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Step 7 (after revision at Step 9)

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

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

Recommended for Adoption
at Step 7 of the VICH Process
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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: Carcinogenicity Testing

1. INTRODUCTION	4
1.1. <i>Objective of the guideline</i>	4
1.2. <i>Background</i>	4
1.3. <i>Scope of the guideline</i>	4
2. CARCINOGENICITY ASSESSMENT	4
2.1. <i>Overall approach</i>	4
2.2. <i>Genotoxic compounds</i>	3
2.3. <i>Non-genotoxic compounds</i>	4
2.4. <i>In vivo carcinogenicity testing</i>	5
2.4.1. Existing relevant guidelines	
2.4.2. Species selection for long-term carcinogenicity testing	
2.4.3. Number of animals and route of administration	
2.4.4. Dose selection for carcinogenicity testing	
2.4.4.1. General	5
2.4.4.2. Dose selection	5
2.5. <i>In-life observations and pathological examination</i>	5
3. REFERENCES	6

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 451¹ 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 451¹, are appropriate for carcinogenicity studies of veterinary drugs. The following tissues should be included with those usually sampled: clitoral or preputial gland (rodents only), Harderian gland, lachrymal gland, larynx, nasal cavity, optic nerves, pharynx, and Zymbal gland (rodents only). 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.