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Guidance for Industry

Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Developmental Toxicity Testing VICH GL32

FINAL GUIDANCE

This version of the guidance replaces the version that was made available in March 19, 2004. This guidance document has been revised to correct the contact information in regard to this document.

This final guidance consolidates developmental toxicity testing recommendations of the EU, Japan, and the USA for establishing the safety of veterinary drug residues in human food.

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. 2002D-0369.

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.

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VICH GL32 (SAFETY: DEVELOPMENTAL TOXICITY)
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For implementation at Step 7 - Final

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

Recommended for Implementation
on October 2002
by the VICH Steering Committee

THIS GUIDANCE 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.

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

Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Developmental Toxicity Testing

This guidance represents the Food and Drug Administration's (FDA's) current thinking for establishing the safety of veterinary drug residues 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 statute(s) and/or regulation(s). 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 number of toxicological evaluations are recommended to establish the safety of veterinary drug residues in human food, including the identification of any potential effects on human prenatal development. The objective of this guidance is to recommend that developmental toxicity assessment be performed according to an internationally harmonized approach. This guidance describes a test designed to provide information concerning the effects on the pregnant test animal and on the developing organism following prenatal exposure to this test animal.

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

The assessment of the potential for developmental toxicity has been identified as one of the key areas to be considered in the evaluation of the safety of residues of veterinary drugs in human food.

The approach to reproductive and developmental toxicity testing of veterinary drugs differs from that adopted by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)[1]. The ICH guidance advocates a combination of three studies, in which dosing covers a number of stages that include, premating to conception, conception to implantation, implantation to closure of hard palate, closure of the hard palate to the end of pregnancy, birth to weaning and weaning to sexual maturity. While such an approach may be considered appropriate for most human drugs, exposure to veterinary drug residues in human food may be long-term, potentially throughout life. For this reason, the combination of the multi-generation, long-term VICH reproduction guideline (GL22), which addresses stages of exposure not addressed in developmental guidelines, and the current guideline (GL32) is believed to be more appropriate for assessing the safety of

veterinary drug residues in human food. This current guidance focuses on one stage of potential exposure, from implantation through the entire period of gestation to the day before caesarean section of the test animal. This guidance provides harmonized guidance on the conduct of a developmental toxicity study for the safety evaluation of veterinary drug residues in human food and is a core recommendation.

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 should be read in conjunction with the guidance on the general approach for the safety evaluation of veterinary drug residues in human food (VICH GL33). This guidance was developed after consideration of the existing ICH guidance for pharmaceuticals for human use on "Detection of Toxicity to Reproduction for Medicinal Products" [1], in conjunction with the current practices for evaluating veterinary drug residues in human food in the EU, Japan, USA, Australia, New Zealand, and Canada.

1.3. Scope of the guidance

This document provides guidance for developmental toxicity testing for those veterinary medicinal products used in food-producing animals. However, it does not limit the studies that may be performed to establish the safety of residues in human food with respect to developmental toxicity. The guidance does not preclude the possibility of alternative approaches that may offer an equivalent assurance of safety, including scientifically based reasons as to why developmental toxicity data may not need to be provided.

1.4. General principles

The aim of developmental toxicity testing is to detect any adverse effects on the pregnant female test animal and development of the embryo and fetus consequent to exposure of the female from implantation through the entire period of gestation to the day before caesarean section. Such adverse effects may include enhanced toxicity relative to that observed in non-pregnant female test animals, embryo-fetal death, altered fetal growth, and structural changes in the fetus of the test animal. For the purpose of this guidance, teratogenicity is defined as the capability of producing a structural change in the fetus considered detrimental to the animal, which may or may not be compatible with life.

The design of the test should be such that if any adverse effects on development are detected, the dose(s) at which they occur and the dose(s) producing no adverse effects are clearly identified. Some observations may suggest further study to fully characterize the nature of the response or of the dose-response relationship.

Traditionally, two species, one rodent and one non-rodent have been used for developmental toxicity testing. Two species are still recommended under the ICH testing guidance for developmental toxicity testing for human drugs.

However, a review of an extensive database for veterinary products indicated that a tiered approach would provide sufficient data to evaluate veterinary drugs for developmental toxicity while reducing the number of animals used in testing[2]. The recommended tiered strategy for developmental toxicity testing of veterinary products for

food animals was developed based on an evaluation of positive and negative teratogenic findings from the published Summary Reports of the EU Committee for Veterinary Medicinal Products and Joint FAO/WHO Expert Committee of Additives (JECFA) reports on veterinary drug residues in food. The data showed: (1) considerable concordance between test species; (2) no single test species was consistently more sensitive; and (3) in cases where the rabbit was more sensitive than the rat, the difference in sensitivity was well within the 10-fold safety factor used to account for interspecies variability.

This recommended approach is described below.

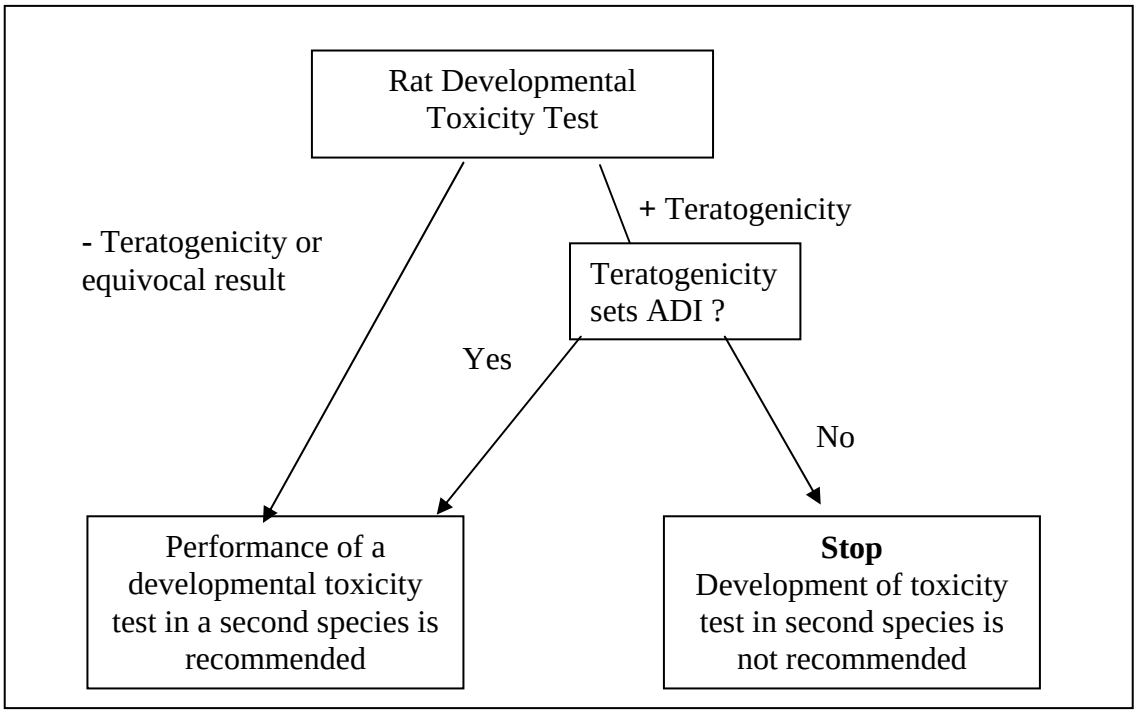
2. GUIDANCE

2.1. Number of species

The tiered approach (see Figure 1) should begin with developmental toxicity testing in the rat. If clear evidence of teratogenicity is observed, regardless of maternal toxicity, testing in a second species would not be recommended, except under the circumstances described in the next paragraph. If a negative or an equivocal result for teratogenicity is observed in the rat, a developmental test in a second species, preferably the rabbit, should be conducted. In the absence of teratogenicity in the rat, a developmental toxicity test in a second species would be recommended even if there were other signs of developmental toxicity in the rat (i.e. fetotoxicity or embryolethality).

If, upon review of all the core studies, it is apparent that the ADI would be based on teratogenicity occurring in the rat, a developmental toxicity study should be conducted in another species in order to determine whether the second species shows greater sensitivity for developmental effects. It is therefore recommended that a tiered approach beginning with a test in the rat be conducted. The outcome of this initial test should indicate whether a developmental test in a second species should be conducted.

Figure 1



2.2. Recommended test protocol

One appropriate reference method for a developmental toxicity test to establish the safety of veterinary drugs used in food-producing animals is the OECD Test Guideline 414 "Prenatal Developmental Toxicity Study". [3] This test guidance includes discussion of the number of the test animals, administration period, selection of doses, observations of the dams, examination of the fetuses and reporting of results.

3. REFERENCES

1. ICH. 1993. ICH Harmonised Tripartite Guidance S5A. Detection of Toxicity to Reproduction for Medicinal Products. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

2. Hurtt, M.E., Cappon, G.D., and Browning, A. (2003). Proposal for a tiered approach to developmental toxicity testing for veterinary pharmaceutical products for food producing animals. Food Chem. Toxicol. 41(5), 611-619.

3. OECD. 2001. Test Guideline 414. Prenatal Developmental Toxicity Study. In: OECD Guidances for the Testing of Chemicals. Organisation for Economic Cooperation & Development, Paris.