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Guidance for Industry

Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Repeat-Dose (Chronic) Toxicity Testing VICH GL-37

FINAL GUIDANCE

(This version of the guidance replaces the version that was made available in February 4, 2005. This guidance document has been revised to correct the contact information in regard to this document.)

Comments and suggestions regarding the document should be submitted to Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov/. All comments should be identified with the Docket No. 2003D-0466.

For questions regarding this document, contact the Division of Human Food Safety, Center for Veterinary Medicine, (HFV-150), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 240-276-8208.

Additional copies of this guidance document may be requested from the Communications Staff (HFV-12), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm.

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STUDIES TO EVALUATE THE SAFETY OF RESIDUES OF VETERINARY DRUGS IN HUMAN FOOD: REPEAT-DOSE CHRONIC TOXICITY TESTING

Recommended for implementation by May 2005
by the VICH SC at its meeting held in May 2004

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

This final guidance represents the agency's current thinking on the safety of residues of veterinary drugs in human food. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

1. INTRODUCTION

1.1. Objective of the guidance

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

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word "should" in Agency guidances means that something is suggested or recommended, but not required.

1.2. Background and scope of the guidance

The current guidance is one of a series of guidances 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 guidance 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 guidance recommends the framework for chronic toxicity testing of veterinary drugs, it is important that the design of the test remains flexible. This guidance 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 guidance, 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 should include 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. GUIDANCE

2.1. Repeat-dose (chronic) toxicity testing

2.1.1. Purpose

Chronic toxicity testing is recommended 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 consider the relevance to human metabolism, pharmacokinetics and pharmacodynamics. If testing in two species is to be conducted, one should be a rodent and the other a non-rodent. Generally, the default rodent species recommended is the rat, and the default non-rodent species recommended is the dog.

A review of available data on a large number of chemicals resulted in differing but equally valid interpretations as to whether one or two species should be used for chronic toxicity testing in the EU, USA, and Japan. 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 should be performed in the most appropriate species chosen on the basis of all available scientific data, including 90-day studies. The default species recommended 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 should 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 should be 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

In Japan, Justifications 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.