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Safety Pharmacology Studies for Human Pharmaceuticals

Step 5

NOTE FOR GUIDANCE ON SAFETY PHARMACOLOGY STUDIES FOR HUMAN PHARMACEUTICALS

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NOTE FOR GUIDANCE ON SAFETY PHARMACOLOGY STUDIES FOR HUMAN PHARMACEUTICALS

1. INTRODUCTION

1.1 Objectives Of The Guideline

This guideline was developed to help protect clinical trial participants and patients receiving marketed products from potential adverse effects of pharmaceuticals, while avoiding unnecessary use of animals and other resources.

This guideline provides a definition, general principles and recommendations for safety pharmacology studies.

1.2 Background

Pharmacology studies have been performed worldwide for many years as part of the non-clinical evaluation of pharmaceuticals for human use. There have been, however, no internationally accepted definitions, objectives or recommendations on the design and conduct of safety pharmacology studies. (Note 1)

The term "safety pharmacology studies" first appeared in the ICH topics, "Timing of Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (M3)" and "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (S6)" as studies that should be conducted to support use of therapeutics in humans (1, 2). Details of the safety pharmacology studies, including their definition and objectives, were left for future discussion.

1.3 Scope Of The Guideline

This guideline generally applies to new chemical entities and biotechnology-derived products for human use. This guideline can be applied to marketed pharmaceuticals when appropriate (e.g. when adverse clinical events, a new patient population, or a new route of administration raises concerns not previously addressed).

1.4 General Principle

It is important to adopt a rational approach when selecting and conducting safety pharmacology studies. The specific studies that should be conducted and their design will vary based on the individual properties and intended uses of the pharmaceuticals. Scientifically valid methods should be used, and when there are internationally recognized methods that are applicable to pharmaceuticals, these are preferable. Moreover, the use of new technologies and methodologies in accordance with sound scientific principles is encouraged.

Some safety pharmacology endpoints can be incorporated in the design of toxicology, kinetic, clinical studies, etc., while in other cases these endpoints should be evaluated in specific safety pharmacology studies. Although adverse effects of a substance may be detectable at exposures that fall within the therapeutic range in appropriately designed safety pharmacology studies, they may not be evident from observations and measurements used to detect toxicity in conventional animal toxicity studies.

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1.5 Definition Of Safety Pharmacology

Pharmacology studies can be divided into three categories: primary pharmacodynamic, secondary pharmacodynamic and safety pharmacology studies.

For the purpose of this document, safety pharmacology studies are defined as those studies that investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure in the therapeutic range and above. (See Note 2 for definitions of primary pharmacodynamic and secondary pharmacodynamic studies.)

In some cases, information on the primary and secondary pharmacodynamic properties of the substance may contribute to the safety evaluation for potential adverse effect(s) in humans and should be considered along with the findings of safety pharmacology studies.

2. GUIDELINE

2.1 Objectives Of Studies

The objectives of safety pharmacology studies are: 1) to identify undesirable pharmacodynamic properties of a substance that may have relevance to its human safety; 2) to evaluate adverse pharmacodynamic and/or pathophysiological effects of a substance observed in toxicology and/or clinical studies; and 3) to investigate the mechanism of the adverse pharmacodynamic effects observed and/or suspected. The investigational plan to meet these objectives should be clearly identified and delineated.

2.2 General Considerations In Selection And Design Of Safety Pharmacology Studies

Since pharmacological effects vary depending on the specific properties of each test substance, the studies should be selected and designed accordingly. The following factors should be considered (the list is not comprehensive):

(1) Effects related to the therapeutic class of the test substance, since the mechanism of action may suggest specific adverse effects (e.g., proarrhythmia is a common feature of antiarrhythmic agents);

(2) Adverse effects associated with members of the chemical or therapeutic class, but independent of the primary pharmacodynamic effects (e.g., anti-psychotics and QT prolongation);

(3) Ligand binding or enzyme assay data suggesting a potential for adverse effects;

(4) Results from previous safety pharmacology studies, from secondary pharmacodynamic studies, from toxicology studies, or from human use that warrant further investigation to establish and characterize the relevance of these findings to potential adverse effects in humans.

During early development, sufficient information (e.g., comparative metabolism) may not always be available to rationally select or design the studies in accordance with the points stated above; in such circumstances, a more general approach in safety pharmacology investigations can be applied.

A hierarchy of organ systems can be developed according to their importance with respect to life-supporting functions. Vital organs or systems, the functions of which are acutely critical for life, such as the cardiovascular, respiratory and central nervous systems, are considered to be the most important ones to assess in safety pharmacology studies. Other organ systems, such as the renal or gastrointestinal system, the functions of which can be transiently disrupted by adverse pharmacodynamic effects without causing irreversible harm, are of less immediate investigative concern. Safety pharmacology evaluation of effects on these other systems may

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be of particular importance when considering factors such as the likely clinical trial or patient population (e.g. gastrointestinal tract in Crohn's disease, renal function in primary renal hypertension, immune system in immunocompromised patients.).

2.3 Test Systems

2.3.1 General Considerations On Test Systems

Consideration should be given to the selection of relevant animal models or other test systems so that scientifically valid information can be derived. Selection factors can include the pharmacodynamic responsiveness of the model, pharmacokinetic profile, species, strain, gender and age of the experimental animals, the susceptibility, sensitivity, and reproducibility of the test system and available background data on the substance. Data from humans (e.g., in vitro metabolism), when available, should also be considered in the test system selection. The time points for the measurements should be based on pharmacodynamic and pharmacokinetic considerations. Justification should be provided for the selection of the particular animal model or test system.

2.3.2 Use Of In Vivo And In Vitro Studies

Animal models as well as ex vivo and in vitro preparations can be used as test systems. Ex vivo and in vitro systems can include, but are not limited to: isolated organs and tissues, cell cultures, cellular fragments, subcellular organelles, receptors, ion channels, transporters and enzymes. In vitro systems can be used in supportive studies (e.g., to obtain a profile of the activity of the substance or to investigate the mechanism of effects observed in vivo).

In conducting in vivo studies, it is preferable to use unanesthetized animals. Data from unrestrained animals that may be chronically instrumented for telemetry, other suitable instrumentation methods for conscious animals, or animals conditioned to the laboratory environment are preferable to data from restrained or unconditioned animals. In the use of unanesthetized animals, the avoidance of discomfort or pain is a foremost consideration.

2.3.3 Experimental Design

2.3.3.1 Sample Size And Use Of Controls

The size of the groups should be sufficient to allow meaningful scientific interpretation of the data generated. Thus, the number of animals or isolated preparations should be adequate to demonstrate or rule out the presence of a biologically significant effect of the test substance. This should take into consideration the size of the biological effect that is of concern for humans. Appropriate negative and positive control groups should be included in the experimental design. In well-characterized in vivo test systems, positive controls may not be necessary. The exclusion of controls from studies should be justified.

2.3.3.2 Route Of Administration

In general, the expected clinical route of administration should be used when feasible. Regardless of the route of administration, exposure to the parent substance and its major metabolites should be similar to or greater than that achieved in humans when such information is available. Assessment of effects by more than one route may be appropriate if the test substance is intended for clinical use by more than one route of administration (e.g. oral and parenteral), or where there are observed or anticipated significant qualitative and quantitative differences in systemic or local exposure.

2.4 Dose Levels Or Concentrations Of Test Substance

2.4.1 In Vivo Studies

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Safety pharmacology studies should be designed to define the dose-response relationship of the adverse effect observed. The time course (e.g., onset and duration of response) of the adverse effect should be investigated, when feasible. Generally, the doses eliciting the adverse effect should be compared to the doses eliciting the primary pharmacodynamic effect in the test species or the proposed therapeutic effect in humans, if feasible. It is recognized that there are species differences in pharmacodynamic sensitivity. Therefore, doses should include and exceed the primary pharmacodynamic or therapeutic range. In the absence of an adverse effect on the safety pharmacology parameter(s) evaluated in the study, the highest tested dose should be a dose that produces moderate adverse effects in this or in other studies of similar route and duration. These adverse effects can include dose-limiting pharmacodynamic effects or other toxicity. In practice, some effects in the toxic range (e.g., tremors or fasciculation during ECG recording) may confound the interpretation of the results and may also limit dose levels. Testing of a single group at the limiting dose as described above may be sufficient in the absence of an adverse effect on safety pharmacology endpoints in the test species.

2.4.2 In Vitro Studies

In vitro studies should be designed to establish a concentration-effect relationship. The range of concentrations used should be selected to increase the likelihood of detecting an effect on the test system. The upper limit of this range may be influenced by physico-chemical properties of the test substance and other assay specific factors. In the absence of an effect, the range of concentrations selected should be justified.

2.5 Duration Of Studies

Safety pharmacology studies are generally performed by single dose administration. When pharmacodynamic effects occur only after a certain duration of treatment, or when results from repeat dose non-clinical studies or results from use in humans give rise to concerns about safety pharmacological effects, the duration of the safety pharmacology studies to address these effects should be rationally based.

2.6 Studies On Metabolites, Isomers And Finished Products

Generally, any parent compound and its major metabolite(s) that achieve, or are expected to achieve, systemic exposure in humans should be evaluated in safety pharmacology studies. Evaluation of major metabolites is often accomplished through studies of the parent compound in animals. If the major human metabolite(s) is (are) found to be absent or present only at relatively low concentrations in animals, assessment of the effects of such metabolite(s) on safety pharmacology endpoints should be considered. Additionally, if metabolites from humans are known to substantially contribute to the pharmacological actions of the therapeutic agent, it may be important to test such active metabolites. When the in vivo studies on the parent compound have not adequately assessed metabolites, as discussed above, the tests of metabolites can use in vitro systems based on practical considerations.

In vitro or in vivo testing of the individual isomers should also be considered when the product contains an isomeric mixture.

Safety pharmacology studies with the finished product formulation(s) should be conducted only for formulations that substantially alter the pharmacokinetics and/or pharmacodynamics of the active substance in comparison to formulations previously tested (i.e. through active excipients such as penetration enhancers, liposomes, and other changes such as polymorphism).

2.7 Safety Pharmacology Core Battery

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The purpose of the safety pharmacology core battery is to investigate the effects of the test substance on vital functions. In this regard, the cardiovascular, respiratory and central nervous systems are usually considered the vital organ systems that should be studied in the core battery. In some instances, based on scientific rationale, the core battery should be supplemented (see section 2.8) or need not be implemented (see also section 2.9).

The exclusion of certain test(s) or exploration(s) of certain organs, systems or functions should be scientifically justified.

2.7.1 Central Nervous System

Effects of the test substance on the central nervous system should be assessed appropriately. Motor activity, behavioral changes, coordination, sensory/motor reflex responses and body temperature should be evaluated. For example, a functional observation battery (FOB) (3), modified Irwin's (4), or other appropriate test (5) can be used.

2.7.2 Cardiovascular System

Effects of the test substance on the cardiovascular system should be assessed appropriately. Blood pressure, heart rate, and the electrocardiogram should be evaluated. In vivo, in vitro and/or ex vivo evaluations, including methods for repolarization and conductance abnormalities, should also be considered. (Note 3)

2.7.3 Respiratory System

Effects of the test substance on the respiratory system should be assessed appropriately. Respiratory rate and other measures of respiratory function (e.g., tidal volume (6) or hemoglobin oxygen saturation) should be evaluated. Clinical observation of animals is generally not adequate to assess respiratory function, and thus these parameters should be quantified by using appropriate methodologies.

2.8 Follow-up and Supplemental Safety Pharmacology Studies

Adverse effects may be suspected based on the pharmacological properties or chemical class of the test substance. Additionally, concerns may arise from the safety pharmacology core battery, clinical trials, pharmacovigilance, experimental in vitro or in vivo studies, or from literature reports. When such potential adverse effects raise concern for human safety, these should be explored in follow-up or supplemental safety pharmacology studies, as appropriate.

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2.8.1 Follow-up Studies For Safety Pharmacology Core Battery

Follow-up studies are meant to provide a greater depth of understanding than, or additional knowledge to, that provided by the core battery on vital functions. The following subsections provide lists of studies to further evaluate these organ systems for potential adverse pharmacodynamic effects. These lists are not meant to be comprehensive or prescriptive, and the studies should be selected on a case-by-case basis after considering factors such as existing non-clinical or human data. In some cases, it may be more appropriate to address these effects during the conduct of other non-clinical and/or clinical studies.

2.8.1.1 Central Nervous System

Behavioral pharmacology, learning and memory, ligand-specific binding, neurochemistry, visual, auditory and/or electrophysiology examinations, etc.

2.8.1.2 Cardiovascular System

Cardiac output, ventricular contractility, vascular resistance, the effects of endogenous and/or exogenous substances on the cardiovascular responses, etc.

2.8.1.3 Respiratory System

Airway resistance, compliance, pulmonary arterial pressure, blood gases, blood pH, etc.

2.8.2 Supplemental Safety Pharmacology Studies

Supplemental studies are meant to evaluate potential adverse pharmacodynamic effects on organ system functions not addressed by the core battery or repeated dose toxicity studies when there is a cause for concern.

2.8.2.1 Renal/Urinary System

Effects of the test substance on renal parameters should be assessed. For example, urinary volume, specific gravity, osmolality, pH, fluid/electrolyte balance, proteins, cytology, and blood chemistry determinations such as blood urea nitrogen, creatinine and plasma proteins can be used.

2.8.2.2 Autonomic Nervous System

Effects of the test substance on the autonomic nervous system should be assessed. For example, binding to receptors relevant for the autonomic nervous system, functional responses to agonists or antagonists *in vivo* or *in vitro*, direct stimulation of autonomic nerves and measurement of cardiovascular responses, baroreflex testing, and heart rate variability can be used.

2.8.2.3 Gastrointestinal System

Effects of the test substance on the gastrointestinal system should be assessed. For example, gastric secretion, gastrointestinal injury potential, bile secretion, transit time in vivo, ileal contraction in vitro, gastric pH measurement and pooling can be used.

2.8.2.4 Other Organ Systems

Effects of the test substance on organ systems not investigated elsewhere should be assessed when there is a reason for concern. For example, dependency potential or skeletal muscle, immune and endocrine functions can be investigated.

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2.9 Conditions Under Which Studies Are Not Necessary

Safety pharmacology studies may not be needed for locally applied agents (e.g., dermal or ocular) where the pharmacology of the test substance is well characterized, and where systemic exposure or distribution to other organs or tissues is demonstrated to be low.

Safety pharmacology studies prior to the first administration in humans may not be needed for cytotoxic agents for treatment of end-stage cancer patients. However, for cytotoxic agents with novel mechanisms of action, there may be value in conducting safety pharmacology studies.

For biotechnology-derived products that achieve highly specific receptor targeting, it is often sufficient to evaluate safety pharmacology endpoints as a part of toxicology and/or pharmacodynamic studies, and therefore safety pharmacology studies can be reduced or eliminated for these products.

For biotechnology-derived products that represent a novel therapeutic class and/or those products that do not achieve highly specific receptor targeting, a more extensive evaluation by safety pharmacology studies should be considered.

There may be additional exceptions where safety pharmacology testing is not needed, for example, in the case of a new salt having similar pharmacokinetics and pharmacodynamics.

2.10 Timing Of Safety Pharmacology Studies In Relation To Clinical Development

When planning a safety pharmacology program, section 2.9 should be reviewed to determine whether or not specific studies are recommended.

2.10.1 Studies Prior To First Administration In Humans

The effects of a test substance on the functions listed in the safety pharmacology core battery should be investigated prior to first administration in humans. Any follow-up or supplemental studies identified as appropriate, based on a cause for concern, should also be conducted. Information from toxicology studies adequately designed and conducted to address safety pharmacology endpoints can result in reduction or elimination of separate safety pharmacology studies.

2.10.2 Studies During Clinical Development

Additional studies may be warranted to clarify observed or suspected adverse effects in animals and humans during clinical development.

2.10.3 Studies Before Approval

Safety pharmacology effects on systems listed in section 2.8 should be assessed prior to product approval, unless not warranted, in which case this should be justified. Available information from toxicology studies adequately designed and conducted to address safety pharmacology endpoints, or information from clinical studies, can support this assessment and replace safety pharmacology studies.

2.11 Application Of Good Laboratory Practice (GLP)

It is important to ensure the quality and reliability of non-clinical safety studies. This is normally accomplished through the conduct of the studies in compliance with GLP. Due to the unique design of, and practical considerations for, some safety pharmacology studies, it may not be feasible to conduct these in compliance with GLP. It has to be emphasized that data quality and integrity in safety pharmacology studies should be ensured even in the absence of formal adherence to the principles of GLP. When studies are not conducted in compliance with GLP, study reconstruction should be ensured through adequate documentation of study conduct and archiving of data. Any study or study component not

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conducted in compliance with GLP should be adequately justified, and the potential impact on evaluation of the safety pharmacology endpoints should be explained.

The safety pharmacology core battery should ordinarily be conducted in compliance with GLP. Follow-up and supplemental studies should be conducted in compliance with GLP to the greatest extent feasible. Safety pharmacology investigations can be part of toxicology studies; in such cases, these studies would be conducted in compliance with GLP.

Primary pharmacodynamic studies do not need to be conducted in compliance with GLP.

Generally, secondary pharmacodynamic studies do not need to be conducted in compliance with GLP. Results from secondary pharmacodynamic studies conducted during the compound selection process may contribute to the safety pharmacology evaluation; when there is no cause for concern (e.g., there are no findings for the safety pharmacological endpoint or the chemical or therapeutic class), these studies need not be repeated in compliance with GLP. In some circumstances, results of secondary pharmacodynamic studies may make a pivotal contribution to the safety evaluation for potential adverse effects in humans, and these are normally conducted in compliance with GLP.

3. NOTES

1. General pharmacology studies have been considered an important component in drug safety assessment. General pharmacology studies were originally referred to as those designed to examine effects other than the primary therapeutic effect of a drug candidate. Safety pharmacology studies were focused on identifying adverse effects on physiological functions. All three regions have accepted data from general pharmacology studies (Japan and EC) or safety pharmacology studies (USA) in the assessment of a marketing application. The Japanese Ministry of Health and Welfare (MHW) issued the "*Guideline for General Pharmacology* " in 1991. In this MHW guideline, general pharmacology studies include those designed to identify unexpected effects on organ system function, and to broaden pharmacological characterization (pharmacological profiling). However, there has been no internationally accepted definition of the terms "primary pharmacodynamics", "secondary pharmacodynamics" and "safety pharmacology." The need for international harmonization of the nomenclature and the development of an international guideline for safety pharmacology has been recognized.
2. Studies on the mode of action and/or effects of a substance in relation to its desired therapeutic target are primary pharmacodynamic studies. Studies on the mode of action and/or effects of a substance not related to its desired therapeutic target are secondary pharmacodynamic studies (these have sometimes been referred to as part of general pharmacology studies).
3. There is no scientific consensus on the preferred approach to, or internationally recognized guidance on, addressing risks for repolarization-associated ventricular tachyarrhythmia (e.g., Torsade de Pointes). A guideline (S7B) will be prepared to present some currently available methods and discuss their advantages and disadvantages. Submission of data to regulatory authorities to support the use of these methods is encouraged.

4. REFERENCES

1) ICH Harmonized Tripartite Guideline (M3) "Timing of Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals" (1997)

2) ICH Harmonized Tripartite Guideline (S6) "Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals" (1997)

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