (Central/peripheral nervous system drugs, sensory organ drugs (except drugs classified in category 6-1), narcotics)**	39
Category 4 (Antibacterial agents, vermifuge agents, antifungal agents, antiviral agents (except anti-HIV agents))	16
Anti-AIDS drugs	0
Category 5 (Reproductive system drugs, genitourinary system drugs, combination drugs)	14
Category 6-1 (Respiratory tract drugs, anti-allergy drugs, sensory organ drugs for inflammatory diseases)	26
Category 6-2 (Hormone drugs, drugs for metabolic disorders (excluding combination drugs))	31
Oncology drugs	50
Biological products (Vaccines, antitoxins)	13
Cell/tissue-derived products	9
Blood products (Blood coagulation factor products, confirmation of gene therapy, confirmation of Cartagena)	5
Consultations on compliance with conformity criteria***	0
Total number of consultations	281
Withdrawn	21
Total including withdrawn applications	302

\*Consultations covering several categories are classified according to their main category.  
\*\*Category 3 was subdivided into two categories as of 1 December 2008.  
\*\*\*Consultations on compliance with conformity criteria are all conducted by the Office of Conformity Audit, regardless of consultation category.

on the sufficiency of the data for the NDA submission, either after completion or shortly before completion of the clinical trial.

**6 Consultation on procedures for commencing clinical trials.** Guidance and advice are provided on procedures for the start of a clinical trial, mainly for investigator-initiated clinical trials.

**7 Consultation on bioequivalence studies.** Suggestions and advice are offered on the evaluation of data from bioequivalence studies.

**8 Consultation on drug quality.** Guidance and suggestions are provided on the quality of investigational products, such as specifications, test methods, stability, etc.

**9 Consultation on drug safety.** Suggestions and advice are provided on the safety issues related to nonclinical data such as ADME, pharmacology and toxicology.

**10 Additional consultation for drugs.** Second or subsequent consultation meetings are held after having conducted one of the consultation meetings listed above.

**11 Consultations on document preparation for cell/tissue-derived drugs.** Suggestions and advice are offered on the efficient preparation of the documents for preclinical assurance applications\*, clinical trial notifications and marketing approval applications. However, issues on data evaluation, validity of the clinical trial endpoints, appropriateness of the data package, etc, are beyond the scope of this consultation. [*\*Drugs obtained by processing human or animal-derived cells or tissues need to be reviewed by the MHLW for their safety and quality before submitting a clinical trial notification.*]

In addition to the above, the PMDA recently announced the implementation of the following evaluation consultations prior to J-NDA applications from 1 April 2009:

- Quality
- Toxicity
- Pharmacology
- Pharmacokinetics
- Phase I study result
- Phase II study result.

The documents for the J-NDA (including the result of each study and commonly CTD Module 2) are evaluated at these meetings. Causes for concern are identified, and an evaluation report of the study results is prepared. In principle, the nonclinical results (including toxicity, pharmacology and pharmacokinetics) should be discussed and evaluated comprehensively at the consultation meeting, but separate discussions may be acceptable in some cases. These new consultation meetings are currently being held on a trial basis, so there is no guarantee that all requests for such consultations will be accepted at this time.

One further consultation meeting has recently been implemented, relating to pharmacogenomics and biomarkers. The agency's general view on the use of pharmacogenomics and biomarkers in drug development is given at such consultations, as well as suggestions on data evaluation, albeit not focused on a specific drug.

### Step-by-step process for consultation meeting requests

The procedure for organising face-to-face consultation meetings is shown in Figure 1. This process enables all applicants to have a consultation meeting with the PMDA either in the requested month or in the preceding or following month.

In 2007, to improve the quality of consultation meetings, the PMDA introduced an additional step, in which the agency's view of the consultation meeting is provided to the applicant prior to the meeting. And in August 2008, as the consultation meetings became increasingly

popular, the PMDA began offering paper-based consultations. The application procedures for these are the same as the face-to-face consultation meetings, the only difference being that the guidance is instead given in writing.

### Contents of the briefing documents

The applicant should prepare briefing documents specifying the items to be discussed, together with attachments giving the applicant's reasons for wanting to initiate trials of the investigational new drug. The following are examples of attachments to support the applicant's view or to provide background information related to the drug's development:

- The existing treatment(s) for the intended indication of the new drug (including comparisons with similar drugs on indication, dosage and administration, and precautions, if any)
- Unmet medical needs of the existing treatment(s) and the expected benefit of the new drug
- US package insert and/or EU SmPCs (if applicable) together with the corresponding Japanese translation
- History of the new drug's development (chronological table)
- Complete clinical data package. (If the use of foreign data is planned, these data must be separated into overseas data and Japanese data. If a bridging strategy is proposed, the bridging study and its corresponding study to be bridged must be clearly indicated)
- The latest version of the investigator's brochure
- Draft protocol and draft explanation sheet for patient informed consent
- List of clinical studies (in a tabular format such as CTD guideline Exhibit 5, Table 5.1)
- List of toxicity studies (in a tabular format such as CTD guideline Exhibit 4, Table 2.6.7.1, Toxicology overview)
- Relevant important articles
- Minutes of previous face-to-face consultation meetings (if applicable)
- The latest Periodic Safety Update Report (if applicable).

Preliminary consultation meetings are offered, free of charge, to discuss the compilation of consultation points and other relevant matters that will enable the PDMA to provide a more efficient consultation service. A separate application is needed for this preliminary service.

### Priority clinical trial consultations

A system to 'designate and review products for priority face-to-face advice', in which guidance on developing certain drugs and medical devices on a priority basis is provided to drug developers, was implemented in 2004. The purpose of this system is to expedite approval of specific priority drugs or medical devices from the development stage. Priority face-to-face consultations are offered for pharmaceuticals that are designated as orphan drugs by the MHLW, as well as other drugs perceived to meet a particularly high medical need (ie, new drugs for serious diseases that may show promise of distinctly superior efficacy or safety compared with existing pharmaceuticals or treatment methods).

To receive these priority consultation services, all applications (except those for orphan drugs) must be reviewed to determine if they warrant this service. When the PMDA receives an application for priority designation, it consults with its internal and external experts before conducting an overall assessment of the seriousness of the indicated disease and the medical usefulness of the product, to determine if the application merits priority face-to-face advice. The outcome of this review is notified to the applicant and reported to the CDfS.

Developers of drugs designated as a priority for face-to-face consultations may be offered consultations on compliance with reliability criteria, to enable applicants to compile complete and accurate documents to be attached to marketing approval applications.

#### How the consultation process is working

In fiscal year (FY) 2007, in addition to consultation applications for domestic clinical trials, the PMDA conducted 56 consultations on multinational clinical trials for new active ingredients. In the same year, the agency issued a notification entitled: 'Basic principles on Global Clinical Trials' (ELD/PFSB Notification No 0928010). The numbers of clinical trial consultations by therapeutic category are shown in Figure 2.

#### Initiatives for the future

Through efficient, prioritised and prompt reviews, the PMDA plans to reduce the 'drug lag' – the time lag between pharmaceuticals already approved in the US and EU not yet having been approved in Japan, and thus not being available to Japanese citizens. The aim is to reduce this time lag by two and a half years (consisting of 18 months for development and a year for approval review) by FY 2011. To achieve this target, measures being taken include reducing the development period by a significant expansion of, and improvement in, consultation services.

In addition to reducing the drug lag, plans for further improvement include the introduction of a consultation and review system for the preliminary evaluation of application descriptions.

The PMDA aims to increase the total number of consultation meetings to 1,200 a year by FY 2011.

Technical matters relating to clinical trial consultation meetings are now handled by a working group established jointly with the Japan Pharmaceutical Manufacturers Association (JPMA), the Pharmaceutical Research and Manufacturers of America (PhRMA) and the European Federation of Pharmaceutical Industries and Associations (EFPIA). This working group has collaborated to ensure large-scale improvements in consultation services and an expanded consultation menu aimed at reducing waiting times for both drug development and approvals.

#### Conclusion

Clearly, then, the clinical trial consultation system in Japan has been increasingly effective in enabling the conduct of clinical trials and in gaining marketing approval for new drugs and medical devices. With the PMDA in the process of making approval reviews speedier and more efficient to resolve the current issue of drug lag, further improvements are expected in the clinical trial consultations system in the near future.

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