

## **Current Status and Perspectives of Placebo-controlled Studies**

Subcommittee on Placebo-controlled Studies

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### **1. Background on Placebo-controlled Studies and Objectives of the Subcommittee**

The Subcommittee on Placebo-controlled Studies of the Pharmaceuticals and Medical Devices Agency (PMDA) Science Board (hereinafter referred to as the “Subcommittee”) discussed and summarized basic perspectives on the need for placebo-controlled studies for the assessment of the efficacy of pharmaceuticals. Given that various factors may hinder the conduct of placebo-controlled studies, clarifying these factors and assessing their validity will provide important information for determining the application of placebo-controlled studies for future individual clinical trials.

Placebo-controlled studies are difficult to be clearly defined, but they generally mean clinical studies in which subjects are randomly assigned to either an investigational drug or placebo with the same appearance. Most placebo-controlled studies are conducted as double-blinded trials. Randomization and blinding are usually considered as preconditions for placebo-controlled studies. Nevertheless, randomization, blinding, and placebo-controlled are three independent concepts, with different points of discussion.

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In particular, the necessity of randomization should usually be discussed before determining the necessity of placebo-controlled studies. Randomization therefore includes scientific and ethical issues that are different from those associated with placebo-controlled trials. Randomization is thus not a main topic of this report.

One of the criteria for determining the appropriateness of using placebo as a comparator is whether standard treatment is available for the target disease. If avoiding a therapy is considered by experts to cause obvious disadvantages to patients, the therapy might as well be called “standard treatment.” The most basic and convincing rationale for considering a therapy as a standard treatment is efficacy proven by a placebo-controlled study. However, such a narrow definition of “standard treatment” influences the judgment on the necessity of placebo-controlled studies; therefore the Subcommittee’s discussion was based on the assumption that “standard treatment” refer to therapies considered by experts to possess high scientific needs with a favorable benefit-risk balance. In this report, “standard treatment” means widely used treatments that have been medically validated by being covered by health care insurance or recommended by medical society guidelines. Clinical trials in which the investigational drug or placebo is added to standard treatment (i.e. add-on studies) are not considered as “placebo-controlled studies” in this report because these studies are considered to be qualitatively different. (However, add-on studies may be classified as “placebo-controlled studies” in some sections of this report.) Specifically, “add-on studies” are relatively feasible in terms of ethical issues, a main topic of this report, but raise other questions such as whether an investigational drug “added” to other therapy can demonstrate its real efficacy; this clearly shows qualitative difference between add-on and placebo-controlled studies.

As a general rule, placebo-controlled studies are required to assess the efficacy of pharmaceuticals. This also applies to cases where a standard treatment is available. Specifically, if an investigational drug is compared with a standard treatment, appropriate comparison should be made with an appropriate treatment; otherwise, drugs equivalent to placebo in efficacy may be used in clinical practice. Placebo-controlled studies are particularly needed for trials that are expected to generate strong placebo effects. In some cases, however, placebo-controlled studies are difficult to conduct because of ethical and other issues. The Subcommittee has therefore discussed issues and concerns that may impact the decision on the necessity of placebo-controlled studies for investigational new drugs, in view of the current clinical practice and other considerations.

## **2. Current Status of Placebo-controlled Studies in Japan**

### **2.1 History of Placebo-controlled Studies for the Development of Pharmaceuticals in Japan**

In the past in Japan, comparisons with approved drugs, if available, tended to be considered important for assessing the efficacy of investigational new drugs. There were therefore many investigational new drugs that were not evaluated by placebo-controlled studies. Infrequent placebo-controlled studies were also due to inadequate environment for clinical trials or many technical problems associated with the conduct of clinical trials.

Subsequently, basic guidelines on the conduct of clinical trials were established through activities of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Specifically, the ICH-Good Clinical Practice (GCP) was introduced to the Japanese regulatory system (ICH-E6 guidelines, Ordinance No. 28 of the Ministry of Health, Labour and Welfare [MHLW] dated March 27, 1997), and the following guidelines were enforced: “General Considerations for Clinical Trials” (ICH-E8 guidelines, Pharmaceutical and Medical Safety Bureau (PMSB)/Evaluation and Licensing Division (ELD) Notification No. 380 dated April 21, 1998); “Statistical Principles for Clinical Trials” (ICH-E9 guidelines, PMSB/ELD Notification No. 1047 dated November 30, 1998); and “Choice of Control Group and Related Issues in Clinical Trials” (ICH-E10 guidelines, PMSB/ELD Notification No. 136 dated February 27, 2001). These guidelines formed the basis for assessing the efficacy of new drugs under development, providing an environment to conduct scientifically and ethically appropriate trials.

### **2.2 Current Status of Placebo-controlled Studies for the Development of Pharmaceuticals in Japan**

Through the aforementioned sequence of events, a certain number of placebo-controlled studies have come to be conducted in Japan now. Shown below is summary results of a questionnaire survey conducted by the Japan Pharmaceutical Manufacturers Association in 2015. The survey has revealed a part of the current situation. (For details, refer to “Status of the conduct of placebo-controlled studies among industry-sponsored clinical trials [Document No.1 for the 4th meeting of the Subcommittee on Placebo-

controlled Studies].” In the survey, add-on studies were categorized as placebo-controlled studies.)

The purpose of the survey was to understand the actual situations of placebo-controlled studies conducted in recent years, i.e., trials for which clinical trial notifications were submitted from January 2010 onward; pharmaceutical companies were requested to complete a questionnaire about their clinical trials using placebo (5 trials or less per company). In total, 22 of 27 companies answered the questionnaires about 65 trials: 2 Phase I trials, 21 Phase II trials, 7 Phase II/III trials, and 35 Phase III trials. Of the 65 trials, 24 were conducted globally and 40 in Japan alone (unreported for the remaining 1 trial).

Of the 65 trials, 58% simply compared an investigational drug with placebo without administering background therapy (i.e., studies fitting the definition of “placebo-controlled studies” used in this report), and 37% were add-on studies. Placebo-controlled trials were conducted in various disease areas, being particularly common in neuropsychiatric disorders (25% of the 65 trials) and cancers (16%), followed by endocrine and metabolic disorders (8%), respiratory disorders (8%), gastrointestinal disorders (6%), cardiovascular disorders (5%), etc. Placebo-controlled studies were also conducted for infectious diseases, orthopedic surgery, urology, ophthalmology, etc., although the number of studies was limited. Of the 65 trials, 85% involved subjects 18 years or older, and 15% involved subjects younger than 18 years (of which 4% involved subjects younger than 11 years).

The survey has shown that placebo has been used in many trials in various disease areas including pediatric disorders. This suggests that there is no specific area in which placebo cannot be used. (Although add-on studies account for approximately 40% of the 65 trials.)

### 2.3 PMDA’s Position on the Necessity of Placebo-controlled Studies

The Japanese regulatory authorities’ position on placebo-controlled studies is presented in the document entitled “Points to be Considered by the Review Staff Involved in the Evaluation Process of New Drug” published on April 17, 2008

(<https://www.pmda.go.jp/files/000153830.pdf>). (Note that add-on studies are categorized as “placebo-controlled studies” in the document.)

The document states that, when deciding whether to approve a drug, PMDA should consider several points including the following: “Is the efficacy in the study population considered to be more effective than placebo according to the results of properly designed clinical studies?” Points to be checked during regulatory review may differ between individual pharmaceuticals according to the characteristics of the drugs, submitted study results, or other considerations. Nevertheless, the document lists the following points that should be considered: “Has superiority been confirmed against placebo or other doses in the efficacy evaluation?” and “Has non-inferiority/superiority against an active control been confirmed in the efficacy evaluation?”

In regards to handling of placebo, the document states that “in a disease area where the placebo responder rate is presumed to be constant, results showing the investigational drug’s non-inferiority against an existing drug or results from an objective and appropriate clinical study even without a control group may be sufficient for the evaluation.” The document also notes that when a standard treatment is used as a comparator, the appropriateness of the comparator and their doses should be confirmed.

The document describes basic principles used by PMDA when providing consultations on clinical trials and reviewing new drugs, although individual trials or drugs should be assessed on a case-by-case basis according to their characteristics.

### **3. How to Address Situations Where a Placebo-controlled Study Is Difficult to Conduct**

Ethical issues are the main reason for the difficulty in conducting placebo-controlled studies, although there are also technical and other problems. This section thus focuses on ethical issues and how to overcome them (e.g., modifications of study designs), and then discuss feasibility issues and how to address them.

### 3.1 Ethical Issues

As a general rule, randomized placebo-controlled studies are required to assess the efficacy and safety of a new drug. They are considered necessary, in particular, when placebo effect, such as that on subjective complaints, is expected to be strong and when symptoms fluctuate due to the natural course of the disease.

Meanwhile, ethical issues may hinder the use of placebo. For example, the Declaration of Helsinki by the World Medical Association (amended in 2013) clearly states that, if a standard treatment is available, the use of placebo is acceptable only when the following two conditions are satisfied: “where the use of placebo is necessary for compelling and scientifically sound methodological reasons” and “the patients who receive placebo will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.” The Council for International Organizations of Medical Science (CIOMS) established similar conditions in the “International Ethical Guidelines for Biomedical Research Involving Human Subjects” (2002).

Of the two conditions, the latter should be discussed from an ethical viewpoint, namely, whether patients who do not receive a standard treatment will suffer “serious or irreversible harm.” This condition concerns trials in which placebo is administered in place of standard treatment to patients with serious, life-threatening diseases such as malignant tumors and severe infectious diseases. In addition, a certain degree of consideration is required for placebo-controlled studies that will not cause any “serious or irreversible harm” despite lack of standard treatment but will impose a heavy burden on subjects. This specifically relates to circumstances that require long-term and invasive administration methods.

In any case, however, it does not mean that a placebo-controlled study may be avoided just because it is not feasible. The conduct of a placebo-controlled study should be carefully discussed on a case-by-case basis for individual clinical trials based on the severity and irreversibility of the target disease, and, if appropriate, relief measures may be prepared. Clinical assessment guidelines for each disease area may describe points to be considered when selecting study designs and conducting placebo-controlled studies; such guidelines may be referred to as well. The relationship between social benefits and benefits or burdens on individual patients should be extensively discussed

by Institutional Review Boards (IRB) and at other occasions, and efforts should be made to seek patients' understanding of the importance of scientific assessment of new drugs.

### 3.2 Issues Related to Modifications of Trial Designs

If avoiding the use of an available standard treatment causes non-negligible risks or burdens on subjects, measures should be taken to lessen the risk or burden. One measure is modifications of study designs.

For example, the ICH guideline "Choice of Control Group and Related Issues in Clinical Trials" (ICH-E10) discusses the modifications of placebo-controlled study designs, including three-arm trials, additional doses, add-on studies,<sup>1</sup> replacement studies,<sup>2</sup> early escape/rescue treatment,<sup>3</sup> limited placebo period,<sup>4</sup> and randomized withdrawal.<sup>5</sup> If these modifications sufficiently lower risk to subjects, using placebo rather than standard treatment as a comparator may be acceptable.

However, each study design has its own unique scientific limit, and may not necessarily be useful for minimizing risk or burden to subjects. The decision on whether to conduct a study with a modified design should therefore be carefully considered according to individual protocols.

For instance, randomized withdrawal trials are primarily designed to prove long-term efficacy or the suppression of recurrence; thus, in terms of scientific assessment, they cannot be used as an alternative to demonstrate efficacy in the acute phase of disease. Moreover, sudden withdrawal of treatment may lead to exacerbation of symptoms in individual patients with diseases requiring continuous treatment. Ethical issues associated with modified study designs should thus also be carefully considered.

The CIOMS guidelines recommend that, in addition to appropriate modifications of study design, interim analysis be reviewed by an independent data monitoring committee to avoid continuing treatment that is useless and inferior. Other than this, additional measures to ensure the safety of subjects (e.g., enhanced monitoring, strict eligibility criteria) are useful to reduce risk to subjects.

In some designs of placebo-controlled studies, fewer subjects are assigned to placebo than to investigational product, such as 1:2, instead of 1:1. The ICH-E10 guideline, however, does not recommend the modification of assignment ratio. Although such modification reduces the number of subjects receiving placebo, it does not reduce risk

to individual subjects receiving placebo. In clinical trials that may pose high risk to subjects, modification of assignment ratio thus does not change ethical acceptability.

<sup>1</sup> Add-on study: Study method where investigational drug or placebo is added to standard treatment. In terms of assessing the investigational drug, the ICH-E10 guideline considers this study design to be useful only when standard treatment already administered is not fully effective.

<sup>2</sup> Replacement study: Study method where the investigational drug or placebo is added by random assignment to conventional treatment given at an effective dose and the conventional treatment is gradually tapered. After replacement, the ability to maintain the subjects' baseline status is assessed according to predefined success criteria.

<sup>3</sup> Early escape/rescue treatment: Study method where subjects are promptly removed from the study if clinical symptoms worsen, subjects fail to improve to a defined level, subjects suffer from an event that the treatment was intended to prevent, or subjects who otherwise require rescue treatment. In such studies, the need to change treatment becomes a study endpoint.

<sup>4</sup> Limited placebo period: Study method where placebo group is used for a short period at the beginning of an active control trial in situations where long-term placebo treatment would not be acceptable.

<sup>5</sup> Randomized withdrawal: Study method where subjects receiving an investigational drug for a specified time are randomly assigned to continued treatment with the investigational drug or to placebo (i.e. withdrawal of active treatment).



### 3.3 Challenges Regarding Feasibility

In addition to the aforementioned ethical issues, the discussion by the Subcommittee revealed that in some cases placebo-controlled studies may be difficult to conduct due to feasibility issues, which can be categorized into 4 groups:

- 1) Recruiting patients or collecting cases is difficult.
- 2) Patients' consent cannot be obtained or dropout rate after assignment is high (because a similar drug is already on the market and has been used by a significant number of patients, or because the investigational drug has long been on the overseas markets and has been widely imported and used by Japanese individual patients, or because the investigational drug is already available for another indication and its off-label use is common among patients, or for other reasons).
- 3) Healthcare professionals are reluctant to use placebo (because off-label use of the investigational drug is common since it is referred to by treatment guidelines, or because experimental use has suggested the efficacy of the investigational drug and treatment success of the drug has been published, or for other reasons).
- 4) The IRB does not approve the use of placebo (because of the reasons presented in 2) and 3), or because a board member[s] refuses any control arm that does not use standard treatment or places excessive importance on the disadvantages of not using standard treatment, or for other reasons).

Among the feasibility issues presented above, some can be resolved by measures taken by medical and scientific societies, by thorough discussion among relevant parties before the beginning of a study, or through other measures, but others require political measures.

With regard to the feasibility issue 1), placebo-controlled studies may be conducted by securing as many patients as possible by organizing a disease registry or by using global clinical trials.

Extensive off-label use is a cause of the feasibility issues 2) and 3). In clinical practice, off-label use of drugs has been allowed to expand gradually without robust assessment of the drugs. However, the "Investigational Committee for Usage of Unapproved/Off-label Drugs with High Medical Needs," established in February 2010, has promoted efforts to

gain approval for unapproved or off-label drugs with high medical needs. These efforts are expected to help resolve the feasibility issues 2) and 3) relating to placebo-controlled studies.

Finally, political measures should be discussed towards integration of several IRBs and enhancement of the quality of IRBs, to resolve the feasibility issue 4), namely, IRB's disapproval of all placebo-controlled studies with no exception. Such measures should be promoted in a manner consistent with the current MHLW's accreditation system for Ethics Review Committees (not for IRBs).

#### **4. Conclusion and Issues for Future Discussion**

##### **4.1 Conclusion**

The Subcommittee confirmed that placebo-controlled studies are necessary for evaluating the efficacy of new drugs. The Subcommittee also discussed the necessity of placebo-controlled studies and cases where placebo-controlled studies are difficult to conduct, examining what is causing the difficulty and how to overcome the difficulty.

The discussion revealed that the difficulties can be categorized into ethical or feasibility issues, which should be addressed separately.

Ethical issues are related to cases where avoiding the use of standard treatment will pose severe risk to subjects or administration of placebo itself will be a large burden on subjects. Even in such cases, however, placebo-controlled studies may be conducted by reducing risk or burden to subject through modifications of study designs or by other measures. Feasibility issues are (1) "Recruiting patients or collecting cases is difficult," (2) "Patients' consent cannot be obtained," (3) "Healthcare professionals are reluctant to use placebo," and (4) "The IRB does not approve the use of placebo." The Subcommittee's discussion suggested that some of the 4 issues can be resolved by future political measures.

## 4.2 Issues for Future Discussion

The Subcommittee also raised other issues, which were not fully discussed. In particular, the following three issues should be discussed in the future.

- 1) The necessity of placebo-controlled studies for fields including medical devices and regenerative medicines (including the necessity of sham surgeries)

In general, placebo-controlled studies are absent in the evaluation of medical devices or regenerative medicines. Conducting a placebo-controlled study may be impossible for products for which placebo cannot be manufactured, for rare disease, or for other cases. In cases where a placebo-controlled study is feasible, however, an untreated group may be used based on the necessity in terms of endpoint. In particular, it should be noted that sham surgery may be required in a controlled trial that evaluates an investigational treatment that includes surgery. The Subcommittee noted that the necessity of controlled studies and placebo-controlled trials for medical devices, regenerative medicines, surgical treatment, etc. should be discussed. However, no consensus exists among experts over the ethical acceptability of such study designs, which should therefore be carefully discussed in view of overseas situations as well.

Furthermore, discussion of this issue should involve not only the necessity of placebo-controlled studies but also the necessity of randomized controlled trials. Some members of the Subcommittee commented that clinical trials without a control group may be acceptable if they can properly evaluate the efficacy of investigational treatment. In such circumstances, a single-arm study may be conducted, and therefore the necessity of placebo-controlled studies need not be discussed.

- 2) The necessity of placebo-controlled studies in the face of public health crisis

Placebo-controlled studies may be difficult to conduct even in cases where no standard treatment is available. Such cases include the experimental use of a new drug in the face of public health crisis, including epidemic of serious and unknown infections. The Subcommittee indicated that, in such crisis situations, placebo-controlled studies may be avoided even if there is no standard treatment. Particularly in Europe and the United States, a debate, triggered by the conduct of clinical trials for Ebola virus disease, is

taking place on the necessity of placebo-controlled studies of investigational new drugs that address public health crisis. The progress of the debate should be closely monitored.

### 3) Setting the margins for non-inferiority or equivalence trials

The Subcommittee discussed situations in which placebo-controlled studies are recommended even if standard treatment is available. If conducting a placebo-controlled study is still difficult, however, non-inferiority or equivalence trials using an active comparator may be considered.

Non-inferiority and equivalence trials have an advantage that subjects in the control arm receive an active treatment. As mentioned in the ICH-E10 guidelines, however, there is no assurance that an active comparator is superior to placebo in efficacy (assay sensitivity). Moreover, non-inferiority trials require a “non-inferiority margin” (i.e., the maximum acceptable level of inferiority in the efficacy of investigational treatment relative to an active comparator), and equivalence trials require an “equivalence margin” (i.e. the maximum acceptable difference within which the investigational treatment is considered equivalent in efficacy to an active comparator). If the predetermined margins are too wide, an investigational drug which is actually inferior in efficacy to an active comparator may be considered non-inferior or equivalent. Defining appropriate margins is thus extremely important for non-inferiority or equivalence trials.

Non-inferiority or equivalence margins should therefore be defined to ensure clinical relevance as well as superiority over placebo. Furthermore, if an active comparator to be used in a trial is a drug that was approved based on a non-inferiority or equivalence study, it is necessary to ensure that the drug was appropriately compared with an active comparator in the non-inferiority or equivalence study.

Although the ICH-E9 guideline describes the approach for setting margins over an active comparator, there are no definite criteria for determining non-inferiority or equivalence margins applicable to all trials. This issue should therefore continue to be discussed.

Abbreviations:

CIOMS: Council for International Organizations of Medical Science

ELD: Evaluation and Licensing Division

GCP: Good Clinical Practice

ICH: International Conference on Harmonisation of Technical Requirements for  
Registration of Pharmaceuticals for Human Use

IRB: Institutional Review Board

MHLW: Ministry of Health, Labour and Welfare

PFSB: Pharmaceutical and Food Safety Bureau

PMDA: Pharmaceuticals and Medical Devices Agency