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

VICH GL28 (SAFETY: CARCINOGENITICY)
October 2002
For implementation at Step 7 - Final

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

Recommended for Implementation
on October 2002
by the VICH Steering Committee

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: Carcinogenicity testing

Studies to evaluate the safety of residues of veterinary drugs in human food: Carcinogenicity testing

1. Introduction

1.1. Objective of the guideline

In order to establish the safety of veterinary drug residues in human food, a number of toxicological evaluations are required including the assessment of potential to induce neoplasia. The objective of this guideline is to ensure that the assessment of carcinogenic potential is appropriate for human exposure to veterinary drug residues in human food.

1.2. Background

The assessment of carcinogenic potential has been identified as one of the key areas to be considered in the evaluation of the safety of veterinary drug residues in human food. Exposure to residues of veterinary drugs will usually occur at extremely low levels, but potentially for long periods, possibly over a lifetime. To ensure that substances that could pose carcinogenic potential at relevant exposure levels are adequately assessed, it is necessary to consider a number of issues, including genotoxicity, metabolic fate, species differences, and cellular changes.

1.3. Scope of the guideline

This guideline sets out a data-driven decision pathway to determine the need to conduct carcinogenicity studies. It also provides guidance on the conduct of carcinogenicity studies.

2. Carcinogenicity Assessment

2.1. Overall approach

The decision to undertake carcinogenicity testing should take into consideration, 1) the results of genotoxicity tests, 2) structure-activity relationships, and 3) findings in systemic toxicity tests that may be relevant to neoplasia in longer term studies. It should also take into consideration any known species specificity of the mechanism of toxicity. Any differences in metabolism between the test species, target animal species, and human beings should be taken into consideration.

2.2. Genotoxic compounds

Many carcinogens have a genotoxic mode of action and it is prudent to regard genotoxicants as carcinogens unless there is convincing evidence that this is not the case. Clearly negative results for genotoxicity will usually be taken as sufficient evidence of a lack of carcinogenic potential via a genotoxic mechanism.

2.3. Non-genotoxic compounds

Because it is generally believed that non-genotoxic compounds exhibit a threshold dose for carcinogenicity and human exposure to residues of veterinary drugs is low, non-genotoxic

compounds do not need to be routinely tested for carcinogenicity. Such tests may however be required if, for example, 1) the compound is a member of a chemical class known to be animal or human carcinogens, 2) available systemic toxicity studies with the compound identify potentially preneoplastic lesions or findings indicative of neoplasia, or 3) systemic toxicity studies indicate that the compound may be associated with effects known to be linked with epigenetic mechanisms of carcinogenicity that are relevant to humans.

2.4. *In vivo* carcinogenicity testing

2.4.1. Existing relevant guidelines

The OECD Test Guideline 451 "Carcinogenicity Studies"[1] contains study protocol guidelines and approaches for testing chemicals for carcinogenicity using experimental animals. This document serves as the basis for carcinogenicity testing of veterinary drugs with clarifications outlined in the following paragraphs.

Note: Information derived from a combined assay for carcinogenicity and chronic toxicity (OECD Test Guideline 453 "Combined Chronic Toxicity/Carcinogenicity Studies"[2]) would also be acceptable.

2.4.2. Species selection for long-term carcinogenicity testing

Carcinogenicity bioassays consisting of a two-year rat study and an 18-month mouse study are generally required. With appropriate scientific justification, carcinogenicity studies may be carried out in one rodent species, preferably the rat. A positive response in either test species will be considered indicative of carcinogenic potential.

2.4.3. Number of animals and route of administration

Consistent with OECD Test Guideline 451[1] and common practice, a minimum of 50 rats and/or mice per dose (including concurrent controls) per sex is appropriate for carcinogenicity testing. The route of administration for carcinogenicity testing of veterinary drug residues in human food is oral, preferably dietary. Other routes of administration are not generally relevant for risk assessment of veterinary drug residues in human food.

2.4.4. Dose selection for carcinogenicity testing

2.4.4.1. General

It is recommended that at least three dose levels, in addition to a concurrent control group(s), be used for typical rodent carcinogenicity studies.

2.4.4.2. Dose selection

The high dose should be set to demonstrate a minimum toxic effect without affecting survivability due to effects other than carcinogenicity. Demonstration of a toxic effect in the carcinogenicity study, without compromising survivability or physiological homeostasis, ensures that the animals were sufficiently challenged and provides confidence in the reliability of a negative outcome.

Factors to be considered in establishing other doses include linearity of pharmacokinetics, saturation of metabolic pathways, anticipated human exposure levels, pharmacodynamics in the test species, the potential for threshold effects in the test species, available mechanistic information, and the unpredictability of the progression of toxicity observed in short-term

rodent studies. One generally accepted default paradigm is to set the lowest dose at a level that does not induce significant toxicity and is not lower than 10% of the highest dose.

2.5. In-life observations and pathological examination

In-life observations and pathological examination, consistent with OECD Test Guideline 451[1], are appropriate for carcinogenicity studies of veterinary drugs. Clinical pathology (hematology, urinalysis, and clinical chemistry) is not considered necessary or contributory to the assessment of neoplastic endpoints.

3. REFERENCES

OECD. 1981. Test Guideline 451. Carcinogenicity Studies. In: OECD Guideline for the Testing of Chemicals. Organization for Economic Cooperation & Development, Paris.

2. OECD. 1981. Test Guideline 453. Combined ChronicToxicity/Carcinogenicity Studies. In: OECD Guideline for the Testing of Chemicals. Organization for Economic Cooperation & Development, Paris.

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VICH GL31 (SAFETY: REPEAT-DOSE TOXICITY)
October 2002
For implementation at Step 7 - Final

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

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.

REPEAT-DOSE (90-DAY) 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 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 (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.

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

VICH GL32 (SAFETY: DEVELOPMENTAL TOXICITY)
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STUDIES TO EVALUATE THE SAFETY OF RESIDUES OF VETERINARY DRUGS IN HUMAN FOOD: DEVELOPMENTAL TOXICITY TESTING

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DEVELOPMENTAL TOXICITY TESTING

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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.

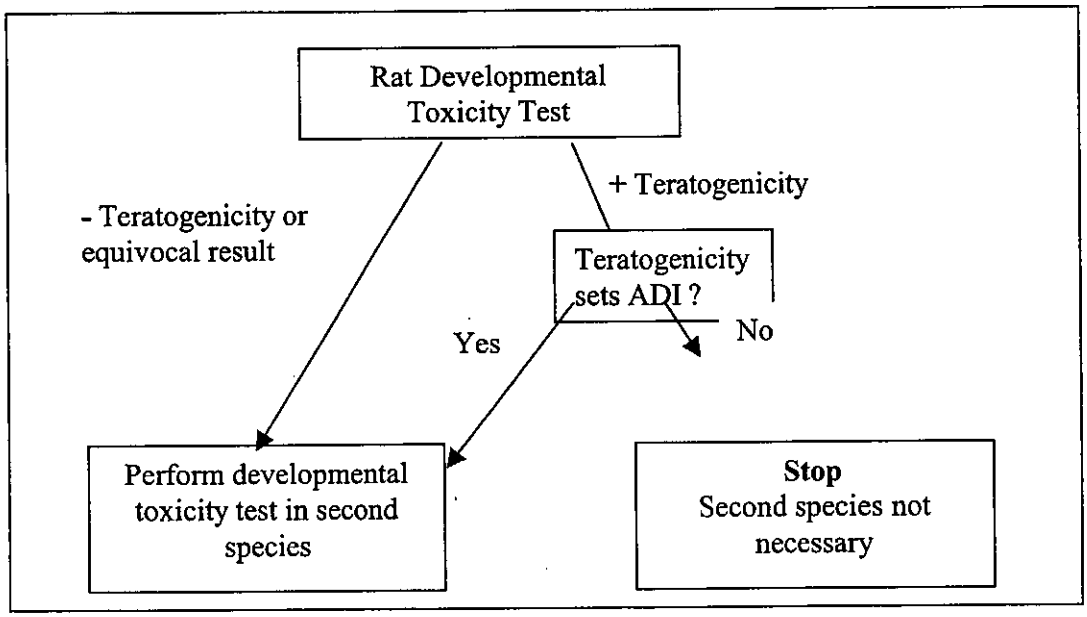
2. GUIDELINE

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.