Health Canada Santé Canada

Therapeutic Products Programme
Holland Cross, Tower "B"
1600 Scott Street
Address Locator # 3102D1
OTTAWA, Ontario
K1A 1B6
March 24, 2000

00-003535

To: Main Trade Associations, Registrars of Medicine, Registrars of Pharmacy

I am pleased to inform you of the release of the *International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use* (ICH)/Therapeutic Products Programme Guidance, **Addendum to "Dose Selection for Carcinogenicity Studies of Pharmaceuticals" Addition of a Limit Dose and Related Notes (ICH Topic S1C(R))**.

This guidance 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. The ICH Steering Committee has endorsed the final draft and recommended its adoption by the regulatory bodies of the European Union, Japan and USA.

In adopting this ICH guidance, the Therapeutic Products Programme (TPP) endorses the principles and practices described therein. This document should be read in conjunction with this covering letter and with the relevant sections of other applicable Programme guidances.

The Programme recognizes that the scope and subject matter of current TPP guidances may not be entirely consistent with those of the ICH guidances that are being introduced as part of the Programme's commitment to international harmonization and the ICH Process. In such circumstances, the ICH guidances adopted by the TPP take precedence. In this regard, the TPP will be examining necessary changes to the Programme's 1990 *Toxicological Evaluation Guideline.*

The TPP is committed to eliminating discrepancies through the implementation of a phased-in work plan that will examine the impact associated with the adoption of ICH guidances. This will result in the amendment or, depending on the extent of revisions required, withdrawal of some TPP guidances.

.../2

This and other Guidance documents are available on the Therapeutic Products Programme (TPP) Website (**http://www.hc-sc.gc.ca/hpb-dgps/therapeut**). The availability of printed copies of TPP guidances may be confirmed by consulting the Programme's *Guidelines and Publications Order Form* (available on the TPP Website) or by contacting the Publications Coordinator.[1]

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

Dr. Peter Grosser
Clinical Trials & Special Access Programme
Bureau of Pharmaceutical Assessment
Therapeutic Products Programme
Health Canada
A.L. 0202C1
Finance Building, Tunney's Pasture
OTTAWA, Ontario
K1A 1B6

Telephone: (613) 941-2132
Facsimile: (613) 941-2121

(Original signed by)

Dann M. Michols
Director General

Enclosure

[1] Tel: (613) 954-6466; E-mail: publications_coordinator@hc-sc.gc.ca

Disclaimer

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

Health Canada Santé Canada

GUIDANCE FOR INDUSTRY

Addendum to "Dose Selection for Carcinogenicity Studies of Pharmaceuticals"
Addition of a Limit Dose and Related Notes
ICH Topic S1C(R)

Published by authority of the
Minister of Health

Date Adopted by the TPP	1999/12/16
Effective Date	2000/03/24

Therapeutic Products Programme
Guidance Document

Canada

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

Health Canada

Our mission is to ensure that the drug, medical devices, and other therapeutic products available in Canada are safe, effective and of high quality and that narcotic and restricted substances are not abused or diverted from legitimate uses.

Therapeutic Products Programme

THERAPEUTIC PRODUCTS PROGRAMME 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 Programme Website
at
www.hc-sc.gc.ca/hpb-dgps/therapeut

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

Également disponible en français sous le titre : *Annexe à "Sélection des doses pour les études de carcinogénicité des produits pharmaceutiques"*
Ajout d'une dose limite avec remarques

Catalogue No. H42-2/67-15-1999E
ISBN 0-662-28442-9

FOREWORD

This guidance 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. The ICH Steering Committee has endorsed the final draft and recommended its adoption by the regulatory bodies of the European Union, Japan and USA.

In adopting this ICH guidance, the Therapeutic Products Programme (TPP) endorses the principles and practices described therein. This document should be read in conjunction with the accompanying covering letter and with the relevant sections of other applicable Programme guidances.

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with the TPP policies and governing statutes and regulations. They also serve to provide review and compliance guidance to TPP staff, thereby ensuring that the Programme's mandate is implemented in a fair, consistent and effective manner.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document ***may be*** acceptable provided they are supported by adequate scientific justification. Alternate approaches should be discussed in advance with the Programme to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that the Programme reserves the right to request information or material, or define conditions not specifically described in this guidance, in order to allow the Programme to adequately assess the safety, efficacy or quality of a therapeutic product. The TPP is committed to ensuring that such requests are justifiable and decisions clearly documented.

Limit Dose

In determining the high dose for carcinogenicity studies using the approaches outlined in this guidance, 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 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 lower rodent to human is equal to about a 25-fold mg/m^2 ratio or a 150-fold mg/kg ratio (150 = 25 x 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.