European Medicines Agency
Veterinary Medicines and Inspections

CVMP/VICH/485/02-FINAL
Updated in June 2004
London, 16 June 2004

VICH Topic GL32

Step 7

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

ADOPTION BY CVMP FOR RELEASE FOR CONSULTATION	May 2002
TRANSMISSION TO INTERESTED PARTIES	May 2002
END OF CONSULTATION	15 September 2002
FINAL ADOPTION BY CVMP	13 November 2002
UPDATE ADOPTED BY CVMP	16 June 2004
DATE OF COMING INTO EFFECT	*To be determined*

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

DEVELOPMENTAL TOXICITY TESTING

Recommended for Implementation
at Step 7 of the VICH Process
on June 2001
by the VICH Steering Committee

EDITORIAL CHANGES

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 draft will be 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

1. Introduction

1.1. Objective of the guideline

A number of toxicological evaluations are required to establish the safety of veterinary drug residues in human food, including the identification of any potential effects on prenatal development. The objective of this guideline is to ensure that developmental toxicity assessment is performed according to an internationally harmonized guideline. This guideline describes the test designed to provide information concerning the effects on the pregnant animal and on the developing organism following prenatal exposure.

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 guideline 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 is considered appropriate for most human drugs, exposure to veterinary drug residues in human food may be long-term, potentially throughout life. For this reason, this VICH guideline in conjunction with the Reproduction Testing Guideline (see VICH GL22), is believed to be more appropriate for assessing the safety of veterinary drug residues in human food. This guideline focuses on one stage of potential exposure, from implantation through the entire period of gestation to the day before caesarean section. This guideline 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 requirement.

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 should be read in conjunction with the guideline on the general approach for the safety evaluation of veterinary drug residues in human food (VICH GL33). It was developed after consideration of the existing ICH guideline 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 guideline

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 guideline 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 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 include enhanced toxicity relative to that observed in non-pregnant females, embryo-fetal death, altered fetal growth, and structural changes in the fetus. For the purpose of this guideline, 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 require 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 guideline 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 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 approach is described below.

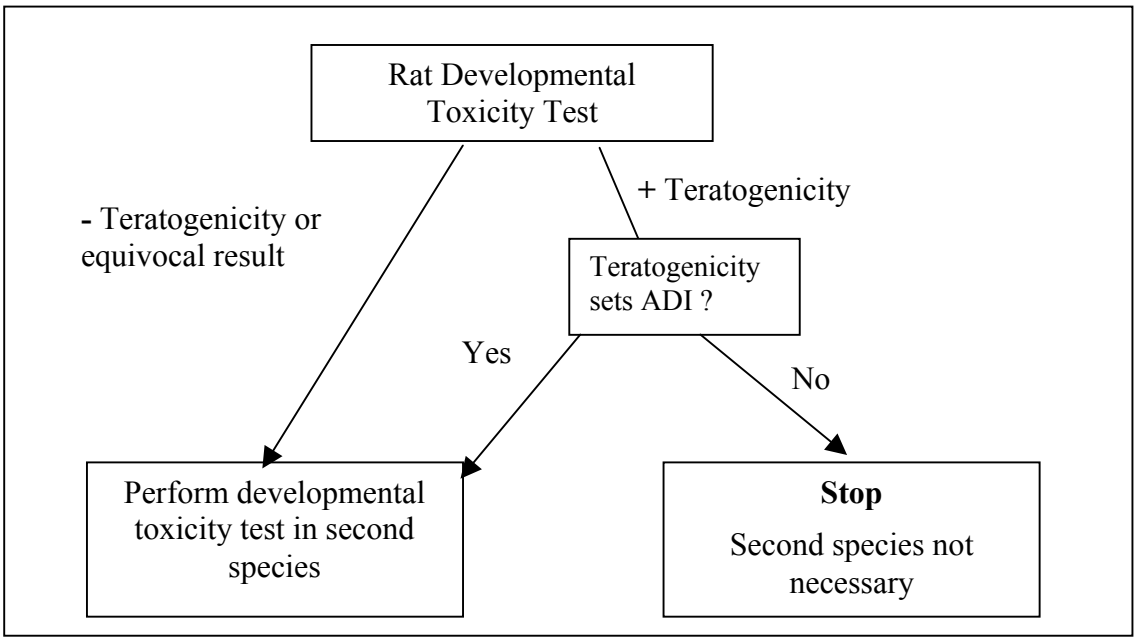
2. GUIDELINE

2.1. Number of species

The tiered approach (see Figure 1) begins 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 required, 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 required 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 will indicate the necessity of a developmental test in a second species.

Figure 1



2.2. Recommended test protocol

The OECD Test Guideline 414 “Prenatal Developmental Toxicity Study” [3] is an appropriate reference method for a developmental toxicity test to establish the safety of veterinary drugs used in food-producing animals. This test guideline 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 Guideline 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. Proposal for a Tiered Approach to Developmental Toxicity Testing For Veterinary Pharmaceutical Products for Food Producing Animals. Food & Chemical Toxicology (submitted).

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