事　務　連　絡
平成２４年４月１８日

各都道府県衛生主管部（局）
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厚生労働省医薬食品局審査管理課

「医薬品開発におけるヒト初回投与試験の安全性を確保するためのガイダンス」等の英文版の送付について

医薬品開発おけるヒト初回投与試験の安全性を確保するためのガイダンス及びその質疑応答集（Ｑ＆Ａ）について、添付の英文版を作成しましたので、業務の参考としてご活用下さい。

（添付資料）
①Guidance For Establishing Safety in First-in-Human Studies during Drug Development
②Guidance for Establishing Safety in First-In-Human Studies during Drug Development　Q&A

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

CONTENTS

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

SUMMARY

This Guidance shows the framework of our basic concept to support the smooth transition from non-clinical to early clinical study during the drug development process. It identifies risk factors in first-in-human trials, discusses the quality of the investigational products, and describes the planning and implementation of non-clinical studies and first-in-human trials. Strategies are provided for the calculation of the initial dose to be used in humans, for subsequent dose escalation, and for the mitigation of risk to subjects that is associated with the implementation of the clinical trial.

1. INTRODUCTION

The safety of subjects is the paramount consideration, particularly in first-in-human studies. Assessment of the safety of the investigational products has to be based on previously collected scientific findings, and needs to be evaluated on a case-by-case basis. This Guidance has been prepared to point out the risk factors which the sponsor should consider during the planning of non-clinical studies and first-in-human trials, and which should also be considered by the personnel responsible for study implementation, in order to ensure the safety of study subjects. In this Guidance, the term "first-in-human trial" refers to a phase I clinical trial, defined by the General Considerations for Clinical Trials (ICH E8), that uses a novel active ingredient and that is being implemented for the first time in the world at a Japanese study site.

Generally, risk factors in human subjects can be identified from earlier scientific findings for similar drug products and investigational products. However, the ability of non-clinical studies to predict safety issues in humans may be limited because of the specific nature of the target in humans and the other factors.

The designing of a protocol for a first-in-human trial in healthy individuals or patients should be based on information gathered from many sources, and the protocol should include the estimation of the initial dose to be used in humans, subsequent dose escalation, intervals between dosing, and the management of risk.

Particular consideration should be given to investigational product quality where it may give additional risk to subjects in first-in-human studies.

This Guidance should be read in conjunction with existing reference materials (see Reference Materials), as a general guideline. Application to individual diseases and investigational products should be on a case-by-case basis, using the most recent scientific findings.

2. SCOPE

This Guidance applies to all new chemical and biological investigational drugs (biotechnological/biological products), except drugs for cellular, tissue and gene therapy. It focuses primarily on issues for consideration prior to the first administration in humans, including investigational product quality and non-clinical studies, and on the design and implementation of first-in-human studies.

For early-stage exploratory studies, including microdose clinical studies as described in Japanese guidelines and documents such as ICH M3 (R2) please refer to the applicable guidelines.

3. MAIN GUIDANCE TEXT

For many new investigational products, safety data for estimating risk prior to the first-in-human study can be collected from non-clinical studies. However, in some cases non-clinical study findings are not sufficient to predict serious adverse events in humans; therefore closely examined the design of the non-clinical studies and the first-in-human study requires special consideration. When planning a first-in-human trial, sponsors and investigators should identify risk factors and apply risk mitigation strategies.

3.1 Risk Factors

Predicting the development of potentially severe adverse reactions to the investigational product necessitates the identification of the risk factors involved.

There is an increased risk of first-in-human study in case of deficiency of sufficient information with regard to (1), (2), or (3) or difficulty on predicting the safety in human when in the view of the following; (1) the mechanism of action, (2) the characteristics of the target molecule (site of action), or (3) the relevance of animal models, or if adequate information is unavailable.

For a first-in-human trial, the sponsor must consider each of the following items for each investigational product.

3.1.1 Mechanism of Action of the Investigational Product

In order to understand the primary pharmacological action and the side effects of the investigational product, review of the available information on the presumed mechanism of action is required. The correlation between the presumed mechanism of action and the pharmacological action observed in *in vitro* and *in vivo* study systems (duration of action and dose-response relationship) must be understood, insofar as possible, in terms of the characteristics of the molecules specifically targeted by the investigational product and the receptor/target binding affinity and occupancy of the investigational product. Such understanding will also help to predict factors such as species differences in pharmacological action, effects of genetic polymorphisms, and drug interactions.

In addition, if the investigational product binds to multiple active sites, the possibility should be considered that effects may occur other than those noted at individual active sites.

The following points need to be considered when reviewing risk factors that are related to the mechanism of action.

(1) Safety as determined from past human exposure to compounds having a related mechanism of action

(2) Any serious risk of toxicity from primary or secondary pharmacological action in animal models (including transgenic and knockout animals)

(3) Any novel feature of the molecular structure of the active ingredient

The minimal anticipated biological effect level (MABEL) can be used for dose-setting in the first-in-human study where the risk of adverse reaction development may not be anticipated from the results of non-clinical studies. The followings are cases where MABEL should be exercised: (1) no information is available on existing drugs that act on the identified target molecule, (2) the target molecule activates/blocks multiple signal pathways (for example, the target molecule elicits pleiotropic biological activities), (3) the drug elicits systemic actions in living organism such as an immune response, or (4) pharmacological action may be elicited that exceeds the organism's maximum permissible limit (for example, cytokine release induced by anti-CD3- or anti-CD28-superagonist). The pharmacodynamics(PD) studies that provide the basis for MABEL are not required to be conducted in accordance with GLP, but they should be highly reliable. (Details related to MABEL are provided in Section 3.4.2.b.)

3.1.2 Characteristics of the Target Molecule

The sponsors should review the risks of first-in-human administration, based on the following aspects of the target molecule and available data:

(1) Factors including structure, tissue distribution (including expression in/on cells of the human immune system), cell specificity, disease specificity, *in vivo* regulation, level of expression and "downstream" effects of the reaction cascade, and the variations between healthy individuals and patients.

(2) A description of genetic polymorphisms, if present, in the target molecule

3.1.3 Relevance of Animal Models in Non-Clinical Studies

Where necessary, the sponsor should draw comparisons between humans and the animal models used in non-clinical studies and predict potential differences assessing structural homology, tissue distribution, signal transduction pathways, and biological activity of the target molecules (see Section 3.3.1).

3.2 Investigational Product Quality

The process and product quality control of the investigational product for use in a first-in-human trial should be based on "Good Manufacturing Practices (GMP) for Study Products" (Pharmaceutical and Food Safety Bureau (PFSB) Notification No. 0709002, dated July 9, 2008). In addition, in order to proceed with the drug development process efficiently toward a future New Drug Application, it is desirable to establish provisional specifications. In establishing these specifications, please refer to the ICH guidelines Q6A and Q6B.

For investigational product quality, the contents of Sections 3.2.1 through 3.2.3 should be taken into account.

3.2.1 Elucidation of Structure and Other Characteristics

Appropriate analytical methods should be used to gain a better understanding of the structure and physicochemical properties of the investigational product. For highly heterogeneous investigational products such as glycoproteins, if this heterogeneity could potentially affect the pharmacological profile, the correlation between the heterogeneity and the pharmacological action of the drug should be clearly characterized.

When determining a safe starting dose, reliable methods of quantification must be established to quantify the amount of substance. If the investigational product is a substance such as a protein, in addition to the methods of quantification for the active ingredient, a potency assay should also be established based on the biological properties of the investigational product, and specific activity should be determined. If no public reference standard is available as the standard for the potency assay, a reference material should be established. For example, the active ingredient may degrade during storage, or be adsorbed onto the inner surface of the container in some cases. Therefore, the stability of the investigational product and factors such as adsorption onto the container should be investigated to confirm assurance of the intended dose.

3.2.2 Control of Impurities

Consideration should be given to the manufacturing process and stability of the investigational product during storage. If the presence of impurities that might

adversely affect safety cannot be ruled out, acceptable criteria should be established for assuming that these impurities will not adversely affect human health.

For impurities detected above the specified threshold in chemically synthesized investigational products such as low-molecular-weight compounds, they should be shown why there is no problems with safety as considering ICH guidelines Q3A, Q3B, and Q6A, when needed, related information reported in scientific literature and results from non-clinical studies.

For investigational products having a biological substance as the active ingredient, potential contaminants include product-related impurities (such as aggregates and degradation products), process-related impurities (such as host cell proteins), and infectious agents such as viruses and mycoplasmas. Unintended aggregates and host-cell-derived proteins can directly or indirectly increase immunogenicity, giving rise to adverse events, and should be removed to the extent possible. When human-derived and animal-derived cell lines are used as cell substrates, it is necessary to ensure the safety of the investigational products through characterization of cell substrates, and through testing for the absence of contaminating infectious viruses at appropriate steps during the production process (see ICH Q5A and Q5D). If biologically-derived raw materials including human-derived or those derived from other organisms (with the exception of plant-derived materials) are used in the production process, the "Japanese Standards for Biological Ingredients" (the Ministry of Health, Labour and Welfare, Notice 210, dated May 20, 2003) will be strictly observed. In the event of the unavoidable use of a substance, such as a bovine serum, that does not meet the Japanese Standards for Biological Ingredients, subjects enrolled in the clinical study will be informed accordingly.

Depending on the dosage form, procedures such as sterility tests, foreign insoluble matter tests, insoluble particulate matter tests, and endotoxin tests are needed in order to ensure that the quality of the drug is appropriate for administration in humans. Test procedures in General Tests of the Japanese Pharmacopoeia can be used.

3.2.3 Consistency in Quality between Non-Clinical Studies and Clinical Studies

The investigational product used in first-in-human administration should not differ from the investigational product used in non-clinical studies in ways that might adversely affect safety or efficacy, either with regard to structure or other properties

as described in Section 3.2.1, or with regard to the impurities profile as described in Section 3.2.2.

For investigational products that are biological products, refer to ICH guidelines Q5E and S6. If the manufacturing process of the investigational product was changed after non-clinical studies had been implemented, and if differences in quality are detected between the drug produced before and after these changes, the drug cannot be used in first-in-human studies unless it can be reasonably assumed, based on previous findings, that those differences will have no adverse impact on efficacy or safety. If this cannot be assumed, follow-up non-clinical studies should be conducted to confirm that the quality differences do not negatively influence the non-clinical study results, before the drug is used in first-in-human studies.

3.3 Non-Clinical Studies

3.3.1 Relevance of the Animal Model

There are qualitative and quantitative differences in biological responses in animals and humans for a specific investigational product. In particular, the following points should be understood as prerequisite for the satisfactory assessment of human safety and efficacy in animal models. In animal studies with an investigational product having high species specificity, the study will be designed with consideration for the mechanism of action and the characteristics of the target molecule (site of action). In addition, the study should use appropriate animal species that similar human biological responses as closely as possible.

(1) The intended pharmacological effects in humans may not be expressed in animals.

(2) Relationships between pharmacokinetic (PK) and pharmacodynamic (PD) results may not be evaluated appropriately.

(3) Relevant toxic effects in humans may not be predicted.

(4) For biological investigational products, in case of antibody formation, the risk to subjects may vary depending on how similar the biological products are to a human endogenous substance. However, these biological products cannot always be appropriately assessed in animal models.

The relevance of animal models should be demonstrated from following points;

(1) Expression, tissue distribution, and primary structure of the target molecule

However, a high degree of structural homology between humans and animals does not necessarily imply the same pharmacological effects.

(2) Cross-reactivity studies of biologics, such as monoclonal antibodies, using human and animal samples (including humanized model systems)

(3) Pharmacodynamics (PD)

- Binding affinity and occupancy of receptor/target, and pharmacological activity

- Data related to the activity of additional functional domains in animals, if necessary and available (such as Fc receptor* system for monoclonal antibodies) *Fc receptor: receptor for the Fc region of the immunoglobulin (antibody) molecule.

(4) Metabolism and other pharmacokinetic (PK) aspects

The reasons for selection of an animal model should be specified. If no appropriate animal species is available, the use of homologous proteins or the use of relevant transgenic animals expressing the human target molecules may be considered. For the assessment of risk in humans, the data obtained is useful if the biological activity predicted for the investigational product in humans is elicited by the interaction between a homologous protein and the target molecule. Moreover, there are some cases which *in vitro* studies using human cells provide relevant additional information.

The relevance and limitations of all animal models used in the non-clinical safety assessment of the investigational product should be carefully considered and fully discussed in the supporting documentation.

3.3.2 Pharmacodynamics

Pharmacodynamics (PD) studies must be something to provide information on correlation between biological effects and the target molecules, or the mode of action of the investigational products. This data will help to characterize the

pharmacological properties of the investigational product and to identify the most appropriate animal models. The primary and secondary pharmacodynamics (PD) of the investigational product should be clearly elucidated in *in vitro* studies used animal/human cells and *in vivo* studies. These studies should include target affinity which should preferably be linked to functional response, such as receptor/target binding and occupancy, duration of effect of the pharmacological action, and the dose-response relationship.

The dose/concentration-response correlation of the pharmacological effect(s) should be established with sufficient dose levels to detect significant pharmacological effects and to identify the active form of the drug.

3.3.3 Pharmacokinetics

Before starting first-in-human studies (see ICH guidelines S3, S6, and M3 (R2)), the following results should be made available:

- Results from *in vitro* studies of drug metabolism in animals and humans, and results from plasma protein binding
- Results from systemic exposure data from the animal species used in safety studies

The correlation between pharmacological effects and exposure dose (AUC/Cmax) should be determined when pharmacological effects in an appropriate animal model may contribute to potential safety concerns in humans.

3.3.4 Safety Pharmacology

Effects on major physiological functions (e.g. those of the cardiovascular, respiratory, and central nervous systems) should be clearly characterized prior to the first administration in human subjects (see ICH guidelines S7A, S7B, S6, and M3 (R2)). Additional studies to investigate effects in other organ systems should be carried out on a case-by-case basis. In particular, *in vitro* testing in human samples must be performed for investigational products that are highly species-specific.

3.3.5 Toxicity

Toxicological studies should be performed in appropriate animal species, and should include toxicokinetics as a general rule. When factors that increase risk in humans are identified (section 3.1), the inclusion of additional relevant endpoints should be considered on a case-by-case basis.

Toxicological studies in non-relevant species may give rise to misinterpretation. Valuable information for the assessment of investigational product safety may be obtained through studies in homologous proteins and in transgenic animals, as well as through *in vitro* studies in human cells. It should be noted that humanized proteins are likely to be immunogenic in animal species. Therefore, repeated-dose toxicity studies in animals may not predict the toxicologic effects of such substances in humans (e.g. the presence of neutralizing antibodies).

Animal models that are thought to be similar to the human disease may provide useful information with regard to the pharmacological action, the pharmacokinetics (PK), the disease-related expression of the target molecule, dosage and method of administration in a clinical setting, and safety of the investigational product. Therefore, in certain cases, studies performed in animal models of disease may be used as an acceptable alternative to normal animal species generally used in non-clinical studies. In such cases, the scientific justification should be provided for the use of these animal models of disease in the assessment of safety.

3.4 Clinical Studies

3.4.1 General Principle

The safety of participants in first-in-human trials can be enhanced by identification and planned mitigation of factors associated with the risk of adverse events. The trial should be designed to mitigate these risk factors, including in the following areas:

(1) Risk related to investigational product quality

(2) Toxicity concerns

(3) Findings in appropriate animal models (non-clinical studies)

(4) Relevant subject population (healthy individuals, patients)

(5) Tolerability of anticipated adverse events/adverse drug reactions in subjects

(6) Potential differences in reaction to the investigational product due to variability of genetic predisposition in subjects

(7) Possibility that patients might benefit from other available drugs and/or medical procedures

(8) Anticipated concentration range for the investigational product

3.4.2 Clinical Study Protocol

The clinical study protocol should discuss the following items, based on the knowledge available on the target molecule for that investigational product, and should provide justification for giving first consideration to assuring the safety of subjects to the extent possible.

(1) Study subjects

(2) Study site

(3) Initial dose and dose-setting rationale

(4) Route and rate of administration

(5) Administration period and observation period

(6) Number of subjects per dose increment (cohort)

(7) Sequence and interval between dosing of subjects within the same cohort

(8) Dose escalation increments

(9) Transition to next dose cohort

(10) Stopping rules, and rules for suspending and resuming the study

(11) Safety assessment procedures that serve as determining criteria for (8) to (10) above

(12) A system where the responsibilities lie for decisions with respect to subject dosing, dose escalation, and procedures for modifying or discontinuing the clinical study

In general, when pharmaceutical effect associated with investigational product will make a considerable influence on vital organs functions, or when administration of investigational product will make a considerable health concern, it is essential to establish the safe dose and minimize the risk in the first-in-human study. In such cases, particular consideration should be given to preventative measures in establishing the initial dose and in designing the first-in-human trial. The protocol should describe the strategy for managing risk, including a specific plan to monitor for and manage likely adverse events or adverse drug reactions, as well as the procedures for modifying or stopping the trial if necessary, and a system where the responsibilities lie for making these decisions. The protocol should also describe the criteria for deciding whether or not to administer to the next subject within the same cohort and escalate the dose. The sponsor should arrange for expert review of the protocol and the associated risk factors, and assure that responses to the results of such review have been properly included in the protocol.

It is recognized that placebo is often included as part of the design of first-in-human studies. In such cases, the protocol should describe the conditions for opening the allocation code.

For first-in-human trials where there is uncertainty about the risk to subjects, discussion is recommended regarding biomarkers or other pharmacodynamic (PD) measures that can be linked with information from non-clinical findings on pharmacological/toxicological effects of the investigational product.

3.4.2.a Choice of Subjects for First-In-Human Trials

Except in a few studies, subjects are not generally expected to derive any therapeutic benefit from participation in a first-in-human trial. The most important considerations should always be the safety and human rights of the subjects regardless of patients or healthy individuals, and the value of what can be learned from the clinical trial.

Even in studies that enroll patients as subjects, the concurrent use of other medications should be avoided during administration of the investigational product except in special circumstances. This is because drug interactions may increase the patient's response, and it will be difficult to determine whether or not the investigational product is responsible for adverse events. If a subject is participating or has participated in another clinical trial, that subject should not be included in first-in-human trials unless a sufficient time period has elapsed between the two trials, or unless there is sufficient justification for such participation. It is important to include clear exclusion criteria in the protocol, in order to prevent concomitant or immediate consecutive exposure to other investigational products.

3.4.2.b Setting the Dose for First-In-Human Administration

It is important to select the first-in-human dose with great care in order to assure the safety of subjects. Selection of the first-in-human dose should be based on all available information; decisions on what information is used, and how that information is used, should be determined on a case-by-case basis.

Generally, the first-in-human dose will be selected as follows. First, the No Observed Adverse Effect Level (NOAEL) will be determined for the most highly sensitive animal species used in non-clinical studies. Next, the Human Equivalent Dose (HED) will be calculated based on those values, with the appropriate application of allometric correction or pharmacokinetic (PK) information. Considerations will include a safety factor based on the investigational product properties and the clinical study design. Other procedures can be considered in special cases, such as, for example, cancer patients who have previously been treated with cytotoxic investigational products (see entry (8) in the reference section on Clinical Studies).

When there is some concern that the investigational product has specific risk factors (section 3.1), additional procedures should be used in dose-setting. Information related to the pharmacodynamics (PD) of the investigational product may be helpful. If the MABEL is used to determine the first-in-human dose, investigations should be made to ensure no differences in bioactivity of the investigational product between humans and animals. All PK/PD information from *in vitro* and *in vivo* studies should be used (including from PK/PD models) including the information shown below.

(1) Studies of receptor/target binding affinity and occupancy, using target human cells or cells from appropriate animal species

(2) Dose-response curves in target human cells or cells from appropriate animal species

(3) Estimated exposure in humans at pharmacological doses in appropriate animal species. In order to avoid the potential for adverse reactions in humans, a safety factor may be applied in the calculation of the first-in-human dose from the MABEL. This should take into account risk factors such as the novelty, bioactivity, and mode of action of the investigational product, the degree of species specificity, the shape of the dose-response curve, and the degree of uncertainty in the calculation of the MABEL. The appropriate safety factors should be set.

When the methods of calculation (e.g. NOAEL, MABEL) give different estimates, the first-in-human dose should be determined on the basis of scientific evidence.

3.4.2.c Administration Route and Administration Rate

The choice of route and rate of administration of the first dose in humans should be justified based on the non-clinical data. For intravenous administration, a slow infusion is generally safer than a bolus infusion. Slow infusion allows easy monitoring for an adverse reaction, and it can be promptly discontinued if a serious adverse event develops.

3.4.2.d Study Design

It should be usually appropriate to design the administration of the first dose so that a single subject receives a single dose of the investigational product. Further dose administration should be sequential within each cohort (including a number of subjects in the placebo group in some cases). It may be also appropriate to assess the safety of a higher dose at the first time in a single subject to mitigate the risk. If this is done, there must be an adequate period of observation between the administration of the investigational product to the first, second, and subsequent subjects in a cohort, in order to observe and interpret reactions and adverse events. Information available based on comparable drug substances and identified risk factors should be taken into account when determining the period of observation.

The number of subjects per dose (the cohort size) depends on the variability of both pharmacokinetic (PK) and pharmacodynamic (PD) parameters, and also depends on the study objectives and the information required to progress to the next dose level or the next clinical study.

3.4.2.e Progression to the Next Dose Level

In dose-escalation studies, in order to mitigate risk when progressing to a subsequent cohort, pre-specified criteria should be used to mitigate risk at the next dose level by assessing previously identified risk factors in the low-dose cohort. Criteria for dose increase should be based on non-clinical study data and data from comparable similar drug substances, and should be described in the protocol. Data and results from subjects in each cohort need to be assessed fully, in accordance with the protocol, before advancing to the next cohort. Unanticipated adverse events may require a revision in dose escalation, including possible adjustment of the number of dose levels, the dose increment between two dose levels, and the time interval between doses.

3.4.2.f Dose Escalation Scheme

Dose increases should be implemented with caution, taking into account identified risk factors from non-clinical studies such as steep dose-response, exposure-response, and dose-toxicity curves.

The dose increment between two dose levels should be guided by either the dose-toxicity curve or the dose-effect curve, as determined in non-clinical studies, depending on whichever is steeper. The steeper the increase in the dose-toxicity or dose-effect curve, the lower the dose increment that should be selected. The choice of the next dose level should include some estimate of the potential pharmacodynamic (PD) effects and the risk of adverse reactions.

Reference should be made to any available information in humans on investigational product exposure, pharmacological effects, and safety from previous studies including microdose studies. Since the initial doses are generally very low, it is anticipated that early cohorts may not show any pharmacological response. If the

cohort shows no clinical symptoms or abnormal laboratory findings, the precautions for the next cohort should be the same as for the previous cohort.

In the absence of human information, a certain degree of uncertainty will be unavoidable in the setting of dose escalation increments. 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 dose escalation modification, and the procedures for such modification.

3.4.2.g Stopping Rules Clinical Study and Decision-Making about Resuming Administration

The protocol should define rules for dose escalation in each cohort, and for suspension or discontinuation of the clinical trial. It should define processes and responsibilities for making decisions about dosing of subjects, dose escalation, and stopping the cohort or the trial. In the case of multicenter trials, it is also important to define processes and responsibilities for decision-making and immediate communication among sites.

3.4.2.h Monitoring Adverse Events and Adverse Reactions

The trial design should provide a specific plan for monitoring for adverse events or adverse reactions. The mode of action of the investigational product, findings in the non-clinical safety studies, and any anticipated responses should be used to identify likely adverse reactions. All clinical staff should be trained to identify both the anticipated responses and any unanticipated serious adverse events or adverse reactions. In cases where there is a predictable risk of a certain type of adverse reaction occurring in humans, a treatment strategy should be described in the protocol. This should include the availability of specific medicines when they exist, and a clear plan of availability of medical staff and medical facilities. For clinical studies involving the administration of anticancer drugs, methods for supportive and emergency treatment should be clearly identified.

The length of the monitoring period and matters of monitoring should be justified on the bases of pharmacokinetic (PK), pharmacodynamic (PD), and safety studies.

Special consideration should be given to potential long-term consequences with regard to physiological changes and to poor-prognosis toxicity.

3.4.3 Clinical Study Site Facilities and Personnel

First-in-human trials should take place in appropriate clinical facilities and be conducted by trained investigators who have acquired the necessary expertise and experience in conducting early-phase trials (i.e. phase I-II), and medical staff with appropriate levels of training and previous experience. The investigator(s) and medical staff should understand the study design and the investigational product, its target, its mechanism of action, and any anticipated adverse reactions, and should include individuals with an in-depth understanding of clinical pharmacology.

Units should have immediate access to equipment and doctors for responding to acute emergency situations (such as cardiac emergencies, anaphylaxis, cytokine syndrome, loss of consciousness, convulsions, and shock), and ready availability of a medical emergency facilities. Procedure should be established between the clinical research unit and a medical emergency facilities (including facilities outside the study site) regarding to the responsibilities and undertakings of each in the transfer and care of patients.

With the exception of studies of substances such as some anticancer drugs, first-in-human trials should preferably be conducted under a single protocol at a single site. When multiple sites are involved, an appropriate plan needs to an adequate system of information communication for the well-being of all study subjects assuring. This information system should ensure that the unpredicted/predicted important adverse events/reactions regarding to the investigational product are transmitted promptly to the participating study sites.

References

Related to Quality of Investigational Products

(1) GMP for Investigational Products: July 9, 2008, Pharmaceutical and Food Safety Bureau (PFSB) Notification No. 0709002. Good Manufacturing Practices (GMP) for Clinical Investigational Products

(2) Biopharmaceuticals: February 22, 2000, Evaluating and Licensing Division of the Pharmaceutical and Medical Safety Bureau (PMSB/ELD) Notification No. 329. Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin (ICH Q5A)

(3) January 6, 1998, PMSB/ELD Notification No. 3. Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products (ICH Q5B)

(4) January 6, 1998, PMSB/ELD Notification No. 6. Stability Testing of Biotechnological / Biological Products (ICH Q5C)

(5) July 14, 2000, PMSB/ELD Notification No. 873. Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products (ICH Q5D)

(6) April 26, 2005, PFSB/ELD Notification No. 0426001. Comparability of Biotechnological/Biological Products (ICH Q5E)

(7) May 1, 2001, PMSB/ELD Notification No. 571. Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (ICH Q6B)

(8) Chemically Synthesized Drugs: June 3, 2003,PMSB/ELD Notification No. 0603001. Stability Testing of New Drug Substances and Products (ICH Q1A (R2))

(9) December 16, 2002, PMSB/ELD Notification No. 1216001. Impurities in New Drug Substances (ICH Q3A)

(10) June 24, 2003, PMSB/ELD Notification No. 0624001. Impurities in New Drug Products (ICH Q3)

(11) May 1, 2001, PMSB/ELD Notification No. 568. Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products (ICH Q6A)

(12) March 30, 1998, PMSB/ELD Notification No. 307. Guideline for Residual Solvents (ICH Q3C)

(13) Infectious substance-related: May 20, 2003, MHLW Notification No. 210. Japanese Standards for Biological Ingredients

(14) August 1, 2003, PFSB/ELD Notification No. 0801001. Handling of Risk Assessment in Application for Approval of Partial Change in Pharmaceutical Product or Medical Device Using Bovine-derived Raw Materials

(15) November 7, 2003, PFSB/ELD Notification No. 1107001, PFSD/Safety Division (SD) Notification No. 1107001, PFSB/CND Division Notification No. 1107001, PFSD/Blood and Blood Products Division (BBPD) Notification No. 1107001. Measures for Safety from Viral Contamination of Plasma Fractionated Products

(16) Study-related: March 31, 2006, MHLW Notification No. 285 (most recent revision July 30, 2010) MHLW Notification No. 322. The Japanese Pharmacopoeia

(17) March 30, 2004, MHLW Notification No. 155 (most recent revision October 16, 2009) MHLW Notification No. 446. Minimum Requirements for Biological Products

Related to Non-clinical Studies

(1) February 19, 2010, PFSB/ELD Notification No. 0219-4. "Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals" (ICH M3 (R2))

(2) February 22, 2010, PMSB/ELD Notification No. 326. "Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals" (ICH S6)

(3) June 4, 2010, PFSB/ELD Notification No. 0604-1. "Guidelines for Preclinical Safety Evaluation of Anti-cancer Drugs " (ICH S9)

(4) October 23, 2009, PFSB/ELD Notification No. 1023-4. "Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals" (ICH Q7B)

(5) June 21, 2001, PMSB/ELD Notification No. 902. "Safety Pharmacology Studies for Human Pharmaceuticals" (ICH Q7A)

(6) June 26, 2008, PMSB/ELD Notification No. 496. "Guidelines for Non-clinical Pharmacokinetic Studies"

Related to Clinical Studies

(1) March 27, 1997, MHLW Ordinance No. 28. "The Ordinance on Good Clinical Practice"

(2) April 21, 2008, PMSB/ELD Notification No. 380. "General Considerations for Clinical Trials" (ICH E8)

(3) June 1, 2001, PMSB/ELD Notification No. 796. "Clinical Pharmacokinetics Studies on Drugs"

(4) June 3, 2008, PFSB/ELD Notification No. 0603001. Guidance for the Performing of Microdose Clinical Trials"

(5) EUDRALEX- Vol. 10 – Clinical trials. In particular: Chapter I: Application and Application Form and Chapter II: Monitoring and Pharmacovigilance.

(6) Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medical products. EMEA/CHMP/SWP/ 28367/07

(7) Sims J. Member of ABPI/BIA Early Stage Clinical Trials Taskforce. Calculation of the Minimum Anticipated Biological Effect Level (MABEL) and 1st dose in human. In: EMEA Workshop on the Guideline for first-in human clinical trials for potential high-risk medicinal products. 12 June 2007 London. Available from: http://www.emea.europa.eu/pdfs/conferenceflyers/first_in_man/05-J_Sims_AstraZeneca.pdf

(8) Guidance for Industry: Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers (July 2005)

2

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)