

Guidance for Industry

Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Carcinogenicity Testing VICH GL28

FINAL GUIDANCE

(This version of the guidance replaces the version that was made available in May 24, 2004. This guidance document has been revised to correct the contact information in regard to this document.)

This final guidance is to ensure that the assessment of carcinogenic potential is appropriate to human exposure through residues of veterinary drugs in 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.fda.gov/dockets/ecomments>. All comments should be identified with the Docket No. 2001D-0357.

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, 301-594-1626.

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VICH GL28 (SAFETY: CARCINOGENICITY)

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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 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.

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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

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

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 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, a number of issues should be considered, including genotoxicity, metabolic fate, species differences, and cellular changes.

1.3. Scope of the guidance

This guidance sets out a recommended data-driven decision pathway to determine whether carcinogenicity studies should be conducted. 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 should 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 should not be routinely tested for carcinogenicity. Such tests may however be recommended 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. OECD Test Guideline 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 recommended. With appropriate scientific justification, carcinogenicity studies may be carried out in one rodent species, preferably the rat. A positive response in either test species should be considered indicative of carcinogenic potential.

2.4.3. Number of animals and route of administration

Consistent with OECD Test Guideline 451¹ and common practice, a minimum of 50 rats and/or mice per dose (including concurrent controls) per sex is recommended for carcinogenicity testing. The route of administration for carcinogenicity testing of veterinary drug residues in human food should be oral, preferably dietary. Other routes of administration are not generally recommended 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 recommended 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. It is recommended 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 451¹, are recommended 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

1. 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 Chronic Toxicity/Carcinogenicity Studies. In: OECD Guideline for the Testing of Chemicals. Organization for Economic Cooperation & Development, Paris.