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CLINICAL TRIALS HANDBOOK
Asia Pacific

JAPAN

Japan

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Introduction

The regulator of clinical trials in Japan is the Ministry of Health, Labour and Welfare (**MHLW**). The sponsoring, preparation, management and execution of clinical trials for the purpose of applying for product approvals in Japan must be in accordance with MHLW's Ordinance on Standards of Implementation of Clinical Studies on Drugs (Ministerial Ordinance No. 28 of March 27, 1997), MHLW's Ordinance on Standards of Implementation of Clinical Studies on Medical Devices (Ministerial Ordinance No. 36 of March 23, 2005), and MHLW's Ordinance on Standards of Implementation of Clinical Studies on Regenerative Medicine Products (Ministerial Ordinance No. 89 of July 30, 2014) (Good Clinical Practices or **GCP**).

In addition, investigations on the compliance with GCP are carried out by the Pharmaceuticals and Medical Devices Agency (Article 14-2(1) of the Act of Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices ("**PMD Act**").

Different regulatory regimes apply to clinical trials for purposes other than applying for product approvals. The rest of this article is dedicated to clinical trials for the purpose of applying for product approvals.

Regulatory framework

The main piece of legislation in Japan governing pharmaceuticals and medical devices administration is the PMD Act, which regulates clinical research, manufacturing, marketing, labelling, and safety of drugs, diagnostics, regenerative medicines and medical devices. The handling of clinical trials and government review of clinical trial plans for the purpose of applying for product approvals are governed by Articles 80-2 and 80-3 of the PMD Act and Articles 268 to 280-2 of the PMD Act Enforcement Regulations (Ministerial Ordinance No. 1 of February 1, 1961).

Based on the relevant regulations, a person intending to sponsor clinical trials must:

- **Comply with the provisions of GCPs**
    - The sponsoring, execution and management of clinical trials must be in compliance with GCPs (Article 80-2(1), (4) and (5) of the PMD Act).
- **Submit a clinical trial plan (different rules apply to the submission of clinical trial plans based on drug type)**

A clinical trial plan must be submitted to the MHLW for the following medicinal substances, instruments and processed cells:

- Medicinal substances with active ingredients that differ from those of drugs listed in the Japanese Pharmacopoeia and those of drugs already approved for marketing
- Medicinal substances that have the same active ingredients as those of drugs listed in the Japanese Pharmacopoeia and those of drugs already approved for marketing and differ from them in terms of routes of administration
- Medicinal substances that have the same active ingredients as those of drugs listed in the Japanese Pharmacopoeia and those of drugs already approved for marketing but differ from them in terms of

percentage of active ingredients in the drug composition, indications and effects, and dosage and administration

- Medicinal substances with the same active ingredients as those of drugs that have already been approved for marketing as drugs that differ in active ingredients from drugs listed in the Japanese Pharmacopoeia and drugs already approved for marketing, and for which the reexamination period specified under the PAL has not passed from the date of marketing approval
- Medicinal substances that are expected to be biological products
- Medicinal substances that are manufactured by using genetic modification technology
- Instruments whose structure, usage, efficacy, effect and performance are different from those already approved
- Instruments that are medical devices approved as those that are clearly different in structure, usage, efficacy, effect and performance from medical devices approved and that have the same characteristics in structure, usage, efficacy, effect and performance as those whose post marketing usage result survey period has not passed
- Instruments that are expected to be biological products
- Instruments manufactured by using genetic modification technology
- Processed cells that are expected to be regenerative medicine products

The person submitting a clinical trial plan must not sponsor the clinical trial or itself conduct the clinical trial for 30 days after the date of the submission of the plan.

Submit a notification of adverse effects, etc.

When a person sponsoring clinical trials becomes aware of any of the matters specified by the MHLW Ministerial Ordinance, including the occurrence of disease, disability or death suspected to be attributable to the tested product, or matters relating to the efficacy and safety of the tested product, the person must report to the Minister of Health, Labour and Welfare (Article 80-2(6) of the PMD Act).

Other matters

(i) Requiring report and on-site examination

When the MHLW deems it necessary, it may request necessary reports from a person sponsoring clinical trials or a person conducting clinical trials, or have the competent officer perform on-site examination (Article 80-2(7) of the PMD Act).

(ii) Cancellation / change of clinical trial

When the MHLW deems it necessary to prevent the occurrence or spread of hazards to public health and hygiene, it may order the person intending to sponsor the clinical trial, or the person sponsoring the clinical trial, the person intending to conduct or is conducting the clinical trial to cancel the sponsoring of the clinical trial, or to suspend or change the clinical trial. The Minister may also issue other necessary instructions (Article 80-2(9) of the PMD Act).

Clinical trial agreements (CTAs)

There is no specific requirement to obtain the approval of a CTA. However, the parties are required to enter into a CTA providing for the matters prescribed in Article 13 of the GCPs. Such matters include:

- Date of the agreement
- Name and address of the sponsor
- If responsibilities relating to the clinical trial are to be outsourced to a contract research organization (**CRO**), name and address of the CRO and the scope of outsourcing
- Name and address of the medical institution carrying out the clinical trial
- Name and position of the persons responsible for the agreement
- Name and position of the investigator
- Term of the clinical trial
- Matters concerning the management of the tested product
- Matters concerning the maintenance of records
- Matters concerning notifications
- Matters concerning the maintenance of confidentiality regarding trial subjects
- Matters concerning the costs of the clinical trial
- Provision to the effect that the medical institution will carry out the clinical trial in accordance with the clinical trial plan
- Matters concerning indemnity for health hazard to trial subjects
- Other necessary matters

The sponsor must take necessary measures, such as arranging insurance coverage beforehand, to provide compensation for any health hazard to trial subjects (including those arising from the operations of a CRO) caused by the clinical trial (Article 14 of the GCPs). More specifically, together with the establishment of protocols concerning indemnifications for costs for treatments and other expenses, in order to ensure that such indemnifications are carried out, it is necessary to take measures such as insurance coverage.

In addition, the CRO should also establish protocols concerning indemnifications for damages concerning health hazard, and carry out indemnifications in accordance with such protocol.

CRO and in-county clinical caretaker

A sponsor initiates, operates, monitors and manages a clinical trial, including preparation of standard operating procedures; completes studies on the quality; and prepares clinical trial protocol, etc. While the sponsor may entrust part of the operations concerning a clinical trial to a CRO within the appropriate scope, the final responsibilities concerning the quality and completeness of clinical trial data always rest with the sponsor.

The sponsor is not required to be located in Japan. However, if a person who intends to sponsor a clinical trial is not located in Japan, the sponsor or prospective sponsor will need to appoint an in-country clinical caretaker who has residency in Japan (including the representative of a foreign legal person holding office in Japan) so that person can carry out the necessary procedures for sponsoring a clinical trial and ensure that necessary measures are taken to prevent the occurrence or spread of hazards to public health and hygiene.

A sponsor may delegate part of his or her duties and functions related to sponsoring and managing a clinical trial (or post-marketing usage result survey of a product) to a CRO. A CRO may perform any or all of the following services:

- Planning development strategy
- Conduct of Phases I to III trials
- Preparation of approval application form, approval application summary and attachment documentation as well as application
- Post-marketing usage result survey
- Carrying out the responsibilities of the in-country clinical caretaker and designated marketing approval holder (D-MAH)
- Trial-related services other than those mentioned above
- Consultation regarding development and approval/license
- Consultation regarding statistical analysis
- Quality assurance/audit and consultation regarding quality assurance/audit
- Training services
- Cooperation for the establishment of a clinical trial system

In principle, the sponsor retains ultimate legal responsibilities.

The CRO should ensure that the client (prospective sponsor) has taken out clinical trial insurance or taken other actions to ensure that the client can indemnify or compensate trial subjects for any health hazard prior to concluding part of the duties and functions related to sponsoring and managing a clinical trial for the client.

If the health hazard is caused due to the CRO's intentional or negligent acts (failure to exercise due care), and if causal relation is established between the intentional or negligent acts and the health hazard suffered by the trial subjects, the CRO must assume responsibility for such delinquency (damage).

If the CRO acts as an in-country clinical caretaker, then it should take the necessary measures to indemnify/compensate trial subjects in the same manner as the sponsor.

No specific requirements governing the appointment of a CRO are provided in the GCPs. However, the sponsor must enter into an agreement with the CRO, which covers the following:

- Scope of the functions and obligations
- Procedures for the conduct of the delegated tasks
- Provision that the sponsor may ascertain if delegated tasks are carried out properly and smoothly in accordance with the above procedures

- Matters concerning instructions to the CRO
- Provision that the sponsor may ascertain if its instructions are observed and that the delegated tasks are carried out properly and smoothly in accordance with the instructions
- Matters relating to reporting by the CRO to the sponsor
- Matters relating to indemnification to trial subjects
- Other necessary matters concerning the delegated tasks

The clinical trial agreements are not subject to review by regulatory authorities.

Investigator

An investigator must have sufficient education, training and clinical experience to be able to conduct the clinical trial properly. His or her functions include:

- Selecting trial subjects in accordance with the objectives of the trial from the ethical and scientific standpoints and taking into account candidates' health conditions, symptoms, ages, capacity to give consent and other relevant factors
- Taking measures beforehand so that appropriate treatment can be given to subjects when adverse events occur
- Reporting certain incidents, such as deaths suspected of being caused by adverse reactions of the investigational product or other serious adverse events

Investigator-initiated trials are allowed (Article 15-2 of the GCPs). In addition, the investigator may delegate part of the execution and management of clinical trials (Article 15-8 of the GCPs). Further, pharmaceutical companies are allowed to support such trials.

Tested products

As stated above, when MHLW deems it necessary to prevent the occurrence or spread of hazards to public health and hygiene, it may order the person intending to sponsor a clinical trial or the person sponsoring a clinical trial, or the person intending to conduct or is conducting the clinical trial, to cancel the sponsoring of the clinical trial, or to suspend or change the clinical trial. The approval of the MHLW is therefore necessary for the administration of a tested product.

In addition, explanation regarding the purposes, methods, expected results/efficacy and expected side effects must be provided to the trial subjects, and the written informed consent of the trial subjects must be obtained.

There are no specific rules concerning financing the supply of tested products. However, in principle, it seems that it is presumed that tested products will be provided to volunteers/patients without consideration. As a result, in the event considerations are demanded for tested products, the reasons for demanding payments must be stated in the clinical trial plan.

According to the GCPs, the allocation of costs for clinical trials must be provided in the CTA.

The provision of the tested product after the termination of the clinical trial is not allowed.

Intellectual property (IP) and data

According to the Patent Act, an inventor of an invention that has industrial applicability may obtain a patent for the said invention. In the case of clinical studies, therefore, the investigator may have the IP rights as a result of the trial. Such rights may be transferred (Article 33-1 of the Patent Act).

The following contractual clause is recommended for the transfer of the IP rights:

> "All IP rights and deliverables arising out of the clinical trial shall belong to ____."

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