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Guidance for Establishing Safety in First-In-Human Studies during Drug Development

Q&A

Q1 This Guidance refers the reader to ICH guidelines in several places. We understand that the ICH guideline requirements are also required for Japanese NDAs, but does this Guidance say that ICH guidelines must also be followed prior to the first-in-human study?

A This Guidance does not mandate that ICH guidelines be followed prior to the first-in-human study. However, before the start of the first-in-human study, those guidelines must be used for reference to determine whether all of the studies and tests that are considered prerequisite have been completed.

Q2 Section 3.4.2.f of this Guidance, "Dose Escalation Scheme," states that "The dose and dose escalation method may be reconsidered in light of PK/PD and safety information obtained from the previous cohort. To allow for such situations, the protocol should describe the possibility of dose modification and does escalation, and the procedures for such modification." If the dose can be modified, how should the maximum dose would be described?

A If a modification is made in the maximum dose stipulated in the initial clinical trial notification, a notification of clinical trial modification will be required. If the initial intention is to increase the maximum dose, an appropriate maximum dose should instead be selected initially, based on scientific evidence and with careful consideration for the safety of subjects.

Q3 In this Guidance, section 3.4.2.b "Setting the Dose for First-In-Human Administration" states that, "Other procedures can be considered in special cases, such as, for example, cancer patients who have previously been treated with cytotoxic investigational products." What kinds of procedures are meant by "other procedures"?

A According to the guidelines, when working with most of the cytotoxic anticancer drugs of low molecular weight, the initial selected dose is usually 1/10 the amount that causes serious toxicity in 10% of rodents studied (STD_{10}). If a non-rodent animal is the most relevant species, the appropriate maximum

initial dose is generally considered to be 1/6 of the maximum dose that does not cause serious toxicity (maximum dose not resulting in death, lethal toxicity, or irreversible toxicity).

Q4 In section 3.4.2.b "Setting the Dose for First-In-Human Administration," please explain within the document, using examples, rather than referring to the literature, because this section is the core of this Guidance. We would like you to provide specific illustrations of methodology.

A Provided specific examples of does setting in first-in-human administration using two model cases of monoclonal antibody drags which have pharmacological action that provided receptor blocking against target molecules (although the NOAEL from toxicological studies was 10 mg/kg in both cases). We would like to add that these are only examples and the decisions on the first-in-human dose should be made from scientific evidence.

Case1 is the case approaching the Minimal Anticipated Biological Effect Level (MABEL) and Case2 differs from the conventional use of the No Observed Adverse Effect Level (NOAEL). When calculating the first-in-human dose, the majority of cases will fall into the following categories: cases in which the dose per unit body weight will be obtained from the MABEL or NOAEL (mg/kg) and will then be divided by a safety factor; cases in which the dose (mg/m^2) per unit body surface area (m^2) will be used for conversion to the Human Equivalent Dose (HED) to ensure equivalence between study animals and human subjects. In general, for drugs based on antibodies and receptor fusion proteins, body weight (kg) conversion is appropriate for extrapolation to humans, based on reasons such as previous clinical experience and similarity of pharmacokinetic(PK)- pharmacodynamic (PD) analyses. However, with further escalation in the development of products such as non-natural modified antibodies, new approaches should be considered based on new findings and accumulated experience.

(Case 1)

In this case, clinical dose and Mechanism of Action (MoA) of the investigational products are already clear from currently available similar drag products with the same target molecule. Therefore the initial dose in first-in-human administration is calculated from the NOAEL based on toxicological text using cynomolgous monkey as an animal model.

That is, the initial dose is obtained by dividing NOAEL 10mg/kg by the safety factor 10, so it can be calculated at 1 mg/kg. Since this dose is not considerably higher than the effective clinical dose, which anticipated from the pharmacokinetic (PK) and pharmacodynamic (PD) data comparing with similar drag products and so on, there is no problem in using it as the initial dose.

(Case 2)

In this case, the calculation of the clinical initial dose was used the MABEL based on applied pharmacodynamic (PD) test using cynomolgous monkey as an animal model, which is determined by knowledge of the histological distribution of the target molecules on the mode of action, *in vitro* studies and so on, because the target is a novel molecule.

The MABEL levels can anticipate from *in vivo* and *in vitro* studies were 0.5 mg/kg and 10μg/ml (which estimate appropriate 0.1 mg/kg in *in vivo* equivalent) respectively. In this case, a specific biomarker was available for the quantification of pharmacologic activities in studies used an appropriate animal model. Therefore, the initial dose can be calculated based on the MABEL (0.5 mg/kg) anticipated from *in vivo* model. That is, the initial dose is obtained by dividing MABEL 0.5mg/kg by the safety factor 10, so it can be calculated at 0.05 mg/kg.

	Case 1	Case 2
Molecule type	Monoclonal antibody	Monoclonal antibody
MoA of the study drug	Blocking activation of specific receptor	Blocking activation of specific receptor
Nature of the target	Similar drug products are already commercially available for the target of this same molecule.	New target.
Animal models	Cynomolgus monkey was adapted as an animal model by the knowledge of similar drugs products.	Cynomolgus monkeys was adapted as an animal model by the histological distribution of the target molecules, *in vitro* studies and so on, There are not considerable differences in effect obtained by *in vitro* studies between inter-species.
Administration route	Intravenous administration	Intravenous administration
Indication	Chronic disease	Chronic disease
Toxicological studies	Performed in cynomolgus monkeys (No rodent species) → NOAEL considered to be 10 mg/kg (high-dose group)	Performed in cynomolgus monkeys (No rodent species) → NOAEL considered to be 10 mg/kg (high-dose group)
Related knowledge of PK/PD	Performed in cynomolgus monkeys Compared with the related data of the similar drugs products, the anticipated clinical dose is estimated at 10 mg/kg.	Performed in cynomolgus monkeys Minimal Anticipated Biological Effect Level(MABEL) of *in vivo* estimated at 0.05 mg/kg MABELof *in vitro* estimated at 1 μg/mL(which estimate appropriate 0.01 mg/kg in *in vivo* equivalent)