



European Medicines Agency
Veterinary Medicines and Inspections

London, 20 April 2009
Doc. Ref.: EMEA/CVMP/VICH/486/02-Rev.2

VICH Topic GL33

Step 7

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

ADOPTION BY CVMP	13 November 2002
DATE OF COMING INTO EFFECT	1 October 2003
REVISION ADOPTED BY CVMP	16 June 2004
FURTHER REVISION ADOPTED BY CVMP	20 April 2009
DATE OF COMING INTO EFFECT	1 February 2010

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 47

E-mail: mail@emea.europa.eu <http://www.emea.europa.eu>

© European Medicines Agency, 2009. Reproduction is authorised provided the source is acknowledged.

VICH GL33 (SAFETY: GENERAL APPROACH)

Revision 2 at step 9

February 2009

For implementation at Step 7 – Final

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

Recommended for Adoption
at Step 7 of the VICH Process
in February 2009 by the VICH SC
for implementation in February 2010

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.

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

1. INTRODUCTION.....	3
1.1 <i>Objective of the guideline.....</i>	3
1.2 <i>Background.....</i>	3
1.3 <i>Scope of the guideline.....</i>	3
2. GUIDELINES.....	4
2.1. <i>Basic tests.....</i>	4
2.1.1 <i>Repeat-dose toxicity testing.....</i>	4
2.1.2 <i>Reproduction toxicity testing.....</i>	4
2.1.3 <i>Developmental toxicity testing.....</i>	4
2.1.4 <i>Genotoxicity testing.....</i>	4
2.2. <i>Additional tests.....</i>	5
2.2.1. <i>Testing for effects on the human intestinal microflora.....</i>	5
2.2.2. <i>Pharmacological effects testing.....</i>	5
2.2.3. <i>Immunotoxicity testing.....</i>	5
2.2.4. <i>Neurotoxicity testing.....</i>	5
2.2.5 <i>Carcinogenicity testing.....</i>	5
2.3. <i>Special tests.....</i>	5
3. REFERENCES.....	6

1. INTRODUCTION

1.1. Objective of the guideline

This guideline outlines a 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.

VICH seeks to minimize animal testing by supporting the 3R's principle – replacement (replace with non-animal system or with phylogenetically lower species), refinement (lessen or eliminate pain or distress in animals) and reduction (lower the number of test animals needed) of animals in research. One of the expressed goals of VICH is to strive to eliminate repetitious and unnecessary testing through harmonization of regulatory requirements for the registration of veterinary products, a goal that undoubtedly leads to a reduction in the number of animals used for product development and registration. Whenever possible, flexibility, minimum number of animals, as well as alternative in vivo and in vitro tests have been recommended.

When designing and carrying out the studies recommended below due regard for the welfare of the study animals should be given. The use of animals in the studies described below should adhere to these protocols and should conform to general ethical standards and to the national standards for the use and care of experimental animals.

While the validation of alternative testing protocols falls outside its remit, VICH recognizes that the international status and influence of VICH provide a unique opportunity to encourage the use of validated alternative methods¹. To this end, the Safety EWG that developed these guidelines involving animal experimentation has exercised its responsibility to consider animal welfare, and particularly the possibilities for replacement, refinement and reduction of animal testing.

VICH periodically reviews its guidelines to take into account the development of alternative testing protocols that have been validated, and amends its guidelines where appropriate to assure that they conform to the most recent alternative testing developments.

¹ Validation of alternative testing protocols is the responsibility of regional bodies; ECVAM in Europe, ICCVAM in the USA and JaCVAM in Japan.

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.

The current toxicological testing requirements for veterinary drugs are based on the toxicological tests for human medicines, food additives and pesticides. This guideline indicates 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 selection of concise and appropriate tests was of major concern and a 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 are included in the testing approach. Additional studies, such as tests for effects on human intestinal flora, may be used to evaluate compound specific endpoints. A 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 guideline

The scope of this guideline includes: 1) basic tests required 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 required 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 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 guidelines. 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. GUIDELINES

Testing includes 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 guidelines 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 guideline is subject 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 GL37)^{5,8}

Repeat-dose toxicity testing is 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 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

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 to the fetus.

2.1.4. Genotoxicity testing (VICH GL23)³

A battery of genotoxicity tests is used to identify substances that have the capacity to damage the genetic information within cells. Substances that are considered to be genotoxic are 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 required 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 GL36)⁷

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

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 required for other veterinary drugs when the results from other tests indicate a potential immunological hazard.

2.2.4. Neurotoxicity testing

Evidence of a neurotoxic potential may be identified in repeat-dose tests which may trigger further testing, such as that recommended in OECD Test Guideline 424 "Neurotoxicity Study in Rodents"¹.

2.2.5. Carcinogenicity testing (VICH GL28)⁴

For compounds that are suspected to have carcinogenic potential, carcinogenicity testing by the oral route is required. The decision to require 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 would also be acceptable.

2.3. Special tests

These are 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.

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.
3. VICH (2001). VICH Harmonized Tripartite Guideline GL23. Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Genotoxicity Testing. International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products.
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.