Clinical research database

This guidance 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 guidance provides a definition, general principles, and recommendations for safety pharmacology studies. Pharmacology studies have been performed worldwide for many years as part of the monomaniacal evaluation of pharmaceuticals for human use.

There have been, however, o 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 ICC MM Telling of Monomaniacal Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals and SO Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals 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. A. Scope of the Guidance (13) This guidance generally applies to new chemical entities and biotechnology-derived products for human use. This guidance 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). B. General principle (1.) 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 methods 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, and clinical studies, while In other cases these endpoints should be evaluated in specific safety pharmacology studies. Although adverse effects of a substance may designed safety pharmacology studies, such effects may not be evident from observations and measurements used to detect toxicity in conventional animal toxicity studies. C. Definition of Safety Pharmacology (1. 5) Pharmacology studies can be divided into three categories: primary predominance, secondary predominance, and safety pharmacology studies.

For the purpose of this document, safety pharmacology studies are defined as those studies that investigate the potential undesirable predominance effects of a substance on physiological functions in relation to exposure in the therapeutic range and above. In some cases, information on the primary and secondary predominance repertories of the substance contributes to the safety evaluation for potential adverse effects in humans and should be considered along with the findings of safety pharmacology studies. II. GUIDANCE (2) A.

Objectives of Studies (2. 1) The objectives of safety pharmacology studies are (1) to identify undesirable predominance properties of a substance that may have relevance to its human safety, (2) to evaluate adverse

predominance and/or biotechnological effects of a substance observed in toxicology and/or clinical studies, and (3) to investigate the mechanism of the adverse predominance effects observed and/or suspected. The investigation plan to meet these objectives should be clearly identified and delineated.

B. General Considerations in Selection and Design of Safety Pharmacology Studies (2. 2) 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. , parathyroid is a common feature of antidemocratic agents) .

Adverse effects associated with members of the chemical or therapeutic class, but independent of the primary predominance effects (e. G. , antispasmodics and CT 3. Liking binding or enzyme assay data suggesting a potential for adverse effects 4. Results from previous safety pharmacology studies, from secondary predominance 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 to 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 (e. G. , the cardiovascular, respiratory, and central nervous systems), are considered to be the most important ones to assess in safety pharmacology studies.

Other organ systems (e. G. The renal or gastrointestinal system), the functions of which can be transiently disrupted by adverse predominance effects without causing irreversible harm, are of less immediate investigative concern. Safety pharmacology evaluation of effects on these other systems may be of particular importance when considering factors such as the likely clinical trial or patient population (e. G. , gastrointestinal tract in Crown's disease, renal function in primary renal hypertension, immune system in immune compromised patients).

C. -rest systems (2. 3) 1 . General Considerations on Test Systems (2. 3. 1) 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 predominance responsiveness of the model, pharmaceutics 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 predominance and harmonistic considerations. Justification should be provided for the selection of the particular animal model or test system. 2. Use of In Vivo and In Vitro Studies (2. 3. 2) Animal models as well as ex vivo and in vitro preparations can be used as test organs and tissues, cell

cultures, cellular fragments, sub cellular 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 anesthetized animals. Data from unrestrained animals that are chronically instrumented for telemetry, data gathered using other suitable instrumentation methods for conscious animals, or data from animals conditioned to the laboratory environment are preferable to data from restrained or unconditioned animals.

In the use of anesthetized animals, the avoidance of discomfort or pain is a foremost consideration. 3. Experimental Design (2. 3. 3) a. Sample Size and Use of Controls (2. 3. 3. 1) The size of the groups should be sufficient to allow meaningful scientific interpretation of the data generated. Thus, the number of animals or isolated reparations should be adequate to demonstrate or rule out the presence of a biologically significant effect of the test substance. The sample size 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. B. Route of Administration (2. 3. 3. 2) In general, the expected clinical route of administration should be used when seeable. 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 parental) or where there are observed or anticipated significant qualitative and quantitative differences in systemic or local exposure. D. Dose Levels or Concentrations of Test Substance (2. 4) 1. In VIVO studies (2. 4. 1) In vivo 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 therapeutic effect in humans, if feasible. It is recognized that there are species differences in predominance sensitivity. Therefore, doses should include and exceed the primary predominance or therapeutic range. In the absence of an adverse effect on the safety pharmacology parameters evaluated in the study, the shiest 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 predominance effects or other toxicity. In practice, some effects in the toxic range (e. G. , tremors or fasciculation during EGG 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. In Vitro studies (2. 4. 2)

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 physics-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. E. Duration of Studies (2. 5) Safety pharmacology studies are generally performed by single-dose administration.

When predominance effects occur only after a certain duration of treatment, or hen 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. F. Studies on Metabolites, Isomers, and Finished Products (2. 6) Generally, any parent compound and its major metabolites 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 metabolites are found to be absent or present only at relatively low concentrations in animals, assessment of the effects of such metabolites 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 could 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 Safety pharmacology studies with the finished product formulations should be conducted only for formulations that substantially alter the pharmaceutics and/or pharmacologists of the active substance in comparison to formulations previously tested (I. E. Through active expedients such as penetration enhancers, lollipops, and other changes such as polymorphism). G. Safety Pharmacology Core Battery (2. 7) The purpose of the safety pharmacology core battery is to investigate the effects of he 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. The exclusion of certain tests or explorations of certain organs, systems or functions should be scientifically Justified. 1.

Central Nervous System (2. 7. 1) 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 Orrin's (4), or other appropriate test (5) can be used. 2. Cardiovascular System (2. 7. 2) 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 revitalization and conductance abnormalities, should also be considered.

(Note 3) 3. Respiratory System (2. 7. 3) 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.

H. Follow-up and Supplemental Safety Pharmacology Studies (2. 8) Adverse effects may be suspected based on the pharmacological properties or chemical class of the test substance. Additionally, concerns may arise from the safety 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 fatty pharmacology studies, as appropriate. 1 . Follow-up Studies For Safety Pharmacology Core Battery (2. 8.) 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 predominance 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 monomaniacal or human data. In some eases, it may be more appropriate to address these effects during the conduct of other monomaniacal and/or clinical studies. . Central Nervous System (2. 8. 1 . 1) Behavioral pharmacology, learning and memory, liking-specific binding, neuropsychiatry, visual, auditory, and/or electrophoresis's examinations b. Cardiovascular System (2. 8. 1. 2) Cardiac output, ventricular contractually,

vascular resistance, the effects of endogenous and/or exogenous substances on the cardiovascular responses c. Respiratory System (2. 8. 1. 3) Airway resistance, compliance, pulmonary arterial pressure, blood gases, blood pH . Supplemental Safety Pharmacology Studies (2. 8.) Supplemental studies are meant to evaluate potential adverse predominance effects on organ system functions not addressed by the core battery or repeated dose toxicity studies when there is a cause for concern. A. Renal/Urinary System (2. 8. 2. 1) Effects of the test substance on renal parameters should be assessed. For example, urinary volume, specific gravity, commonality, pH, fluid/electrolyte balance, proteins, cytology, and blood chemistry determinations such as blood urea nitrogen, creating, and plasma proteins can be used. B. Autonomic Nervous System (2. 8. 2.) For example, binding to receptors relevant for the autonomic nervous system, functional responses to Zionists or antagonists in vivo or in vitro, direct stimulation of autonomic nerves and measurement of cardiovascular responses, affordable testing, and heart rate variability can be used. C. Gastrointestinal System (2. 8. 2. 3) 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, ilea contraction in vitro, gastric pH measurement, and lolling can be used. . Other Organ Systems (2. 8. 2. 4) 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. L. Conditions Under Which Studies Are Not Necessary (2. 9) 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 isotonic agents for treatment of end-stage cancer patients. However, for isotonic agents with novel mechanisms of action, there may be value in conducting 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 predominance studies; therefore, safety pharmacology studies can be reduced or eliminated for these products.

For biotechnology-derived products that represent a novel therapeutic class and/or hose 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 pharmaceutics and pharmacologists. J. Timing of Safety Pharmacology Studies in Relation to Clinical Development (2. 10) determine whether or not specific studies are recommended. 1 .

Studies Prior to First Administration in Humans (2. 10. 1) The effects of a test substance on the functions listed in the safety pharmacology ore 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. Studies During Clinical Development (2. 10.) Additional studies may be warranted to clarify observed or suspected adverse effects in animals and humans during clinical development. 3. Studies Before Approval (2. 10. 3) Safety pharmacology effects on systems listed in section H (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.

K. Application of Good Laboratory Practice (GLOP) (2. 11) It is important to ensure the quality and reliability of monomaniacal safety studies. This is normally accomplished through the conduct of the studies in compliance with GLOP. 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 GLOP. 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 GLOP.

When studies are not conducted in compliance with GLOP, study reconstruction should be ensured through adequate documentation of study conduct and archiving of data. Any study or study component not conducted in compliance with GLOP should e 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 GLOP. Follow-up and supplemental studies

should be conducted in compliance with GLOP 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 GLOP. GLOP. Generally, secondary predominance studies do not need to be conducted in compliance with GLOP. Results from secondary predominance studies conducted ruing 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 GLOP.

In some circumstances, results of secondary predominance studies may make a pivotal contribution to the safety evaluation for potential adverse effects in humans, and these are normally conducted in compliance with GLOP. Ill. NOTES (3) 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 Pan and CE) or safety pharmacology studies (USA) in the assessment of a marketing application. The Japanese Ministry of Health and Welfare (MAW) issued the Guideline for General Pharmacology in 1991. In this MAW

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 pharmacologists, secondary pharmacologists and safety pharmacology.

The need for international harmonistic of the nomenclature and the development of an international guidance 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 predominance studies. Studies on the ode of action and/or effects of a substance not related to its desired therapeutic target are secondary predominance studies (these have sometimes been referred to as part of general pharmacology studies). .
There is no scientific consensus on the preferred approach to, or internationally recognized guidance on, addressing risks for revitalization-associated ventricular tachycardia's (e. G. , Toreadors De Pointed). A guidance (SUB) 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.