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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, **Duration of Chronic Toxicity Testing in Animals (Rodent and Non Rodent Toxicity Testing) ICH Topic S4A**.

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 such 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.

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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 Forms* (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

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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

Duration of Chronic Toxicity Testing in Animals (Rodent and Non Rodent Toxicity Testing)

ICH Topic S4A

Published by authority of the
Minister of Health

Date Adopted by the TPP	1999/12/16
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Therapeutic Products Programme
Guidance Document

Canada

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

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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

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Également disponible en français sous le titre : *Durée des essais de toxicité chronique chez les animaux (essais de toxicité chez les rongeurs et les autres animaux)*

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FOREWORD

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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 that decisions are clearly documented.

1. OBJECTIVE

The objective of this guidance is to set out the considerations that apply to chronic toxicity testing in rodents and non rodents as part of the safety evaluation of a medicinal product. Since guidance is not legally binding, an applicant may submit justification for an alternative approach.

2. SCOPE

This guidance has been prepared for the development of medicinal products with the exception of those already covered by the ICH Guidance on Safety Studies for Biotechnological Products, e.g. Monoclonal antibodies, recombinant DNA proteins.

3. BACKGROUND

During the first International Conference on Harmonisation in 1991, the practices for the testing of chronic toxicity in the 3 regions (EU, Japan, and US) had been reviewed. Arising from this it emerged that there was a scientific consensus on the approach for chronic testing in rodents, supporting the harmonised duration of testing of 6 months. However, for chronic toxicity testing in non-rodents, there were different approaches to the duration of testing.

The lack of harmonised duration led to the need for pharmaceutical companies to perform partially duplicative studies for both 6 and 12 months duration when developing new medicinal products. As the objective of ICH is to reduce or eliminate the need to duplicate testing during development of medicinal products and to ensure a more economical use of material, animal and human resources, while at the same time maintaining safeguards to protect public health, further scientific evaluation was undertaken.

Each of the regulatory authorities in EU, Japan and US undertook a review to determine whether a single duration for chronic toxicity testing in non-rodents could be identified. From this analysis it emerged that in 16 cases a more detailed evaluation of 6 versus 12 months data should be undertaken. This evaluation was conducted as a joint exercise by the competent authorities in the 3 regions.

In some of the cases analysed at the tripartite meetings, there were no additional findings at 12 months. For some other cases, there was not complete agreement among the regulators with respect to the comparability in study design and conduct to allow assessment of whether there were differences in the findings at 6 and 12 months due to duration of treatment alone.

In a number of cases there were findings observed by 12 months, but not by 6 months. It was concluded that these would, or could have been detected in a study of nine months duration. Varying degrees of concern for the differences in findings detected between the studies of different durations were expressed. An agreement on the clinical relevance of these findings could not be reached.

Studies of 12 months duration are usually not necessary and studies of shorter than 9 months duration may be sufficient.

In the EU, studies of 6 months duration in non-rodents are acceptable according to Council Directive 75/318/EEC, as amended. To avoid duplication, where studies with a longer duration have been conducted, it would not be necessary to conduct a study of 6 months.

4. GUIDANCE ON DURATION OF CHRONIC TOXICITY TESTING FOR TRIPARTITE DEVELOPMENT PLAN

Arising from the extensive analysis and review of the above mentioned data in non-rodents and based upon the achievements of ICH1 for testing in rodents, and so as to avoid duplication and follow a single development plan for chronic toxicity testing of new medicinal products, the following studies are considered acceptable for submission in the 3 Regions:

1) Rodents: a study of 6 months duration;

2) Non-rodents: a study of nine months duration.