

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

ICH HARMONISED TRIPARTITE GUIDELINE

DURATION OF CHRONIC TOXICITY TESTING IN ANIMALS
(RODENT AND NON RODENT TOXICITY TESTING)

S4

Current *Step 4* version
dated 2 September 1998

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.

S4
Document History

First Codification	History	Date	New Codification November 2005
S4A	Approval by the Steering Committee under <i>Step 2</i> and release for public consultation.	16 July 1997	S4

Current *Step 4* version

S4	Approval by the Steering Committee under <i>Step 4</i> and recommendation for adoption to the three ICH regulatory bodies.	2 September 1998	S4
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DURATION OF CHRONIC TOXICITY TESTING IN ANIMALS (RODENT AND NON RODENT TOXICITY TESTING)

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 2 September 1998, this guideline is recommended for adoption to the three regulatory parties to ICH

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 Guideline 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.