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

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Guidance for Industry

Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Testing VICH GL33

FINAL GUIDANCE

(This version of the guidance replaces the version that was made available in May 18, 2004. This guidance document has been revised to correct the contact information in regard to this document.)

This final guidance outlines a testing approach to assure human food safety following the consumption of food products derived from animals treated with veterinary drugs.

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. 2002D-0326.

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

This guidance outlines a recommended testing approach to assure the safety of human food derived from animals treated with veterinary drugs. The tests should provide an adequate amount of toxicological data to ensure human food safety, while reducing the number of animals used in testing and conserving resources. Whenever possible, flexibility, minimum number of animals, as well as alternative *in vivo* and *in vitro* tests have been recommended.

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 hazards associated with the consumption of food containing residues of veterinary drugs are generally assessed in laboratory animals treated with the drugs. International harmonization of testing requirements aims to assure that the development and registration of valuable animal drugs is achieved with maximum efficiency. The efficiency of the approval process has an impact on the expenditure of resources, time from discovery to new product approval, and the introduction of innovative drugs into the market.

Current toxicological testing for veterinary drugs are based on the toxicological tests for human medicines, food additives and pesticides. This guidance suggests use of those tests particularly relevant to the identification of a no-observed adverse effect level (NOAEL) for veterinary drugs.

The appropriateness of a test for the purpose of assessing human food safety is determined by its ability to predict an adverse effect in humans. The recommendation of concise and appropriate tests was of major concern. A recommended testing regimen was selected based on a minimum number of tests after consideration of extensive historical data and a review of widely accepted protocols. To increase the chance of identifying a potential adverse effect, both rodent and non-rodent models should be included in the testing approach. Additional studies, such as tests for effects on human intestinal flora, may be used to evaluate compound specific endpoints. The recommended testing approach is designed to determine a dose that causes an adverse effect and a dose that can be identified as the NOAEL. A NOAEL is used to establish a human acceptable daily intake (ADI), which represents the amount of drug that can be safely consumed by a person on a daily basis for a lifetime.

1.3. Scope of the guidance

The scope of this guidance includes: 1) basic tests recommended for all new animal drugs used in food-producing animals in order to assess the safety of drug residues present in human food, 2) additional tests that may be recommended depending on specific toxicological concerns such as those associated with the structure, class, and mode of action of the drug, and 3) special tests which might be recommended to assist in the interpretation of data obtained in the basic or additional tests.

Guidance on the design of protocols for basic and selected additional tests will be provided in separate VICH guidances. Selection and protocol design of special tests and any other tests will be left to the discretion of the various regulatory authorities and/or drug sponsors.

2. GUIDANCE

Testing should include an assessment of systemic toxicity, reproduction toxicity, developmental toxicity, genotoxicity, carcinogenicity, and effects on the human intestinal flora. In general, oral administration is the route of choice for *in vivo* tests. The guidances do not preclude the possibility of alternative approaches that may offer an equivalent assurance of safety, including scientifically based reasons as to why such data may not need to be provided. Testing described in this guidance should be conducted pursuant to national standards and/or compliance with Good Laboratory Practice.

2.1. Basic tests

2.1.1. Repeat-dose toxicity testing (VICH GL31 and VICH GL*37*)[5,8]

Repeat-dose toxicity testing should be performed to define (1) toxic effects based on repeated and/or cumulative exposures to the compound and/or its metabolites, (2) the incidence and severity of the effect in relation to dose and/or duration of exposure, (3) doses associated with toxic and biological responses, and (4) a NOAEL.

2.1.2. Reproduction toxicity testing (VICH GL22)[2]

Multigeneration reproduction studies are recommended and are designed to detect any effect on mammalian reproduction. These include effects on male and female fertility,

mating, conception, implantation, ability to maintain pregnancy to term, parturition, lactation, survival, growth and development of the offspring from birth through to weaning, sexual maturity and the subsequent reproductive function of the offspring as adults.

2.1.3. Developmental toxicity testing (VICH GL32)[6]

Developmental toxicity testing should be used 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 to the fetus.

2.1.4. Genotoxicity testing (VICH GL23)[3]

A battery of genotoxicity tests should be used to identify substances that have the capacity to damage the genetic information within cells. Substances that are considered to be genotoxic should be regarded as potential carcinogens. Those that cause genetic damage in germ cells also have the potential to cause reproductive/developmental effects.

2.2. Additional tests

These tests are recommended to address safety concerns such as those based on compound structure, class, and mode of action. Some examples of these studies are:

2.2.1. Testing for effects on the human intestinal flora (VICH GL*36*)[7]

For compounds with antibacterial properties, information to determine the effects of residues of the drug on the human intestinal flora is recommended.

2.2.2. Pharmacological effects testing

Some veterinary drugs produce pharmacological effects in the absence of a toxic response or at doses lower than those required to elicit toxicity. The pharmacological NOAEL should be identified and taken into account in the setting of the ADI for the drug.

2.2.3. Immunotoxicity testing

For some classes of drugs such as beta-lactam antibiotics, the potential for the drug to elicit an allergic reaction in sensitive individuals should be investigated. Immunotoxicity testing may be appropriate for other veterinary drugs when the results from other tests indicate a potential immunological hazard.

2.2.4. Neurotoxicity testing

If evidence of a neurotoxic potential is identified in repeat-dose tests, further testing, such as that recommended in OECD Test Guideline 424 “Neurotoxicity Study in Rodents” may be recommended.

2.2.5. Carcinogenicity testing (VICH GL28)[4]

For compounds that are suspected to have carcinogenic potential, carcinogenicity testing by the oral route is recommended. The decision to recommend carcinogenicity testing is based on all available data including results of genotoxicity testing, structure activity relationship (SAR) information and results of repeat-dose and mechanistic studies. It is recommended that carcinogenicity testing be performed using a carcinogenicity bioassay. However, information derived from a combined assay for carcinogenicity and chronic toxicity may also be acceptable.

2.3. Special tests

Special tests, performed to understand the mode of action of the drug and used to aid in the interpretation of, or the assessment of the relevance of the data obtained in the basic and/or additional tests, may also be recommended.

3. REFERENCES

1. OECD. 1997. Test Guideline 424. Neurotoxicity Study in Rodents. In: OECD Guidelines for the Testing of Chemicals. Organization for Economic Cooperation & Development, Paris.

2. VICH (2001). VICH Harmonized Tripartite Guideline GL22. Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Reproduction Toxicity Testing. International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products.

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4. VICH (2002). VICH Harmonized Tripartite Guideline GL28. Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Carcinogenicity Testing. International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products.

5. VICH (2002). VICH Harmonized Tripartite Guideline GL31. Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Repeat-Dose (90-Day) Toxicity Testing. International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products.

6. VICH (2002). VICH Harmonized Tripartite Guideline GL32. Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Developmental Toxicity Testing. International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products.

7. VICH (2004). VICH Harmonized Tripartite Guideline GL36. Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish a Microbiological ADI. International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products.

8. VICH (2004). VICH Harmonized Tripartite Guideline GL37. Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Repeat-Dose (Chronic) Toxicity Testing. International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products.