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

ICH HARMONISED TRIPARTITE GUIDELINE

DOSE SELECTION FOR CARCINOGENICITY STUDIES OF PHARMACEUTICALS & LIMIT DOSE
S1C(R1)

Current *Step 4* version
Parent Guideline dated 27 October 1994
(Addendum on a Limit Dose dated 17 July 1997
incorporated in November 2005)

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 final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

S1C(R1)
Document History

First Codification	History	Date	New Codification **November 2005**

Parent Guideline: Dose Selection for Carcinogenicity Studies of Pharmaceuticals

S1	Approval by the Steering Committee under *Step 2* and release for public consultation.	27 October 1993	S1
S1C	Approval by the Steering Committee under *Step 4* and recommendation for adoption to the three ICH regulatory bodies.	27 October 1994	S1C

Addendum to the Parent Guideline: Addition of a Limit Dose and Related Notes

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Current *Step 4* version

S1C and S1C(R)	The parent guideline is now renamed S1C(R1) as the Addendum has been incorporated to the parent guideline. The new title is: "Dose Selection for Carcinogenicity Studies of Pharmaceuticals & Limit Dose".	November 2005	S1C(R1)

PART I:
DOSE SELECTION FOR CARCINOGENICITY STUDIES OF PHARMACEUTICALS

ICH Harmonised Tripartite Guideline

Having reached Step 4 of the ICH Process at the ICH Steering Committee meeting on 27 October 1994, this guideline is recommended for adoption to the three regulatory parties to ICH

Introduction

Traditionally, carcinogenicity studies for chemical agents have relied upon the maximally tolerated dose (MTD) as the standard method for high dose selection. (NOTE 1) The MTD is generally chosen based on data derived from toxicity studies of 3 months' duration.

In the past, the criteria for high dose selection for carcinogenicity studies of human pharmaceuticals have not been uniform among international regulatory agencies. In Europe and Japan, dose selection based on toxicity endpoints or attaining high multiples of the maximum recommended human daily dose (>100x on a mg/kg basis) have been accepted. However, in the United States, dose selection based on the MTD has traditionally been the only acceptable practice. All regions have used a maximum feasible dose as an acceptable endpoint.

For pharmaceuticals with low rodent toxicity, use of the MTD may result in the administration of very large doses in carcinogenicity studies, often representing high multiples of the clinical dose. The usefulness of an approach developed for genotoxic substances or radiation exposure where a threshold carcinogenic dose is not necessarily definable may not be appropriate for non-genotoxic agents (NOTE 2). For non-genotoxic substances where thresholds may exist and carcinogenicity may result from alterations in normal physiology, linear extrapolations from high dose effects have been questioned. This has led to the concern that exposures in rodents greatly in excess of the intended human exposures may not be relevant to human risk; because they so greatly alter the physiology of the test species, the findings may not reflect what would occur following human exposure.

Ideally, the doses selected for rodent bioassays for non-genotoxic pharmaceuticals should provide an exposure to the agent that (1) allow an adequate margin of safety over the human therapeutic exposure, (2) are tolerated without significant chronic physiological dysfunction and are compatible with good survival, (3) are guided by a comprehensive set of animal and human data that focus broadly on the properties of the agent and the suitability of the animal (4) and permit data interpretation in the context of clinical use.

In order to achieve international harmonisation of requirements for high dose selection for carcinogenicity studies of pharmaceuticals, and to establish a rational basis for high dose selection, the ICH Expert Working Group on Safety initiated a process to arrive at mutually acceptable and scientifically based criteria for high dose selection. Several features of pharmaceutical agents distinguish them from other environmental chemicals and can justify a guideline which may differ in some respects from other guidelines. This should enhance the relevance of the carcinogenicity study for pharmaceuticals. Thus, much knowledge may be available on the pharmacology, pharmacokinetics, and metabolic disposition in humans. In addition, there will usually be information on the patient population, the expected use

pattern, the range of exposure, and the toxicity and/or side effects that cannot be tolerated in humans. Diversity of the chemical and pharmacological nature of the substances developed as pharmaceuticals, plus the diversity of non-genotoxic mechanisms of carcinogenesis calls for a flexible approach to dose selection. This document proposes that any one of several approaches may be appropriate and acceptable for dose selection, and should provide for a more rational approach to dose selection for carcinogenicity studies for pharmaceuticals. These include: 1) toxicity-based endpoints; 2) pharmacokinetic endpoints; 3) saturation of absorption; 4) pharmacodynamic endpoints; 5) maximum feasible dose; 6) additional endpoints.

Consideration of all relevant animal data and integration with available human data is paramount in determining the most appropriate endpoint for selecting the high dose for the carcinogenicity study. Relevant pharmacokinetic, pharmacodynamic, and toxicity data should always be considered in the selection of doses for the carcinogenicity study, regardless of the primary endpoint used for high dose selection.

In the process of defining such a flexible approach, it is recognised that the fundamental mechanisms of carcinogenesis are only poorly understood at the present time. Further, it is also recognised that the use of the rodent to predict human carcinogenic risk has inherent limitations, although this approach is the best available option at this time. Thus, while the use of plasma levels of drug-derived substances represents an important attempt at improving the design of the rodent bioassay, progress in this field will necessitate continuing examination of the best method to detect human risk. This guideline is therefore intended to serve as guidance in this difficult and complex area, recognising the importance of updating the specific provisions outlined below as new data become available.

General considerations for the conduct of dose-ranging studies

The considerations involved when undertaking dose-ranging studies to select the high dose for carcinogenicity studies are the same regardless of the final endpoint utilised.

1. In practice, carcinogenicity studies are carried out in a limited number of rat and mouse strains for which there are reasonable information on spontaneous tumour incidence. Ideally, rodent species/strains with metabolic profiles as similar as possible to humans should be studied (NOTE 3).

2. Dose-ranging studies should be conducted for both males and females for all strains and species to be tested in the carcinogenicity bioassay.

3. Dose selection is generally determined from 90-day studies using the route and method of administration that will be used in the bioassay.

4. Selection of an appropriate dosing schedule and regimen should be based on clinical use and exposure patterns, pharmacokinetics, and practical considerations.

5. Ideally, both the toxicity profile and any dose-limiting toxicity should be characterised. Consideration should also be given to general toxicity, the occurrence of preneoplastic lesions and/or tissue-specific proliferative effects, and disturbances in endocrine homeostasis.

6. Changes in metabolite profile or alterations in metabolising enzyme activities (induction or inhibition) over time, should be understood to allow for appropriate interpretation of studies.

Toxicity endpoints in high dose selection

ICH 1 agreed to evaluate endpoints other than the MTD for the selection of the high dose in carcinogenicity studies. These were to be based on the pharmacological properties and toxicological profile of the test compound. There is no scientific consensus the use of toxicity endpoints other than the MTD. Therefore, the ICH Expert Working Group on Safety has agreed to continue use of the MTD as an acceptable toxicity-based endpoint for high dose selection for carcinogenicity studies.

The following definition of the MTD is considered consistent with those published previously by international regulatory authorities (NOTE 1): The top dose or maximum tolerated dose is that which is predicted to produce a minimum toxic effect over the course of the carcinogenicity study. Such an effect may be predicted from a 90-day dose range-finding study in which minimal toxicity is observed. Factors to consider are alterations in physiological function which would be predicted to alter the animal's normal life span or interfere with interpretation of the study. Such factors include: no more than 10% decrease in body weight gain relative to controls; target organ toxicity; significant alterations in clinical pathological parameters.

Pharmacokinetic endpoints in high dose selection

A systemic exposure representing a large multiple of the human AUC (at the maximum recommended daily dose) may be an appropriate endpoint for dose selection for carcinogenicity studies for non-genotoxic pharmaceuticals (NOTE 2) which have similar metabolic profiles in humans and rodent and low organ toxicity in rodents (high doses are well tolerated in rodents), The level of animal systemic exposure should be sufficiently great, compared to exposure to provide reassurance of an adequate test of carcinogenicity.

It is recognised that the doses administered to different species may not correspond to tissue concentrations because of different metabolic and excretory patterns, Comparability of systemic exposure is better assessed by blood concentrations of parent drug and metabolites than by administered dose. The unbound drug in plasma is thought to be the most relevant indirect measure of tissue concentrations of unbound drug. The AUC is considered the most comprehensive pharmacokinetic endpoint since it takes into account the plasma concentration of the compound and residence time in vivo,

There is, as yet, no validated scientific basis for use of comparative drug plasma concentrations in animals and humans for the assessment of carcinogenic risk to humans. However, for the present, and based on an analysis of a database of carcinogenicity studies performed at the MTD, the selection of a high dose for carcinogenicity studies which represents a 25-fold ratio of rodent to human plasma AUC of parent compound and/or metabolites is considered pragmatic (NOTE 4).

Criteria for comparisons of AUC in animals and man for use in high dose selection

The following criteria are especially applicable for use of a pharmacokinetically-defined exposure for high dose selection.

1. Rodent pharmacokinetic data are derived from the strains used for the carcinogenicity studies using the route of compound administration and dose ranges planned for the carcinogenicity study (NOTES 5, 6 and 7).

2. Pharmacokinetic data are derived from studies of sufficient duration to take into account potential time-dependent changes in pharmacokinetic parameters which may occur during the dose ranging studies,

3. Documentation is provided on the similarity of metabolism between rodents and humans (NOTE 8).

4. In assessing exposure, scientific judgement is used to determine whether the AUC comparison is based on data for the parent, parent and metabolite(s) or metabolite(s). The justification for this decision is provided.

5. Interspecies differences in protein binding are taken into consideration when estimating relative exposure (NOTE 9).

6. Human pharmacokinetic data are derived from studies encompassing the maximum recommended human daily dose (NOTE 10).

Saturation of absorption in high dose selection

High dose selection based on saturation of absorption measured by systemic availability of drug-related substances is acceptable. The mid and low doses selected for the carcinogenicity study should take into account saturation of metabolic and elimination pathways.

Pharmacodynamic endpoints in high dose selection

The utility and safety of many pharmaceuticals depend on their pharmacodynamic receptor selectivity. Pharmacodynamic endpoints for high dose selection will be highly compound-specific and are considered for individual study designs based on scientific merits. The high dose selected should produce a pharmacodynamic response in dosed animals of such magnitude as would preclude further dose escalation. However, the dose should not produce disturbances of physiology or homeostasis which would compromise the validity of the study. Examples include hypotension and inhibition of blood clotting (because of the risk of spontaneous bleeding).

Maximum feasible dose

Currently, the maximum feasible dose by dietary administration is considered 5% of diet. International regulatory authorities are re-evaluating this standard. It is believed that the use of pharmacokinetic endpoints (AUC ratio) for dose selection of low toxicity pharmaceuticals, discussed in this guideline, should significantly decrease the need to select high doses based on feasibility criteria.

When routes other than dietary administration are appropriate, the high dose will be limited based on considerations including practicality and local tolerance,

Additional endpoints in high dose selection

It is recognised that there may be merit in the use of alternative endpoints not specifically defined in this guidance on high dose selection for rodent carcinogenicity studies. Use of these additional endpoints in individual study designs must be based on scientific rationale. Such designs are evaluated based on their individual merits. (NOTE 11)

Selection of middle and low doses in carcinogenicity studies

Regardless of the method used for the selection of the high dose, the selection of the mid and low doses for the carcinogenicity study should provide information to aid in assessing the relevance of study findings to humans. The doses should be selected following integration of rodent and human pharmacokinetic, pharmacodynamic and toxicity data. The rationale for the selection of these doses should be provided. While not all encompassing, the following points should be considered in selection of the middle and low doses for rodent carcinogenicity studies:

1. Linearity of pharmacokinetics and saturation of metabolic pathways.
2. Human exposure and therapeutic dose.
3. Pharmacodynamic response in rodents.
4. Alterations in normal rodent physiology.
5. Mechanistic information and potential for threshold effects.
6. The unpredictability of the progression of toxicity observed in short-term studies.

Summary

This guidance outlines four generally acceptable criteria for selection of the high dose for carcinogenicity studies of therapeutics: maximum tolerated dose, 25-fold AUC ratio (rodent:human), dose-limiting pharmacodynamic effects, saturation of absorption, and maximum feasible dose. The use of other pharmacodynamic-pharmacokinetic- or toxicity-based endpoints in study design is considered based on scientific rationale and individual merits. In all cases, appropriate dose ranging studies need to be conducted. All relevant information should be considered for dose and species/strain selection for the carcinogenicity study. This information should include knowledge of human use, exposure patterns and metabolism. The availability of multiple acceptable criteria for dose selection will provide greater flexibility in optimising the design of carcinogenicity studies for therapeutic agents.

NOTE 1

The following are considered equivalent definitions of the toxicity based endpoint describing the maximum tolerated dose:

The US Interagency Staff Group on Carcinogens has defined the MTD as follows: "The highest dose currently recommended is that which, when given for the duration of the chronic study, is just high enough to elicit signs of minimal toxicity without significantly altering the animal's normal lifespan due to effects other than carcinogenicity. This dose, sometimes called the maximum tolerated dose (MTD), is determined in a subchronic study (usually 90 days duration) primarily on the basis of mortality, toxicity and pathology criteria. The MTD should not produce morphologic evidence of toxicity of a severity that would interfere with the interpretation of the study. Nor should it comprise so large a fraction of the animal's diet that the nutritional composition of the diet is altered, leading to nutritional imbalance."

"The MTD was initially based on a weight gain decrement observed in the subchronic study; i.e., the highest dose that caused no more than a 10% weight gain decrement, More recent studies and the evaluation of many more bioassays indicate refinement of MTD selection on the basis of a broader range of biological information, Alterations in body and organ weight and clinically significant changes in haematologic, urinary, and clinical chemistry measurements can be useful in conjunction with the usually

more definitive toxic, pathologic or histopathologic endpoints." (Environmental Health Perspectives, Vol. 67, pp. 201-281, 1986)

The Ministry of Health and Welfare in Japan prescribes the following: "The dose in the preliminary carcinogenicity study that inhibits body weight gain by less than 10% in comparison with the control and causes neither death due to toxic effects nor remarkable changes in the general signs and laboratory examination findings of the animals is the highest dose to be used in the full-scale carcinogenicity study." (Toxicity test guideline for pharmaceuticals, Chapter 5, pg. 127, 1985)

The Committee on Proprietary Medicinal Products of the European Community prescribes the following: "The top dose should produce a minimum toxic effect, for example a 10% weight loss or failure of growth, or minimal target organ toxicity. Target organ toxicity will be demonstrated by failure of physiological functions and ultimately by pathological changes." (Rules Governing Medicinal Products in the European Community, Vol. III, 1987)

NOTE 2

While it is recognised that standard test batteries may not examine all potential genotoxic mechanisms, for the purposes of this guideline, a pharmaceutical is considered non-genotoxic with respect to the use of pharmacokinetic endpoints for dose selection, if it is negative in the standard battery of assays required for pharmaceutical registration.

NOTE 3

This does not imply that all possible rodent strains will be surveyed for metabolic profile. But rather, that standard strains used in carcinogenicity studies will be examined.

NOTE 4

In order to select a multiple of the human AUC that would serve as an acceptable endpoint for dose selection for carcinogenicity studies, a retrospective analysis was performed on data from carcinogenicity studies of therapeutics conducted at the MTD for which there was sufficient human and rodent pharmacokinetic data for comparison of AUC values.

In 35 drug carcinogenicity studies carried out at the MTD for which there was adequate pharmacokinetic data in rats and humans, approximately, 1/3 had a relative systemic exposure ratio less than or equal to 1, another 1/3 had ratios between 1 and 10.

An analysis of the correlation between the relative systemic exposure ratio, the relative dose ratio (rat mg/kg: human mg/kg MRD) and the dose ratio adjusted for body surface area (rat mg/M2 MTD:human mg/M2 MRD), performed in conjunction with the above-described database analysis indicates that the relative systemic exposure corresponds better with dose ratios expressed in terms of body surface area rather than body weight. When 123 compounds in the expanded FDA database were analysed by this approach, a similar distribution of relative systemic exposures was observed.

In the selection of a relative systemic exposure ratio (AUC ratio, to apply in high dose selection, consideration was given to a ratio value that would represent an adequate margin of safety, would detect known or probable human carcinogens, and could be attained by a reasonable proportion of compounds,

To address the issue of detection of known or probable human carcinogenic pharmaceuticals, an analysis of exposure and/or dose ratios was performed on IARC class 1 and 2A pharmaceuticals with positive rat findings. For phenacetin, sufficient rat and human pharmacokinetic data is available to estimate that a relative systemic exposure ratio of at least 15 is necessary to produce positive findings in a rat carcinogenicity study. For most of 14 IARC 1 and 2A drugs evaluated with positive carcinogenicity findings in rats, there is a lack of adequate pharmacokinetic data for analysis. For these compounds, the body surface area adjusted dose ratio was employed as a surrogate for the relative systemic exposure ratio. The results of this analysis indicated that using doses in the rodent corresponding to body surface area ratios of 10 or more would identify the carcinogenic potential of these pharmaceuticals.

As a result of the evaluations described above, a minimum systemic exposure ratio of 25 is proposed as an acceptable pharmacokinetic endpoint for high dose selection. This value was attained by approximately 25% of compounds tested in the FDA database, is high enough to detect known or probable (IARC 1, 2A) human carcinogenic drugs and represents an adequate margin of safety. Those pharmaceuticals tested using a 25 fold or greater AUC ratio for the high dose will have exposure ratios greater than 75% of pharmaceuticals tested previously in carcinogenicity studies performed at the MTD.

NOTE 5

The rodent AUCs and metabolite profiles may be determined from separate steady-state kinetic studies, as part of the subchronic toxicity studies, or dose-ranging studies.

NOTE 6

AUC values in rodents are usually obtainable using a small number of animals, depending on the route of administration and the availability of data on the pharmacokinetic characteristics of the test compound.

NOTE 7

Equivalent analytical methods of adequate sensitivity and precision are used to determine plasma concentrations of pharmaceuticals in rodents and humans.

NOTE 8

It is recommended that in vivo metabolism be characterised in humans and rodents, if possible. However, in the absence of appropriate *in vivo* metabolism data, *in vitro* metabolism data (e.g. from liver slices, uninduced microsomal preparations) may provide adequate support for the similarity of metabolism across species.

NOTE 9

While in vivo determinations of unbound drug may be the best approach, in vitro determinations of protein binding using parent and/or metabolites as appropriate (over the range of concentrations achieved in vivo in rodents and humans) may be

used in the estimation of AUC unbound. When protein binding is low in both humans and rodents or when protein binding is high and the unbound fraction of drug is greater in rodents than in humans, the comparison of total plasma concentration of drug is acceptable, When protein binding is high and the unbound fraction is greater in humans than in rodents, the ratio of the unbound concentrations should be used.

NOTE 10

Human systemic exposure data may be derived from pharmacokinetic monitoring in normal volunteers and/or patients. The possibility of extensive inter-individual variation in exposure should be taken into consideration. In the absence of knowledge of the maximum recommended human daily dose, at a minimum, doses producing the desired pharmacodynamic effect in humans are used to derive the pharmacokinetic data.

NOTE 11

Additional pharmaceutical-specific endpoints to select an appropriate high dose are currently under discussion (e.g. additional pharmacodynamic, pharmacokinetic and toxicity endpoints as well as alternatives to a maximum feasible dose).

PART II:
ADDITION OF A LIMIT DOSE AND RELATED NOTES

ICH Harmonised Tripartite Guideline

Having reached Step 4 of the ICH Process at the ICH Steering Committee meeting on 17 July 1997, this addendum is recommended for adoption to the three regulatory parties to ICH

Limit Dose

In determining the high dose for carcinogenicity studies using the approaches outlined in this guideline, it may not be necessary to exceed a dose of 1500 mg/kg/day (*Note 1*). This limit dose applies only in cases where there is no evidence of genotoxicity, and where the maximum recommended human dose does not exceed 500 mg/day (*Note 2*).

Data should be provided comparing exposure of rodents and humans to drug and metabolites primarily to support dose selection for and interpretation of the carcinogenicity study. Based on such information, there may be cases where the limit of 1500 mg/kg/day is not acceptable because it cannot be assured that animal exposure after 1500 mg/kg/day is sufficiently high compared to the exposure achieved in humans. The rodent systemic exposure at 1500 mg/kg/day should be greater by at least an order of magnitude than human exposure measured at the intended human therapeutic dose. [If this is not the case, efforts should be made to increase the rodent exposure or to reconsider the animal model in a case-by-case approach]. If the human dose exceeds 500 mg/day the high dose may be increased up to the maximum feasible dose.

Note 1:

Review of the FDA carcinogenicity database of nearly 900 carcinogenicity tests indicated that about 20 tests had been conducted that used doses of 1000 mg/kg or greater as the highest dose tested. About 10 of these tests were considered as having demonstrated a carcinogenic response. Seven of these were positive only at or above 1000 mg/kg including 2 that were positive in two species (in neither case were doses above 1000 mg/kg necessary to detect the carcinogenic response in both species, but rather in only one of the two species was a dose greater than 1000 mg/kg necessary).

Some of the one species positives were also only positive at doses greater than 1000 mg/kg. In one case where the drug was considered as demonstrating a significant tumor response only above 1000 mg/kg it was positive in several non-standard genotoxicity assays, but not in standard genotoxicity studies. Regulatory action has resulted from some of these cases. Based on these results, the limit dose for carcinogenicity testing should be 1500 mg/kg rather than 1000 mg/kg to eliminate the risk that a genotoxic carcinogen will not be able to be identified as a result of adoption of a limit dose of 1000 mg/kg.

Note 2:

It has been agreed that if a non-genotoxic drug is only positive in rodents at doses above those producing a 25-fold exposure over humans, such finding would not be considered likely to pose a relevant risk to humans.

It has been shown that systemic exposure comparisons between rodents and humans are better estimated by dose using mg/m^2 than using mg/kg (NOTE 4 of the S1C document "Dose Selection for Carcinogenicity Studies of Pharmaceuticals"). Therefore, the human dose should be at least 25-fold lower on a mg/m^2 basis than the high dose in the carcinogenicity study. The factor, 6-7 (6.5), is used to convert rat doses from mg/kg to mg/m^2 and 40 is used to convert human doses from mg/kg to mg/m^2. Thus, the estimated systemic exposure ratio of 25-fold rodent to human is equal to about a 25-fold mg/m^2 ratio or a 150-fold mg/kg ratio ($150 \approx 25 \times 40/6.5$). Therefore a human dose below 10 mg/kg/day (about 500 mg/day or less) could be tested in rats at 1500 mg/kg as the high dose.