Health Canada Santé Canada

Therapeutic Products Programme /
Programme des produits thérapeutiques
Tunney's Pasture / Pré Tunney
A.L. / L.A. # 0702A
OTTAWA (Ontario)
K1A 0L2

June 18, 1998 / Le 18 juin 1998

97-036022

To: Associations

I am pleased to inform you of the release of the ICH (*International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use*)/Therapeutic Products Programme guideline,"Timing of Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals".

This guideline was developed by an expert working group under the auspices of ICH. The ICH Steering Committee has endorsed the final draft and recommended its adoption by regulatory bodies of the European

Aux : Associations

J'ai le plaisir de vous annoncer la publication de la ligne directrice de la CIH (*Conférence internationale sur l'harmonisation des exigences techniques pour l'enregistrement des médicaments à usage humain*) et du Programme des produits thérapeutiques, intitulée « Calendrier des études d'innocuité non cliniques pour la conduite d'essais cliniques de produits pharmaceutiques sur des sujets humains ».

Cette ligne directrice a été mise au point par un groupe d'experts, sous les auspices de la CIH. Le Comité directeur de la CIH a approuvé la version définitive et en a recommandé l'adoption par les organismes de réglementation de l'Union

.../2

Union, Japan and the United States.

The Therapeutic Products Programme has adopted this international guideline. In accordance with ICH rules, the document was adopted verbatim. The guideline outlines those safety data that are mandatory prior to human exposure. It also provides the minimum duration of toxicity studies that must be available prior to the inclusion of subjects into clinical trials of various duration. Regarding the inclusion of women of childbearing potential into clinical trials, the principles outlined in the Therapeutic Products Programme's guideline "Inclusion of Women in Clinical Trials" are to be followed.

Please note that this document provides only general guidance. Depending on the findings of the various toxicity studies, the importance of the new therapeutic agent and the risk/benefit assessment in general, additional data may be required prior to the

européenne, du Japon et des États-Unis.

Le Programme des produits thérapeutiques a adopté cette ligne directrice internationale, textuellement comme l'exige la CIH. La ligne directrice décrit les données d'innocuité à obtenir obligatoirement avant d'exposer des sujets humains à des produits pharmaceutiques. Elle précise également la durée minimale des études toxicologiques qui doivent être faites avant d'inclure des sujets humains dans des essais cliniques de durée variable. En ce qui concerne l'inclusion, dans des essais cliniques, de femmes aptes à procréer, il faut observer les principes énoncés dans la ligne directrice du Programme des produits thérapeutiques intitulée « Inclusion des femmes dans les essais cliniques ».

Je vous signale que ce document ne donne qu'une orientation générale. Selon les conclusions des différentes études toxicologiques, l'importance du nouvel agent thérapeutique et l'évaluation des risques et des avantages en général, il faudra peut-être obtenir

exposure of patients/ volunteers to a given agent.

de l'information supplémentaire avant d'exposer des malades ou des volontaires à un agent donné.

The guideline is available through Internet at www.hc-sc/hpb-dgps/therapeut. For those clients who do not have access to Internet, printed copies will be available through Health Canada Publications, telephone (613)954-5995 or fax (613)941-5366.

La ligne directrice est disponible sur Internet à www.hc-sc/hpb-dgps/ therapeut. Les clients qui n'ont pas accès à Internet peuvent obtenir le document en s'adressant au service des publications de Santé Canada, par téléphone au (613) 954-5995 ou par télé-copieur au (613) 941-5366.

Should you have any questions regarding the content of the guideline, please contact:

Pour toutes questions au sujet du contenu de la ligne directrice, veuillez communiquer avec :

Dr. Kitty Voith
Bureau of Pharmaceutical

Dre Kitty Voith
Bureau de l'évaluation des

Assessment
A.L. # 3102B
Therapeutic Products
Programme
Health Canada
Tower "B", Holland Cross
1600 Scott Street
Ottawa, Ontario
K1A 1B6

Telephone: (613) 941-3178
Facsimile: (613) 941-1668

produits pharmaceutiques
L.A. # 3102B
Programme des produits
thérapeutiques
Santé Canada
Tour B, Holland Cross
1600, rue Scott
Ottawa (Ontario)
K1A 1B6

Téléphone : (613) 941-3178
Télécopieur :(613) 941-1668

Original signed by / Original signé par

Dann M. Michols
Director General /Directeur général

Health Canada Santé Canada

THERAPEUTIC PRODUCTS DIRECTORATE GUIDELINES

ICH HARMONISED TRIPARTITE GUIDELINE

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

TIMING OF NON-CLINICAL SAFETY STUDIES FOR THE CONDUCT OF HUMAN CLINICAL TRIALS FOR PHARMACEUTICALS

Published by authority of the
Minister of Health

For more information, please contact:

Therapeutic Products Directorate
Health Canada
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

Disclaimer

The material herein was prepared under the direction of the Drugs Programme, Health Canada. No changes are permitted.

Avertissement

Le document ci-joint a été préparé sous la direction de la Programme des médicaments, Santé Canada. Aucune modification n'est permise.

Canada

Our mission is to help the people of Canada
Maintain and improve their health.
Health Canada

THERAPEUTIC PRODUCTS DIRECTORATE WEBSITE
(TP-Web)

LET YOUR COMPUTER DO THE SEARCHING!

... Need to know how to market a new drug in Canada?
... Want information on the drug regulatory process?
... Need to know what the newest drugs on the Canadian market are?
... Want direct access to forms and policies?
... Need to know the requirements for labelling drugs?

All this and more is available on the

Therapeutic Products Directorate Website
at
www.hc-sc.gc.ca/hpb-dgps/therapeut

Therapeutic Products Directorate Webmaster : Pete Nilson
Telephone - (613) 941-1601

Available in Canada through
Health Canada
Publications
Brooke Claxton Building, A.L. #0913A
Tunney's Pasture
Ottawa, Ontario
K1A 0K9

Tel: (613) 954-5995
Fax: (613) 941-5366

Internet: www.hc-sc.gc.ca/hpb-dgps/therapeut
tp_webmaster@inet.hwc.ca

Également disponible en français sous le titre :
Calendrier des études d'innocuité non cliniques pour la conduite d'essais cliniques de produits pharmaceutiques sur des sujets humains

Catalogue No. H42-2/67-13-1997IN
ISBN 0-662-26386-3

FOREWORD

The ICH harmonised tripartite guideline: "Timing of Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals" has been developed by an ICH Expert Working Group and has been subject to consultation, in accordance with the ICH process, by regulatory parties which include Canada. The ICH Steering Committee has endorsed the final draft and recommended its adoption by the regulatory bodies of the European Union, Japan, and the USA.

The guideline delineates those safety data that are mandatory prior to human exposure. The guideline also provides the minimum duration of toxicity studies that must be available prior to the inclusion of subjects into clinical trials of various duration.

Regarding the inclusion of women of childbearing potential into clinical trials, the principles outlined in the Therapeutic Products Directorate's guideline "Inclusion of Women in Clinical Trials" should be followed.

The present document provides only general guidance. Depending on the findings of the various toxicity studies, the importance of the new therapeutic agent and the risk/benefit assessment in general, additional data may be required prior to the exposure of patients/ volunteers to a given agent.

TABLE OF CONTENTS

1. INTRODUCTION

1.1 Objectives of the Guideline

The purpose of this document is to recommend international standards for and promote harmonisation of the non-clinical safety studies needed to support human clinical trials of a given scope and duration.

Harmonisation of the guidance for non-clinical safety studies will help to define the current recommendations and reduce the likelihood that substantial differences will exist between regions.

This guidance should facilitate the timely conduct of clinical trials and reduce the unnecessary use of animals and other resources. This should promote safe and ethical development and availability of new pharmaceuticals.

1.2 Background

The recommendations for the extent of non-clinical safety studies to support the various stages of clinical development differ among the regions of Europe, USA and Japan. This raises the important question of whether there is scientific justification for these differences and whether it would be possible to develop a mutually acceptable guidance.

The present guideline represents the consensus that exists regarding the scope and duration of non-clinical safety studies to support the conduct of human clinical trials for pharmaceuticals.

1.3 Scope of Guideline

The non-clinical safety study recommendations for the marketing approval of a pharmaceutical usually include single and repeated dose toxicity studies, reproduction toxicity studies, genotoxicity studies, local tolerance 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 non-clinical studies include pharmacology studies for safety assessment (safety pharmacology) and pharmacokinetic (ADME) studies. These types of studies and their relation to the conduct of human clinical trials are presented in this guideline.

This guideline applies to the situations usually encountered during the conventional development of pharmaceuticals and should be viewed as providing general guidance for drug development. Animal safety studies and human clinical trials should be planned

and designed to represent an approach that is scientifically and ethically appropiate for the pharmaceutical under development.

There have been marked changes in the kinds of therapeutic agents being developed (e.g., biotechnology derived products), and the existing paradigms for safety evaluation may not always be appropriate or relevant. The safety evaluation in such cases should be considered on a case by case basis as described in the ICH guideline, "Safety Studies for Biotechnological Products"(1). Similarly, pharmaceuticals under development for indications in life threatening or serious diseases without current effective therapy may also warrant a case by case approach to both the toxicological evaluation and clinical development to optimise and expedite drug development. In these cases, particular studies may be abbreviated, deferred or omitted.

1.4 General Principles

The development of a pharmaceutical is a stepwise process involving an evaluation of both the animal and human safety information. The goals of the non-clinical safety evaluation include: a characterisation of toxic effects with respect to target organs, dose dependence, relationship to exposure, and potential reversibility. This information is important for the estimation of an initial safe starting dose for the human trials and the identification of parameters for clinical monitoring for potential adverse effects. The non-clinical safety studies, although limited at the beginning of clinical development, should be adequate to characterise potential toxic effects under the conditions of the supported clinical trial.

Human clinical trials are conducted to demonstrate the efficacy and safety of a pharmaceutical, starting with a relatively low exposure in a small number of subjects. This is followed by clinical trials in which exposure usually increases by dose, duration and/or size of the exposed patient population. Clinical trials are extended based on the demonstration of adequate safety in the previous clinical trial(s) as well as additional non-clinical safety information that is available as the clinical trials proceed. Serious adverse clinical or non-clinical findings may influence the continuation of clinical trials and/or suggest the need for additional non-clinical studies and a re-evaluation of previous clinical adverse events to resolve the issue.

Clinical trials are conducted in phases for which different terminology has been utilised in the various regions. This document uses the terminology as defined in the ICH guideline "General Considerations for Clinical Trials" (2). Clinical trials may be grouped by their purpose and objectives. The first human exposure studies are generally single dose studies, followed by dose escalation and short term repeated dose studies to evaluate pharmacokinetic parameters and tolerance (Phase I studies - Human Pharmacology

studies). These studies are often conducted in healthy volunteers but may also include patients. The next phase of trials consists of exploratory efficacy and safety studies in patients (Phase II studies - Therapeutic Exploratory studies). This is followed by confirmatory clinical trials for efficacy and safety in patient populations (Phase III studies - Therapeutic Confirmatory studies).

2. SAFETY PHARMACOLOGY

Safety pharmacology includes the assessment of effects on vital functions, such as cardiovascular, central nervous and respiratory systems, and these should be evaluated prior to human exposure. These evaluations may be conducted as additions to toxicity studies or as separate studies.

3. TOXICOKINETIC AND PHARMACOKINETIC STUDIES

Exposure data in animals should be evaluated prior to human clinical trials (3). Further information on absorption, distribution, metabolism and excretion in animals should be made available to compare human and animal metabolic pathways. Appropriate information should usually be available by the time the Phase I (Human Pharmacology) studies have been completed.

4. SINGLE DOSE TOXICITY STUDIES

The single dose (acute) toxicity for a pharmaceutical should be evaluated in two mammalian species prior to the first human exposure (Note 1). A dose escalation study is considered an acceptable alternative to the single dose design.

5. REPEATED DOSE TOXICITY STUDIES

The recommended duration of the repeated dose toxicity studies is usually related to the duration, therapeutic indication and scale 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 (Tables 1 and 2).

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

5.1 Phase I and II Studies

A repeated dose toxicity study in two species (one non-rodent) for a minimum duration of 2-4 weeks (Table 1) would support Phase I (Human Pharmacology) and Phase II (Therapeutic Exploratory) studies up to 2 weeks in duration. Beyond this, 1, 3 or 6 months toxicity studies would support these types of human clinical trials for up to 1, 3 or 6 months, respectively. Six month rodent and chronic non-rodent studies (11) would support clinical trials of longer duration than 6 months.

Table 1

Duration of Repeated Dose Toxicity Studies to Support Phase I and II Trials in EU and Phase I, II and III Trials in the US and Japan*

Duration of Clinical Trials	**Minimum Duration of Repeated Dose Toxicity Studies**	
	Rodents	**Non-rodents**
Single Dose	2-4 Weeks**	2 Weeks
Up to 2 Weeks	2-4 Weeks**	2 Weeks
Up to 1 Month	1 Month	1 Month
Up to 3 Months	3 Months	3 Months
Up to 6 Months	6 Months	6 Months***
> 6 Months	6 Months	Chronic***

* In Japan, if there are no Phase II clinical trials of equivalent duration to the planned Phase III trials, conduct of longer duration toxicity studies should be considered as given in Table 2.

** In EU and US, 2 week studies are the minimum duration. In Japan, 2 week non-rodent and 4 week rodent studies are needed (Also see Note 2). In the US, as an alternative to 2 week studies, single dose toxicity studies with extended examinations can support single-dose human trials (4).

*** See (11). Data from 6 months of administration in non-rodents should be available before the initiation of clinical trials longer than 3 months. Alternatively, if applicable, data from a 9 month non-rodent study should be available before the treatment duration exceeds that which is supported by the available toxicity studies.

5.2 Phase III Studies

For the Phase III (Therapeutic Confirmatory) studies, the recommendations for the US and Japan are the same as those in Table 1. In EU, a one month toxicity study in two species (one non-rodent) would support clinical trials of up to 2 weeks duration (Table 2). Three month toxicity studies would support clinical trials for up to 1 month duration, while 6 month toxicity studies in rodents and 3 month studies in non-rodents would support clinical trials of a duration up to 3 months. For longer term clinical trials, a 6 month study in rodents and a chronic study in non-rodents are recommended.

Table 2

Duration of Repeated Dose Toxicity Studies to Support Phase III Trials in the EU and Marketing in all Regions*

Duration of Clinical Trials	Minimum Duration of Repeated Dose Toxicity Studies	
	Rodents	**Non-rodents**
Up to 2 Weeks	1 Month	1 Month
Up to 1 Month	3 Months	3 Months
Up to 3 Months	6 Months	3 Months
> 3 Months	6 Months	Chronic**

* The above Table also reflects the Marketing recommendations in the 3 Regions except that a chronic non-rodent study is recommended for clinical use > 1 month.

** See (11).

6. LOCAL TOLERANCE STUDIES

Local tolerance should be studied in animals using routes relevant to the proposed clinical administration. The evaluation of local tolerance should be performed prior to human exposure. The assessment of local tolerance may be part of other toxicity studies.

7. GENOTOXICITY STUDIES

Prior to first human exposure, in vitro tests for the evaluation of mutations and chromosomal damage are generally needed. If an equivocal or positive finding occurs, additional testing should be performed (5).

The standard battery of tests for genotoxicity (6) should be completed prior to the initiation of Phase II studies.

8. CARCINOGENICITY STUDIES

Completed carcinogenicity studies are not usually needed in advance of the conduct of clinical trials unless there is cause for concern. Conditions relevant for carcinogenicity testing, are discussed in the ICH document (7).
For pharmaceuticals developed to treat certain serious diseases, carcinogenicity testing, if needed, may be concluded post-approval.

9. REPRODUCTION TOXICITY STUDIES

Reproduction toxicity studies (8, 9) should be conducted as is appropriate for the population that is to be exposed.

9.1 Men

Men may be included in Phase I and II trials prior to 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 should be completed prior to the initiation of Phase III trials (8, 9).

9.2 Women Not of Childbearing Potential

Women not of childbearing potential (i.e., permanently sterilised, postmenopausal) may be included in clinical trials without reproduction toxicity studies provided the relevant repeated dose toxicity studies (which include an evaluation of the female reproductive organs) have been conducted.

9.3 Women of Childbearing Potential

For women of childbearing potential there is a high level of concern for the unintentional exposure of an embryo/fetus before information is available concerning the potential benefits versus potential risks. There are currently regional differences in the timing of reproduction toxicity studies to support the inclusion of women of childbearing potential in clinical trials.

In Japan, assessment of female fertility and embryo-fetal development should be completed prior to the inclusion of women of childbearing potential using birth control in any type of clinical trial. In the EU, assessment of embryo-fetal development should be completed prior to Phase I trials in women of childbearing potential and female fertility studies prior to Phase III trials.

In the US women of childbearing potential may be included in early, carefully monitored studies without reproduction toxicity studies provided appropriate precautions are taken to minimise risk. These precautions include pregnancy testing (for example, based on the beta-subunit of HCG), use of a highly effective method of birth control (Note 3) and entry after a confirmed menstrual period. Continued testing and monitoring during the trial should be sufficient to ensure compliance with the measures not to become pregnant during the period of drug exposure (which may exceed the length of study). To support this approach, informed consent should include any known pertinent information related to reproductive toxicity, such as a general assessment of potential toxicity of pharmaceuticals with related structures or pharmacological effects. If no relevant information is available, the informed consent should clearly note the potential for risk.

In the US, assessment of female fertility and embryo-fetal development should be completed before women of childbearing potential using birth control are enrolled in Phase III trials.

In the 3 Regions, the pre- and post-natal development study should be submitted for marketing approval or earlier if there is cause of concern. For all regions, all female reproduction toxicity studies (8) and the standard battery of genotoxicity tests (6) should be completed prior to the inclusion, in any clinical trial, of women of childbearing potential not using highly effective birth control (Note 3) or whose pregnancy status is unknown.

9.4 Pregnant Women

Prior to the inclusion of pregnant women in clinical trials, all the reproduction toxicity studies (8,9) and the standard battery of genotoxicity tests (6) should be conducted. In addition, safety data from previous human exposure are generally needed.

10. SUPPLEMENTARY STUDIES

Additional non-clinical studies may be needed if previous non-clinical or clinical findings with the product or related products have indicated special safety concerns.

11. CLINICAL TRIALS IN PEDIATRIC POPULATIONS

When pediatric patients are included in clinical trials, safety data from previous adult human exposure would usually represent the most relevant information and should

generally be available before pediatric clinical trials. The necessity for adult human data would be detemined on a case by case basis.

In addition to appropriate repeated dose toxicity studies all reproduction toxicity studies (8) and the standard battery of genotoxicity tests (6) should be available prior to the initiation of trials in pediatric populations. Juvenile animal studies should be considered on an individual basis when previous animal data and human safety data are insufficient . The need for carcinogenicity testing should be addressed prior to long term exposure in pediatric clinical trials considering the length of treatment or cause for concern (7).

12. CONTINUING EFFORTS TO IMPROVE HARMONISATION

It is recognised that significant advances in harmonisation of the timing of non-clinical 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. These include toxicity studies to support first entry into man and the recommendations for reproduction toxicity studies for women of childbearing potential. Regulators and industry will continue to consider these differences and work towards further improving the drug development process.

13. ENDNOTES

Note 1
For the conduct of single dose toxicity studies, refer to the ICH-1 recommendations (10) and the regional guidelines.

Note 2
There are currently regional differences for the minimum duration of repeated dose toxicity studies; 2 weeks in the EU and US and 2 weeks non-rodent and 4 weeks rodent in Japan. In Japan, unlike the EU and US, the male fertility study has usually been conducted prior to the inclusion of men in clinical trials. However, an assessment of male fertility by careful histopathological examination in the rodent 4 week repeated dose toxicity study has been found to be more sensitive in detecting effects on male reproductive organs than fertility studies (9), and is now recommended to be performed prior to the first clinical trial in Japan. In the EU and US, 2 week repeated dose studies are considered adequate for an overall assessment of the potential toxicity of a drug to support clinical trials for a short duration.

Note 3

A highly effective method of birth control is defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some IUDs, sexual abstinence or vasectomised partner. For subjects using a hormonal contraceptive method, information regarding the product under evaluation and its potential effect on the contraceptive should be addressed.

14. REFERENCES

1. ICH Topic S6 Document "Safety Studies for Biotechnological Products"
2. ICH Topic E8 Document "General Considerations for Clinical Trials"
3. ICH Harmonised Tripartite Guideline (S3A) "Note for Guidance on Toxicokinetics-The Assessment of Systemic Exposure in Toxicity Studies"
4. United States DHHS Federal Register notice August 26, 1996 (61 FR 43934)
5. ICH Harmonised Tripartite Guideline (S2A) "Guidance on Specific Aspects of Regulatory Genotoxicity Tests"
6. ICH Topic S2B Document "Standard Battery of Genotoxicity Tests"
7. ICH Harmonised Tripartite Guideline (SIA) "Guideline on the Need for Carcinogenicity Studies for Pharmaceuticals"
8. ICH Harmonised Tripartite Guideline (S5A) "Detection of Toxicity to Reproduction for Medicinal Products"
9. ICH Harmonised Tripartite Guideline (S5B) "Toxicity to Male Fertility"
10. P.F. Arcy and D.W.G. Harron, "Proceeding of The First International Conference on Harmonisation, Brussels 1991. Queen's Univ. of Belfast, pp 183-184 (1992)
11. ICH Topic S4 Document "Duration of Chronic Toxicity Testing in Animals (Rodent and Non Rodent Toxicity Testing)