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Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Reproduction Testing (Revision 1)

VICH GL22

Guidance for Industry

Draft Guidance

This guidance document is being distributed for comment purposes only.

This version of the guidance replaces the version made available July 2006. This revision updates the guidance with the inclusion of the extended one-generation reproductive toxicity study as an alternative to the two-generation reproductive toxicity study.

Submit comments on this draft guidance by the dated provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with docket number FDA-2000-D-0784.

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Additional copies of this draft guidance document may be requested from the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville MD 20855, and may be viewed on the Internet at https://www.fda.gov/animal-veterinary, https://www.fda.gov/regulatory-information/search-fda-guidance-documents, or http://www.regulations.gov.

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STUDIES TO EVALUATE THE SAFETY OF RESIDUES OF VETERINARY DRUGS IN HUMAN FOOD: REPRODUCTION TESTING (REVISION 1)

Revision at Step 9

Recommended for Consultation at Step 4 of the VICH Process
in January 2024
by the VICH Steering Committee

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Draft Guidance for Industry

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

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 needed, including the assessment of any effects on reproduction. The objective of this guidance is to ensure international harmonization of reproduction testing that is appropriate for the evaluation of effects on reproduction from long-term, low-dose exposures; these effects may be encountered from the presence of veterinary drug residues in food.

In general, FDA's guidance documents 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

There was a considerable overlap in the reproduction and developmental toxicity testing recommendations of the EU, Japan, and the USA for establishing the safety of veterinary drug residues in human food. Although each region differed in some aspects of detail, all needed a multigeneration study in at least one rodent species, dosing beginning with the parental (P) group and continuing through at least two subsequent (F1 and F2) generations. All three regions also recommended developmental toxicity (teratogenicity) studies. Developmental toxicity studies are the subject of a separate guideline (see GFI #148 (VICH GL32), "Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Developmental Toxicity Testing"[1]) and will not be further addressed in this guidance, except to note that it is no longer recommended that a developmental toxicity phase be included as part of a reproduction toxicity study.

[1] https://www.fda.gov/media/69968/download (July 2006).

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

This guidance is one of a series of guidances developed to facilitate the mutual acceptance by the relevant regulatory authorities of safety data for the determination of Acceptable Daily Intakes (ADIs) for veterinary drug residues in human food. 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 GFI #149 (VICH GL33), "Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Testing"[2]). It was developed after consideration of the existing GFI (ICH) S5(R3) (Ref. 1) and the European Chemicals Agency publication on "Evaluating results from 55 extended one-generation reproductive toxicity studies under REACH: Final report of the EOGRTS review project" (Ref. 2), in conjunction with the current practices for evaluating veterinary drug residues in human food in the EU, Japan, the USA, Australia, Canada, New Zealand, and the UK.

1.3. Scope of the Guideline

This document provides guidance on the core recommendations for a multigeneration study including EOGRTS for those veterinary drugs that leave residues in human food. However, it does not seek to limit the studies that may be performed to establish the safety of veterinary drug 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 needed to establish the safety of veterinary drug residues with respect to reproduction in the target species.

1.4. General Principles

The aim of a multigeneration reproduction toxicity study including EOGRTS is to detect any effects of veterinary drug residues (i.e., the drug substance and/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 the reproduction studies are

[2] https://www.fda.gov/media/69960/download (March 2009).

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.

Reproduction testing intends to detect not only any effects on adult reproduction, but also 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. Effects on reproductive tract development and function in males and females following exposure to sex hormones and their analogues during this critical period are well known. 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 effects in successive generations.

The design of the study should be able to detect any effects on reproduction, the dose(s) at which they occur and the dose(s) giving rise to no adverse effects. The highest dose level should be chosen with the aim to induce toxicity but not death or severe suffering (Ref. 3 and 4).

2. Guidance

2.1. Test Species

A multigeneration test including EOGRTS in one animal species is normally sufficient. In practice, these studies for all classes of chemicals have been conducted in the rat, which will continue to be the species of choice for most 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 test substance.

The rat is the preferred species for testing. If other species (such as mouse) are used, justification should be given. For example, studies on test substances originally used for other purposes but later proposed for veterinary use have sometimes been conducted in mice. Also, there may be scientific reason to conduct a study in other species, such as when the mouse is a more appropriate model due to metabolism in common with the target animal species or similar metabolites formed as those predicted in humans.

2.2. Number of Generations

Studies in one generation have been the normal testing requirement 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 is 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 from the prenatal to pubertal period. A multigeneration reproduction toxicity study including EOGRTS is therefore considered necessary for this assessment and to evaluate the reproductive effects of long-term exposures (see section 1.4. *General Principles*).

A study of more than one generation will also allow confirmation of any effects in the first generation, clarify equivocal effects at any stage in the test, or give an indication of effects that are not observed in the first generation.

The minimum number of generations necessary to give clear and interpretable results in most cases is considered to be two. In some cases, an extended one-generation test protocol as described in OECD Test Guideline 443 may also be an acceptable alternative (Ref. 4). A decision on whether to assess the second (F2) generation should reflect existing knowledge of the chemical being evaluated. Criteria for internal triggers for extending the study to the second generation are described in OECD Guidance Documents 117 and 151 (Ref. 5 and 6).

It is therefore recommended that a study of two generations be conducted as default.

2.3. Number of Litters per Generation

A study with one litter per dam and per generation is sufficient if the results clearly show either absence of any effects or presence of adverse effects with well-defined no-observed-adverse-effect levels (NOAELs). Under certain circumstances, however, it may be appropriate to extend the study to produce second litters. 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, due to chance, or due to poor reproductive performance unrelated to treatment. Poor reproductive performance in controls can be minimized by avoidance of nutritional problems and other disturbances, ensuring the weight variation of the parental (P) generation animals is not too large, 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 dam and per generation be conducted. It may be appropriate, under certain circumstances mentioned above, to extend the study by producing second litters and it is recommended that results from the study be closely monitored to enable such a decision to be taken, if warranted.

2.4. Recommended Study Protocol

OECD Test Guideline 416 (Ref. 3) is an appropriate reference method for a multigeneration study to establish the safety of reproduction of veterinary drug residues in human food. This guideline includes discussion of the selection of test animals, selection of doses, timing of commencement of treatment, timing of mating, observations, evaluation, and reporting of results, all of which are relevant for the testing of veterinary drugs for the safety evaluation of residues in human food.

If an extended one-generation study is planned, OECD Test Guideline 443 (Ref. 4) is an appropriate reference method. In addition to evaluating the reproduction safety, the EOGRTS protocol allows additional investigation on the developing nervous and immune systems. However, VICH considers that the males of the parental (P) generation in the pre-mating period should be dosed to cover at least one complete spermatogenic cycle, e.g., a minimum of 10 weeks in the pre-mating period rather than the 2 weeks for rats, as described in the EOGRTS protocol. It is important to leverage existing data and knowledge and use a weight-of-evidence approach to help determine whether an EOGRTS is appropriate.

If a benchmark dose approach is intended as an alternative to the NOAEL approach, the study design, such as dose selection, number of dose groups and number of animals per group, should be considered accordingly.

3. References

1. GFI (ICH S5(R3)), "Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals," (May 2021).

2. ECHA. 2023. Evaluating results from 55 extended one-generation reproductive toxicity studies under REACH: final report of the EOGRTS review project. ECHA-23-R-04-EN. European Chemicals Agency. (Accessed on May 10, 2024).

3. OECD (2001), *Test No. 416: Two-Generation Reproduction Toxicity*, OECD Guidelines for the Testing of Chemicals, Section 4, OECD Publishing, Paris, https://doi.org/10.1787/9789264070868-en. (Accessed May 10, 2024).

4. OECD (2018), *Test No. 443: Extended One-Generation Reproductive Toxicity Study*, OECD Guidelines for the Testing of Chemicals, Section 4, OECD Publishing, Paris, https://doi.org/10.1787/97892"64185371-en. (Accessed May 10, 2024).

5. OECD. 2011. OECD Environment, Health and Safety Publications, Series on Testing and Assessment, No. 117. Guidance document 117 on the current implementation of internal triggers in Test Guideline 443 for an extended one generation reproductive toxicity study, in the United States and Canada. Organisation for Economic Cooperation & Development. (Accessed May 10, 2024).

6. OECD. 2013. OECD Environment, Health and Safety Publications, Series on Testing and Assessment, No. 151. Guidance document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test. Organisation for Economic Cooperation & Development. (Accessed May 10, 2024).