December 23, 2002

NOTICE

Our file number: 02-122028-691

Withdrawal of *Toxicological Evaluation Guidelines* and Re-issuance of *ICH*[1] *Safety Guidances*

The Health Canada *Toxicological Evaluation* guidances (revised 1996) are being withdrawn following an internal review by a Safety Expert Working Group which concluded that they no longer reflected current toxicological methodologies. Furthermore, the review revealed substantial areas of overlap and inconsistency between these guidances and their more recently adopted ICH counterparts.

The following Health Canada-adopted ICH Safety (Nonclinical) guidances, previously available as part of the *Toxicological Evaluation* guidances, are being re-issued as stand alone documents:

1. S1A Need for Carcinogenicity Studies of Pharmaceuticals
2. S2A Guidance on Specific Aspects of Regulatory Genotoxicity Tests For Pharmaceuticals
3. S3A Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies
4. S3B Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies
5. S5A Detection of Toxicity to Reproduction for Medicinal Products

These ICH guidances have been developed by the appropriate ICH Expert Working Group and have 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 these ICH guidances, Health Canada as observer to ICH, endorses the principles and practices described therein. These documents should be read in conjunction with this covering notice and with the relevant sections of other applicable Health Canada guidances.

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[1] *ICH - International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use*

These and other guidance documents are currently available on the **Therapeutic Products Directorate / Biologics and Genetic Therapies Directorate Website (s)** (**http://www.hc-sc.gc.ca/hpb-dgps/therapeut**). The availability of printed copies of guidance documents may be confirmed by consulting the *Guidelines and Publications Order Forms* (available on the TPD/BGTD Website) or by contacting the Publications Coordinator[2].

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

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Health Canada Santé Canada

GUIDANCE FOR INDUSTRY

Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies

ICH Topic S3B

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Health Products and Food Branch
Guidance Document

Canada

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Également disponible en français sous le titre: Pharmacocinétique: Ligne directrice sur les études de diffusion tissulaire à doses répétées

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, Health Canada endorses the principles and practices described therein. This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidances.

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with the policies and governing statutes and regulations. They also serve to provide review and compliance guidance to staff, thereby ensuring that mandates are 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 relevant program area 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 Health Canada reserves the right to request information or material, or define conditions not specifically described in this guidance, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

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1. INTRODUCTION

A comprehensive knowledge of the absorption, distribution, metabolism and elimination of a compound is important for the interpretation of pharmacology and toxicology studies. Tissue distribution studies are essential in providing information on distribution and accumulation of the compound and/or metabolites, especially in relation to potential sites of action; this information may be useful for designing toxicology and pharmacology studies and for interpreting the results of these experiments.

In the EC, US and Japan, there has been a general agreement on the need to conduct single dose tissue distribution studies as part of the non-clinical programme. These studies often provide sufficient information about tissue distribution.

There has been no consistent requirement for repeated dose tissue distribution studies. However, there may be circumstances when assessments after repeated dosing may yield important information.

This paper provides guidance on circumstances when repeated dose tissue distribution studies should be considered and on the conduct of such studies.

2. CIRCUMSTANCES UNDER WHICH REPEATED DOSE TISSUE DISTRIBUTION STUDIES SHOULD BE CONSIDERED

1. When single dose tissue distribution studies suggest that the apparent half-life of the test compound (and/or metabolites) in organs or tissues significantly exceeds the apparent half life of the elimination phase in plasma and is also more than twice the dosing interval in the toxicity studies, repeated dose tissue distribution studies may be appropriate.

2. When steady-state levels of a compound/metabolite in the circulation, determined in repeated dose pharmacokinetic or toxicokinetic studies, are markedly higher than those predicted from single dose kinetic studies, then repeated dose tissue distribution studies should be considered.

3. When histopathological changes, critical for the safety evaluation of the test substances, are observed that would not be predicted from short term toxicity studies, single dose tissue distribution studies and pharmacological studies, repeated dose tissue distribution studies may aid in the interpretation of these findings. Those organs or tissues which were the site of the lesions should be the focus of such studies.

4. When the pharmaceutical is being developed for site-specific targeted delivery, repeated dose tissue distribution studies may be appropriate.

3. DESIGN AND CONDUCT OF REPEATED DOSE TISSUE DISTRIBUTION STUDIES

The objectives of these studies may be achieved using radiolabelled compounds or alternative methods of sufficient sensitivity and specificity.

Dose level(s) and species should be chosen to address the problem that led to the consideration of the repeated dose tissue distribution study.

Information from previous pharmacokinetic and toxicokinetic studies should be used in selecting the duration of dosing in repeated dose tissue distribution studies. One week of dosing is normally considered to be a minimum period. A longer duration should be selected when the blood/plasma concentration of the compound and/or its metabolites does not reach steady state. It is normally considered unnecessary to dose for longer than three weeks.

Consideration should be given to measuring unchanged compound and/or metabolites in organs and tissues in which extensive accumulation occurs or if it is believed that such data may clarify mechanisms of organ toxicity.

4. SUMMARY

Tissue distribution studies are an important component in the non-clinical kinetics programme. For most compounds, it is expected that single dose tissue distribution studies with sufficient sensitivity and specificity will provide an adequate assessment of tissue distribution and the potential for accumulation. Thus, repeated dose tissue distribution studies should not be required uniformly for all compounds and should only be conducted when appropriate data cannot be derived from other sources. Repeated dose studies may be appropriate under certain circumstances based on the data from single dose tissue distribution studies, toxicity and toxicokinetic studies. The studies may be most appropriate for compounds which have an apparently long half life, incomplete elimination or unanticipated organ toxicity. The design and timing of repeated dose tissue distribution studies should be determined on a case-by-case basis.