International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

VICH GL37 (SAFETY)
May 2004
For implementation at Step 7 - Final

STUDIES TO EVALUATE THE SAFETY OF RESIDUES OF VETERINARY DRUGS IN HUMAN FOOD:

REPEAT-DOSE CHRONIC TOXICITY TESTING

Adopted at Step 7 of the VICH Process by the VICH Steering Committee
in May 2004
for implementation by May 2005

This Guideline has been developed by the appropriate VICH Expert Working Group and is subject to consultation by the parties, in accordance with the VICH Process. At Step 7 of the Process the final Guideline is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

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VICH (Safety: Repeat-Dose Chronic Toxicity Testing)

VICH SAFETY WORKING GROUP
STUDIES TO EVALUATE THE SAFETY OF RESIDUES OF VETERINARY DRUGS IN HUMAN FOOD

REPEAT-DOSE (CHRONIC) TOXICITY TESTING

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1. INTRODUCTION

1.1. Objective of the guideline

A variety of toxicological evaluations are performed to establish the safety of veterinary drug residues in human food. The objective of this guideline is to establish recommendations for internationally harmonized repeat-dose (chronic) toxicity testing.

1.2. Background and scope of the guideline

The current guideline is one of a series of guidelines developed to facilitate the mutual acceptance of safety data necessary for the determination of acceptable daily intakes (ADIs) for veterinary drug residues in human food. This guideline was developed after consideration of the current practices for evaluating veterinary drug residues in human food in the EU, Japan, USA, Australia, New Zealand, and Canada. It also took account of available data from sub-chronic and chronic toxicity studies.

While this guideline recommends the framework for chronic toxicity testing of veterinary drugs, it is important that the design of the test remains flexible. It is expected that most veterinary drugs will need to be tested for the adverse consequences of chronic exposure, as there is a potential for consumers to be exposed repeatedly throughout their lifetime. However, this guideline does not preclude the possibility of alternative approaches that may offer an equivalent assurance of safety, including scientifically based reasons as to why chronic toxicity testing may not need to be provided. Within the context of this guideline, tests should be tailored to adequately establish the dose-response relationship and a no-observed adverse effect level (NOAEL) for toxicity seen following chronic treatment.

1.3. General principles

Adequate toxicity testing necessitates the administration of repeated doses to assess the effects of prolonged exposure to a parent compound and/or metabolites, to define the toxic effects of compounds following chronic exposure, and to ascertain the highest dose that does not produce toxicity. All available information on the compound should be utilized in

designing the chronic toxicity test. The data obtained in this test may be used to establish a NOAEL for a veterinary drug.

2. GUIDELINE

2.1. Repeat-dose (chronic) toxicity testing

2.1.1. Purpose

Chronic toxicity testing is performed to (1) define toxic effects based on long-term exposures to the compound and/or its metabolites, (2) identify target organs and toxicological endpoints in relation to dose and/or duration of exposure, (3) determine dosages associated with toxic and biological responses, and (4) establish a NOAEL.

2.1.2. Selection of test species

Species selection should always take account of relevance to human metabolism, pharmacokinetics and pharmacodynamics. If testing in two species is required, one should be a rodent and the other a non-rodent. The generally accepted default rodent species is the rat, and the default non-rodent species is the dog.

A review of available data on a large number of chemicals resulted in differing but equally valid interpretation as to whether one or two species are needed for chronic toxicity testing in the regions. Future data may clarify this issue. In Japan, chronic studies are required in two species. However, with appropriate scientific justification, chronic toxicity testing may be performed in only one species (see Appendix A). In the EU and the USA, chronic testing needs to be performed in the most appropriate species chosen on the basis of all available scientific data, including 90-day studies. The default species is the rat.

2.1.3. Experimental design

Chronic toxicity tests should be conducted in accordance with OECD Test Guideline 452 “Chronic Toxicity Studies” [1].

2.1.4. Pathological examination

Gross necropsy and histopathological examination should be performed in accordance with OECD Test Guidelines 408 ("Repeated Dose 90-day Oral Toxicity Study in Rodents" [2]) and 409 ("Repeated Dose 90-day Oral Toxicity Study in Non-rodents" [3]) with the following amendments:

- the following tissues also need to be examined: bone (sternum, femur and joint), clitoral or preputial gland (rodents only), Harderian gland, lachrymal gland, larynx, nasal cavity, optic nerves, pharynx, and Zymbal gland (rodents only).
- for non-rodents, histopathological evaluations are made on all prescribed tissues plus gross lesions from all animals.

3. REFERENCES

1. OECD. 1981. Test Guideline 452. Chronic Toxicity Studies. In: OECD Guidelines for the testing of chemicals Organization for Economic Cooperation & Development, Paris.

2. OECD. 1998. Test Guideline 408. Repeated Dose 90-day Oral Toxicity Study in Rodents. In: OECD Guidelines for the testing of chemicals. Organization for Economic Cooperation & Development, Paris.

3. OECD. 1998. Test Guideline 409. Repeated Dose 90-day Oral Toxicity Study in Non-rodents. In: OECD Guidelines for the testing of chemicals. Organization for Economic Cooperation & Development, Paris.

APPENDIX A

Justification for Performing Chronic Toxicity Studies in Only One Species When Two are Normally Required

Some criteria for eliminating one species:

1. When it is shown that the mechanism/mode of action that is responsible for the occurrence of toxicity of the test substance in one species cannot be extrapolated to humans.

2. When it is demonstrated that the metabolism of the test substance in one species is not applicable to humans.

If these are unknown, then:

3. When it is demonstrated that the absorption rate from the gastrointestinal tract is extremely low in one species, as compared to the other species.