LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

GUIDELINES ON

APPLICATION FOR

CLINIAL TRIALS OF VETERINARY MEDICINAL PRODUCTS IN ANIMALS

January 2022
Version 10

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1. LEGISLATION

Clinical trials of veterinary medicinal products are regulated in Part XI of the Danish Medicines Act No. 1180 of 12 December 2005 (last amended by act no. 534 of 17 June 2008).

A clinical trial of medicinal products can only be conducted if the Danish Medicines Agency has given an authorisation for the trial, cf. section 88(1) of the Danish Medicines Act (Annex 1).

This applies to all prospective clinical trials (including pilot studies) intended to systematically discover or verify knowledge concerning medicinal products' clinical effect and/or side effects (pharmacodynamics) and to investigate the fate of medicinal products in the animal organism (pharmacokinetics). Approval must be obtained for clinical trials for all types of medicinal products in any of the product's clinical assessment phases - irrespective of whether the medicinal product to be trialled has been granted a marketing authorisation.

The obligation to apply also applies to radiopharmaceuticals, herbal medicinal products as well as strong vitamins and mineral products classified as medicinal products.

According to section 2 of the Danish Medicines Act, a medicinal product means “any product that
(i) is presented as a suitable product for the treatment or prevention of disease in human beings or animals, or
(ii) may be used in or administered to humans or animals to restore, change or modify physiological functions by having a pharmacological, immunological or metabolic effect or to make a medical diagnosis.”

The Danish Medicines Act also applies to contraceptives that are not comprised by section (2) or by the Act on medical devices, cf. section 3(2) of the Danish Medicines Act.

Studies with animal models (toxicological, pharmacodynamic, pharmacokinetic, etc. studies in test animals other than the target species, e.g. rats, mice, etc.) are not covered by section 88(1) of the Danish Medicines Act, and the conduct of such studies is therefore not subject to approval by the Danish Medicines Agency.

Trials in which the medicinal product is intended only to produce a known and well-established effect (is used as a tool) and serves no actual medical purpose, and where there is therefore no collection of data on the medicinal product's pharmacodynamics or pharmacokinetics (e.g. studies to clarify physiological mechanisms) do not fall under the definition of a clinical trial and consequently are not to be approved by the Danish Medicines Agency.

For further information concerning a possible obligation to apply, please call +45 4488 9123, or write to:

Danish Medicines Agency
Clinical Trials
Axel Heides Gade 1
2300 Copenhagen S
Email: kf@dkma.dk

Clinical trials with medicinal products must only be started when the Danish Medicines Agency has given its approval. Approval is granted if we assess that the expected therapeutic benefits can justify the risks associated with the trial.

2. FEES

The Danish Medicines Agency charges a fee for the review of applications for the approval of a clinical trial and a fee for the review of amendments to an approved trial protocol in accordance with the executive order on fees for clinical trials of 1st of July 2018.
If several amendments to the same trial protocol are applied for, only one fee is charged.

According to the executive order, fees must be paid no later than one month after the date of the invoice from the Danish Medicines Agency.

There is no legal basis for the Danish Medicines Agency to deviate from the rules regarding fees.

For further information, please see "Fees for clinical trials" on the website of the Danish Medicines Agency.

3. THE APPLICATION

The application can be submitted using a special application form (please see Annex 2). The form is also available as an e-form in Danish, which can be found at the website of the Danish Medicines Agency under “Clinical trials".

An application for authorisation of a clinical trial must be submitted to the Danish Medicines Agency by the person, company or institution undertaking the responsibility for the initiation, management and possibly the financing of the clinical trial (i.e. the sponsor), cf. section 88(3) of the Danish Medicines Act. In this connection, the sponsor has the possibility of arranging representation by another person.

The sponsor or sponsor's representative must have a permanent address in an EU/EEA country, cf. section 88(7) of the Danish Medicines Act.

Please send the application to:

Danish Medicines Agency
Clinical Trials
Axel Heides Gade 1
2300 Copenhagen S
Denmark

3.1 Notification to manufacturer

The sponsor must notify the manufacturer of the medicinal product or the manufacturer’s representative of the application at the same time as the application is submitted to the Danish Medicines Agency, cf. section 88 of the Danish Medicines Act. This allows the manufacturer to raise objections to the sponsor before initiation of the trial. The information given in the notification to the manufacturer or representative should account for the use of the medicinal product in such a manner that the manufacturer/the manufacturer’s representative can gain a clear understanding of how the medicinal product will be employed in the trial. The Danish Medicines Agency requests that a copy of this notification be enclosed with the application for approval of a clinical trial.

3.2 Supplementary notification in connection with multicentre trials

For trials concerning more than one site in Denmark, one full application must be submitted by the sponsor of the trial. From each of the other participating trial sites (preferably jointly and simultaneously with the submission of the application) a special supplementary notification form (Annex 3) is to be ubmitted. An electronic Danish version of the supplementary notification form is available at the website of the Danish Medicines Agency under “Companies, Clinical trials".

If the responsible investigator/veterinarian stops serving as study director, the sponsor must submit an application for an amendment to the trial protocol, and a supplementary notification must be submitted to the Danish Medicines Agency by the succeeding veterinarian to be responsible for the practical execution of the trial at the concerned trial site.

4. CONTENTS OF THE APPLICATION

As part of the review process, the Danish Medicines Agency requests that the following documents and information be submitted with an application for the approval of a clinical trial:

- Application form (Annex 2),
- Supplementary notification forms, if relevant, (Annex 3),
- Trial protocol
- Documentation, cf. section 7,
- Information about species and quantities of active substances (Annex 4),
- Form specifying invoicing details
- A copy of the letter of notification sent to the manufacturer pursuant to the Danish Medicines Act section 88, cf. section 3.1

The Danish Medicines Agency validates the application on receipt, and if documents, etc. are missing, we request the applicant to provide the missing components. If the application is considered invalid and there is no documentation that the expected therapeutic benefit justifies the risk associated with the trial, the likely outcome is that the application will be refused.

5. TRIAL PROTOCOL

Please refer to ”VICH Topic GL 9 (GCP) Guidance on Good Clinical Practices" available at: .
http://www.vichsec.org/component/attachments/attachments/142.html?task=download

According to REGULATION (EU) 2019/6 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC, Article 9, Section 6, must data stemming from clinical trials conducted outside the Union only be taken into consideration for the assessment of an application for a marketing authorisation if those trials were designed, implemented and reported in accordance with the international guidelines on good clinical practice of the VICH.

When the Danish Medicines Agency reviews an application for the approval of a clinical trial, it generally requires that the trial protocol contain the details listed below, some of which may be enclosed as separate annexes to the trial protocol if local conditions so require.

5.1 General information

1. Title and date of the protocol and, if available, the protocol code. All annexes are numbered and dated.
2. Name and address of sponsor in Denmark.
3. Name, title, professional background, address and telephone number of the sponsor’s medical advisers of the trial in Denmark.
4. Description as well as name and address of the farm(s)/veterinary clinic/departments where the trial will be conducted.
5. Name and title of the responsible investigator (veterinarian with a Danish authorisation) in Denmark as well as address and telephone number of the concerned trial centre.
6. In connection with multicentre trials, the name and title of the coordinating investigator in Denmark of all centres (farms), as well as addresses and telephone numbers of all trial centres (farms).
7. Names and addresses of laboratories and/or institutions in Denmark involved in the trial.
8. A declaration stating that the trial will be conducted in compliance with the protocol and applicable regulatory requirements/legislation.

5.2 Background information

1. Product name(s) and description of the active substance(s).
2. Summary of relevant results from non-clinical and already completed clinical trials.
3. Summary of known and potential risks that the animals will be exposed to.
4. Description and justification of dose, route of administration and dosing frequency as well as treatment period.
5. Description of the population.
6. References to literature and data that are relevant and form the basis for the trial.

5.3 Purpose

A detailed description of the purpose of the trial with references to relevant literature.

5.4 Study plan/design

1. A clear indication of the start and end dates of the trial as well as the trial period, treatment period and observation period.
2. Description of the type of trial (controlled, pilot/design (e.g. parallel groups, cross-over design)) and the chosen blinding method.
3. Description of measures taken to reduce or eliminate bias, including:
   - Randomisation; description of randomisation method – including procedure and practical planning.
   - Blinding; description of blinding (single or double blind study) as well as practical procedures to ensure blinding.
4. Description of the trial treatment, dose, route of administration, frequency, packaging and labelling of the investigational product, including placebo and reference product (see section 7.2 for details about documentation requirements for the applied products and section 8 for details about labelling requirements).
5. Description of the rules for stopping a trial or discontinuing treatment.
6. Procedures applied to keep stock of the investigational product, including placebo and reference product.
7. Information about where the randomisation code will be stored as well as rules and procedures for code breaking.

5.5 Selection of animals and criteria for inclusion and exclusion

1. Description of animal species, including details of age, gender, race, etc.
2. Description of inclusion criteria – including methods for ensuring their fulfilment.
3. Description of exclusion criteria – including a description of procedures for removing animals from the trial.
4. Description of animal identification.

5.6 Treatment

1. Description of the treatment, including the product name(s) of all products, dose, route of administration, frequency and treatment period(s), marketed/non-marketed and justification for applied doses.
2. Rules for concomitant treatment/medication before and/or during the trial.
3. Description of measures taken/rules established for ensuring compliance with the treatment regimen for dose, duration of treatment, etc.
4. Description of the treatment of control group(s) or control period(s) (placebo, other products, no treatment etc.)

5. Justification for the time plan – e.g. in light of the extent to which the safety of the active substances/medicinal products has been tested, the concerned disease's life cycle and the expected duration of treatment.
6. Proposals and justification for withdrawal periods. A withdrawal period must also be established for trials with an observation period following the administration of the last dose of the medicinal product, in case animals are excluded from the trial.

5.7 Efficacy evaluation

1. Specification and justification for efficacy parameters.
2. Methods for time points for measurement, registration and analysis of efficacy parameters.
3. Description of special analyses and/or tests that will be performed (pharmacokinetic and clinical investigations, laboratory tests, etc.).

5.8 Adverse incidents/reactions

1. Methods and time points for registration and analysis of adverse incidents/reactions.
2. Information about where the trial code is stored and how to gain access to it in emergencies.
3. Measures established to avoid and deal with complications.
4. Procedures for registration and reporting of adverse incidents/reactions – indicating the person(s) responsible for reporting and the person(s) to whom reporting must be made.

5.9 Practical details

1. A detailed, specified plan of the different steps and procedures established to ensure optimum control and monitoring of the trial.
2. Specification of and instructions for expected deviations from the protocol, e.g. in the case of lack of efficacy.
3. Establishment and coordination of tasks and distribution of responsibilities between persons involved in the trial.
4. Staff instructions - including a description of the trial concerned.
5. Addresses, telephone numbers, etc. of the responsible persons must be kept available for the staff, so that they can reach the investigator/sponsor at all times.

5.10 Handling of data

1. Procedures for handling and dealing with clinical records of treatments, effects, adverse incidents and reactions having occurred during the trial.
2. Procedures for storing special patient lists and patient files for each animal/groups of animals enrolled in the trial. The files must make it possible to clearly identify each animal/group of animals.
3. A copy of the registration forms for each individual animal must be enclosed with the application.

5.11 Evaluation of data

1. Definitions of criteria for measurement of the animal's response, e.g. objective measurements and a scoring system and other methods for measurement of clinical response.
2. Definitions of methods for the establishment and measurement of efficacy.
3. Description of how to process and report information on animals excluded during the course of the trial.

5.12 Statistics

1. Description of statistical methods to be applied.
2. Justification for the planned number of enrolled patients – including considerations/calculations of the power of the trial and clinical justification (the minimum efficacy needed to reach clinical relevance).
3. Description of the statistical unit.
4. The level of significance applied.

5.13 Summary and annexes

The trial protocol must contain a summary and relevant annexes (e.g. staff instructions, description of special procedures).

5.14 Literature references

A list of the literature referred to in the protocol must be enclosed with the application.

6. INSPECTION

The Danish Medicines Agency inspects clinical trials. The Danish Medicines Act entitles us to inspect any company that is or has been carrying out clinical trials of medicinal products, and we may demand all information necessary, including written material, for our control activity. On the presentation of appropriate identification and without a court order, the Danish Medicines Agency has access to companies, hospitals, medical practices and other places affected by the conduct of the trial, cf. Section 90(2) of the Danish Medicines Act. Among other things, we check that the trial is conducted in compliance with the protocol and that the terms and conditions of the trial are observed.

7. DOCUMENTATION

The Danish Medicines Agency generally requires that applications are accompanied by documentation for the product's chemical, pharmaceutical, pharmacological and toxicological properties as well as information about previous clinical experience data related to the product. Where trials on food-producing animals are concerned, we will also emphasise the importance of enclosing results from pharmacokinetic studies for the use of setting withdrawal periods.

Documentation must be in the form of summaries. If we consider it necessary for the review process, we will request the submission of full reports or other additional information.

In the case of medicinal products comprised by a marketing authorisation or medicinal products for which the above-mentioned documentation has already been submitted in connection with a previous application and approval of a clinical trial, it will usually be sufficient to refer to these previously submitted documents.

7.1 Manufacturers

In the case of medicinal products not comprised by a marketing authorisation in Denmark, we ask that all manufacturers be listed on the application form. For products marketed and purchased in Denmark,

it is sufficient to specify the name of the marketing authorisation holder as well as to provide information about the place where a blinded study and labelling, if relevant, will take place.

In this context, manufacture means all the processes involved in producing the finished product and the individual sub-processes, e.g. preparation, mixing, processing, decanting, filling, packaging, labelling and batch release.

7.2 Pharmaceutical-chemical documentation

In the case of pharmaceutical forms and/or strengths for which no marketing authorisation has been granted in Denmark and placebo products, information about the qualitative and quantitative composition must be submitted. This information can be provided using a "cataloguing form" (Annex 4), also available as an e-form (https://laegemiddelstyrelsen.dk/da/godkendelse/kliniske-forsoeg/ansoegning-om-kliniske-laegemiddelforsoeg-med-mennesker/katalogisering-af-indholdsstoffer/vejledning-til-skema-til-brug-ved-katalogisering-af-indholdsstofferne-i-farmaceutiske-specialiteter-mv/) or it may appear from other annexes submitted with the application.

Please specify all raw materials, e.g. in the form of a pharmacopoeia monograph (Ph. Eur., BP, USP, JP etc.). The specifications establish requirements for the raw material's purity, content of impurities as well as analytical tests, etc.
If no pharmacopoeia exists, reference to food specifications is accepted.
Only in cases where neither of the mentioned specifications exist will internal specifications be accepted, in which case they must be enclosed with the application.

In the case of reference products marketed and purchased in an EU/EEA country, the USA or Japan, the package leaflet from the concerned country can be submitted instead of the "cataloguing form". This package leaflet must provide information about the qualitative content of the product as well as the licensed indication and dose applied in the country concerned. We ask that the package leaflet be in English or translated to Danish.

If technical aspects of a trial or other reasons make it necessary to alter a marketed medicinal product's pharmaceutical form, appearance or composition, the applicant is requested to submit information on the full qualitative and quantitative composition and considerations about bioequivalence together with results from in vitro tests (in case of compressed medicinal products, e.g. in the form of dissolution tests) for both the marketed and altered formulation.

In the case of biotechnological medicinal products and medicinal products manufactured based on biological material for which no marketing authorisation has been granted, the applicant is requested to submit information about manufacturing method, including documentation for washing procedures to remove/inactivate virus, DNA as well as other biological/chemical impurities arising in production. The information must be presented in accordance with the relevant EU guidelines. Unauthorised vaccines must be released pursuant to the current requirements established by the Danish National Veterinary Institute DTU for absence of extraneous agents.

If this information has previously been submitted to the Danish Medicines Agency, it is sufficient to refer to this material, if possible, indicating the case number allocated by the Danish Medicines Agency.

8. LABELLING

The Danish Medicines Agency requires the labelling to be in Danish and include the following information:

1. ”Klinisk forsøg” (Clinical trial) and ”Lægemiddel til dyr” (Veterinary medicinal product).
2. Pharmaceutical form, cf. Danish Drug Standards.
3. Code name. Packages for use in unblinded clinical trials may, instead of a code name, be labelled with the name of the product or the active substance. If so, the strength must also be specified.
4. Pack size. Specification of content in g, ml and – for medicine in doses – number.
5. Batch number or another specification allowing for an unambiguous identification of the quantity of a medicinal product manufactured at the same time and intended for use in a clinical trial. In case of subsequent findings of or suspicions about defects in the product, it must thus be possible to withdraw all defective items. The batch numbering must allow for a blinding, if relevant.
6. Name and address of the sponsor. In addition, the Danish representative may be listed (cf. section 18 of the Danish Medicines Act).
7. Expiry date. E.g. ”*Anvendes inden*” / ”*Anvendes før*” (use by). Please specify any other details about limited durability as required and where relevant.
8. Storage conditions, if necessary.
9. Dosage.
10. Name of the person responsible for the trial.
11. Withdrawal period.
12. Small medicine containers, such as vials, that do not allow for complete labelling must as a minimum be labelled with the name/code name of the product and a specification of contents. Individually packaged medicine in doses must similarly be provided with a label identifying each unit.

9. DISPENSING/SALE

Section 11 of the Danish Medicines Act stipulates that no marketing authorisation is required for medicinal products for clinical trials subject to Part XI of the said Act. Under the explanatory notes to the Danish Medicines Act, such medicinal products may be sold and distributed for use in clinical trials approved pursuant to section 88 of the Danish Medicines Act.

When the Danish Medicines Agency has granted its permission for execution of the trial, products may be distributed/sold to:

- the veterinarian/investigator responsible for the practical execution of the trial
- pharmacies with a view to onward distribution to the person responsible for the practical execution of the trial.

Import and export (from third countries) as well as manufacture of medicinal products for clinical trials may only be undertaken by companies authorised pursuant to section 39 of the Danish Medicines Act. The authorisation must include manufacture of medicinal products for clinical trials. The medicinal products must be manufactured under the rules on Good Manufacturing Practice (GMP).

Section 92 of the Danish Medicines Act stipulates that medicinal products for clinical trials must comply with the current standards for good manufacturing practice. Compliance in this respect is comprised by the Danish Medicines Agency's inspection of clinical trials under section 90(2) of the Danish Medicines Act.

No investigational medicinal products may be distributed to the investigator until the Danish Medicines Agency has approved the trial. Distribution to a pharmacy may take place prior to trial approval, but the pharmacy must not dispense any of the medicinal products concerned to the investigator before the trial is approved. We furthermore refer to Danish executive order no. 1242 of 12 December 2005 on the manufacture and import of medicinal products and intermediary products, as amended by executive order no. 1101 of 12 November 2008 (the executive order on GMP) and to Annex 13.

Distribution of narcotics for use in clinical trials is only permitted when the Danish Medicines Agency has granted its approval, cf. section 4(5) of Danish executive order no. 749 of 1 July 2008 on euphoriant substances. Likewise, companies' receipt and storage of euphoriant substances requires that the Danish Medicines Agency has granted its permission, cf. the above executive order.

10. INFORMED CONSENT

Before any animal participates in a clinical trial, the animal owner must give his/her consent after being thoroughly informed about the trial both orally and in writing.
The information to the animal owner must include the following details:

1. That the animal will participate in a trial with other animals.
2. The purpose of the trial.
3. The main aspects of the trial – including if it involves randomisation, the procedures followed, periods without treatment, and if any unlicensed medicinal products or blinded products are used (placebo).
4. Predictable risks and drawbacks – including any undesired effects (adverse reactions).
5. How the trial is expected to benefit the animal concerned and/or may benefit other animals in future.
6. Alternative treatment options, if the animal owner refuses participation.

and for animals for consumption

7. Withdrawal periods.

The information must clearly state that consent is voluntary and may be withdrawn at any time.
The consent must be in writing.

It is usually not necessary to enclose the written information, but the Danish Medicines Agency may demand it to be submitted.

11. TRIAL INITIATION AND CONDUCT

11.1 Authorisation

The trial may be initiated once the Danish Medicines Agency has granted its permission. No medicinal products to be used in the trial may be distributed to the investigator(s) responsible for the trial until the permission is granted.

The Danish Medicines Agency is entitled to set terms for the trial to the sponsor and the veterinarian responsible for the practical conduct of the trial (investigator), cf. section 90(1) of the Danish Medicines Act. It is a condition that the sponsor and veterinarian/investigator comply with any such terms for the trial.

11.2 Amendments

Any later additions and amendments to the protocol must be sent to and approved by the Danish Medicines Agency before implementation.
For example, the following amendments must be sent to and approved by the Danish Medicines Agency:

- dose
- duration of treatment
- number of animals
- other age group of animals
- trial design
- inclusion and exclusion criteria
- efficacy parameters and sampling procedures
- product (original/parallel imported (specify country of origin for the latter)).

If any animals are included in a trial before the change is implemented, please submit considerations as to whether the change may influence the final outcome of the trial.

We ask that the application includes a protocol number and the date of the latest accepted trial protocol. Please also send a clear specification of all amendments. The sponsor must sign for approval of all amendments, and no amendments may be implemented until the Danish Medicines Agency has approved them.

Major amendments may cause the material submitted to be considered as a new application.

If the trial is terminated earlier than planned, information about why the trial was terminated prematurely and the reason for this must be notified to the Danish Medicines Agency. Section 89(2)(ii) of the Danish Medicines Act stipulates that the sponsor must inform the Danish Medicines Agency within 15 days if a trial needs to be terminated earlier than planned and give the Danish Medicines Agency a clear reason for the interruption.

12. ADVERSE REACTIONS/INCIDENTS

The sponsor must immediately inform the Danish Medicines Agency if any suspected unexpected and serious adverse reactions occur during a trial, cf. section 89(2)(i) of the Danish Medicines Act. An unexpected adverse reaction is an adverse reaction whose character or gravity is not consistent with either the product information in the Investigator's Brochure for an unlicensed investigational medicinal product or the summary of product characteristics for a licensed medicine.

12.1. Adverse reactions

An adverse reaction is any suspected harmful and unintended reaction from a medicinal product, regardless of the dose.

12.2 Adverse incidents

An adverse incident is any unwanted incident occurring to an animal that has been administered a medicinal product, regardless if the incident is expected to have a causal relation to this treatment.

An adverse incident can thus be any unfavourable or unexpected result (including abnormal laboratory findings), symptom or disease temporarily related to the use of a medicinal product – regardless if the incident is expected to have any relation to the medicinal product.

12.3 Serious adverse reactions or incidents

Any incident, regardless of dose, which:

- causes death
- is life-threatening,
- causes significant disability, reduction in production output or inability to work
- is a congenital anomaly or birth trauma
- causes persistent or long-term symptoms in the animal treated.

12.4 Adverse reactions and incidents seen in trials in Denmark

The trial protocol should generally specify which adverse reactions and incidents the investigator must report to the sponsor, and when this must be done after the adverse reaction/incident is discovered. The protocol should generally also state how long the animals are observed after they have stopped using the trial medication. This is for the purpose of registering any adverse reactions/incidents occurring late.

The following must be reported to the Danish Medicines Agency:
Under section 89(2)(i) of the Danish Medicines Act, the sponsor must immediately inform the Danish Medicines Agency if any suspected unexpected and serious adverse reactions occur during the trial.

The Danish Medicines Agency is entitled to set terms for the trial to the sponsor, cf. section 90(1) of the Danish Medicines Act, and in connection with approval of a trial, The Danish Medicines Agency requires the sponsor to ensure that all information about suspected unexpected serious adverse reactions, which are fatal or life-threatening, is registered and reported to the Danish Medicines Agency as quickly as possible and within 7 days after such a suspected adverse reaction comes to the knowledge of the sponsor. Moreover, within 8 days after the reporting, the sponsor must provide the Danish Medicines Agency with all relevant information about how the sponsor and investigator have followed up on the reporting.

In addition, the Danish Medicines Agency requires that all other suspected unexpected and serious adverse reactions must be reported to the Danish Medicines Agency within 15 days after they come to the sponsor's knowledge.

All adverse reactions and incidents (including the serious ones) must be included in the final reporting to the Danish Medicines Agency at the end of the trial. Section 89(2)(iv) of the Danish Medicines Act stipulates that the sponsor must submit the trial results to the Danish Medicines Agency no later than one year after the trial is completed.

12.5 Serious adverse reactions and serious incidents seen in trials outside Denmark

Serious adverse reactions and serious incidents occurring outside Denmark in connection with a clinical trial of medicinal products, which are also used in a trial in Denmark, should generally not be reported to the Danish Medicines Agency as single reports. However, if any such serious adverse reactions/incidents seen abroad require changes to be made to a protocol for ongoing trials in Denmark, these incidents must be reported as single reports, and they must immediately be taken into account in the form of an addition to the protocol.

If any suspected unexpected and serious adverse reactions occur in connection with safety studies carried out outside Denmark, but with medicines approved for marketing in Denmark, the marketing authorisation holder (MAH) must report these adverse reactions to the Danish Medicines Agency as single reports under section 7 of Danish executive order no. 1238 of 12 December 2005 on monitoring of adverse reactions from medicinal products. In addition, the MAH must report any adverse reactions

from licensed medicinal products in connection with periodic safety update reports (PSURs), cf. section 4 of Danish executive order no. 1214 of 7 December 2005 on requirements for the layout of adverse reaction reports and periodic safety update reports. These reports are in principle independent from the rules on clinical trial reporting in Denmark.

12.6 Reporting form

Adverse reactions and incidents seen in trials in Denmark can be reported on the Danish Medicines Agency's reporting form (see Annex 5) or via a Danish e-form. The reporting form is available at the Danish Medicines Agency's website https://laegemiddelstyrelsen.dk/en/sideeffects/side-effects-of-medicines/report-a-side-effect/animals/.

13. REPORT

After completion of the trial, the sponsor must submit information about the results to the Danish Medicines Agency, cf. section 89(2)(iv) of the Danish Medicines Act. The sponsor must summarise information about the number of animals treated, the doses used, duration of dosing and the trial results as well as any observed adverse reactions in connection with the trial.

If deemed necessary, the Danish Medicines Agency will request additional information about the trial results.

Annex 1
EXTRACT FROM THE DANISH MEDICINES ACT

Extract from the Danish Medicines Act, no. 1180 of 12 December 2005, as last amended by Act No. 534 of 17 June 2008:

" **Clinical trials of medicinal products, etc.**
88.-(1) A clinical trial of medicinal products can only be conducted if the Danish Medicines Agency has given an authorisation for the trial. However, non-interventional trials may be implemented without the authorisation of the Danish Medicines Agency. Furthermore, trials on humans must be approved by a scientific ethical committee, cf. Act on a Scientific Ethical Committee System and the Processing of Biomedical Research Projects.

(2) Trials of medicinal products on humans must be conducted in accordance with Good Clinical Practice. The Danish Medicines Agency shall lay down rules on Good Clinical Practice, including quality standards for the planning, conducting and reporting of clinical trials.

(3) Application for authorisation of a clinical trial must be submitted to the Danish Medicines Agency by the person, company or institution undertaking the responsibility for the initiation, management and possibly the financing of a clinical trial (sponsor).

(4) If the Danish Medicines Agency has a reasoned objection, the sponsor may amend the application once to allow for the objection. If the application is not amended according to the objection, the application is rejected.

(5) The sponsor must inform the manufacturer of the medicinal product or the manufacturer's representative of the application at the same time as the application is submitted to the Danish Medicines Agency.

(6) In connection with applications for trials of medicinal products on humans the Danish Medicines Agency must make its decision of authorisation under subsection (1) or of rejection of application for authorisation known to the scientific ethical committee concerned, cf. Act on a Scientific Ethical Committee System and the Processing of Biomedical Research Projects.

(7) The sponsor or sponsor's representative must have a permanent address in an EU/EEA country.

(8) The Minister for the Interior and Health shall lay down specific rules on which information should be included in applications for authorisation of clinical trials and on the Danish Medicines Agency's processing of such applications.

89.-(1) When a trial has been initiated, sponsor can only amend the trial protocol according to rules laid down by the Minister for the Interior and Health.

(2) The sponsor shall

(i) immediately inform the Danish Medicines Agency if presumed unexpected and serious adverse reactions occur during the trial,

(ii) inform the Danish Medicines Agency within 15 days if a trial needs to be interrupted earlier than planned and give the Agency a clear reason for the interruption,

(iii) once a year throughout the entire trial period draw up a list of all serious suspected adverse reactions which have occurred during the trial period, and a report on the safety of the trial subjects and submit the list and the report to the Danish Medicines Agency, and

(iv) no later than 90 days after the end of the trial, inform the Danish Medicines Agency that the trial has been completed and as soon as possible and no later than one year after submit the result of the trial to the Agency.

(3) The Minister for the Interior and Health shall lay down rules on information specified in subsection (2).

(4) The Minister for the Interior and Health shall lay down rules on sponsor's obligation to inform others, including those responsible for clinical trials and the national authorities responsible for medicinal products in the other EU/EEA countries of the information submitted under subsection (2).

90.-(1) The Danish Medicines Agency is entitled to set terms for the trial to the sponsor and the doctor, dentist or veterinarian responsible for the practical conduct of the trial (investigator).

(2) The Danish Medicines Agency is entitled to inspect any company, etc. that is or has been carrying out clinical trials of medicinal products, and the Agency is entitled to demand all information necessary, including written material, for its control activity. As part of the control, the Danish Medicines Agency's representatives shall:

(i) on the presentation of appropriate identification and without a court order, have access to companies, hospitals, medical practices and other places affected by the implementation of the trial and
.
(ii) have access to patient records, etc., provided that the trial subject, his or her relatives or guardian has consented to or authorised this.

(3) For trials of medicinal products for humans, the Danish Medicines Agency's control pursuant to subsection (2) shall comprise observation of good clinical practice. The Minister for the Interior and Health shall lay down specific rules on this control activity.

(4) If an investigator or any other party involved in the trial fails to comply with the established obligations for a trial of medicinal products for humans, the Danish Medicines Agency shall present such parties with suggestions for remedying the problem, and also submit the proposal to the scientific ethical committee concerned, the European Commission and the national authorities responsible for medicinal products in the other EU/EEA countries.

(5) During the trial, the Danish Medicines Agency shall be entitled to demand from the sponsor and the investigator that the trial should be altered or temporarily suspended, or the Agency shall be entitled to prohibit the trial. The Minister for the Interior and Health shall lay down specific rules to this effect.

(6) In deciding to stop or prohibit a trial of medicinal products for humans, the Danish Medicines Agency shall immediately notify its decision and the grounds for it to the scientific ethical committee concerned, the European Medicines Agency, the European Commission and the national authorities responsible for medicinal products in the other EU/EEA countries.

91.-(1) The Danish Medicines Agency must enter information on all clinical trials of medicinal products for humans which the Agency has authorised in a European database. The Minister for the Interior and Health shall lay down specific rules on what information the Danish Medicines Agency must report and on the Agency's processing of the information.

(2) The Danish Medicines Agency is entitled to disclose relevant information on clinical trials to the European Medicines Agency, the European Commission, the national authorities responsible for medicinal products in the other EU/EEA countries and the scientific ethical committee concerned. The Minister for the Interior and Health shall lay down specific rules to this effect.

92.-(1) The medicinal products for clinical trials must comply with the current standards for good manufacturing practice. Compliance in this respect is comprised by the Danish Medicines Agency's monitoring of clinical trials under section 90(2).

(2) In response to a reasoned request, the Danish Medicines Agency is entitled to disclose information from the monitoring under section 90(2) to the European Medicines Agency, the national authorities responsible for medicinal products in the other EU/EEA countries and scientific ethical committee concerned.

(3) The Danish Medicines Agency shall lay down specific rules on the manufacture, import, labelling, distribution and monitoring of medicinal products for clinical trials."

REGULATION (EU) 2019/6 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC

LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

Application form for authorisation of clinical trials of veterinary medicinal products in animals

Protocol title:

Protocol code/number:

Phase:

Design:

Applicant (name and address):

Investigators (name and address):

Investigational medicinal products (name/code name, if any):

Active substance:

Manufacturer of the investigational medicinal product:

Placebo, if used: manufacturer of placebo:

Information on reference documents (usually Investigator's Brochure (IB) or summary of product characteristics (SPC)) to assess whether an adverse reaction is unexpected:
Please copy the above if several investigational medicinal products are included in the trial.

Trial site:

Number of centres in Denmark:

Expected start date date **and expected end date** date

Will the Clinical Trial be conducted in compliance with the veterinary GCP rules (VICH GL9)?

Invoice details:

List of appendices (see checklist)
http://laegemiddelstyrelsen.dk/en/licensing/clinical-trials/trials-in-animals/

Applicant's signature (sponsor or on behalf of sponsor)

Date	Signature

Please complete the form, sign it and send it to:
Danish Medicines Agency, Clinical Trials, Axel Heides Gade 1, 2300 Copenhagen S, Denmark

Annex 3

Supplementary notification to the Danish Medicines Agency about

clinical trials of veterinary medicinal products in animals.

Danish Medicines Agency's case no.:

MEDICINES USED IN THE TRIAL:
(Name and code name used in the trial (if any))

PROTOCOL
Title:
code number(if any):

SPONSOR:
(Name and address):

Trial site (participating centre) Address:

clinical practice	university	farm
company	other	
☐	☐	☐
☐	☐	

The undersigned hereby confirms my participation in the above clinical trial.
I understand and accept that the trial sponsor or applicant is the Danish Medicines Agency's contact persons for all questions regarding the trial. The Danish Medicines Agency's permission, terms, deadlines and other orders as well as any information concerning the trial will only be notified to the sponsor or applicant.

SIGNATURE

Date: (stamp)

Please complete the form, sign it and send it to:
Danish Medicines Agency, Clinical Trials, Axel Heides Gade 1, 2300 Copenhagen S, Denmark

Is also available as an e-form: Clinical Trials - composition form (e-form, Digital Signature)

Annex 4

Clinical trials

Form for cataloguing active substances of proprietary medicinal products etc.

1) Name of the

2) Dispensing form/strength (only one dispensing form/strength on each form):

3 **Name of substance***	**4)** **Quantity per***	**5)** **Specification***	**6** **Type of**

Date _____ Signature _____

* See the next page

Please complete the form, sign it and send it to:
Danish Medicines Agency, Clinical Trials, Axel Heides Gade 1, 2300 Copenhagen S, Denmark

Instructions

Column 3: Substance name, i.e. the actual active substance (not a possible declared active substance). Example: Tetracycline hydrochloride and *not* Tetracycline (as chloride). The active substance names to be used are those listed in the Danish Drug Standards (Danske Lægemiddelstandarder). If no name is listed here, please use the INN, NFN, BAN or USAN name. If none of these names are determined, use the trade name or the chemical name. As regards dyes, please also specify the Colour Index numbers as used in the publication Colour Index, 3rd edition, 1971.

Column 4: The quantitative composition of the product in mg or g, excl. any excess of active substances. If an excess of active substance is added, please write this in percentage in a parenthesis after the quantity stated. The quantities are specified per unit (ml, g, tablet, etc.) with as few digits as possible, and the unit concerned is listed at the top of the column. If it is impossible to specify an exact quantity, add "approx." in front of the quantity indication.

Column 5: Specification of identity and purity of all active substances. If it is not possible to refer to a pharmacopoeia or the like (e.g. Ph.Eur, Ph.Nord, BP, UPS or DLS), please refer to an enclosed document or appendix to the material submitted.

Column 6: After each substance, please write a letter identifying the type of substance. Please use the following letters:

A: Active substances
F: Dyes
K: Preservatives
X: Flavouring
C: Other inactive substances

Is also available as an e-form (in Danish only): Form for the reporting of suspected adverse reactions to a veterinary medicinal product (e-form in Danish only)

Form for the reporting of suspected adverse reactions to a veterinary medicinal product (A written copy of the case with relevant information may be enclosed)

Submitter: Name Address Postcode and city		**Filled in by the Danish Medicines Agency** Case no.: Received Causality Central reg.
Veterinarian ☐ Owner ☐ Company ☐ Other ☐		
Animal owner: Name The animal's location Postcode and city		Is the pharmaceutical company informed yes ☐ no ☐ May your name and address be disclosed to the pharmaceutical company yes ☐ no ☐ Human reaction yes ☐ no
Animal species **Breed**		
Gender	**Age**	**Weight**
Medicinal product Trade name Active substance Strength Company Batch number Dosage Quantity administered Place of administration Form of administration		Number of animals treated in this incident Number of animals with adverse reactions Number of dead animals Date of adverse reaction Duration of adverse reaction
Other medicines used concurrently		
Reason for treatment		
Adverse reaction incl. subsequent reactions (use the back of the form if		
Previous treatment with the same medicine? Reaction?		
Subsequent treatment laboratory examination/ autopsy, if relevant (send a copy, if possible)		**Date** **Signature**

Please complete the form, sign it and send it to: Danish Medicines Agency, Clinical Trials, Axel Heides Gade 1, 2300 Copenhagen S, Denmark