Points to Consider for nonclinical safety matters when submitting the initial clinical trial notification (Early Consideration)

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Center for Product Evaluation
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When an initial clinical trial notification (CTN) is submitted to the PMDA, the toxicology reviewer check issues related to ensuring the safety of clinical trial participants based mainly on non-clinical study data. In this document, common inquiries frequently raised during the recent review of initial CTNs are summarized, and the basic principles regarding the provision of information on non-clinical safety, avoidance of pregnancy, and inclusion of lactating women in clinical trials, are presented. In addition, wording examples for CTN-related documents such as the informed consent form are provided as an attachment for your reference when preparing materials for the initial CTN. If there are concerns about the sufficiency of non-clinical safety studies to commence a clinical trial, or about ensuring the safety of trial participants, etc., sponsors are recommended to consider using PMDA's consultation services prior to submitting the initial CTN in order to ensure the smooth progress of the 30-day-CTN review.

1. Handling of information on the safety concerns of the investigational medicinal product (IMP)

Information obtained from nonclinical studies should be appropriately provided to the investigators and participants in the clinical trial in order to ensure the proper conduct of the trial. In this context, the safety concerns predicted from non-clinical safety studies, the pharmacological effects and class effects of the IMP, etc., for which the safety margin between the clinical dose and NOAEL and the mechanisms of toxicity findings suggest the possibility of their occurrence in humans, should be clearly and understandably communicated to trial participants through the informed consent document. In particular, findings that are difficult to monitor in clinical settings or those that were irreversible in non-clinical safety studies must be handled with care, such as providing information on such findings even when their relevance to humans is not clear.

It is not necessary to provide information on toxicity findings observed in non-clinical safety studies if they are related to adverse drug reactions that have already been identified in clinical trials. However, it is desirable to provide information on any toxicity findings detected in non-clinical safety studies that are more serious than the adverse drug reactions identified in clinical trials. It is also necessary to appropriately provide information on safety risks related to excipients, etc. contained in IMPs used in clinical studies.

In addition, in the case of biotechnology-derived pharmaceuticals where a sufficient period of non-

*: This English version of the Japanese early consideration is provided for reference purposes only. In the event of any inconsistency between the Japanese original and English translation, the former shall prevail.

clinical safety studies has not been conducted to justify the conduct of clinical trials for reasons such as anti-drug antibodies being produced in animals, or where adequate, guideline-compliant non-clinical safety studies have not been conducted due to the specificity of the IMP (e.g. targeting an exogenous antigen or only reacting in humans), it is necessary to appropriately inform trial participants of these circumstances.

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2. Phototoxicity assessment

The discussion of phototoxic potential is often missing in the investigator's brochure and other documents. It is necessary to include information on the initial evaluation of phototoxicity potential in accordance with the “Guidelines for the Photosafety Evaluation of Pharmaceuticals" (ICH S10 : PFSB/ELD Notification No. 0521-1 dated May 21, 2014) and other guidelines. If the phototoxic potential of the IMP cannot be ruled out, it is necessary to either take appropriate photoprotection measures for trial participants or conduct an additional phototoxicity assessment to rule out any concern for phototoxicity. For IMPs that are already in clinical use overseas, it is possible to discuss their phototoxicity potential based on the available clinical study results or other data. When utilizing clinical data, it is important to consider the extent of clinical experience (e.g. the number of trial participants and duration of exposure), whether the participants were outpatients or inpatients, and whether any photoprotective measures were implemented during the administration of the IMP. Specific examples of photoprotection measures should be adjusted as appropriate based on the phototoxic potential of the IMP.

3. Avoidance of pregnancy

If concerns of pregnancy during treatment with the IMP cannot be ruled out because embryo-fetal toxicity has been observed in toxicity studies, or because appropriate reproductive and developmental toxicity studies have not been conducted at the time of submission of the CTN, it is necessary to specify appropriate contraceptive methods in the study protocol for trial participants who may become pregnant or whose partners may become pregnant. An appropriate, specific contraception period has to be set in accordance with the "Guidance on the Need for Contraception Related to Use of Pharmaceuticals" (PSEHB/PED Notification No. 0216-1 dated February 16, 2023) and based on the genotoxic potential, reproductive and developmental toxicity risks, pharmacokinetic parameters, and other properties of the IMP.

When selecting the contraceptive methods and duration specified in the clinical trial, particular attention should be paid to the following points.

・ The number and combination of contraceptive methods should be evaluated, taking into account

the degree of risks and the nature of the IMP (e.g., oral contraceptives should be avoided if the IMP is a potent CYP inducer).

- Strict abstinence (i.e., no sexual intercourse) may be selected as a contraceptive method, but should be adequately explained to the participants.
- The use of condoms alone does not fall under the category of “methods with an annual failure rate of less than 1% when used consistently and correctly, either alone or in combination” as specified in the "Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals" (PFSB/ELD Notification No. 0219-4 dated February 19, 2010).
- When it is necessary to prescribe strict contraception for male trial participants, taking into account the properties of the IMP, it may be necessary to prescribe contraception not only for male trial participants receiving the IMP but also for their female partners.
- If contraception is required, it is necessary to specify the period for which contraception must be continued, both during and after completion of IMP administration.

It is desirable to provide information on the acceptable contraceptive methods (including the approval/certification status in Japan) and the period of contraception as specifically as possible in the informed consent form. Some wording examples are provided in the attachment, but this is not intended to be a definitive list. The content should be adjusted based on the characteristics of the trial participants (healthy adults or patients) and the risks of the IMP.

When a pregnancy is discovered in a trial participant or the partner of a trial participant during the trial period (this may include a certain period after completion of IMP administration, depending on the properties of the product), the need to follow up on the outcome of the pregnancy may arise, and this should be specified as necessary.

4. Inclusion of lactating women

For lactating women, the decision to include them in the clinical trial should be made after considering information such as the properties of the IMP and whether or not it is secreted into breast milk. If lactating women are defined as an exclusion criterion, it should also be specified whether or not lactating women can be included in the clinical trial if breastfeeding is interrupted. In such cases, the time when breastfeeding can be resumed after the completion of IMP administration should also be specified. These provisions should also be clearly communicated in the informed consent form.

[Attachment]

Specific wording examples that take into account the important considerations regarding the initial CTN described in this document are provided below for your reference when preparing materials for the initial CTN.

1. Handling of information on the safety concerns of the IMP

(1) Toxicological information predicted from non-clinical study results, pharmacological action, etc.

< Sample wording in the informed consent form >

- Myocardial necrosis was observed in cynomolgus monkeys treated with this drug. This finding was observed at doses higher than approximately ● times the dose administered in clinical studies.
- In pregnant rats given this drug, fetal death and teratogenicity (the property of causing malformations in fetuses) were observed.
- This drug can be genotoxic (toxicity to substances that transmit genetic information to the next generation in cells) and carcinogenic.
- Radioactivity in this drug may be genotoxic, carcinogenic, and affect germ cells (cells that produce sperm or egg).
- By suppressing the expression of genes that are not originally intended, this drug may cause adverse events that were not anticipated based on the data obtained so far.

(2) When an adequate, guideline-compliant toxicity study has not been conducted:

< Sample wording in the informed consent form >

- Repeat-dose studies in animals with this drug have been conducted for only up to ● weeks, and no longer-term studies have been conducted.
- There is no animal species suitable for evaluating the safety of this drug, meaning that no adequate toxicity evaluation has been conducted in accordance with internationally accepted guidelines for safety evaluation of pharmaceuticals.

2. Phototoxicity assessment

< Sample wording in the investigator's brochure >

- This drug does not exhibit molar absorptivity greater than 1000 $Lmol^{-1}cm^{-1}$ within the wavelength range of 290 to 700 nm, suggesting no phototoxic potential.
- Because the possibility of this drug being phototoxic cannot be ruled out, trial participants should

be advised not to be exposed to intense light. They should also be instructed that if they have to go outside, they should minimize skin exposure and take photoprotective measures such as using sunscreen and wearing sunglasses.

3. Avoidance of pregnancy

(1) Contraceptive methods for fertile participants

< Sample wording in the informed consent form >

When including only methods that are approved/certified in Japan:

The following contraceptive methods should be used correctly during the study period and for 4 weeks after the completion of IMP administration:

For male participants: Strict abstinence (i.e., no sexual intercourse), condoms

For female participants: Strict abstinence (i.e., no sexual intercourse), oral hormonal contraceptives (progesterone + estrogen), intrauterine devices, intrauterine hormone-releasing systems

For the informed consent form for a global clinical trial that also includes contraceptive methods used overseas, as well as whether they are approved/certified in Japan:

The following contraceptive methods should be used correctly during the study period and for 4 weeks after the completion of IMP administration:

For male participants: Strict abstinence, condoms, condoms with spermicide*

For female participants: Strict abstinence, oral hormonal contraceptives (progesterone + estrogen), female condoms*, cervical caps*, diaphragms*, contraceptive sponges*, spermicides*, intrauterine devices, intrauterine hormone-releasing systems

(*: Not approved/certified in Japan)

When specific methods are specified in the protocol, and the informed consent form only states that the investigator will explain the details:

You are required to use contraception during the study period and for 4 weeks after the completion of IMP administration. Please ask your study doctor about specific contraceptive methods.

(2) Contraceptive period for fertile participants

< Sample wording in the informed consent form >

Contraception should continue until 3 months after the completion of treatment with this drug for male participants, and until 6 months after the completion of treatment with this drug for female participants.

(3) Non-fertile participants

< Sample wording in the informed consent form >

For male participants: Vasectomized men with no sperm found in their semen.

For female participants: Women who have undergone hysterectomy, bilateral oophorectomy, bilateral tubal ligation, or bilateral salpingectomy, or who have been amenorrheic for 12 months (excluding amenorrhea due to medical reasons such as treatment with antineoplastic agents), and who are determined to be menopausal based on blood hormone levels.

(4) Actions to be taken when pregnancy is confirmed

< Sample wording in the informed consent form >

For male participants:

If your partner is found to be pregnant, contact the study doctor immediately. You will be asked to cooperate in follow-up on the outcome of your partner's pregnancy and the preborn baby.

For female participants:

If you are suspected or found to be pregnant, contact the study doctor immediately. You will be asked to cooperate in follow-up on the outcome of your pregnancy and the preborn baby.

4. Inclusion of lactating women

< Sample wording in the informed consent form >

- If you are breastfeeding, you cannot participate in this clinical trial (you cannot participate in the trial even if you stop breastfeeding).
- If you are breastfeeding, you cannot participate in this clinical trial, but if you stop breastfeeding, you can participate in the study. Breastfeeding can be resumed 4 weeks after the completion of IMP administration.