30 December 2010 Dnro 4848/03.01.01/2010

Clinical trials on medicinal products for veterinary use

Legal bases

Section 88a, paragraph 4 of the Medicines Act (395/1987), as amended by 773/2009

Target group

Those conducting clinical trials on medicinal products for veterinary use

Period of validity

This regulation enters into force on 1 January 2011 and is in force until further notice.

Regulation repealed

National Agency for Medicine regulation 3/2005: Clinical trials on veterinary medicinal products

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1. Definitions

Adverse event (AE) A harmful event in an animal that has been administered a medicinal product or is otherwise being studied, which is not necessarily caused by a medicinal product.

Serious adverse event
An adverse event occurring during the course of a trial, which results in death, is life-threatening, results in significant disability, incapacity or permanent or long-term effects. Human exposure to a medicinal product, causing an adverse effect, also constitutes a serious adverse event.

Adverse reaction
A reaction to a veterinary medicinal product which is harmful and unintended and which occurs at doses normally used in animals for the prophylaxis, diagnosis or treatment of disease or to restore, correct or modify a physiological function.

Serious adverse reaction
An effect occurring in an animal during the course of a trial, which results in death, is life-threatening, results in significant disability, incapacity or permanent or long-term effects. Human exposure to a medicinal product in the course of a study, causing an adverse effect, also constitues a serious adverse reaction (human adverse reaction).

Unexpected adverse reaction
An adverse effect, the nature, severity or outcome of which is not consistent with the summary of the product characteristics (SPC) or the Investigator's Brochure (IB).

Unexpected serious adverse reaction
A serious adverse reaction that is unexpected.

Maximum residue limit (MRL) The maximum permissible concentration of medicinal residues in foodstuffs of animal origin.

Veterinary clinical trial A study designed to investigate the pharmacodynamics (safety and efficacy), the pharmacokinetics (absorption, distribution, metabolism and excretion) or the residues of a veterinary medicinal product in the target species.

Target species The animal species, for the treatment of which a marketing authorisation has been granted for a veterinary medicinal product. In the context of a clinical trial, the target species is the animal species to which the investigational veterinary product is intended for use.

Multi-centre trial A study conducted according to a single study protocol in more than one study site.

Substantial protocol amendment A significant change to the study protocol, affecting the selection, management, safety and welfare of study animals or the procedures performed on the animals, or affecting the quality or safety of the investigational veterinary product, or having an impact on the interpretation of the trial results or the overall scientific value of the trial.

Sponsor An individual, company, institution or organisation, which assumes responsibility for the financing, or financing and management of a veterinary clinical trial. The individual responsible for the study is considered the sponsor where no external sponsor exists.

Food-producing animals Animals bred, raised, kept, slaughtered or harvested for the purpose of producing food.

Investigator's brochure (IB) A summary of pre-clinical, clinical and other information regarding the investigational veterinary product that is significant for the use of the investigational veterinary product in the animal or for user safety.

Supervising veterinarian A scientifically and professionally qualified authorised veterinarian responsible for all aspects of the clinical trial at the trial site. In multi-centre trials, each site must have a dedicated veterinarian in place.

Principal investigator The person responsible for ensuring that the clinical trial is conducted in an appropriate, competent and safe manner and also responsible for the welfare of the study animals.

Study site A scientific or commercial unit, to which the sponsor may allocate tasks and responsibilities related to the conduct of a trial.

Investigational veterinary product is a medicinal product used as an investigational or control product, which may contain an active substance or a placebo. The investigational veterinary product may or may not be subject to a marketing authorisation.

2. Guidance and other legislation on clinical trials on medicinal products for veterinary use

Guidance has been issued within the European Union on good clinical practice in veterinary clinical trials (Guideline on Good Clinical Practices CVMP/VICH/595/98-final)[1].
Further guidance concerning clinical veterinary trials within the EU should be taken into consideration, as published in the following EU guidelines:
The rules governing medicinal products in the European Union, in Eudralex Volume 7A (Guidelines, Veterinary Medicinal Products, General,

[1] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004343.pdf

Efficacy, Environmental Risk Assessment)[2], the European Medicines Agency (EMA) website[3] and the European Pharmacopoeia [4].

For maximum residue limits (MRLs) in foodstuffs of animal origin, please refer to Council Regulation (EEC) 470/2009[5]. Guidance on maximum residue limits for medicinal products for veterinary use is available in Volume 8, Maximum Residue Limits Guidelines[6].

3. Scope of the regulation

This Regulation governs the conduct of clinical trials of veterinary medicinal products in target species. Clinical trials on veterinary medicinal products may be conducted to investigate the product's desired effects, adverse reactions or interactions with other substances, or its pharmacokinetics, metabolism or residue levels. Toxicity studies conducted on laboratory animals are excluded from the scope of this regulation.

4. General requirements

The purpose of veterinary clinical trials must be scientifically justified, and sufficient pharmacological, toxicological and pharmaceutical/immunological information should be available on the investigational veterinary product.

The sponsor has primary responsibility for ensuring that sufficient and scientifically valid information is available to justify the conduct of the trial. The sponsor appoints **a principal investigator** who has sufficient competence and experience for the conduct of a veterinary clinical trial. If the principal investigator is not a licensed veterinarian, a supervising veterinarian must be appointed by the principal investigator to assume responsibility for all veterinary aspects of the trial.

The principal investigator must ensure that all information on the management and monitoring of the animal is available to responsible members of staff in case of an emergency. If the principal investigator chooses to allocate any task within his/her area of responsibility to another party, such as the sponsor or supervising veterinarian, this must be recorded in writing, with individual tasks itemised in detail.

[2] http://ec.europa.eu/health/documents/eudralex/vol-7/index_en.htm
[3] http://www.ema.europa.eu/ema
[4] http://www.edqm.eu/en/Homepage-628.html
[5] http://ec.europa.eu/health/files/eudralex/vol-5/reg_2009-470/reg_470_2009_fi.pdf
[6] http://ec.europa.eu/health/documents/eudralex/vol-8/index_en.htm

5. Advance notification

In accordance with Section 88a, paragraph 1 of the Medicines Act, advance notification of a clinical trial of veterinary medicinal products must be submitted to the Finnish Medicines Agency (Fimea).

The advance notification may be submitted when the sponsor and the principal investigator consider that sufficient information on the relevant medicinal products is available.

Advance notification is required for all those veterinary clinical trials that are intended to be conducted in target species and that involve medicines, which have not been granted a marketing authorisation as a medicinal product for veterinary use, as set out under Section 21 of the Medicines Act.

In cases of uncertainty, those planning a veterinary clinical trial should contact the Finnish Medicines Agency to ascertain whether advance notification is required.

The advance notification is made using the dedicated Finnish Medicines Agency form entitled *Advance notification of veterinary clinical trials*, which is available on the Finnish Medicines Agency website. The form should be signed by the trial sponsor. The principal investigator is required to sign a declaration included in the form.

Multi-centre trials are considered a single trial, requiring one complete notification, including the study protocol and information of the medicinal products to be used and any previous trials conducted on them. In addition, each site participating in a multi-centre trial is required to complete a separate notification, confirming the site's participation in the study and including relevant details for the site. If the study is to be conducted as an international multi-centre trial, this must be stated on the form along with details of what proportion of the work is to be carried out in Finland.

The Finnish Medicines Agency will assess the advance notification and appendices and, where necessary, requests further information. Confirmation of receipt will be sent to the sponsor, indicating the date on which the processing will begin. In the event of a trial involving immunological veterinary medicinal products, the Finnish Medicines Agency will consult the Finnish Food Safety Authority (Evira).

5.1. Documents required

The following documents must be included in the application:

- A covering letter listing all appended documents
- Completed notification form[7]
- Copy of study protocol

[7] A printable version of the form is available on the Finnish Medicines Agency website at www.fimea.fi > veterinary medicines > clinical trials on veterinary medicinal products

- Justification that the trial in question is exempt from the requirement for animal experiment authorisation, as set out in Section 20 of the Act on the Use of Animals for Experimental Purposes (62/2006) or a copy of the authorisation or a copy of an authorisation application
- Where necessary, a summary of the relevant MRL application for clinical trials or confirmation of a confirmed MRL for a clinical trial.

If the veterinary medicinal product has been granted a marketing authorisation in Finland, a reference to the data submitted in conjunction with the application will be sufficient. If no marketing authorisation is in place, the following information should be included:

- Data on the pharmacological or immunological properties of the medicine
- Data on pharmacology and pre-clinical toxicology
- Data on the origin of the active ingredients of the immunological product
- Information on any previous experiments conducted on animals

The extent of the information required will depend on the nature of the trial. For clinical trials involving food-producing animals, the information submitted much be sufficient to allow a withdrawal period to be determined for the investigational veterinary product. The notification must be submitted in Finnish or Swedish. The appendices may be in Finnish, Swedish or English.

The protocol must include the following information:

- The objective and scientific justification for the trial, including ethical and animal welfare considerations
- Design (controlled or uncontrolled), experimental procedures, randomisation and blinding (single or double blind). The application should also include details of the methods adopted to ensure that any control product cannot be distinguished from the investigational product
- An outline of the information available on the study animals, details of the inclusion and exclusion criteria and an assessment of the extent to which the disease in the study animals is representative of the disease under investigation
- Estimated number of trial animals to be used and the scientific justification for it
- Details of how written consent is to be obtained from the study animals' owners or keepers. Copies of the consent form and guidance and other information provided to owners and keepers are to be included in the application
- Recruitment methodology, e.g. full text to be used if volunteers sought through printed or other media
- Dosage of the veterinary medicinal product and possible control product, the method and frequency of administration and the duration of the treatment period
- Control groups and control treatments (placebo, other, etc.)
- Proposed withdrawal period for investigational veterinary products administered to food-producing animals
- Details of any concomitant treatments, including administration instructions provided

- Investigator’s Brochure (IB)
- Instructions provided to veterinarians and other staff
- Details of procedures to be adopted to ensure safe handling of all medicinal products and compliance with instructions provided. Where necessary, instructions on any precautionary measures should also be included
- Description of how the effects and safety of the investigational medicinal products will be observed (including defining and measuring the effects, descriptions and assessment of measurement methods and the timing of measurements);
- Procedures for monitoring adverse events and effects and a description of how they are to be recorded as well as any systematic follow-up survey. The notification should also set out details for precautionary measures to be adopted in an emergency;
- Details of how the study records and animal monitoring forms are to be stored, including where these records and the study codes are to be placed and instructions for how to access the information in an emergency;
- Contact details for the principal investigator and other investigators in the group in the event of an emergency;
- Details of infection control measures adopted for trials involving immunological agents;
- A summary of the procedures for study animal disposal in the event that a preparation or substance is administered to food-producing animals, for which no MRL has been set;
- Notwithstanding the above, for horses treated with a substance without a MRL and which is not included in the Commission’s list of substances subject to a six-month withdrawal period, a description of procedures to ensure exclusion from the food chain should be provided
- Trial timetable
- Handling of results, including statistical methodology
- Care arrangements for the study animals following the conclusion of the trial.

The advance notification can also include details of the marketing authorisation status in other countries and a description of other clinical trials of the product conducted in Finland, if applicable.

6. Commencing the clinical trial

Clinical trials on food-producing animals may be commenced only after the Finnish Medicines Agency has confirmed the required withdrawal period in writing to the sponsor or principal investigator. The Finnish Medicines Agency will communicate this information or issue a request for further clarification within 60 days of receiving the fully completed notification. Clinical trials of immunological agents may not be commenced until written confirmation of clinical trial approval has been issued to the sponsor and principal investigator by the Finnish Medicines Agency. Other trials may be commenced 60 days after the fully completed advance notification has been received by the Finnish Medicines Agency, unless the Agency has requested further information.

7. Consent of study animal owner or keeper

Animals may participate in a clinical trial only if written consent has been obtained from their owner or keeper. Prior to securing consent, the relevant veterinarian or investigator conducting the trial must explain to the owner or keeper, in clear layman's terms, their rights as well as the purpose, nature and methods to be used in the trial. The owner or keeper must also be given sufficient information of the potential adverse reactions and risks involved. With regard to food-producing animals in particular, an explanation is required of how the study animal or products derived from it can be supplied for use as foodstuffs. In addition, the veterinarian or investigator must also clarify to the owner or keeper of food-producing animals that all medicines administered to the animal must be recorded in the animal's medical records. The entry must specify that the medicine has been administered as part of a clinical veterinary trial approved by the Finnish Medicines Agency.

The above information on the trial must be made available in writing and, where practicable, verbally. Consent must be confirmed with the dated signature of the person concerned.

8. Investigational veterinary product

Medicinal products used in veterinary clinical trials must be produced in a pharmacy, subsidiary pharmacy or by an industrial manufacturer, licensed under Section 8 of the Medicines Act. Detailed information on the origin of investigational medicinal products used in veterinary clinical trials, including details of the licensing status and operation of the plant must be submitted to the Finnish Medicines Agency. These data will be used to assess the acceptability of the manufacturing site. A site is, however, not required to adhere to the GMP code.

9. Product labelling

Where feasible, the following information should be displayed on the investigational veterinary product label:

- Trial code number
- Investigational veterinary product code
- Batch number
- Expiry date
- Storage instructions, if special instructions are necessary
- Name of manufacturer and/or sponsor
- Name of investigator and/or trial site
- Study animal identifier
- Withdrawal period for products administered to food-producing animals
- Dosage and posology
- Technical instructions, where required

Where stipulated by the trial protocol, the packaging information must be displayed in Finnish and Swedish.

All packaging used in clinical veterinary trials, including control products, must display the following in Finnish and Swedish: "Kliiniseen tutkimukseen - eläimille"/”För klinisk prövning - för djur" (For veterinary clinical trials only) and "Ei lasten ulottuville eikä näkyville"/"Förvaras utom syn- och räckhåll för barn" (Keep out of reach of children).

10. Distributing investigational veterinary products

Industrial medicinal product manufacturers, pharmaceutical wholesalers and pharmacies may supply medicinal products required for a clinical trial to the principal investigator against a signature.

The principal investigator must ensure that any unused investigational veterinary products are returned to the supplier or are disposed of appropriately.

11. Reporting adverse reactions

The principal investigator must report to the sponsor all serious and unexpected adverse events, excluding those, which under the trial protocol do not require immediate notification. The principal investigator or sponsor must report all serious suspected and confirmed expected and unexpected adverse reactions to the Finnish Medicines Agency within 15 days of receiving information on them.

12. Protocol amendments

In the event that substantial amendments to the protocol are required, the sponsor or principal investigator must notify the Finnish Medicines Agency in writing. The report must include the reasons and scientific justification for the amendment. The sponsor must also inform the Agency in writing of any change to the principal investigator.

If a veterinary clinical trial is repeated, the sponsor must submit all documentation required for clinical trials to the Finnish Medicines Agency. A reference to the previous advance notification will not be sufficient.

13. Reporting trial results

The sponsor or principal investigator must notify the Finnish Medicines Agency of the conclusion of the trial in writing within 30 days. A report on the trial results must be submitted no later than one year following the conclusion of the trial. If the report has been submitted to the Finnish Medicines Agency as an appendix to a marketing authorisation or amendment application, details of where the report can be found in the application will suffice.

The sponsor or principal investigator must provide any information or documentation on the trial, if requested to do so by the Finnish Medicines Agency.

14. Information and guidance

Information and guidance concerning this regulation is available from the Finnish Medicines Agency on request.

15. Other considerations

The Finnish Medicines Agency notifies the Ministry of Agriculture and Forestry and Provincial State Offices of all prospective veterinary clinical trials.

16. Entry into force

This regulation entered into force on 1 January 2011.

Director General Sinikka Rajaniemi

Veterinary Officer Kristina Lehmann

Recipient list

Medicinal product manufacturers
Pharmaceutical wholesalers
Staff responsible for placing proprietary medicinal products on the market
Finnish Food Safety Authority (Evira)
Finnish Game and Fisheries Research Institute
MTT Agrifood Research Finland
Faculty of Veterinary Medicine, University of Helsinki
Veterinary Teaching Hospital, University of Helsinki
Faculty of Agriculture and Forestry, University of Helsinki
Faculty of Pharmacy, University of Helsinki
Faculty of Health Sciences, University of Eastern Finland
Department of Biosciences, Division for Natural Sciences and Technology, Åbo Akademi University
Animal Experiment Board

For information

Ministry of Social Affairs and Health
Ministry of Agriculture and Forestry
Eläinlääketeollisuus ry
Pharmaindustry Finland
Association of Pharmaceutical Distributors (ATY)
Finnish Veterinary Association
Consumer Ombudsman
Federation for the Protection of Animals (Animalia)
Finnish Federation for Animal Welfare Associations (SEY)