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

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STUDIES TO EVALUATE THE SAFETY OF RESIDUES OF VETERINARY DRUGS IN HUMAN FOOD: REPEAT-DOSE (90 DAYS) TOXICITY TESTING

Recommended for Implementation
on October 2002
by the VICH Steering Committee

EDITORIAL CHANGES

THIS GUIDELINE HAS BEEN DEVELOPED BY THE APPROPRIATE VICH EXPERT WORKING GROUP AND WAS SUBJECT TO CONSULTATION BY THE PARTIES, IN ACCORDANCE WITH THE VICH PROCESS. AT STEP 7 OF THE PROCESS THE FINAL DRAFT IS RECOMMENDED FOR ADOPTION TO THE REGULATORY BODIES OF THE EUROPEAN UNION, JAPAN AND USA.

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STUDIES TO EVALUATE THE SAFETY OF RESIDUES OF VETERINARY DRUGS IN HUMAN FOOD: REPEAT-DOSE (90-DAY) TOXICITY TESTING

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 90-day repeat-dose 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.

While this guideline recommends the framework for 90-day toxicity testing of veterinary drugs, it is important that the design of the test remains flexible. Within the context of this guideline, tests should be tailored to adequately establish the dose-response and a NOAEL (no-observed adverse effect level) for toxicity following 90-day compound treatment.

1.3. General principles

Adequate toxicity testing necessitates assessment of the effects of repeated exposure to a parent compound and/or metabolites. It should also ascertain a dose that does not produce toxicity. As with other types of toxicity testing, available information on the compound should be utilized in designing the test. Repeat-dose toxicity tests should be performed in sensitive/appropriate species. While species selection should always take account of relevance to human metabolism, pharmacokinetics and pharmacodynamics, the generally accepted default species are the rat and the dog. Exposure should begin early enough in life to encompass the growth phase of the test animals. In general, the highest dose should be sufficient to produce toxicity. The data obtained from this test may be used to establish a NOAEL for a veterinary drug.

2. GUIDELINE

2.1. Repeat-dose (90-day) toxicity test

2.1.1. Purpose

Repeat-dose (90-day) toxicity testing should be performed in a rodent and a non-rodent species in order to (1) identify target organs and toxicological endpoints, (2) provide information that will help the setting of dose levels to be used in repeat-dose (chronic) toxicity testing, and, when necessary, (3) identify the most appropriate species for subsequent repeat-dose (chronic) toxicity testing. A NOAEL should be identified from the results of each repeat-dose (90-day) toxicity test.

2.1.2. Experimental design for a 90-day toxicity test

Repeat-dose (90-day) toxicity tests should be conducted in accordance with OECD Test Guidelines 408 “Repeated Dose 90-day Oral Toxicity Study in Rodents”[1] and 409 “Repeated Dose 90-day Oral Toxicity Study in Non-rodents”[2].

2.1.2.1. Pathological examination

Gross necropsy and histopathological examination should be performed in accordance with OECD Test Guidelines 408[1] and 409[2] with the following exception: for non-rodents, histopathological evaluations are made on a standardized set of tissues plus gross lesions from all animals in all groups.

3. REFERENCES

1. OECD. 1998. Test Guideline 408. Repeated Dose 90-day Oral Toxicity Study in Rodents. In: OECD Guidelines for the Testing of Chemicals. Organisation for Economic Cooperation & Development, Paris.

2. OECD. 1998. Test Guideline 409. Repeated Dose 90-day Oral Toxicity Study in Non-rodents. In: OECD Guidelines for the Testing of Chemicals. Organisation for Economic Cooperation & Development, Paris.