INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

GUIDANCE ON NONCLINICAL SAFETY STUDIES FOR THE CONDUCT OF HUMAN CLINICAL TRIALS AND MARKETING AUTHORIZATION FOR PHARMACEUTICALS

M3(R2)

Current *Step 4* version

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This guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the draft is recommended for adoption to the regulatory bodies of the European Union, Japan and the USA.

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GUIDANCE ON NONCLINICAL SAFETY STUDIES FOR THE CONDUCT OF HUMAN CLINICAL TRIALS AND MARKETING AUTHORIZATION FOR PHARMACEUTICALS

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on June 11, 2009, this guideline is recommended for adoption to the three regulatory parties to ICH.

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LIST OF ABBREVIATIONS

AUC	Area Under the Curve
C_{max}	Maximum Plasma Concentration
EU	European Union
GLP	Good Laboratory Practices
HCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
i.v.	Intravenous
MFD	Maximum Feasible Dose
MTD	Maximum Tolerated Dose
NOAEL	No Observed Adverse Effect Level
PET	Positron Emission Tomography
PK	Pharmacokinetics
PD	Pharmacodynamics
SAR	Structure-Activity Relationship
siRNA	Small Interfering RNA
WOCBP	Women of Childbearing Potential

GUIDANCE ON NONCLINICAL SAFETY STUDIES FOR THE CONDUCT OF HUMAN CLINICAL TRIALS AND MARKETING AUTHORIZATION FOR PHARMACEUTICALS

1. INTRODUCTION

1.1 Objectives of the Guideline

The purpose of this document is to recommend international standards for, and promote harmonisation of, the nonclinical safety studies recommended to support human clinical trials of a given scope and duration as well as marketing authorization for pharmaceuticals.

Harmonisation of the guidance for nonclinical safety studies will help to define the current recommendations and reduce the likelihood that substantial differences will exist among regions.

This guidance should facilitate the timely conduct of clinical trials, reduce the use of animals in accordance with the 3R (reduce/refine/replace) principles and reduce the use of other drug development resources. Although not discussed in this guidance, consideration should be given to use of new *in vitro* alternative methods for safety evaluation. These methods, if validated and accepted by all ICH regulatory authorities, can be used to replace current standard methods.

This guidance promotes safe, ethical development and availability of new pharmaceuticals.

1.2 Background

The recommendations of this revised guidance further harmonise the nonclinical safety studies to support the various stages of clinical development among the regions of European Union (EU), Japan, and the United States. The present guidance represents the consensus that exists regarding the type and duration of nonclinical safety studies and their timing to support the conduct of human clinical trials and marketing authorization for pharmaceuticals.

1.3 Scope of the Guideline

The nonclinical safety assessment for marketing approval of a pharmaceutical usually includes pharmacology studies, general toxicity studies, toxicokinetic and nonclinical pharmacokinetic studies, reproduction toxicity studies, genotoxicity studies and, for drugs that have special cause for concern or are intended for a long duration of use, an assessment of carcinogenic potential. Other nonclinical studies to assess phototoxicity, immunotoxicity, juvenile animal toxicity and abuse liability should be conducted on a case-by-case basis. The need for nonclinical safety studies and their relation to the conduct of human clinical trials is delineated in this guidance.

This document applies to the situations usually encountered during the development of pharmaceuticals and should be viewed as general guidance for drug development. Nonclinical safety studies and human clinical trials should be planned and designed to represent an approach that is scientifically and ethically appropriate.

For biotechnology-derived products (as defined in Ref. 1), appropriate nonclinical safety studies should be determined in accordance with ICH S6. For these products, ICH

M3(R2) only provides guidance with regard to timing of nonclinical studies relative to clinical development.

Pharmaceuticals under development for indications in life-threatening or serious diseases (e.g., advanced cancer, resistant HIV infection, and congenital enzyme deficiency diseases) without current effective therapy also warrant a case-by-case approach to both the toxicological evaluation and clinical development in order to optimise and expedite drug development. In these cases and for products using innovative therapeutic modalities (e.g., siRNA), as well as vaccine adjuvants, particular studies can be abbreviated, deferred, omitted, or added. Where ICH guidances for specific product areas exist, they should be consulted.

1.4 General Principles

The development of a pharmaceutical is a stepwise process involving an evaluation of both animal and human efficacy and safety information. The goals of the nonclinical safety evaluation generally include a characterisation of toxic effects with respect to target organs, dose dependence, relationship to exposure, and, when appropriate, potential reversibility. This information is used to estimate an initial safe starting dose and dose range for the human trials and to identify parameters for clinical monitoring for potential adverse effects. The nonclinical safety studies, although usually limited at the beginning of clinical development, should be adequate to characterise potential adverse effects that might occur under the conditions of the clinical trial to be supported.

Human clinical trials are conducted to investigate the efficacy and safety of a pharmaceutical, starting with a relatively low systemic exposure in a small number of subjects. This is followed by clinical trials in which exposure to the pharmaceutical usually increases by duration and/or size of the exposed patient population. Clinical trials should be extended based on the demonstration of adequate safety in the previous clinical trial(s), as well as on additional nonclinical safety information that becomes available as clinical development proceeds.

Serious adverse clinical or nonclinical findings can influence the continuation of clinical trials. Within the overall clinical context, these findings should be evaluated to determine the appropriateness and design of additional nonclinical and/or clinical studies.

Clinical trials are conducted in phases for which different terminology has been utilised in the various regions. This document generally uses the terminology as defined in the ICH E8 guideline (Ref. 2). However, as there is a growing trend to merge phases of clinical development, in some cases this document also relates the nonclinical studies to the duration and size of clinical trials and the characteristics of the subjects included.

1.5 High Dose Selection for General Toxicity Studies

Generally, in toxicity studies, effects that are potentially clinically relevant can be adequately characterized using doses up to the maximum tolerated dose (MTD). It is not essential to demonstrate the MTD in every study. Other equally appropriate limiting doses include those that achieve large exposure multiples or saturation of exposure or use the maximum feasible dose (MFD). These limit doses (see additional details below and Figure 1) prevent the use of doses in animals that would not add value to predicting clinical safety. These recommendations are consistent with those for reproduction and carcinogenicity study designs that already have defined limit doses and/or exposures (Refs. 3 and 4).

Limit doses for acute, subchronic, and chronic toxicity studies of 1000 mg/kg/day for rodents and non-rodents are considered appropriate in all cases except those discussed

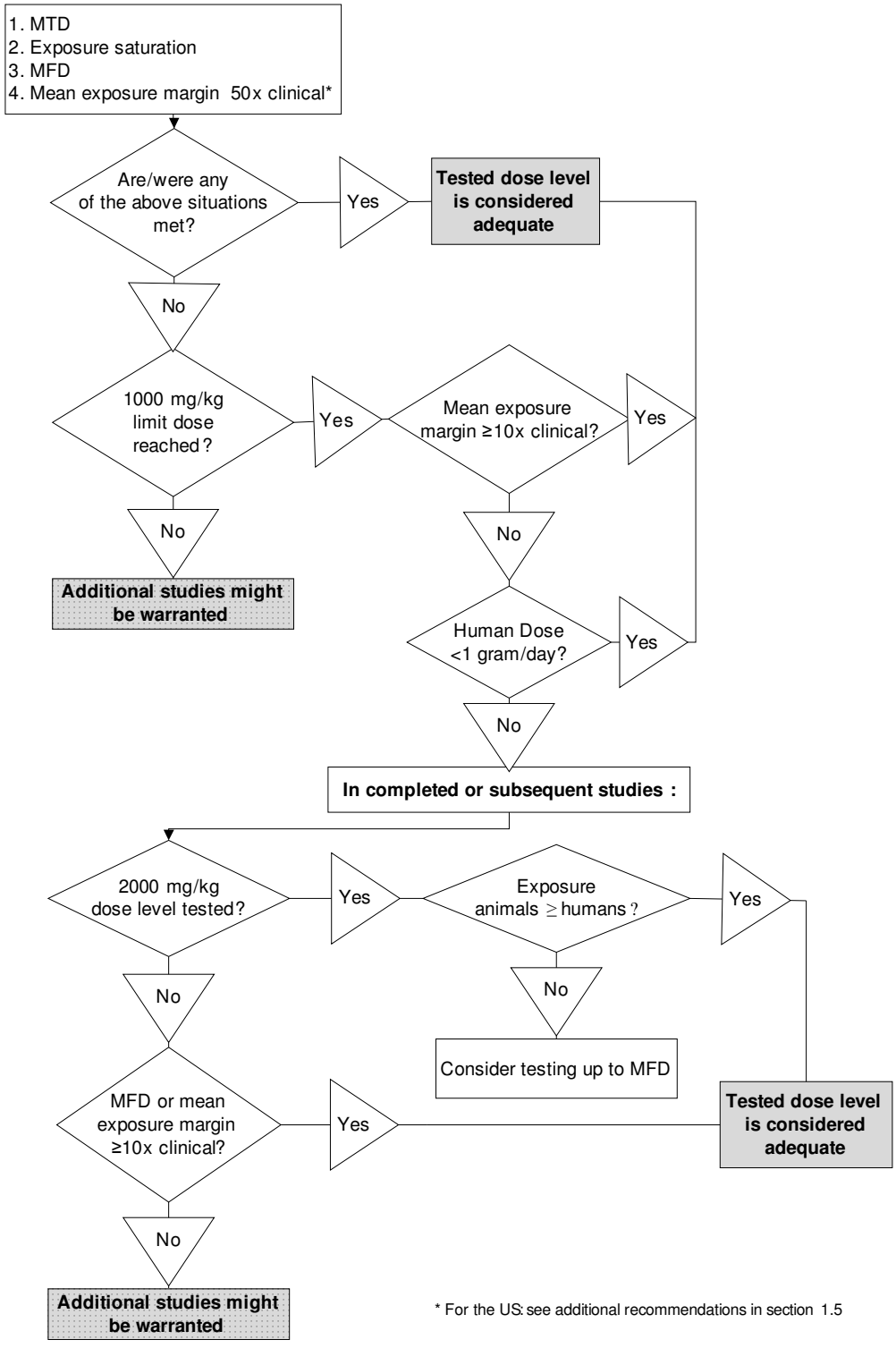
below. In the few situations where a dose of 1000 mg/kg/day does not result in a mean exposure margin of 10-fold to the clinical exposure and the clinical dose exceeds 1 g per day, then the doses in the toxicity studies should be limited by a 10-fold exposure margin or a dose of 2000 mg/kg/day or the MFD, whichever is lower. In those rare situations in which the dose of 2000 mg/kg/day results in an exposure that is less than the clinical exposure, a higher dose up to the MFD can be considered.

Doses providing a 50-fold margin of exposure (usually based on group mean AUC values [see Note 1] of the parent drug or the pharmacologically active molecule of a pro-drug) to the clinical systemic exposure generally are also considered acceptable as the maximum dose for acute and repeated-dose toxicity studies in any species.

To support Phase III clinical trials for the United States, dose-limiting toxicity generally should be identified in at least one species when using the 50-fold margin of exposure as the limit dose. If this is not the case, a study of one-month or longer duration in one species that is conducted at the 1000 mg/kg limit dose, MFD or MTD, whichever is lowest, is recommended. However, on a case-by-case basis this study might not be warranted if a study of a shorter duration identifies dose-limiting toxicity at doses higher than those resulting in a 50-fold exposure margin.

If genotoxicity endpoints are to be incorporated into a general toxicity study, then an appropriate maximum dose should be selected based on a MFD, MTD or limit dose of 1000 mg/kg/day.

Figure 1 Recommended high dose selection for general toxicity studies



2. PHARMACOLOGY STUDIES

Safety pharmacology and pharmacodynamic (PD) studies are defined in ICH S7A (Ref. 5).

The core battery of safety pharmacology studies includes the assessment of effects on cardiovascular, central nervous and respiratory systems, and should generally be conducted before human exposure, in accordance with ICH S7A and S7B (Refs. 5 and 6). When warranted, supplemental and follow-up safety pharmacology studies can be conducted during later clinical development. Consideration should be given to inclusion of any *in vivo* evaluations as additions to general toxicity studies, to the extent feasible, in order to reduce animal use.

In addition, primary PD studies (*in vivo* and/or *in vitro*) are intended to investigate the mode of action and/or effects of a substance in relation to its desired therapeutic target. Such studies are generally conducted during the discovery phase of pharmaceutical development and as such, are not generally conducted in accordance with Good Laboratory Practices (GLP). These studies can contribute to dose selection for both nonclinical and clinical studies.

3. TOXICOKINETIC AND PHARMACOKINETIC STUDIES

In vitro metabolic and plasma protein binding data for animals and humans and systemic exposure data (ICH S3A, Ref. 7) in the species used for repeated-dose toxicity studies generally should be evaluated before initiating human clinical trials. Further information on pharmacokinetics (PK) (e.g., absorption, distribution, metabolism and excretion), in test species and *in vitro* biochemical information relevant to potential drug interactions should be available before exposing large numbers of human subjects or treating for long duration (generally before Phase III). These data can be used to compare human and animal metabolites and for determining if any additional testing is warranted.

Nonclinical characterization of a human metabolite(s) is only warranted when that metabolite(s) is observed at exposures greater than 10% of total drug-related exposure and at significantly greater levels in humans than the maximum exposure seen in the toxicity studies. Such studies should be conducted to support Phase III clinical trials. For drugs for which the daily administered dose is <10 mg, greater fractions of the drug related material might be more appropriate triggers for testing. Some metabolites are not of toxicological concern (e.g., most glutathione conjugates) and do not warrant testing. The nonclinical characterization of metabolites with an identified cause for concern (e.g., a unique human metabolite) should be considered on a case-by-case basis.

4. ACUTE TOXICITY STUDIES

Historically, acute toxicity information has been obtained from single-dose toxicity studies in two mammalian species using both the clinical and a parenteral route of administration. However, such information can be obtained from appropriately conducted dose-escalation studies or short-duration dose-ranging studies that define an MTD in the general toxicity test species (Refs. 8 and 9).

When this acute toxicity information is available from any study, separate single-dose studies are not recommended. Studies providing acute toxicity information can be limited to the clinical route only and such data can be obtained from non-GLP studies if clinical administration is supported by appropriate GLP repeated-dose toxicity studies. Lethality should not be an intended endpoint in studies assessing acute toxicity.

In some specific situations (e.g., microdose trials; see Section 7) acute toxicity or single-dose studies can be the primary support for studies in humans. In these situations, the high dose selection can be different from that described in Section 1.5 but should be appropriate for supporting the intended clinical dose and route. These studies should be performed in compliance with GLP.

Information on the acute toxicity of pharmaceutical agents could be useful to predict the consequences of human overdose situations and should be available to support Phase III. An earlier assessment of acute toxicity could be important for therapeutic indications for which patient populations are at higher risk for overdosing (e.g., depression, pain, and dementia) in out-patient clinical trials.

5. REPEATED-DOSE TOXICITY STUDIES

The recommended duration of the repeated-dose toxicity studies is usually related to the duration, therapeutic indication and scope of the proposed clinical trial. In principle, the duration of the animal toxicity studies conducted in two mammalian species (one non-rodent) should be equal to or exceed the duration of the human clinical trials up to the maximum recommended duration of the repeated-dose toxicity studies (Table 1). Limit doses/exposures that are considered appropriate in repeated-dose toxicity studies are described in Section 1.5.

In circumstances where significant therapeutic gain has been shown, trials can be extended beyond the duration of supportive repeated-dose toxicity studies on a case-by-case basis.

5.1 Clinical Development Trials

Repeated-dose toxicity studies in two species (one non-rodent) for a minimum duration of 2 weeks (Table 1) would generally support any clinical development trial up to 2 weeks in duration. Clinical trials of longer duration should be supported by repeated-dose toxicity studies of at least equivalent duration. Six month rodent and 9 month non-rodent studies generally support dosing for longer than 6 months in clinical trials (for exceptions see Table 1 footnotes).

Table 1 Recommended Duration of Repeated-Dose Toxicity Studies to Support the Conduct of Clinical Trials

Maximum Duration of Clinical Trial	**Recommended Minimum Duration of Repeated-Dose Toxicity Studies to Support Clinical Trials**	
	Rodents	**Non-rodents**
Up to 2 weeks	2 weeks[a]	2 weeks[a]
Between 2 weeks and 6 months	Same as clinical trial[b]	Same as clinical trial[b]
> 6 months	6 months[b, c]	9 months [b, c, d]

a. In the United States, as an alternative to 2 week studies, extended single-dose toxicity studies (see footnote **c** in Table 3) can support single-dose human trials. Clinical studies of less than 14 days can be supported with toxicity studies of the same duration as the proposed clinical study.

b. In some circumstances clinical trials of longer duration than 3 months can be initiated, provided that the data are available from a 3-month rodent and a 3-month non-rodent study, and that complete data from the chronic rodent and non-rodent study are made available, consistent with local clinical trial regulatory procedures, before extending dosing beyond 3 months in the clinical trial. For serious or life-threatening indications or on a case-by-case basis, this extension can be supported by complete chronic rodent data and in-life and necropsy data for the non-rodent study. Complete histopathology data from the non-rodent should be available within an additional 3 months.

c. There can be cases where a pediatric population is the primary population, and existing animal studies (toxicology or pharmacology) have identified potential developmental concerns for target organs. In these cases, long-term toxicity testing starting in juvenile animals can be appropriate in some circumstances (see Section 12).

d. In the EU, studies of 6 months duration in non-rodents are considered acceptable. However, where studies with a longer duration have been conducted, it is not appropriate to conduct an additional study of 6 months.

The following are examples where non-rodent studies of up to 6 months duration can also be appropriate for Japan and the United States:

- When immunogenicity or intolerance confounds conduct of longer term studies.
- Repeated short-term drug exposure even if clinical trial duration exceeds 6 months, such as intermittent treatment of migraine, erectile dysfunction, or herpes simplex.
- Drugs administered on a chronic basis to reduce the risk of recurrence of cancer.
- Drugs for indications for which life expectancy is short.

5.2 Marketing Authorization

Because of the size of the population at risk and the relatively less controlled conditions in clinical practice in contrast to clinical trials, longer durations of nonclinical testing can be valuable. The durations of repeated-dose toxicity studies to support marketing for different treatment durations are outlined in Table 2. However, for a small number of conditions in which the indicated use is between 2 weeks and 3 months, but for which there is extensive clinical experience suggesting both widespread and long-term use beyond that recommended (e.g., anxiety, seasonal allergic rhinitis, pain), the duration of testing might more appropriately be equivalent to that recommended for treatment of greater than 3 months.

Table 2 Recommended Duration of Repeated-Dose Toxicity Studies to Support Marketing

Duration of Indicated Treatment	Rodent	Non-rodent
Up to 2 weeks	1 month	1 month
>2 weeks to 1 month	3 months	3 months
>1 month to 3 months	6 months	6 months
>3 months	6 months[c]	9 months [c,d]

N.B., See footnotes **c** and **d** in Table 1.

6. ESTIMATION OF THE FIRST DOSE IN HUMAN

The estimation of the first dose in humans is an important element to safeguard subjects participating in first-in-human studies. All of the relevant nonclinical data, including the pharmacological dose response, the pharmacological/toxicological profile, and pharmacokinetics, should be considered when determining the recommended starting dose in humans.

In general, the No Observed Adverse Effect Level (NOAEL) determined in nonclinical safety studies performed in the most appropriate animal species gives the most important information. The proposed clinical starting dose will also depend on various factors, including PD, particular aspects of the molecule, and the design of the clinical trials. See available regional guidance for specific approaches that can be used.

Exploratory clinical trials (see Section 7) in humans can be initiated with less, or different, nonclinical support than is generally warranted for clinical development trials (see Section 5.1); therefore, the estimation of the clinical starting (and maximal) dose can differ. The recommended criteria for starting doses for various exploratory clinical trial designs are described in Table 3.

7. EXPLORATORY CLINICAL TRIALS

It is recognized that in some cases earlier access to human data can provide improved insight into human physiology/pharmacology, knowledge of drug candidate characteristics and therapeutic target relevance to disease. Streamlined early exploratory approaches can accomplish this end. Exploratory clinical studies for the purpose of this guidance are those intended to be conducted early in Phase I, involve limited human exposure, have no therapeutic intent, and are not intended to examine clinical tolerability. They can be used to investigate a variety of parameters such as PK, PD and other biomarkers, which could include PET receptor binding and displacement or other diagnostic measures. The subjects included in these studies can be patients from selected populations or healthy individuals.

The amount and type of nonclinical supporting data that is appropriate in these situations will be dependent on the extent of proposed human exposure, both with respect to the maximum clinical dose used and the duration of dosing. Five different examples of exploratory clinical approaches are summarized below and in more detail in Table 3, together with the nonclinical testing programs that would be recommended in these particular approaches. However, alternative approaches not described in this guidance can also be used, including strategies to support biotechnology-derived

products. It is recommended that these alternative approaches be discussed and agreed upon with the appropriate regulatory authority. The use of any of these approaches can reduce overall animal use in drug development.

Recommended starting doses and maximal doses for the five approaches are included in Table 3. In all cases, characterization of PD and pharmacology using *in vivo* and/or *in vitro* models as noted in Table 3 and Section 2 is important and should be used in support of human dose selection.

7.1 Microdose Trials

Two different microdose approaches are described below with details provided in Table 3.

The first approach would involve not more than a total dose of 100 µg that can be administered as a single dose or divided doses in any subject. This could be useful to investigate target receptor binding or tissue distribution in a PET study. A second use could be to assess PK with or without the use of an isotopically labelled agent.

A second microdose approach is one that involves $\leq$ 5 administrations of a maximum of 100 µg per administration (a total of 500 µg per subject). This can be useful for applications similar to the first microdose approach described above, but with less active PET ligands.

In some situations it could be appropriate to carry out a clinical microdose study using the i.v. route on a product intended for oral administration and for which an oral nonclinical toxicology package already exists. In this case the i.v. microdose can be qualified by the existing oral toxicity studies as described in Table 1 or Table 3, Approach 3, where adequate exposure margins have been achieved. It is not recommended to investigate i.v. local tolerance of the drug substance in this situation because the administered dose is very low (100 µg maximum). If a novel i.v. vehicle is being employed then local tolerance of the vehicle should be assessed.

7.2 Single-Dose Trials at Sub-therapeutic Doses or into the Anticipated Therapeutic Range

The third approach involves a single-dose clinical study typically starting at subtherapeutic doses and possibly escalating into the pharmacological or anticipated therapeutic range (see Table 3). The maximum allowable dose should be based on the nonclinical data, but could be further limited based on emerging clinical information obtained during the course of the study. This approach could allow, for example, determination of PK parameters with non-radiolabeled drug at or near the predicted pharmacodynamically active dose. Another example could be assessment of target engagement or pharmacology after a single dose. This approach is not intended to support the determination of the maximum tolerated clinical dose (see exception, Table 1, footnote **a**).

7.3 Multiple Dose Trials

Two different nonclinical approaches (numbers 4 and 5) to support multiple dose clinical trials are provided in Table 3. These approaches support up to 14 days of dosing for determination of PK and PD in human in the therapeutic dose range, but are not intended to support the determination of maximum tolerated clinical dose.

Approach 4 involves 2-week repeated-dose toxicity studies in rodents and non-rodents where dose selection in animals is based on exposure multiples of anticipated AUC at the maximum clinical dose.

Approach 5 involves a 2-week toxicity study in a rodent species and a confirmatory non-rodent study that is designed to investigate whether the NOAEL in the rodent is also not a toxic dose in the non-rodent. If toxic effects are observed in the non-rodent at the rodent NOAEL exposure, clinical administration should be deferred until further nonclinical studies in this species have been conducted (usually a standard toxicity study (see Section 5)).

Table 3 Recommended Non-Clinical Studies to Support Exploratory Clinical Trials

Clinical:		**Non clinical:**		
Dose to be Administered	**Start and Maximum Doses**	**Pharmacology**	**General Toxicity Studies[a]**	**Genotoxicity[b] / Other**
Approach 1: Total dose ≤ 100 µg (no inter-dose interval limitations) AND Total dose ≤ 1/100th NOAEL and ≤1/100th pharmacologically active dose (scaled on mg/kg for i.v. and mg/m^2 for oral).	Maximal and starting doses can be the same but not exceed a total accumulated dose of 100 µg.	*In vitro* target/ receptor profiling should be conducted. Appropriate characterization of primary pharmacology (mode of action and/or effects) in a pharmacodynamically relevant model should be available to support human dose selection.	Extended single dose toxicity study (see footnotes **c** and **d** in one species, usually rodent, by intended route of administration with toxicokinetic data, or via the i.v. route. A maximum dose of 1000-fold the clinical dose on a mg/kg basis for i.v. and mg/m^2 for oral administration can be used.	Genotoxicity studies are not recommended, but any studies or SAR assessments conducted should be included in the clinical trial application. For highly radioactive agents (e.g., PET imaging agents), appropriate PK and dosimetry estimates should be submitted.
Approach 2: Total cumulative dose ≤ 500 µg, maximum of 5 administrations with a washout between doses (6 or more actual or predicted half-lives) AND each dose ≤ 100 µg AND each dose ≤ 1/100th of the NOAEL and ≤ 1/100th of the pharmacologically active dose.	Maximal daily and starting doses can be the same, but not exceed 100 µg.	*In vitro* target/receptor profiling should be conducted. Appropriate characterization of primary pharmacology (mode of action and/or effects) in a pharmacodynamically relevant model should be available to support human dose selection.	7-day repeated-dose toxicity study in one species, usually rodent, by intended route of administration with toxicokinetic data, or via the i.v. route. Hematology, clinical chemistry, necropsy, and histopathology data should be included. A maximum dose of 1000-fold the clinical dose on a mg/kg basis for i.v. and mg/m^2 for oral administration can be used.	Genotoxicity studies are not recommended, but any studies or SAR assessments conducted should be included in the clinical trial application. For highly radioactive agents (e.g., PET imaging agents), appropriate PK and dosimetry estimates should be submitted.

Table 3 Recommended Non-Clinical Studies to Support Exploratory Clinical Trials

Clinical:		**Non clinical:**		
Dose to be Administered	**Start and Maximum Doses**	**Pharmacology**	**General Toxicity Studies[a]**	**Genotoxicity[b]**
Approach 3 Single Dose Studies at Sub-therapeutic Doses or into the Anticipated Therapeutic Range.	Starting dose should be based on the types of toxicity findings observed in the most sensitive species and a consideration of the pharmacologically active dose. For other considerations on initial dosing in humans, regional guidances should be consulted. Maximum dose can be that yielding up to ½ NOAEL exposure in the more sensitive species, in cases where any relevant toxicity observed in animals is anticipated to be monitorable and reversible in humans.	*In vitro* target/receptor profiling should be conducted. Appropriate characterization of primary pharmacology (mode of action and/or effects) in a pharmacodynamically relevant model should be available to support human dose selection. Core battery of safety pharmacology (see Section 2).	Extended single dose toxicity studies in both the rodent and non-rodent (see footnote **c** by intended clinical route of administration with toxicokinetics, hematology, clinical chemistry, necropsy, and histopathology data. For this situation the top dose should be MTD, MFD or limit dose (see Section 1.5).	Ames assay (or an alternative assay if Ames is inappropriate, for example, for an antibacterial product).

Table 3 Recommended Non-Clinical Studies to Support Exploratory Clinical Trials

Clinical:		**Non clinical:**		
Dose to be Administered	**Start and Maximum Dose**	**Pharmacology**	**General toxicity studies[a]**	**Genotoxicity[b]**
Approach 4: Dosing up to 14 days into the therapeutic range but not intended to evaluate clinical MTD.	With toxicity in both species, follow appropriate regional guidance for clinical starting dose. If toxicity is not seen in either species (i.e., the NOAELs are the highest dose tested and doses used were not otherwise limited, e.g., not an MFD), or is seen only in one species, the clinical starting dose should be one that gives a predicted clinical AUC value (based on either interspecies PK modelling or mg/m^2 conversion) that is approximately 1/50th of the AUC at the NOAEL from the species yielding the lower exposure. For other considerations on initial dosing in humans, e.g., predicted PD activity, regional guidance should be consulted. Without toxicity in both species, it is recommended that the maximum clinical dose not exceed 1/10th the lower exposure (AUC) in either species at the highest dose tested in the animals. When only one species demonstrates toxicity, the maximum clinical dose should	*In vitro* target/receptor profiling should be conducted. Appropriate characterization of primary pharmacology (mode of action and/or effects) in a pharmacodynamically relevant model should be available to support human dose selection. Core battery of safety pharmacology (see Section 2) using doses similar to those used for the toxicity studies.	2-week repeated-dose toxicity studies in rodent and non-rodent with standard parameters assessed and where dose selection in animals is based on exposure multiples of anticipated clinical AUC at maximum dose.	Ames assay (or an appropriate alternative assay if Ames is inappropriate, for example, for an antibacterial product) and an assay (*in vitro* or *in vivo*) capable of detecting chromosomal damage in a mammalian system.

	not be higher than the NOAEL in the species showing toxicity, or 1/2 the AUC at the highest dose tested in the species not showing toxicity, whichever is lower. With toxicity in both species, the maximum clinical dose should be based on standard risk assessment approaches and, in this specific case, the clinical MTD can be explored.			

Table 3 Recommended Non-Clinical Studies to Support Exploratory Clinical Trials

Clinical:		**Non clinical:**		
Dose to be Administered	**Start and Maximum Doses**	**Pharmacology**	**General Toxicity Studies[a]**	**Genotoxicity[b]**
Approach 5: Dosing up to 14 days and not to exceed duration of dosing in non-rodent; into therapeutic range but not intended to evaluate clinical MTD.	Starting dose predicted exposures should not exceed 1/50th the NOAEL in the more sensitive species on a mg/m^2 basis. For other considerations on initial dosing in humans, regional guidance should be consulted. The maximum exposure in humans should not be higher than the AUC at the NOAEL in the non-rodent species or higher than ½ the AUC at the NOAEL in the rodent species, whichever is lower[e].	*In vitro* target/receptor profiling should be conducted Appropriate characterization of primary pharmacology (mode of action and/or effects) in a pharmacodynamically relevant model should be available to support human dose selection. Core battery of safety pharmacology (see Section 2) using doses similar to those used for the toxicity studies.	Standard 2-week repeated-dose toxicity study in rodents (with justification of the rodent as an appropriate species). The top dose should be the MTD, MFD or limit dose (see Section 1.5). Confirmatory study in non-rodent (n=3) at the anticipated NOAEL exposure in rodent, with duration of a minimum of 3 days and at least the intended clinical study duration. Alternatively, an escalating dose study in the non-rodent with duration of a minimum of 3 days and at least the intended clinical study duration at the anticipated NOAEL exposure in the rodent.	Ames assay (or an appropriate alternative assay if Ames is inappropriate, for example, for an antibacterial product) and an assay (*in vitro* or *in vivo*) capable of detecting chromosomal damage in a mammalian system. If an *in vivo* assessment is used then this could be part of the rodent toxicity study.

a. General toxicity studies should be conducted according to GLP regulations.

b. See Ref. 10 for genotoxicity study design and dose selection.

c. Generally, extended single dose toxicity studies should be designed to evaluate hematology, clinical chemistry, necropsy, and histopathology data (control and high dose only if no treatment-related pathology is seen at the high dose) after a single administration, with further evaluations conducted 2 weeks later to assess delayed toxicity and/or recovery. The usual design for rodents consists of 10 animals/sex/group to be assessed on the day following dosing, and 5 animals/sex at the dose level(s) selected to be assessed on day 14 post-dose. The usual design for non-rodents consists of 3/sex/group for all groups on day 2 and 2/sex for the dose level(s) assessed on day 14.

d. A single dose level to assess reversibility/delayed toxicity on day 14 can support the microdose approach. The dose level used need not be the high dose but should be a dose that is at least 100 times the clinical dose.

e. In the absence of adverse effects in the clinical trial, escalation above this AUC can be appropriate if the findings in the toxicity studies are anticipated to be monitorable, reversible, and of low severity in humans.

8. LOCAL TOLERANCE STUDIES

It is preferable to evaluate local tolerance by the intended therapeutic route as part of the general toxicity studies; stand alone studies are generally not recommended.

To support limited human administration by non-therapeutic routes (e.g., a single i.v. dose to assist in the determination of absolute bioavailability of an oral drug), a single dose local tolerance study in a single species is considered appropriate. In cases where the anticipated systemic exposure (AUC and C_{max}) from the non-therapeutic administration is covered by the existing toxicology package, the endpoints in the local tolerance study can be confined to clinical signs and macroscopic and microscopic examination of the application site. The formulation delivered for local tolerance need not be identical but should be similar to the clinical formulation.

For an i.v. microdose study that is supported by an oral toxicology package (see Section 7), evaluation of local tolerance of the drug substance is not warranted. If a novel i.v. vehicle is being employed, then local tolerance of the vehicle should be assessed.

For parenteral products, evaluation for local tolerance at unintended injection sites, when appropriate, should be conducted before exposure of large numbers of patients (e.g., Phase III clinical trials). The approach to such studies differs in the various regions. Such studies are generally not recommended in the United States (an example of an exception would be intrathecal for the epidural route). Japan and the EU recommend single dose paravenous administration for the i.v. route. Other parenteral routes should be evaluated on a case-by-case basis.

9. GENOTOXICITY STUDIES

An assay for gene mutation is generally considered sufficient to support all single dose clinical development trials. To support multiple dose clinical development trials, an additional assessment capable of detecting chromosomal damage in a mammalian system(s) should be completed (Ref. 10). A complete battery of tests for genotoxicity should be completed before initiation of Phase II trials (Ref. 10).

If a positive finding occurs, an assessment, and then possibly additional testing (Ref. 10), should be conducted to determine if further administration to humans is still appropriate.

The genotoxicity studies recommended to support Exploratory Clinical Study approaches are discussed in Section 7.

10. CARCINOGENICITY STUDIES

Conditions relevant for carcinogenicity testing are discussed in the ICH S1A document (Ref. 11). If carcinogenicity studies are recommended for the clinical indication, they should be conducted to support the marketing application. Only in circumstances where there is a significant cause for concern for carcinogenic risk should the study results be submitted to support clinical trials. A long clinical study duration alone is not considered to be a significant cause for concern.

For pharmaceuticals developed to treat certain serious diseases for adults or pediatric patients, carcinogenicity testing, if recommended, can be concluded post-approval.

11. REPRODUCTION TOXICITY STUDIES

Reproduction toxicity studies (Ref. 3) should be conducted as is appropriate for the population that is to be exposed.

11.1 Men

Men can be included in Phase I and II trials before the conduct of the male fertility study since an evaluation of the male reproductive organs is performed in the repeated-dose toxicity studies (Note 2).

A male fertility study (Ref. 3) should be completed before the initiation of large scale or long duration clinical trials (e.g., Phase III trials).

11.2 Women Not of Childbearing Potential

Women not of childbearing potential (i.e., permanently sterilised, postmenopausal) can be included in clinical trials without reproduction toxicity studies if the relevant repeated-dose toxicity studies (which include an evaluation of the female reproductive organs) have been conducted. Postmenopausal is defined as 12 months with no menses without an alternative medical cause.

11.3 Women of Childbearing Potential

For women of childbearing potential (WOCBP) there is a high level of concern for the unintentional exposure of an embryo or fetus before information is available concerning the potential benefits versus potential risks. The recommendations on timing of reproduction toxicity studies to support the inclusion of WOCBP in clinical trials are similar in all ICH regions.

It is important to characterize and minimize the risk of unintentional exposure of the embryo or fetus when including WOCBP in clinical trials. One approach to achieve this objective is to conduct reproduction toxicity studies to characterize the inherent risk of a drug and take appropriate precautions during exposure of WOCBP in clinical trials. A second approach is to limit the risk by taking precautions to prevent pregnancy during clinical trials. Precautions to prevent pregnancy include pregnancy testing (e.g., based on the ß-subunit of HCG), use of highly effective methods of birth control (Note 3), and study entry only after a confirmed menstrual period. Testing for pregnancy during the trial and subject education should be sufficient to ensure compliance with the measures designed to prevent pregnancy during the period of drug exposure (which could exceed the length of study). To support these approaches, informed consent should be based on any known pertinent information related to reproduction toxicity, such as a general assessment of potential toxicity of pharmaceuticals with related structures or pharmacological effects. If no relevant reproductive information is available, the potential for unidentified risks to the embryo or fetus should be communicated.

In all ICH regions, WOCBP can be included in early clinical trials without non-clinical developmental toxicity studies (e.g., embryo-fetal studies) in certain circumstances. One circumstance could be intensive control of pregnancy risk over short duration (e.g., 2 weeks) clinical trials. Another circumstance could be where there is a predominance of the disease in women and the objectives of the clinical trial cannot be effectively met without inclusion of WOCBP and there are sufficient precautions to prevent pregnancy (see above).

Additional considerations for the conduct of studies in WOCBP without the non-clinical developmental toxicity studies include knowledge of the mechanism of action of the agent, the type of pharmaceutical agent, the extent of fetal exposure or the difficulty of conducting developmental toxicity studies in an appropriate animal model. For example, for monoclonal antibodies for which embryo-fetal exposure during organogenesis is understood to be low in humans based on current scientific knowledge, the

developmental toxicity studies can be conducted during Phase III. The completed reports should be submitted with the marketing application.

Generally, where appropriate preliminary reproduction toxicity data are available (see Note 4) from two species, and where precautions to prevent pregnancy in clinical trials (see above) are used, inclusion of WOCBP (up to 150) receiving investigational treatment for a relatively short duration (up to 3 months) can occur before conduct of definitive reproduction toxicity testing. This is based on the very low rate of pregnancy in controlled clinical trials of this size and duration (see Note 5), and the ability of adequately designed preliminary studies to detect most developmental toxicity findings that could raise concern for enrolment of WOCBP in clinical trials. The number of WOCBP and the duration of the study can be influenced by characteristics of the population that alter pregnancy rates (e.g., age, disease).

In the United States, assessment of embryo-fetal development can be deferred until before Phase III for WOCBP using precautions to prevent pregnancy in clinical trials (see above). In the EU and Japan, other than the situations described in the above paragraphs, definitive nonclinical developmental toxicity studies should be completed before exposure of WOCBP.

In all ICH regions, WOCBP can be included in repeated-dose Phase I and II trials before conduct of the female fertility study since an evaluation of the female reproductive organs is performed in the repeated-dose toxicity studies (Note 2). Nonclinical studies that specifically address female fertility (Ref. 3) should be completed to support inclusion of WOCBP in large-scale or long-duration clinical trials (e.g., Phase III trials).

In all ICH regions, the pre-postnatal development study should be submitted for marketing approval.

All female reproduction toxicity studies (Ref. 3) and the standard battery of genotoxicity tests (Ref. 10) should be completed before inclusion, in any clinical trial, of WOCBP not using highly effective birth control (see Note 3) or whose pregnancy status is unknown.

11.4 Pregnant Women

Before the inclusion of pregnant women in clinical trials, all female reproduction toxicity studies (Refs. 3) and the standard battery of genotoxicity tests (Ref. 10) should be conducted. In addition, safety data from previous human exposure should be evaluated.

12. CLINICAL TRIALS IN PEDIATRIC POPULATIONS

When pediatric patients are included in clinical trials, safety data from previous adult human experience would usually represent the most relevant information and should generally be available before initiation of pediatric clinical trials. The appropriateness and extent of adult human data should be determined on a case-by-case basis. Extensive adult experience might not be available before pediatric exposures (e.g., for pediatric-specific indications).

Results from repeated-dose toxicity studies of appropriate duration in adult animals (see Table 1), the core safety pharmacology package, and the standard battery of genotoxicity tests should be available before initiation of trials in pediatric populations. Reproduction toxicity studies relevant to the age and gender of the pediatric patient populations under study can also be important to provide information on direct toxic or developmental risks (e.g., fertility and pre-postnatal developmental studies). Embryo-fetal developmental studies are not critical to support clinical studies for males or prepubescent females.

The conduct of any juvenile animal toxicity studies should be considered only when previous animal data and human safety data, including effects from other drugs of the pharmacological class, are judged to be insufficient to support pediatric studies. If a study is warranted, one relevant species, preferably rodent, is generally considered adequate. A study in a non-rodent species can be appropriate when scientifically justified.

Generally, juvenile animal toxicity studies are not considered important for short-term PK studies (e.g., 1 to 3 doses) in pediatric populations.

Depending on the therapeutic indication, age of the pediatric population, and safety data from adult animal and human exposure, the appropriateness of obtaining juvenile animal study results before initiation of short-duration multiple-dose efficacy and safety trials should be considered. The age of the trial participants in relation to the duration of the clinical study (i.e., the fraction of a developmental period of concern during which clinical study participants are exposed) is among the most important considerations. This evaluation can determine whether juvenile animal studies are warranted and, if warranted, their timing in relation to clinical trials.

For long-term clinical trials in pediatric populations when an assessment of juvenile animal toxicity is recommended, the nonclinical studies should be completed before the initiation of the trials.

There can be cases where a pediatric population is the primary population and existing animal studies have identified potential developmental concerns for target organs (toxicology or pharmacology). In some of these cases long-term juvenile animal toxicity testing can be appropriate. A chronic study initiated in the appropriate age and species with the relevant end points to address this developmental concern (e.g., 12 months duration in dog or 6 month in rodent) can be appropriate. A 12-month study can cover the full development period in the dog. For either species, this design could be adapted to replace the corresponding standard chronic study and a separate juvenile animal study in some circumstances.

The appropriateness of carcinogenicity testing should be addressed before long-term exposure in pediatric clinical trials. However, unless there is a significant cause for concern (e.g., evidence of genotoxicity in multiple tests, or concern for pro-carcinogenic risk based on mechanistic considerations or findings from general toxicity studies), carcinogenicity studies are not recommended to support the conduct of pediatric clinical trials.

13. IMMUNOTOXICITY

As stated in the ICH S8 guidance (Ref. 14), all new human pharmaceuticals should be evaluated for the potential to produce immunotoxicity using standard toxicity studies and additional immunotoxicity studies conducted as appropriate based on a weight-of-evidence review, including immune-related signals from standard toxicity studies. If additional immunotoxicity studies are indicated, these should be completed before exposure of a large population of patients (e.g., Phase III).

14. PHOTOSAFETY TESTING

The appropriateness or timing of photosafety testing in relation to human exposure should be influenced by: 1) the photochemical properties (e.g., photoabsorption and photostability) of the molecule; 2) information on the phototoxic potential of chemically related compounds; 3) tissue distribution; and 4) clinical or nonclinical findings indicative of phototoxicity.

An initial assessment of phototoxic potential based on a drug's photochemical properties and pharmacological/chemical class should be performed. If assessment of all the available data and the proposed clinical plan indicates a potential for a significant human phototoxicity risk, appropriate protective measures should be taken during outpatient clinical studies. In addition, a subsequent evaluation of the nonclinical drug distribution to skin and eye should be completed to inform further on the human risk and the need for further testing. Then, if appropriate, an experimental evaluation (nonclinical, *in vitro* or *in vivo*, or clinical) of phototoxic potential should be undertaken before exposure of large numbers of subjects (Phase III).

Alternatively, instead of the above stepwise approach, a direct assessment of phototoxic potential in a nonclinical or clinical study can be undertaken. If this study is negative, an early assessment of eye/skin distribution studies and clinical protective measures are not called for.

If the phototoxicity assessment indicates a potential photocarcinogenic risk, the risk can usually be adequately managed in patients by protective measures including a warning statement in the informed consent for clinical trials and in product information for marketing (Note 6).

15. NONCLINICAL ABUSE LIABILITY

For drugs that produce central nervous system activity, regardless of therapeutic indication, it should be considered whether or not an evaluation of abuse liability is warranted. Nonclinical studies should support the design of clinical evaluations of abuse potential, classification/scheduling by regulatory agencies, and product information. There are regional guidance documents on the conduct of nonclinical abuse liability assessment that can be helpful in designing specific abuse liability packages.

Nonclinical data collected early in the drug development process can be useful in identification of early indicators of abuse potential. These early indicators would typically be available before first human dose and include the PK/PD profile to identify the duration of action, similarity of chemical structure to known drugs of abuse, receptor binding profile, and behavioural/clinical signs from *in vivo* nonclinical studies. When no abuse potential is apparent from these early studies, extensive testing in nonclinical abuse liability models might not be warranted. Generally, if the active substance shows signals associated with known abuse liability patterns or the active substance has a novel mechanism of action on the central nervous system, further nonclinical studies are recommended to support large clinical trials (e.g., Phase III).

When the metabolite profile and the target for drug activity in rodent are consistent with that of human, the nonclinical abuse liability evaluations should be conducted in rodents. Nonhuman primates should be reserved only for those limited cases where there is clear evidence that they would be predictive of human abuse liability and the rodent model is inadequate. Three types of studies are often completed to evaluate the potential for abuse liability: drug discrimination, self-administration of the compound, and an assessment of withdrawal. When conducted, studies of drug discrimination and self-administration are generally stand-alone. Assessments of withdrawal can sometimes be incorporated within the design of the reversibility arm of a repeated-dose toxicity study. A maximum dose that produces a plasma concentration several-fold higher than that obtained at the therapeutic clinical dose is considered appropriate for these nonclinical abuse assessments.

16. OTHER TOXICITY STUDIES

Additional nonclinical studies (e.g., to identify potential biomarkers, to provide mechanistic understanding) can be useful if previous nonclinical or clinical findings with the product or related products have indicated special safety concerns.

The approaches for qualifying impurities and degradants are outlined in ICH Guidelines Q3A and Q3B (Refs. 12 and 13). If specific studies are warranted to qualify an impurity or degradant, generally these studies are not warranted before Phase III, unless there are changes that result in a significant new impurity profile (e.g., a new synthetic pathway, a new degradant formed by interactions between the components of the formulation). In these latter cases, appropriate qualification studies can be warranted to support Phase II or later stages of development.

17. COMBINATION DRUG TOXICITY TESTING

This section covers combination drugs that are intended to be co-packaged or administered in a single dosage form ('fixed formulation'). The principles outlined can also apply when developing products that will have product information recommendations for co-use with a specific drug, even if not in a fixed combination, and for which there is minimal clinical information regarding the combination.

Combinations covered might involve: (1) two or more late stage entities (defined as compounds with significant clinical experience (i.e., from Phase III studies and/ or post marketing)); (2) one or more late stage entity(ies) and one or more early stage entities (defined as compounds with limited clinical experience (i.e., Phase II studies or less)); or (3) more than one early stage entity.

For most combinations which involve two late stage entities and for which there is adequate clinical experience with co-administration, combination toxicity studies would generally not be recommended to support clinical studies or marketing unless there is significant toxicological concern (e.g., similar target organ toxicity). This concern would be modified depending on the margins of safety and the ability to monitor the adverse effects in humans. If a study is being conducted to address a cause for significant toxicological concern it should generally be completed before carrying out clinical studies with the combination.

Where there are two late stage products for which there is not adequate clinical experience with co-administration, but there are no causes for significant toxicological concern based on the available data, nonclinical combination studies generally are not recommended to support small-scale, relatively short-duration clinical studies (e.g., Phase II studies of up to 3 months duration). Nonclinical combination studies, however, are recommended before large-scale or long-term combination trials, as well as for marketing.

For combinations of an early stage entity(ies) with clinical experience with a late stage entity(ies), for which there is no significant toxicological concern, combination toxicity studies are not recommended to support clinical proof-of-concept studies of up to one-month duration. The clinical study of the combination should not be longer than the clinical experience of the individual entities. Later stage or longer duration clinical studies should be supported by a nonclinical combination toxicity study.

For combinations of two early stage entities, nonclinical combination toxicity studies are recommended to support clinical trials.

Provided complete nonclinical development programs are being conducted on the individual entities and a nonclinical combination toxicity study is warranted to support

combination clinical trials, the duration of the combination study should be equivalent to that of the clinical trial, up to a maximum duration of 90 days. A 90-day combination toxicity study would also support marketing. A combination toxicity study of shorter duration can also support marketing, depending on the duration of the intended clinical use.

The design of the nonclinical studies recommended to characterize the combination will depend on the pharmacological, toxicological and PK profiles of the individual entities, the treatment indication(s), the intended patient population, and the available clinical data.

Combination nonclinical studies should generally be limited to a single relevant species. If unexpected toxicity is identified, additional testing can be appropriate.

When complete nonclinical development programs are not conducted on the individual entities, then a complete nonclinical toxicology program with the combination only can be appropriate, provided that the individual agents are only intended for use in combination.

Combination genotoxicity, safety pharmacology, or carcinogenicity studies generally are not recommended to support clinical trials or marketing if the individual agents have been tested according to current standards. In those cases where the patient population includes WOCBP and studies with the individual agent(s) have shown findings indicative of embryo-fetal risk, combination studies are not recommended as a potential human developmental hazard has already been identified. If nonclinical embryo-fetal studies have indicated that neither agent poses a potential human developmental risk, combination studies are not recommended unless concerns exist, based on the properties of individual components, that their combination could give rise to a hazard for humans. In circumstances when the individual agents have been tested in embryo-fetal studies but embryo-fetal studies of the drug combination are warranted, the study(ies) of the combination should be available to support the marketing application.

18. CONTINUING EFFORTS TO IMPROVE HARMONIZATION

It is recognised that significant advances in harmonisation of the timing of nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals have already been achieved and are detailed in this guideline. However, differences remain in a few areas. Regulators and industry will continue to consider these differences and work towards further improving the drug development process.

19. ENDNOTES

Note 1: In this document “exposure” generally means group mean AUC. In some circumstances (e.g., if the compound or compound class is known to produce acute functional cardiovascular changes or central nervous system-related clinical signs) it might be appropriate to base the exposure margin on group mean Cmax values rather than AUC.

Note 2: An assessment of male and female fertility by thorough standard histopathological examination on the testis and ovary in a repeated-dose toxicity study (generally rodent) of at least 2-week duration is considered to be as sensitive as fertility studies in detecting toxic effects on male and female reproductive organs (Refs. 3, 15, 16).

Note 3: Highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used

consistently and correctly. For subjects using a hormonal contraceptive method, information regarding the product under evaluation and its potential effect on the contraceptive should be addressed.

Note 4: A preliminary embryo-fetal study useful for this purpose is one with adequate dose levels; that includes assessment of fetal survival, body weight and external and visceral examinations; that uses a minimum of six dams per group; and that has dams treated over the period of organogenesis. This preliminary nonclinical study should be conducted under high-quality scientific standards with data collection records readily available or under GLP conditions.

Note 5: The pregnancy rate of women initially attempting to become pregnant is ~17% per menstrual cycle. Pregnancy rates estimated from Phase III studies conducted in WOCBP were observed to be <0.1% per menstrual cycle. During these studies, subjects were encouraged to avoid pregnancy and measures were instituted to prevent pregnancy. Survey information from earlier Phase II studies suggests that the pregnancy rates were lower than in Phase III studies but the extent of further reduction could not be estimated due to the limited number of women enrolled. Based on the above Phase III experience, Phase II trials enrolling 150 WOCBP for 3 months are estimated to result in significantly less than 0.5 pregnancies per pharmaceutical under development.

Note 6: Testing for photocarcinogenicity in rodents using currently available models (e.g., hairless rodent) is not considered useful in support of pharmaceutical development and generally is not recommended. If the phototoxicity assessment suggests a potential photocarcinogenic risk and an appropriate assay becomes available, the study should usually be completed before marketing and the results should be considered in the human risk assessment.

20. REFERENCES

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