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

115

Guidance for Industry

Safety Studies for Veterinary Drug Residues in Human Food: Reproduction Toxicity Testing VICH GL22

FINAL GUIDANCE

(This version of the guidance replaces the version that was made available in April 21, 2004. This guidance document has been revised to correct the contact information in regard to this document.)

This document provides guidance on reproduction safety studies for veterinary drug residues in human food.

Comments and suggestions regarding the document should be submitted to Dockets Management Branch (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. 00D-1630.

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.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
July 27, 2006

VICH GL22 (SAFETY: REPRODUCTION)
June 2001
For implementation at Step 7

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

Recommended for Implementation
at Step 7 of the VICH Process
on June 2001
by the VICH Steering Committee

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

This final guidance represents the agency's current thinking and does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative method may be used as long as it satisfies the requirements of the applicable statutes and regulations.

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 any risks to reproduction. The objective of this guidance is to ensure international harmonization of reproduction toxicity testing, which is appropriate for the evaluation of risks to reproduction from long-term, low-dose exposures, such as may be encountered from the presence of veterinary drug residues in food.

1.2. Background

There has been considerable overlap in the reproduction and developmental toxicity testing requirements of the EU, Japan and the US, for establishing the safety of veterinary drug residues in human food. Although each region differed on some aspects of detail, all recommended a multigeneration study in at least one rodent species, dosing beginning with the first parental (P_0) group and continuing through at least two subsequent (F_1 and F_2) generations. All three regions also recommended developmental toxicity (teratology) studies. Developmental toxicity studies are the subject of a separate guidance (see VICH GL-32) and will not be further addressed here, except to note that it is no longer recommended that a developmental toxicity phase be included as part of a multigeneration study.

This approach to reproduction and developmental toxicity testing of veterinary products differs in some respects from that adopted by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).[1,2] The ICH guidance advocates a combination of three studies, in which dosing extends for shorter periods to cover adult fertility and early embryonic development, pre- and postnatal development and embryo-fetal development. While such an approach should be considered appropriate for most human medicines, exposure to veterinary drug residues in human food may be long-term, including exposure throughout life. For long-term, low-dose exposure, a multigeneration study, in which dosing extends through more than one generation is considered more appropriate. This guidance provides harmonized guidance on the core recommendation for a multigeneration study for the safety evaluation of veterinary drug residues in human food.

The current guidance is one of a series of guidances 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 by the relevant regulatory authorities. This guidance should be read in conjunction with the guidance on the overall strategy for the safety evaluation of veterinary residues in human food (see VICH GL-33). It was developed after consideration of the existing ICH guidance for pharmaceuticals for human use on “Detection of Toxicity to Reproduction for Medicinal Products”1 and its Addendum, “Toxicity to Male Fertility”[2], in conjunction with the current practices for evaluating veterinary drug residues in human food in the EU, Japan, the US, Australia, New Zealand and Canada.

1.3. Scope of the guidance

This document provides guidance on the core recommendation for a multigeneration study for those veterinary medicinal products that leave residues in human food. However, it does not seek to limit the studies that may be performed to establish the safety of residues in human food with respect to reproductive function. Neither does it 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. This guidance is not intended to cover the information that may be recommended to establish the safety of a veterinary product with respect to reproduction in the target species.

1.4. General Principles

The aim of a multigeneration reproduction toxicity study is to detect any effect of the parent substance or its metabolites 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 maturation and the subsequent reproductive function of the offspring as adults. While multigeneration studies are not specifically designed to detect developmental abnormalities because malformed offspring may be destroyed by the dams at birth, such studies may provide an indication of developmental toxicity if litter size at birth, birth weight or survival in the first few days after birth are reduced.

The study of more than one generation allows detection not only of any effects on adult reproduction, but also any effects on subsequent generations due to exposure *in utero* and early postnatally. Critical aspects of development, which affect adult reproductive capacity, take place prenatally and early postnatally. Adverse effects of sex hormones and their analogues administered during this critical period on reproductive tract development and function in males and females are well known. More recently, studies of other chemicals with endocrine disrupting potential have illustrated the critical role of exposure during the early developmental period on subsequent reproductive function in adult life. This can result in much greater effects on the reproductive capacity of subsequent generations compared with the original parental generation. Studies of more than one generation may also allow detection of reproductive effects due to bioaccumulation of the test substance. Interference with the developing reproductive tract or bioaccumulation may manifest themselves via increasing degree or severity of adverse effects in successive generations.

The design of the study should be such that where any effects on reproduction are detected, the dose(s) at which they occur and the dose(s) giving rise to no adverse effects are clearly identified. Some observations may indicate further studies to fully characterize the nature of the response or of the dose-response relationship.

2. GUIDANCE

2.1. Number of species

A multigeneration test in one species is normally sufficient. In practice, the majority of multigeneration studies for all classes of chemical have been conducted in the rat and the rat will undoubtedly continue to be the species of choice for most future studies. Provided strains with good fecundity are used, rats generally give more consistent reproductive performance than mice. There is also a much larger historical database available for rats. Reference can also be made, if necessary, to the results of other kinetic, metabolic and toxicity tests on rats within the overall test battery for the compound. However, studies on compounds originally used for other purposes but later proposed for veterinary use have sometimes been conducted in mice for historical reasons. Or there may be good scientific reason to conduct a study in mice (e.g. if there is known metabolic similarity to humans). Provided

reproductive performance is satisfactory, there is no general reason why the mouse should not also be an acceptable test species.

Generally, it is recommended that a study in a single rodent species, preferably the rat, be conducted.

2.2. Number of generations

Studies in one generation only have been the normal testing recommended for pharmaceuticals for human use, where the main concerns are exposure during short-term dosing periods. However, multigeneration studies of two or three generations have long been the usual recommendation for food additives and food contaminants such as pesticides and veterinary drug residues. One-generation studies, in which treatment should be terminated when the first generation of offspring is weaned, do not permit assessment of the reproductive performance of animals that have been exposed to the test substance prenatally through to puberty. A study of more than one generation is therefore considered appropriate (see 1.4.).

A study of more than one generation should also allow confirmation of any effects seen in the first generation or clarification of equivocal effects seen at any stage in the test. It may also give an indication of the effects due to bioaccumulation.

The minimum number of generations appropriate to give clear and interpretable results in most cases is considered to be two. While early multigeneration test protocols for some chemical classes recommended a third generation in certain cases, it is now generally considered that effects which are clear in the third generation should also be adequately detected in the second generation.

Generally, it is recommended that a study of two generations be conducted.

2.3. Number of litters per generation

A study with one litter per generation may be sufficient if the results clearly show either absence of any effects or presence of adverse effects with a well-defined no-adverse-effect level. Under certain circumstances however, it may be appropriate to extend the study to produce second litters and it is recommended that results from the study be closely monitored to enable such a decision to be taken, if appropriate. The value of second litters is that they may help to clarify the significance of any apparently dose-related or equivocal effects in first litters, which may be either the result of treatment, or due to chance, or to poor reproductive performance unrelated to treatment. Poor reproductive performance in controls should be minimized by avoidance of nutritional problems and other disturbances, ensuring the weight variation of the parental (P0) generation animals is not too great, and by not mating animals when they are too young or too old.

It is therefore recommended that in general a study with one litter per generation be conducted. It may be appropriate, under certain circumstances mentioned above, to extend the study by producing second litters.

2.4. Recommended study protocol

The OECD Test Guideline 416 “Two-Generation Reproduction Toxicity Study” [3] is an appropriate reference method for a multigeneration study to establish the safety of any veterinary residues in human food. This OECD Test Guideline includes discussion of the selection of test animals, selection of doses, timing of commencement of treatment, timing of mating, observations and reporting of results, all of which are relevant for the testing of veterinary products for the safety evaluation of residues in human food. It is noted that this Test Guideline is currently being updated. The Revised Draft Guideline 416 (1999 et seq.)[4], in addition to the usual observations included in a multigeneration study conducted according to the 1983 Test Guideline 416[3], also includes evaluation

of adult sperm parameters, sexual maturation of offspring and provision for functional investigations of offspring, if such investigations are not included in other studies. The inclusion of these additional parameters is considered appropriate for the testing of veterinary products to modern standards.

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. ICH. 1995. ICH Harmonised Tripartite Guideline S5B. Toxicity to Male Fertility: An Addendum to the ICH Tripartite Guideline on Detection of Toxicity to Reproduction for Medicinal Products. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

3. OECD. 1987. Test Guideline 416. In: Guidelines for the Testing of Chemicals. Two-Generation Reproduction Toxicity Study. Paris, Organisation for Economic Cooperation & Development.

4. OECD. 1999. Test Guideline 416. Two-Generation Reproduction Toxicity Study. Revised Draft Guideline 416, August 1999. Paris, Organisation for Economic Cooperation & Development.