

DECREE

of June 23 2008

on good clinical practice and detailed conditions of clinical trials on medicinal products

PART ONE

COMMON PROVISIONS

Section 1

Introductory provisions

(1) This Decree incorporates relevant regulations of the European Communities¹⁾ and stipulates the rules of good clinical practice and detailed conditions of clinical trials on medicinal products (hereinafter referred to as “clinical trial”).

(2) For the purposes of this Decree:

- a) the commencement of a clinical trial on a human medicinal product shall mean the moment when the first trial subject referred to in Section 51, paragraph 2 (g) of the Act on Pharmaceuticals or its guardian signs the informed consent with participation in the clinical trial in the Czech Republic; in acute situations referred to in Section 52, paragraph 9 of the Act on Pharmaceuticals, the commencement of a clinical trial shall mean the moment when the investigator decides, in compliance with the Protocol, to enrol the first trial subject to the particular clinical trial and makes a written record thereof in the documentation;
- b) the commencement of a clinical trial on a veterinary medicinal product shall mean the moment when the clinical trial is authorised by the Veterinary Institute;
- c) the completion of a clinical trial shall mean the moment when in respect of trial subjects the last procedure established by the protocol of the clinical trial is performed in the Czech Republic; such procedure, however, shall not mean the follow-up of the trial subject; where the clinical trial protocol defines the completion of the clinical trial in another manner, the completion of the clinical trial shall mean the moment established by the protocol;
- d) residues shall mean all active substances or their metabolites present in the meat or other products obtained from animals in whom the investigational veterinary medicinal product has been applied;
- e) case report forms shall mean documents in paper, picture or electronic format intended for the recording of any information which is pursuant to the clinical trial protocol provided to the sponsor for each trial subject;

- f) a contract research organisation shall mean a natural or legal person having a contractual relationship with the sponsor and safeguarding the performance of one or more activities or functions of the sponsor in respect of the clinical trial;
- g) quality assurance shall mean any planned and systematic procedures which are to safeguard that the clinical trial is conducted and data from the clinical trial obtained, recorded and reported in compliance with good clinical practice and related legal regulations;
- h) quality management shall mean procedures and activities ensuring, within the quality assurance system, compliance with the requirements governing the quality of all activities associated with the clinical trial;
- i) standard operating procedures shall mean detailed written methods of performance of individual actions within the scope of the clinical trial the purpose of which is to achieve a uniform performance of these actions;
- j) trial subject identification code shall mean an explicit identifier allocated by the investigator to every trial subject in order to prevent disclosure of the trial subject's identity;
- k) blinding in a clinical trial shall mean a procedure in which the trial subject and, where applicable, also the investigator or other persons involved in the clinical trial do not have access to the information about the allocation of the investigational medicinal product to individual trial subjects;
- l) a major change to the protocol of the clinical trial shall mean such change which is likely to affect the trial subjects' safety or to alter the scientific hypothesis of the particular clinical trial.

(3) In the conduct of clinical trials on radiopharmaceuticals, the provisions of this Decree shall be without prejudice to the Atomic Act and to legal regulations adopted for its implementation²).

Section 2

General principles of good clinical practice

A clinical trial shall be conducted in compliance with the protocol of the clinical trial as referred to in Annex 1 hereto (hereinafter referred to as the "protocol") and with protocol amendments.

PART TWO

CLINICAL TRIALS ON HUMAN MEDICINAL PRODUCTS

CHAPTER ONE

ETHICS COMMITTEE

Establishment, membership, and operation of ethics committees

Section 3

(1) The establishment of an ethics committee as referred to in Section 53, paragraph 1 of the Act on Pharmaceuticals shall mean the written appointment of the members of the ethics committee. An ethics committee shall comprise of at least five members with adequate qualification and expertise allowing them to assess and evaluate the proposed clinical trial in terms of its scientific, medical, and ethical aspects. Prior to the appointment of ethics committee members, the healthcare facility or the Ministry of Health (hereinafter referred to as the “person”), which establishes the ethics committee, shall request their written consent with their membership in the ethics committee and with adherence to the conditions stipulated in Section 53, paragraph 2 (a) to (c) of the Act on Pharmaceuticals.

(2) When appointing new members of an ethics committee after the committee has already been established, the procedure outlined in paragraph 1 shall apply likewise.

(3) The Institute shall publish a list of ethics committees in the Czech Republic, specifying in particular the contact addressees of the ethics committees, the professional specialisation of their members, date of establishment or dissolution where applicable, and information whether the ethics committee is an ethics committee for multicentric clinical trials and what opinions on proposed clinical trials have been issued by the concerned ethics committee.

(4) Where the ethics committee is to perform also the activities of an ethics committee for multicentric clinical trials, it shall apply with the Ministry of Health for this appointment, and, at the same time, shall provide the Institute with a copy of the application together with the documentation stipulated for the operation of an ethics committee by the Act on Pharmaceuticals and by this Decree. The Institute shall, within the period of 60 days, verify whether this ethics committee complies with the stipulated conditions, and shall forward its opinion to the Ministry of Health. The Ministry of Health shall decide, within the period of 30 days of the delivery of the opinion of the Institute, whether the ethics committee may be designated as an ethics committee for multicentric trials. This appointment shall be notified by the Ministry of Health to the ethics committee, to the establishing healthcare facility and to the Institute.

(5) Where a clinical trial, which has been approved by the ethics committee established by the healthcare facility, is active in the healthcare facility the administrator of the healthcare facility shall create conditions for this ethics committee to operate for the duration of the clinical trial in this healthcare facility, and if changes in its membership occur, to ensure a smooth continuation of its operation as well as its rights and obligations.

Section 4

(1) An ethics committee shall issue its opinions at meetings announced in advance in a manner described in the written operating procedures of the ethics committee as referred to in paragraph 2. Only those members of the ethics committee who participate in the discussion on the concerned clinical trial and who are familiar with it shall express their opinion. The ethics committee may adopt its opinion only if it has a quorum. For an opinion to be adopted, it is

necessary to have the opinion of at least five members of the ethics committee, including a member without healthcare qualification and without expert scientific qualification and a member who is not the employee of or in a similar labour or dependent relationship with the healthcare facility where the proposed clinical trial is to be conducted, and those two members must constitute of two different persons. The investigator shall not take part in the adoption of the opinion of the ethics committee.

(2) The ethics committee shall fulfil its roles in compliance with the written operating procedures which shall include, in particular:

- a) the definition of its membership, giving the name(s) and surname and qualification of its members, and the establishing healthcare facility;
- b) the method of planning of meetings, their announcement to the members of the ethics committee and the conduct of meetings;
- c) the assessment of applications for ethics committee approval of the commencement of clinical trials and the conduct of continuous supervision over the clinical trial;
- d) the method of determining continuous supervision over the clinical trial;
- e) an accelerated assessment and issuance of opinions on administrative changes to active clinical trials;
- f) a specification of the ethics committee's approach to the reports from investigators, to information obtained from the supervision over the clinical trial, or obtained in another way, and a specification of the method how the ethics committee notifies in writing the investigator or the healthcare facility of its opinions on the clinical trial, reasons for their adoption and procedures of review of an opinion, if applicable;
- g) the definition of the method and timelines of the ethics committee communication of data required by the Act on Pharmaceuticals and by this Decree to the investigator or the sponsor, to the Institute, and, where a multicentric ethics committee is concerned, also to ethics committees that may be established at the trial sites;
- h) the operating procedures in compliance with other legal regulations³, if the ethics committee issues its opinions also for spheres of biomedical research other than clinical trials.

(3) The records maintained by the ethics committee must be made accessible upon request of the authorities which perform state administration pursuant to Section 10 of the Act on Pharmaceuticals, and of foreign control authorities in the sphere of pharmaceuticals.

(4) The written operating procedures, a list of members of the ethics committee and a declaration to the effect that the ethics committee has been established and operates in compliance with good clinical practice and related legal regulations shall be provided by the ethics committee upon request to the investigator, sponsor or authorities referred to in paragraph 3.

(5) The minutes of meetings of an ethics committee shall contain the date, hour, and venue, the list of attending members, the list of other invited attendees, main points of discussion, a memorandum of the opinion including the method of adoption of the opinion, a record of announcement of possible conflict of interest and a signature of at least one member of the ethics committee.

(6) Where an ethics committee is dissolved, the person which has established or designated the ethics committee shall announce to the Institute whether the operation of the dissolved ethics committee is being taken over by another ethics committee, and shall provide a list of active clinical trials supervised by the dissolved ethics committee and specify how the storage or hand-over of the documentation of the dissolved ethics committee is safeguarded.

Section 5

Provision of an opinion on the conduct of a clinical trial

(1) The ethics committee shall express its opinion on the conduct of a clinical trial on the basis of a written application and having assessed the submitted documentation. The application for the provision of an opinion on the conduct of a clinical trial shall be submitted to the ethics committee by the investigator or by the sponsor. Documents and source materials shall be submitted to the ethics committee in the Czech language; the ethics committee may allow for the submission of documents and source materials also in another language.

(2) The following shall be submitted to the ethics committee:

- a) the protocol and, where applicable, its amendments;
- b) the text of the informed consent form and other written information provided to trial subjects;
- c) trial subject recruitment procedures, in particular advertising;
- d) investigator's brochure containing available safety data for the investigational medicinal product;
- e) detailed information about compensation of costs and remuneration for trial subjects;
- f) CV of the investigator or other documents certifying the investigator's qualifications;
- g) draft of insurance contract or insurance contract covering the investigator's and sponsor's insurance pursuant to Section 52, paragraph 3 (f) of the Act on Pharmaceuticals;
- h) other documents requested by the ethics committee.

(3) In its assessment of the compensations, insurance and remunerations, the ethics committee shall always assess whether:

- a)

the compensation or provision of damages for the trial subject in the case of death or injury to its health due to its participation in the clinical trial is covered by the insurance contract;

- b) the liability insurance for the investigator as well as for the sponsor is covered by the insurance contract, or, where applicable, whether the liability insurance of the investigator or sponsor may be part of their labour relations;
- c) the compensations exceed the costs incurred by the trial subject or by the investigator in respect of their involvement in the clinical trial and, furthermore, whether the remuneration for the investigators is known in advance and fixed, and whether the sponsor has submitted a written announcement of the amount of this remuneration together with the application;
- d) the amount of remuneration for trial subjects is adequate to the nature of the clinical trial, particularly in respect of those research procedures which are not directly beneficial for the trial subject.

(4) Where clinical trials, in which it is not possible to obtain the trial subject's informed consent prior to its inclusion in the clinical trial, are concerned, the ethics committee shall assess how and at what timelines the protocol covers the request for the informed consent of the guardian of the trial subject or of the trial subject alone, and shall contemplate whether it may be effective to condition the inclusion of each trial subject by the committee's approval.

(5) The ethics committee shall provide its opinion to the sponsor and to the Institute within the timeline stipulated by Section 53, paragraphs 9 and 10 of the Act on Pharmaceuticals.

(6) Where a multicentric clinical trial is concerned, the ethics committee for multicentric clinical trials shall forward its opinion to the local ethics committees of individual trial sites listed in the application, to the sponsor and to the Institute within the timeline stipulated by Section 53, paragraphs 9 and 10 of the Act on Pharmaceuticals. The local ethics committees shall also provide their opinions to the sponsor, to the concerned ethics committee for multicentric clinical trials, and to the Institute in compliance with Section 53, paragraphs 9 and 10 of the Act on Pharmaceuticals.

(7) An opinion of an ethics committee shall contain:

- a) identification data of the assessed clinical trial, in particular the title of the clinical trial, the sponsor and the trial site, protocol number, and, where applicable, the identification number of the EudraCT European database (hereinafter referred to as the "European database"), delivery date of the application, and a list of trial sites in respect of which the ethics committee has provided its opinion and over which it performs supervision;
- b) a list of reviewed documents;
- c) statement and its rationale;
- d)

date of issue of the opinion and a signature of at least one member of the ethics committee authorised for this purpose by the operating procedure referred to in Section 4, paragraph 2;

e)

in the case of clinical trials where it is not possible to obtain the trial subject's informed consent prior to its inclusion in the clinical trial, the ethics committee shall explicitly state whether it agrees with the procedure of trial subject inclusion specified in the protocol, and shall state whether it conditions the inclusion of each individual trial subject by the committee's approval; where it does condition the inclusion of each individual trial subject by the committee's approval, it shall also specify the method of how the investigator shall seek such approval and how the ethics committee shall provide the relevant position without any delay;

f)

where the opinion is issued by an ethics committee for multicentric clinical trials, this fact shall be specified and, at the same time, a list of trial sites on which this committee has issued its opinion and which it supervises shall be provided.

Section 6

Changes to the conditions of a clinical trial

(1) Notification of major changes to the protocol pursuant to Section 56, paragraph 1 (a) of the Act on Pharmaceuticals shall be made in writing, providing a rationale and a draft of the revised relevant part of the dossier to which such change and the protocol amendment pertain to. Where amendments to protocol of administrative or organisational nature are concerned, or those consisting of changes to such data as for example the telephone, fax, e-mail address, necessary for the cooperation of the ethics committees and the Institute with the sponsor, the sponsor shall forthwith inform the Institute and the ethics committees which have provided their position on the given clinical trial. Such amendment shall not be considered a major change to the protocol.

(2) When assessing a protocol amendment and issuing an opinion thereon, the ethics committee shall proceed as per Section 5 likewise.

(3) A revocation of its approval as referred to in Section 53, paragraph 13 of the Act on Pharmaceuticals shall be notified by the ethics committee forthwith in writing to the investigator, the sponsor and the Institute. With the exception of those cases when the trial subjects' safety is compromised, the ethics committee shall, prior to adopting its decision, request the opinion of the sponsor or of the investigator, where appropriate. An ethics committee for multicentric clinical trials shall, prior to adopting its decision, also request the opinions of local ethics committees of individual trial sites.

(4) A revocation of ethics committee approval shall contain:

a)

identification data about the clinical trial, in particular its title, specification of the sponsor and trial sites for which the approval is being revoked, protocol number, and identification number of the European database where applicable;

b)

rationale of the revocation of approval;

- c) measures to terminate the clinical trial, in particular the conversion of the trial subject to another treatment, if the approval is being revoked due to compromised safety of trial subjects and unless the measures have already been specified in the protocol;
- d) approval revocation date and signature of at least one member of the ethics committee authorised therefor by a written operating procedure of the ethics committee.

CHAPTER TWO

INVESTIGATOR

Section 7

Basic activities of the investigator⁴⁾

(1) Prior to the commencement of the clinical trial, the investigator shall familiarise himself/herself with the proper use and characteristics of the investigational medicinal product as described in the protocol and its amendments, in the investigator's brochure and in other information materials provided by the sponsor.

(2) Before enrolling each trial subject in the study, the investigator shall obtain a written informed consent of the trial subject or its guardian; in the case of clinical trials where it is not possible to obtain such consent prior to the enrolment of the trial subject into the clinical trial, procedures outlined in Section 52, paragraph 9 of the Act on Pharmaceuticals and referred to in Section 5, paragraph 4 shall apply.

(3) An investigator who is in a dependant relation to the operator of the healthcare facility⁵⁾ shall obtain the operator's consent with the conduct of the trial prior to the commencement of the clinical trial.

(4) Within the scope of good clinical practice, the investigator shall:

- a) ensure that all persons involved in the conduct of the clinical trial at the particular site have adequate expertise and qualifications and are properly informed about the protocol and its amendments, about the investigational medicinal products, and about their tasks in respect of the clinical trial;
- b) maintain written records of the persons authorised thereby to perform the tasks essential for the conduct of the clinical trial;
- c) ensure that adequate medical care is provided to the trial subject in the case of an adverse event, which has occurred in association with the trial subject's participation in the clinical trial, including clinically significant deviations of laboratory values from normal values;
- d) where he/she finds out about or is informed about a concurrent condition of the trial subject, inform the trial subject to this effect;
- e)

inform the trial subject's attending doctor about the subject's participation in the clinical trial, if the trial subject consents to it;

f)

exert reasonable efforts to identify the reasons for premature withdrawal of the trial subject from the clinical trial without infringing on the trial subject's rights.

(5) The investigator or a person appointed thereby shall keep records of deliveries of the investigational medicinal product to the trial site, of the levels of stock of the investigational medicinal product at the trial site, of the use by each trial subject and of returns of unused investigational medicinal products to the sponsor or of another manner of disposal. These records shall contain the date, amounts, batches, shelf-life, and code numbers allocated to the investigational medicinal product and to the trial subjects. The investigator shall maintain records which provably evidence that trial subjects have been provided with doses of the investigational medicinal product specified in the protocol, and which document the handling of all investigational medicinal products taken from the sponsor.

(6) The investigator shall ensure that the investigational medicinal product is used exclusively in compliance with the approved protocol, and, furthermore, shall safeguard the provision of information to each trial subject regarding the correct use of the investigational medicinal product in intervals appropriate for the concerned clinical trial and shall check whether each trial subject adheres to his/her instructions.

(7) Where a random selection of trial subjects is applied in the clinical trial, the investigator shall ensure that the identification code is disclosed solely in compliance with the protocol.

(8) Where a clinical trial is blinded, the investigator shall forthwith inform the sponsor about any premature unblinding of the investigational medicinal product and shall document this fact.

Section 8

Information for the trial subject and trial subject's informed consent

(1) The particulars of information for the trial subject and informed consent are stipulated in Annex 2 hereto. When the informed consent is being obtained, the trial subject must not be unduly influenced in favour of participation or continued participation in the clinical trial.

(2) In order to obtain an informed consent with participation in the clinical trial the investigator shall use and provide to trial subjects only such information materials which have been approved by the sponsor and authorised by the concerned ethics committee or by the Institute. These information materials shall be updated, approved and authorised any time when new information relevant for trial subjects becomes available.

(3) The investigator or a person authorised thereby shall, prior to obtaining the informed consent, provide an opportunity for the trial subject or its guardian, where applicable, to consider the information necessary for the decision and to ask questions in respect of the clinical trial; these questions shall be answered.

(4) The investigator or a person appointed thereby shall provide the trial subject or its guardian with a counterpart of the signed and dated informed consent form as well as a copy of the written information about the clinical trial intended for trial subjects, including any

changes and amendments, if applicable. Where the informed consent has been granted not only by the guardian but also by the trial subject, the trial subject shall also receive a copy of this consent.

(5) Where clinical trials on minors are concerned:

- a) the investigator shall obtain the informed consent in compliance with Section 52, paragraph 6 (a) of the Act on Pharmaceuticals;
- b) the investigator or a person authorised thereby who is experienced in working with minors shall provide, in the scope of the minor's expected capacity of understanding, the minor with truthful information about the clinical trial, in particular about its risks and benefits, about possible discomfort and potential problems, as well as about the right to withdraw from the clinical trial at any time;
- c) if possible with respect to the capabilities of the minor, the investigator or a person authorised thereby shall provide the minor with written information about the clinical trial within a scope adequate to the stage of development of the minor and shall respect the minor's wish regarding the participation in the clinical trial;
- d) the ethics committee shall perform its supervision at least in six-monthly intervals; if the concerned ethics committee is not experienced in paediatrics, it shall involve a specialist qualified in paediatrics for the purposes of the conduct of supervision.

Section 9

Records and reports

(1) Prior to the commencement of the clinical trial in the healthcare facility where the clinical trial is conducted, documents listed in section I of Annex 3 hereto must be made available to the persons involved in the clinical trial. This Annex, furthermore, in its sections II and III specifies documentation to be maintained in the course of the clinical trial and after its completion. These documents must be made available to the persons involved in the clinical trial, unless stipulated otherwise in the clinical trial authorisation.

(2) The investigator shall ensure accurate, complete, readable and timely recording of data to case report forms and to all reports. The investigator's entries in case report forms shall be in compliance with the source documents; any possible discrepancies must be justified.

(3) Any change or adjustment made in case report forms shall be dated and signed by the person who has done the change and, if applicable, an explanation shall be attached; the change or adjustment shall be attached to the original record. Changes or adjustments shall be made by the investigator, his/her staff authorised to make changes or by persons authorised by the sponsor pursuant to the written operating procedures of the sponsor; such change or adjustment shall be endorsed with the signature of the person who has made the change or adjustment.

(4) Records associated with the clinical trial at the trial site shall be accessible for the sponsor, members of the ethics committee and authorised staff of control authorities as

referred to in Section 4, paragraph 3.

(5) Upon request of the sponsor, of the person referred to in Section 21, paragraph 3 or in Section 22, paragraph 2, of the ethics committee or of control authorities, the investigator shall provide direct access to all requested records associated with the clinical trial.

(6) The investigator shall forthwith inform the sponsor, the concerned ethics committee and the healthcare facility by means of a written report about any changes significantly influencing the conduct of the clinical trial or, if applicable, increasing the risk for trial subjects.

(7) The investigator shall keep clinical trial files in a manner safeguarding the protection of trial subject data pursuant to another legal regulation ⁶⁾. Following the completion of the clinical trial, the investigator shall ensure the storage of source documents in compliance with the regulations governing the storage of healthcare documentation⁷⁾ and in compliance with Section 56, paragraph 7 of the Act on Pharmaceuticals; trial subjects' identification codes shall be maintained for the minimum period of 15 years.

Section 10

Serious adverse event reporting

(1) A serious adverse event report for the sponsor as referred to in Section 58, paragraph 1 of the Act on Pharmaceuticals shall contain information about the trial site, name of the sponsor, title of the clinical trial and protocol number, trial subject identification, description of the event, name of the medicinal product causing the serious adverse event, including the administered dose and method of administration. If the reporting is not done in writing, it shall be forthwith confirmed by a detailed written report. In urgent and, if applicable, follow-up written reports trial subjects shall be preferably identified by their identification codes.

(2) Adverse events, including laboratory deviations, which are defined in the protocol as critical in terms of safety evaluation, shall be reported in compliance with the requirements governing reporting and within timelines specified by the sponsor in the protocol.

Section 11

Suspension of clinical trials and their termination prior to the completion of all procedures specified by the protocol

(1) If a clinical trial is suspended or terminated prior to the completion of all procedures specified by the protocol, the investigator shall forthwith inform trial subjects to this effect and shall arrange for their continued treatment and monitoring of their condition.

(2) Where a clinical trial is suspended or terminated under the conditions referred to in paragraph 1:

a)

by the investigator without prior approval of the sponsor, the investigator shall forthwith inform the Institute, the sponsor and the ethics committee(s) which have provided their opinion on the concerned clinical trial, to this effect; the investigator

shall provide a detailed written explanation to the sponsor and to the ethics committee(s) which have provided their opinion on the concerned clinical trial;

b)

by the sponsor or by the Institute, the investigator shall forthwith inform the ethics committee(s) which have provided their opinion on the concerned clinical trial, to this effect and shall provide a detailed written explanation thereto.

(3) Where a clinical trial is suspended or early terminated due to a permanent or temporary revocation of the approval of the ethics committee, the investigator shall forthwith inform the healthcare facility to this effect.

CHAPTER THREE

THE SPONSOR

Section 12

Basic activities of the sponsor

(1) The sponsor shall safeguard the implementation and maintenance of quality assurance and management systems and the application of written standard operating procedures which guarantee that the clinical trial, including associated laboratory tests and handling of data, is conducted and data are obtained, documented, processed, evaluated, and reported in compliance with the protocol, with the principles of good clinical practice and with other legal regulations⁸), in order to ensure their authenticity and correctness. Where a contract research organisation or another entity is involved in the conduct of the clinical trial, it shall have a quality assurance and management system implemented analogously to the sponsor.

(2) The sponsor shall appoint the investigator with a view to his/her qualification, the nature of the clinical trial and the resources of the healthcare facility where the clinical trial is to be conducted. The sponsor shall conclude a written contract, which may also form an annex to the protocol, with the investigator, the healthcare facility or other persons involved in the clinical trial, on the conditions governing the conduct of the clinical trial, including its funding and compensation of costs of treatment in the case of an injury to the trial subject's health associated with the subject's participation in the trial, responsibility for communication with the ethics committee or the Institute, storage of documentation and provision of reports and information. Before the contract on the conduct of the clinical trial is concluded, the sponsor shall provide the investigator or the healthcare facility with the protocol and with an updated investigator's brochure for them to familiarise themselves with these documents and other provided information.

(3) The sponsor shall ensure that the investigator:

a)

conducts the clinical trial in compliance with good clinical practice, relevant legal regulations, pursuant to the protocol approved by the sponsor and in compliance with the opinion of the ethics committee;

b)

adheres to the procedures for recording and reporting of data.

(4) The sponsor shall, furthermore, ensure that the investigator safeguards that:

- a) essential documents pertaining to the clinical trial are stored until the sponsor notifies the investigator or the healthcare facility that these are no longer required;
- b) access to healthcare facilities conducting the clinical trial and access to source documents and reports is made available for the purposes of monitoring, auditing, inspections by the Institute or by foreign control authorities.

(5) By means of the written contract the sponsor shall, moreover, safeguard an explicit definition of obligations, functions and activities transferred thereby to the contract research organisation, where such organisation is involved in the conduct of the clinical trial; the sponsor's responsibility for the correctness and completeness of obtained data, however, shall not be prejudiced thereby.

(6) Prior to the commencement of the clinical trial, the sponsor shall define, assign and assign all the obligations and functions associated with the clinical trial and shall ensure that that only persons with sufficient qualifications and expertise are involved in any activities associated with the preparation, conduct, evaluation, monitoring, and auditing of the clinical trial, and that these persons are informed about their rights, obligations and, where applicable, functions, and that their qualifications are documented.

(7) For trial subjects and their guardians, the sponsor shall appoint a properly qualified and easily accessible doctor for the provision of consultations about health problems and about issues arising in association with the clinical trial.

(8) The protocol, the selection of the pharmaceutical form, dosage as well as the duration and method of administration of the investigational medicinal product must be supported by sufficient safety and efficacy data from non-clinical studies or, where applicable, from clinical trials.

(9) Where the sponsor identifies a breach of the study protocol, the standard operating procedures, the principles of good clinical practice, legal regulations or the requirements of the Institute by the investigator, by the healthcare facility or by other persons involved in the clinical trial, the sponsor shall forthwith adopt measures to eliminate the identified shortcomings. Where monitoring or audit has discovered a serious or permanent breach referred to in the previous sentence on the part of the investigator or the healthcare facility, the sponsor shall terminate the involvement of the investigator in the clinical trial or shall terminate the clinical trial at this site.

(10) If the sponsor is, at the same time, the investigator, provisions applicable to the investigator shall also apply thereto with the exception of paragraph 4.

(11) In the case of a clinical trial which is conducted at more than one site, the sponsor shall ensure that:

- a)

- prior to the commencement of the clinical trial the responsibilities of the coordinating investigator, if appointed, and of other involved investigators are documented;
- b) all investigators obtain instructions for compliance with the protocol, the uniform set of standards for the assessment of clinical and laboratory results and for the completion of case report forms;
 - c) communication among investigators is made feasible;
 - d) the investigators are informed about serious unexpected adverse reactions to the investigational medicinal products which have occurred at other sites of the clinical trial;
 - e) in the case of a change to the clinical trial or amendment of the application following this trial's non-acceptance by the ethics committee for multicentric clinical trials, a new application shall be submitted to the same ethics committee for multicentric clinical trials.

(12) The sponsor shall ensure that it is verified that each trial subject has provided its written consent with direct access to its original medical records for the purposes of monitoring, auditing, controls by ethics committee and inspection by the control authority in respect of the clinical trial.

Section 13

Application for authorisation and notification of a clinical trial to the Institute

(1) Application for authorisation of a clinical trial or notification of a clinical trial pursuant to Section 55, paragraph 2 of the Act on Pharmaceuticals shall be lodged by the sponsor with the Institute. Where the application or notification is lodged by a person other than the sponsor, the application or notification shall be submitted together with the sponsor's authorisation for this person. Individual parts of the documentation shall be submitted separately, with continuous page numbering and a table of contents. The application shall be accompanied by the proof of payment of costs of the assessment of the application or notification.

(2) The following documentation shall be submitted in two copies together with the application for authorisation of a clinical trial or notification of a clinical trial:

- a) a list of submitted documentation;
- b) the protocol and, if applicable, its amendments, containing data stipulated in Annex 1 hereto;
- c) written information for the investigator, either in the form of the Investigator's brochure containing data referred to in Annex 4 hereto, or in the form of the summary of the product characteristics;
- d) a written informed consent of the trial subject or its guardian in the Czech language with any amendments, if applicable;

- e) written information for trial subjects, including instructions for the trial subject or its guardian in the Czech language;
- f) case report forms;
- g) information on non-acceptance of the clinical trial by any ethics committee or foreign control authority;
- h) pharmaceutical data about the investigational medicinal products pursuant to Annex 5 hereto;
- i) where a multicentric clinical trial is concerned, information on which ethics committee for multicentric trials the application for opinion has been submitted to;
- j) study summary in the Czech language.

Where clinical trials the purpose of which is not to obtain source materials for marketing authorisation or development of the medicinal product and which do not involve manufacturers of medicinal products or persons commercially associated therewith are concerned, the scope of such documentation as well as its maintenance and storage may be amended to reflect the nature of the concerned clinical trial following a discussion with the Institute; this pertains for example to documentation stipulated under letter (h).

(3) Where the clinical trial is subjected to authorisation and the investigational medicinal product is a genetically modified organism⁹⁾, a certificate of inclusion of the genetically modified organism in the List of genetically modified organisms and products approved for marketing in the Czech Republic pursuant to the Act on Handling of Genetically Modified Organisms and Genetic Products shall be submitted together with the application or, if applicable, prior to the issue of the authorisation. Risk assessment referred to in another legal regulation¹⁰⁾ shall be submitted together with the application.

(4) Upon request of the Institute, the sponsor shall submit other source materials necessary for the assessment of the concerned clinical trial, for example information required by the State Office for Nuclear Safety, where clinical trials on radiopharmaceuticals are concerned. The Institute may disclose, by means of publication in its information media, individual parts of the required documentation referred to in paragraph 2, procedures typical for individual types of clinical trials and necessary source materials and requirements implied thereby.

Section 14

Conduct of the clinical trial, data collection and record-keeping

(1) In the course of the clinical trial, the sponsor shall continuously evaluate the progress of the clinical trial, the safety of the investigational medicinal product, and, if applicable, critical efficacy parameters and, on the basis of the findings, shall adopt appropriate measures, including changes to the conditions of the conduct of the clinical trial or its termination.

(2) When electronic or remote system of record-keeping of the data about the clinical trial is

applied, the sponsor shall:

- a) ensure and evidence that these electronic systems comply with the criteria of completeness, accuracy and reliability established by the sponsor and are suitable for the given purpose;
- b) maintain standard operating procedures for the use of these systems;
- c) ensure that the designed systems allow for changes of data to be conducted in a manner which ensure that they are documented and that entered data are not deleted;
- d) maintain a security system preventing unauthorised access to data;
- e) maintain a list of persons who are authorised to make changes to data;
- f) ensure back-ups of data in an adequate manner;
- g) ensure blinding of data, if the clinical trial is blinded, for the duration of the blinding of the clinical trial.

(3) If data or observations obtained in the course of the clinical trial are further processed, comparison of original data and observations with the processed data must be made possible.

(4) The sponsor shall use an explicit identification code for trial subjects allowing for the identification of all monitored data of individual trial subjects.

(5) Prior to the commencement of the clinical trial and in its course the sponsor shall ensure the drafting and maintenance of documentation referred to in Annex 3 hereto. Any change in the ownership of data obtained from the clinical trial and any possible discontinuation of the clinical development of the investigational medicinal product shall be notified by the sponsor to the Institute.

(6) After the completion of the clinical trial, the sponsor shall store documents listed in Annex 3 hereto.

(7) The sponsor shall draw written procedures ensuring that changes made by the representatives of the sponsor to case report forms are necessary, documented, and approved by the investigator. Where such changes are implemented, the representative of the sponsor shall provide the investigator with a change and adjustment log.

(8) In the case of a clinical trial where the sponsor is the investigator, a healthcare facility or a university or the state via its organisational unit and which does not involve a manufacturer of medicinal products or persons commercially associated therewith, and if agreed by the sponsor and the Institute, the Institute shall arrange for the entry of data about suspected serious unexpected adverse reactions to the investigational medicinal product to the European database.

Information about the progress of the clinical trial

(1) Within the maximum of 60 days following the commencement of the clinical trial the sponsor shall inform in writing the Institute and the ethics committee for multicentric clinical trials, if such committee has expressed its opinion on the concerned clinical trial, on the date and site where the clinical trial has commenced in the Czech Republic.

(2) The investigator shall inform the ethics committee which has issued its opinion on the concerned clinical trial and which supervises this clinical trial about the commencement of the clinical trial at the concerned site.

(3) The progress report for the clinical trial shall contain data listed in Annex 6 hereto.

(4) The Annual Safety Report referred to in Section 58, paragraph 8 of the Act on Pharmaceuticals shall contain data listed in Annex 7 hereto. The sponsor shall submit the report annually within the period of 60 days of closing date of data collection.

Section 16

Notification of changes to the conditions of a clinical trial

(1) Amendments to protocol consisting of substantial changes to the documentation, such as changes to the planned number of trial subjects, dosage and duration of administration of investigational medicinal products, changes to inclusion and exclusion criteria, evaluated parameters or sampling procedures and changes to investigational medicinal products affecting their quality, for example changes to their composition, manufacturing process, specifications of storage conditions and shelf-life shall be considered major changes to the clinical trial which are to be notified to the Institute and to the ethics committees which have provided their opinion on the concerned clinical trial. Notification of changes to the conditions of the clinical trial shall be accompanied by the proof of payment of costs of the assessment of the application.

(2) Major changes to the conditions of a clinical trial which alter the nature of the clinical trial, such as changes to the objectives of the clinical trial, substantial changes to the trial subject selection criteria and substantial changes to the investigational medicinal products shall be considered a new clinical trial.

Section 17

Other information about the investigational medicinal product and about the clinical trial

In the course of the clinical trial the sponsor shall forthwith inform in writing the Institute and the ethics committees which have provided their opinions on the concerned clinical trial, about:

- a) changes to its registered office or address;
- b) new findings about the investigational medicinal product;
- c)

- measures adopted by the authorities of foreign countries or by ethics committees which pertain to the concerned clinical trial and may affect the safety of trial subjects;
- d) suspension of the clinical trial or its early termination in the Czech Republic; in this case the information shall be provided within the maximum period of 15 days; this information shall contain data listed in Annex 8 hereto;
 - e) termination of development of the medicinal product.

Section 18

Information about the end of the clinical trial and summary report

- (1) Information about the end of the clinical trial in the Czech Republic referred to in Section 56, paragraph 5 of the Act on Pharmaceuticals shall contain data listed in Annex 8 hereto.
- (2) Following the end of the conduct of the clinical trial, the sponsor shall forthwith draw a summary report, which shall contain the conclusions from the concerned clinical trial and their interpretation. The summary report shall contain particulars listed in Annex 9 hereto.

Section 19

Investigational medicinal products and their labelling

- (1) The sponsor shall ensure that:
 - a) investigational medicinal products are characterised adequately to their stage of development;
 - b) suitable time, temperature and other storage conditions are defined for the investigational medicinal products and, if necessary, also procedures for the preparation or treatment of investigational medicinal products before their administration to trial subjects and aids for their application and that investigational medicinal products are stable for the duration of their use;
 - c) investigational medicinal products are packed, distributed and stored in compliance with good distribution practice so that they are provably protected from contamination and degradation during transport and storage;
 - d) investigational medicinal products are prepared, treated, controlled, stored and dispensed in compliance with good pharmaceutical practice; the persons ensuring the above mentioned activities must comply with professional prerequisites¹¹⁾;
 - e) investigational medicinal products are properly labelled as per paragraph 2 and, where applicable, coded; where a blinded clinical trial is concerned, the sponsor shall ensure that the investigational medicinal products are coded in a manner allowing for blinding and that the coding system allows for a rapid identification of the investigational medicinal product if necessary with regard to the health of the trial subject; any unblinding must be detectable;

f) where clinical trials the purpose of which is not to obtain source materials for marketing authorisation or development of the medicinal product and which do not involve manufacturers of medicinal products or persons commercially associated therewith are concerned, the scope of labelling of investigational medicinal products may be adjusted adequately to the nature of the concerned clinical trial following a discussion with the Institute.

(2) The labelling of the outer and immediate packaging of the investigational medicinal product shall show:

- a) the name of the sponsor, contract research site or investigator;
- b) the pharmaceutical form, route of administration, amount of doses, and, for open-label clinical trials, also the name and strength of the medicinal product;
- c) batch number or code for contents identification;
- d) the reference code of the clinical trial allowing for the identification of the clinical trial, of the trial site, investigator and sponsor, unless shown elsewhere;
- e) trial subject identification code, or if applicable, treatment number and visit number;
- f) the name of the investigator, unless included in the labelling referred to in letter (a) or (d), instructions for use, whereas a reference to the package leaflet or another explanatory document intended for the trial subject or for the person administering the investigational medicinal product may be made;
- g) the text “For clinical trial use only” or another similar wording;
- h) storage conditions;
- i) shelf-life (Use-by date, EXP, or date of retesting where applicable), in the month-and-year format, shown in a manner excluding any confusion;
- j) the text “Store out of reach of children”, with the exception of investigational medicinal products used in such clinical trials where the investigational medicinal product is administered to trial subjects under the supervision of the investigator.

In justified cases, with the objective to ensure safe use of the investigational medicinal product by the trial subject, the immediate packaging shall show at least data allowing for a clear identification of the contents of the packaging.

(3) In the case of a change to the date defining the shelf-life, another label shall be affixed to the packaging of the investigational medicinal product showing the new date and repeating the number identifying the batch. This labelling shall be carried out by a person appointed by the sponsor in compliance with the sponsor’s standard operating procedure.

(4) Where major changes to the pharmaceutical form are implemented in the course of the

clinical development of the investigational medicinal product, the sponsor shall safeguard data about the new pharmaceutical form necessary to assess the extent to which the implemented changes will affect the pharmacokinetic profile of the investigational medicinal product, prior to the application of the new pharmaceutical form in the clinical trial.

(5) The sponsor shall not provide the investigational medicinal product to the investigator or to the healthcare facility until the sponsor obtains all documents necessary at the concerned site for the commencement of the clinical trial, in particular an approval of the ethics committee and authorisation of the conduct of the clinical trial issued by the Institute.

(6) The sponsor shall ensure:

- a) record-keeping evidencing the transportation, receipt, storage, returning, and disposal of investigational medicinal products;
- b) the establishment and application of a system of recalls of investigational medicinal products and documentation thereof, in particular recalls of defective investigational medicinal products, returns of investigational medicinal products after the termination of the clinical trial and returns of investigational medicinal products with expired shelf-life;
- c) the development and application of a system of handling of unused investigational medicinal products, including documentation of this handling.

(7) The sponsor shall ensure sufficient quantities of the investigational medicinal product for the purposes of specification retesting if necessary, and storage of documents about analyses and characteristics of individual batches; the sponsor shall ensure storage of samples of the investigational medicinal product until data obtained from the clinical trial are evaluated, if feasible with respect to the product stability.

Section 20

Change of the sponsor

Application for a change of the sponsor shall contain, in addition to particulars required by the Act, the following data and documentation:

- a) identification of the clinical trial to which the change pertains to;
- b) name(s), surname and address of residence or, if applicable, address of residence outside the territory of the Czech Republic, current employer, where a natural person is concerned, or business or company name and registered office where a legal person is concerned, and name(s), surname and address of residence or, if applicable, address of residence outside the territory of the Czech Republic of the person to whom the decision is to be transferred, where a natural person is concerned, or business or company name and registered office where a legal person is concerned, and proposed date of the implementation of the change;
- c)

declaration of the sponsor and of the person to whom the decision is to be transferred, containing officially authenticated signatures, to the effect that the complete and updated documentation pertaining to the clinical trial or a copy thereof has been made available or handed over to the person to whom the decision is to be transferred, and that this documentation is consistent with the documentation submitted to the Institute within the scope of the application for authorisation or notification of the clinical trial, including updated documentation submitted to the Institute as of the day of the implementation of the change;

d)

a plan safeguarding the provision of information about the change of the sponsor within the scope of the concerned clinical trial, including, for example, an amendment to the protocol, information for the investigators, information for trial subjects and labelling of the investigational medicinal products reflecting the concerned change.

CHAPTER FOUR

MONITORING AND AUDITING OF CLINICAL TRIALS

Section 21

Monitoring of clinical trials

(1) The supervision of the clinical trial shall be secured by the sponsor by means of monitoring the clinical trial, through which it shall be verified, in particular, that:

a)

the rights and safety of all trial subjects are not being compromised;

b)

the recorded data are correct, complete and verifiable on the basis of source documents;

c)

the clinical trial is progressing in compliance with the latest approved version of the protocol and its possible amendments, good clinical practice and related legal regulations.

(2) The scope and method of monitoring shall be determined by the sponsor with a view to the objective, purpose, design, complexity, blinding, scope, and target parameters of the concerned clinical trial. Monitoring is usually performed prior to the commencement of the clinical trial, in its course and after its completion.

(3) The sponsor may appoint persons to monitor the clinical trial at the trial site prior to its commencement, in its course and upon its completion (hereinafter referred to as “monitors”) and to safeguard cooperation between the sponsor and the investigator. These persons shall:

a)

have relevant qualifications and knowledge necessary for the monitoring of the clinical trial; their qualifications shall be documented;

b)

be acquainted with the investigational medicinal products, the protocol, written informed consent form and other written information provided to trial subjects, the sponsor's standard operating procedures, good clinical practice and legal regulations governing the clinical trial.

(4) In the monitoring of the clinical trial, monitors shall proceed in compliance with Annex 10 hereto.

Section 22

Audit

(1) An audit shall be considered a systematic, sponsor-independent assessment of the activities and documents pertaining to the clinical trial, which is to determine whether the activities pertaining to the clinical trial have been implemented and whether data have been recorded, analysed and accurately reported in compliance with the protocol, the sponsor's standard operating procedures, good clinical practice and related legal regulations.

(2) For the purposes of auditing, the sponsor shall appoint persons who are independent of the conducted clinical trial, who are not involved in its monitoring or quality assurance control (hereinafter referred to as the “auditors”); the auditors shall have appropriate qualifications and knowledge necessary for the conduct of audits of the clinical trial and their qualifications shall be documented.

(3) The sponsor shall ensure for the audits to be performed in compliance with the written procedures drafted by the sponsor, which define the subject-matter of the audit, method of auditing, frequency of audits, the form and contents of audit reports.

(4) The plan of audits and selected procedures shall be adapted to the nature of the clinical trial, particularly with a view to the data submitted to control authorities, the number of trial subjects, type and complexity of the clinical trial, degree of risk for trial subjects and, if applicable, also to shortcomings in adherence to the principle of good clinical practice or legal regulations identified in the course of the clinical trial to date.

(5) Observations and findings of the auditors shall be documented and these records shall be stored in compliance with Annex 3 hereto.

(6) Where shortcomings in the activities of the investigator, the healthcare facility or the sponsor in terms of compliance with the protocol, standard procedures, good clinical practice and related legal regulations are identified by the audit, the sponsor shall forthwith adopt corrective action.

(7) If the shortcomings referred to in paragraph 6 are serious or permanent, the sponsor shall terminate the participation of the investigator or of the healthcare facility in the clinical trial and shall forthwith inform the ethics committee and the Institute to this effect. The sponsor shall proceed in the same manner if such shortcomings have been identified by the monitoring of the clinical trial referred to in Section 21.

PART THREE

CLINICAL TRIALS ON VETERINARY MEDICINAL PRODUCTS

Section 23

The investigator

The basic activities of the investigator shall be:

- a) before the commencement of the clinical trial to submit to the sponsor an updated professional CV and, if applicable, a declaration of the conflict of interests, declaration of confidential handling of information and other personal data necessary for the clinical trial to progress in compliance with its protocol;
- b) to ensure that the clinical trial is conducted in compliance with the protocol and that the principles of good clinical practice are adhered to;
- c) to maintain in the documentation of the clinical trial signed and dated copies of the protocol of the clinical trial, including all amendments; each protocol amendment drafted by the sponsor or by the investigator must be signed and dated thereby and must specifically state what has been changed and provide a rationale thereof;
- d) to forthwith notify the sponsor about any deviations from the protocol of the clinical trial;
- e) to ensure a sufficiently qualified staff, including activities conducted on the basis of subcontracts, for the proper conduct of the clinical trial and to provide, in a proper manner, to the staff involved in the clinical trial or taking care of the animals information and relevant materials and information obtained from the sponsor;
- f) to ensure, in the course of the clinical trial, the use of adequate and well maintained equipment and machines and compliance with standard operating procedures;
- g) to secure the informed consent from each breeder of animals prior to their inclusion in the clinical trial, based upon adequate information about the participation in the clinical trial;
- h) to supervise the stabling, feeding and care for animals at the trial site and to inform the breeder about animals stabled outside their permanent stabling;
- i) to document all interventions and procedures, changes in the health of animals and major changes to the environment;
- j) to safeguard the requirements of the protocol governing the use of edible products obtained from food-producing animals, to whom investigational or control veterinary medicinal products have been administered, and to adhere to the measures adopted for the disposal of the tested animals;
- k) to forthwith inform the sponsor about adverse reactions;
- l)

- to ensure that any blinding is disclosed only in compliance with the protocol and with the approval of the sponsor;
- m) to ensure the receipt, storage, distribution and any other handling of the investigational and control veterinary medicinal product and to maintain relevant records, including remaining stock;
- n) to ensure the administration of investigational and control veterinary medicinal products to animals only in compliance with the protocol of the clinical trial;
- o) following the completion of the clinical trial, to compare the records of receipt, use and remains of investigational and control veterinary medicinal products and to explain any arising differences, if applicable;
- p) if the clinical trial is suspended or terminated, to ensure relevant documentation of the safe disposal of the investigational and control veterinary medicinal product, including remains of feedingstuffs medicated therewith;
- q) to document unforeseen events which may affect the course of the clinical trial, and measures adopted;
- r) to maintain complete records of all visits, letters and other contacts with the sponsor, with the representatives of involved authorities as well as with other persons associated with the design, conduct, and documentation of the clinical trial;
- s) to safely store and protect from damage or destruction any documentation of the clinical trial, including copies thereof, for the period stipulated by Section 61, paragraph 4 (e) of the Act on Pharmaceuticals;
- t) to provide the sponsor upon request with signed documentation of the clinical trial or its authenticated copy, keeping one copy and, if applicable, to take part in the drafting of the summary report;
- u) to allow for the monitoring and auditing by means of which the quality of the clinical trial is verified, and enable the Veterinary Institute to conduct inspections of the facilities used by the investigator and of any documentation, including the provision of requested copies for the purposes of compliance with the protocol of the clinical trial.

Section 24

The sponsor

(1) The basic activities of the sponsor shall be:

- a) to ensure scientifically sound information about the efficacy and safety of the investigational veterinary medicinal product on the basis of which it may be explicitly concluded that there are no reasons which would prevent the conduct of the clinical trial;
- b)

- to select the investigator, to ensure his/her qualification, secure his/her availability for the duration of the clinical trial and to verify his/her consent with assuming the responsibility for the clinical trial in compliance with the protocol and with the principles of good clinical practice;
- c) to appoint a qualified monitor;
 - d) in necessary cases to arrange for the preparation of standard operating procedures applied within the scope of the clinical trial;
 - e) following a consultation with the investigator, to prepare the protocol of the clinical trial in compliance with the principles of good clinical practice and to sign it together with the investigator and, furthermore, together with the investigator to approve and sign any amendments to the protocol;
 - f) for a multicentric clinical trial to ensure that all investigators conduct the clinical trial in compliance with the protocol on the basis of a uniform system of data recording and uniform instructions concerning the established procedures;
 - g) to inform the investigator about relevant chemical, pharmaceutical, toxicological, safety and other significant data, which become available in the course of the clinical trial, and to ensure that they are brought also to the attention of the Veterinary Institute;
 - h) to record all identified adverse reactions;
 - i) to safeguard proper disposal of all animals included in the clinical trial and of all edible products obtained from them in compliance with the established requirements;
 - j) to compile and store records of deliveries of the investigational and control veterinary medicinal product; if the clinical trial is suspended or terminated, to ensure proper disposal of all stock thereof, including feedingstuffs medicated therewith;
 - k) to store clinical trial documentation and protect it from damage or destruction for the period stipulated by the Act on Pharmaceuticals;
 - l) to ensure the quality and integrity of data from the clinical trial by means of an audit.

(2) The sponsor may, if effective, by means of a written contract assign the organisation of selected or all of its activities associated with the clinical trial to qualified contract organisations.

Section 25

The monitor

The basic activities of the monitor shall be:

- a) to provide the sponsor with an opinion regarding the appointment of the investigator;

- b) to provide the investigator with necessary information relevant for the clinical trial, by means of a personal or telephone consultation, or in another manner agreed by the monitor and by the investigator, always when required by the circumstances of the clinical trial;
- c) to make sure that the investigator and the staff have enough time to conduct the clinical trial, to ensure that the trial site will have adequate space, facilities, equipment and staffing resources and that the necessary number of animals will be available for the duration of the trial;
- d) to verify that the staff involved in the clinical trial is informed about all major facts relevant to the clinical trial;
- e) to ensure that the investigator understands the requirements of the clinical trial and accepts responsibility for its conduct;
- f) to work in compliance with the requirements of the sponsor, to visit the investigator in adequate frequency, before, in the course of and after the completion of the clinical trial, for the purposes of adherence to the protocol and to the principles of good clinical practice;
- g) to ensure that the breeder's informed consent is secured before the animals are enrolled in the clinical trial;
- h) to guarantee that all data are accurately, correctly and completely recorded and that illegible, missing or corrected documentation is fully explained;
- i) to verify that the storage, dispensing and stock logging of the investigational and control veterinary medicinal product are safe and suitable and that the unused investigational and control veterinary medicinal product is returned to the sponsor or properly disposed of;
- j) to verify primary records and other documentation of the clinical trial necessary for compliance with the study protocol and to check whether information stored by the investigator is complete and accurate;
- k) to prepare and maintain complete records of all visits, letters and other contacts with the investigator, sponsor and representatives of all other involved organisations in sufficient detail for the procedures which may be performed by the investigator and the sponsor;
- l) to endorse compliance with the principles of good clinical practice by the investigator by means of signed and dated reports on the contacts, visits that have taken place, and documented activities during the conduct of the clinical trial; to present them to the sponsor at the end of the clinical trial.

Section 26

Audit

(1) For the purposes of auditing, the sponsor shall appoint auditors (Section 22, paragraph 2), who shall have appropriate qualifications and knowledge necessary for the conduct of audits of the clinical trial. The qualifications of the auditors shall be documented.

(2) The sponsor shall ensure for the audits to be performed in compliance with the written procedures drafted by the sponsor, which define the subject-matter of the audit, method of auditing, frequency of audits, the form and contents of audit reports.

(3) The plan of audits and selected procedures shall reflect the importance and purpose of the clinical trial, the number of trial animals, type and complexity of the trial, degree of risk for trial animals, and existing knowledge of the clinical trial.

(4) Where serious shortcomings are identified, the sponsor shall forthwith adopt corrective action or, if applicable, shall terminate the clinical trial. The sponsor shall forthwith inform the Veterinary Institute about these measures. The same procedure shall apply if such shortcomings are identified by the monitor.

(5) Observations and findings of the auditor shall be documented and the sponsor shall store certificates of performed audits.

Section 27

Investigational veterinary medicinal products and their labelling

Within the scope of good clinical practice, veterinary medicinal products used in a clinical trial shall comply with the following conditions:

- a) they are adequately labelled as per Section 19, paragraph 2 and show the words “For clinical trial use only” and “For animal use only”;
- b) adequate time, temperature and other necessary conditions of their storage have been established;
- c) they have acceptable stability for the duration of their use;
- d) they are in a packaging which protects them from contamination and degradation during transport and storage;
- e) they are stored in sufficient quantities for possible control, and, furthermore, records of analyses and characteristics of samples of individual batches are maintained, until data obtained from the clinical trial are evaluated;
- f) in the case of blinding of the clinical trial, the coding system must allow for rapid identification of these products; any unblinding must be detectable;
- g) they are manufactured in compliance with the principles of good manufacturing practice.

Section 28

Application for clinical trial authorisation

(1) An application for clinical trial authorisation shall be submitted to the Veterinary Institute in two counterparts by the sponsor, using the relevant form.

(2) The following data shall form attachments to the application:

- a) authorisation for use of experimental animals issued by the concerned state authority pursuant to other legal regulations;
- b) consent of the breeder of the animals;
- c) clinical trial protocol, including case report forms for the trial animals, and its amendments, if applicable, drafted in compliance with the requirements outlined in Annex 11 hereto;
- d) written information for the investigator, either in the form of the summary of the product characteristics or a set of available product information, containing data listed in Annex 12 hereto;
- e) written information for breeders in the Czech language, containing data referred to in Annex 13 hereto;
- f) pharmaceutical data about the investigational veterinary medicinal products referred to in Annex 14 hereto;
- g) proof of payment of costs;
- h) information on non-acceptance of the clinical trial by a foreign control authority, if applicable.

(3) Upon request of the Veterinary Institute, the sponsor shall submit other source materials necessary for the assessment of the concerned clinical trial. Specific requirements for individual parts of the dossier, if applicable, shall be published in the information media of the Veterinary Institute.

(4) Where the investigational medicinal product is a genetically modified organism, documents referred to in Section 60, paragraph 4 (b) of the Act on Pharmaceuticals shall be submitted together with the application.

Section 29

Documents, records and reports

(1) Documentation defined in Annex 15 hereto shall be maintained about the conduct of the clinical trial.

(2) Any change or adjustment in the documentation, case report forms for trial animals or reports must be dated and signed, and if necessary, must be explained, whereas the original record must be preserved. Changes or amendments shall be conducted in compliance with the written operating procedures of the sponsor.

(3) Documents, records, and reports associated with the clinical trial must be made available to the sponsor, to the Veterinary Institute, to the monitor and to persons performing audit.

(4) Progress report on the clinical trial shall contain data listed in Annex 16 hereto.

Section 30

Serious adverse reaction reporting

Reports for the Veterinary Institute and for the sponsor shall contain information about the trial site, the name or name(s) and surname of the sponsor, title of the clinical trial, and protocol number, identification of the animal and description of the reaction, name of the investigational and control veterinary medicinal product, including the administered dose and method of application. The reporting to the Veterinary Institute shall be made within the maximum of 15 days of the detection of the event; where a death or jeopardy to the life of the animal is concerned, the information shall be delivered within the maximum of seven days.

Section 31

Suspension and early termination of the clinical trial

If the clinical trial is suspended or terminated early, the investigator shall forthwith inform the breeder, the Veterinary Institute and the concerned Regional Veterinary Administration to this effect and shall provide for further treatment and monitoring of the condition of the trial animals.

Section 32

Information about the completion of the clinical trial and summary report

(1) Information about the completion of the clinical trial shall be submitted by the sponsor to the Veterinary Institute within 60 days of the completion of the clinical trial.

(2) Information about the completion of the clinical trial shall contain data listed in Annex 17 hereto.

(3) Following the completion of the clinical trial, the sponsor shall forthwith draw a summary report, which shall contain conclusions of the concerned clinical trial and their analysis. The summary report shall contain particulars listed in Annex 18 hereto.

PART FOUR

FINAL PROVISIONS

Section 33

Repealing provisions

The following is hereby repealed:

1. Decree No. 472/2000 Coll., on good clinical practice and detailed conditions of clinical trials on pharmaceuticals;
2. Decree No. 301/2003 Coll., amending Decree No. 472/2000 Coll., on good clinical practice and detailed conditions of clinical trials on pharmaceuticals.

Section 34

Coming into force

This Decree comes into force on the first day of the calendar month following the date of enactment.

Minister:

Minister:

Mgr. Gandalovič v. r.

MUDr. Julínek, MBA v. r.

Annex 1 to Decree No. 226/2008
Coll.
Annex 2 to Decree No. 226/2008
Coll.
Annex 3 to Decree No. 226/2008
Coll.
Annex 4 to Decree No. 226/2008
Coll.
Annex 5 to Decree No. 226/2008
Coll.
Annex 6 to Decree No. 226/2008
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Annex 7 to Decree No. 226/2008
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Annex 8 to Decree No. 226/2008
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Annex 9 to Decree No. 226/2008
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Annex 10 to Decree No. 226/2008
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Annex 11 to Decree No. 226/2008
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Annex 12 to Decree No. 226/2008
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Annex 13 to Decree No. 226/2008
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Annex 14 to Decree No. 226/2008
Coll.
Annex 15 to Decree No. 226/2008
Coll.
Annex 16 to Decree No. 226/2008
Coll.
Annex 17 to Decree No. 226/2008
Coll.
Annex 18 to Decree No. 226/2008 Coll.

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- 1) Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, as amended by Regulation (EC) 1901/2006. Commission Directive 2005/28/EC of 9 April 2005, laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products
- 2) For example Decree No 307/2002 Coll., on radiation protection, as amended by o Decree No. 499/2005 Coll.
- 3) For example Act No 123/2000 Coll., on Medical Devices and on Amendments to Some Related Acts, as amended.
- 4) Section 52, paragraph 2 of Act No 378/2007 Coll., on Pharmaceuticals and on Amendments to Some Related Acts (Act on Pharmaceuticals).
- 5) Section 6, paragraph 1 (c) of Act No 378/2007 Coll.
- 6) Act No 101/2000 Coll., on the Protection of Personal Data and on Amendments to Some Acts, as amended.
- 7) Section 67b of Act No 20/1966 Coll., on the Care of the People's Health, as amended. Decree No. 385/2006 Coll., on healthcare documentation, as amended. Act No 499/2004 Coll., on Archiving and Documentary Services and on Amendments to Some Acts, as amended.
- 8) For example Decree No. 229/2008 Coll., on the manufacture and distribution of pharmaceuticals.
- 9) Section 2 (d) of Act No 78/2004 Coll., on the Use of Genetically Modified Organisms and Genetic Products.
- 10)

Section 5 of Decree No. 209/2004 Coll., on detailed conditions governing the handling of genetically modified organisms and genetic products.

11)

Section 79, paragraph 5 of Act No 378/2007 Coll.

Annex 1

Protocol of the clinical trial and amendments to protocol

The protocol of the clinical trial shall contain at least the following data in the below outlined structure. Information specific for individual trial sites may be provided on special pages of the protocol or mentioned in separate documents. If some of the data are provided in other documents of the clinical trial, such as in the investigator's brochure, the protocol shall contain relevant references. The protocol shall have a table of contents and its title page(s) shall show the following:

- a) title of the protocol, its identification number and date of issue; any potential amendments must be identified by amendment number and date;
- b) name and address of the sponsor and of the monitor;
- c) name of the person authorised to sign the protocol and its amendments on behalf of the sponsor;
- d) name, address, and telephone number of the qualified advisor for consultations regarding health issues and issues arising in association with the clinical trial, appointed by the sponsor for the clinical trial in question;
- e) names of investigators responsible for the conduct of the clinical trial, addresses and telephone numbers of trial sites;
- f) name, address, telephone number of the investigator or doctor responsible for medical decisions at the trial site;
- g) name and address of testing facilities performing laboratory tests and of other healthcare or technical departments involved in the clinical trial.

1. Basic information

The name and description of investigational medicinal products shall be provided as well as an overview of findings from non-clinical studies, which may be of clinical significance, and findings from clinical trials related to the study in question. Known and potential risk and benefits for man shall be summarised. The selected method of administration, dosage, dosage scheme, and duration of administration of the investigational medicinal product shall be described and justified. Characteristics of trial subjects to be involved in the clinical trial shall be specified and references to literature and data associated with the clinical trial and representing the basis of the clinical trial shall be provided. This introductory part shall contain a declaration that the clinical trial shall be conducted in compliance with the protocol, principles of good clinical practice, and legal regulations.

2. Objectives of the clinical trial

A detailed description of the objectives and a rationale of the clinical trial.

3. Plan of the clinical trial

Primary and, if applicable, secondary objectives followed in the course of the clinical trial shall be specified. The type and design of the conducted clinical trial shall be described (for

example, double-blind, placebo-controlled, parallel-group study) as well as the scheme of procedures and individual steps, including measures adopted in order to exclude bias (for example method of randomisation or blinding). A description of trial subject treatment, including doses and dosage scheme, pharmaceutical form, packaging and labelling of investigational medicinal products shall be provided. The expected duration of trial subject participation in the trial and the sequence and duration of individual stages of the trial, including follow-up, where applicable, and rules and criteria for termination and for discontinuation of participation of individual trial subjects, parts of or the entire clinical trial shall be specified. Procedures to report accountability of investigational medicinal products, including applied reference products and placebo, where applicable, procedures of handling randomisation codes and of decoding shall be described. Data entered directly in the case report forms (i.e. without previous written or electronic recording) and data which are considered to be source ones shall be specified.

4. Selection of trial subjects and their exclusion

Inclusion, exclusion and withdrawal criteria for the participation of trial subjects in the concerned clinical trial shall be specified. Withdrawal procedures shall include data about when and how a subject is to be withdrawn from the clinical trial or when and how to discontinue the administration of the medicinal product, the nature and timing of data collected for withdrawn subjects, their follow-up and data about whether and how the subjects are to be replaced.

5. Treatment of trial subjects

The treatment, including the names of all administered medicinal products, their dosage, dosage scheme, method of administration and duration of treatment including follow-up of subjects for each administered investigational medicinal product and group shall be described. Acceptable treatment before or during the clinical trial (including rescue therapy) and treatment which is not acceptable during the above mentioned periods shall be specified. Procedures to monitor trial subjects' compliance with all stipulated procedures shall be described.

6. Evaluation of efficacy

Efficacy parameters and methods and timing of assessment, recording, and evaluation of efficacy parameters shall be specified.

7. Evaluation of safety

Safety parameters and methods and timing of assessment, recording, and evaluation of safety parameters, procedures to identify, record and report adverse events and intercurrent diseases and the type and duration of follow-up of subjects after adverse events shall be stated.

8. Statistics

Applied statistical methods, including the timing of scheduled preliminary analyses shall be described. The number of subjects scheduled to participate in the clinical trial shall be specified, for multicentric trials the numbers of subjects planned for individual trial sites shall be given. The selection of the set size shall be justified, including a consideration or calculation of clinical trial statistical cogency. The applied level of significance, criteria for termination of the clinical trial, method of processing of missing, unused and false data, and procedures for the reporting of any deviations from the original statistical plan shall be specified (all deviations from the original statistical plan must be described and justified in the protocol or in the summary report, if appropriate). The selection of subjects for evaluation (for

example all randomised subjects, all subjects to whom the investigational medicinal product has been administered) shall be described.

9. Direct access to source documents

Unless direct access to source documents is safeguarded by a separate written agreement, it shall be stated that the investigator as well as the healthcare facility shall allow for the monitoring of the concerned clinical trial, for audits, supervision by ethics committee, inspections by control authorities and for access to source documents.

10. Quality assurance and management

11. Ethical issues

Ethical principles and issues considered in respect of the clinical trial shall be described.

12. Handling of data and storage of records

13. Funding and insurance

Unless described in a separate contract, the method of funding and insurance shall be specified.

14. Principles of publication

Unless specified in a separate agreement, the principles of publication shall be stated.

Annex 2

Data to be specified in the information for trial subjects and in the written informed consent form

The information for trial subjects and the written informed consent form shall contain the following data:

- a) a notice to the effect that the clinical trial is a research activity;
- b) objectives of the clinical trial;
- c) treatment procedures and a notice of the probability of random assignment to individual groups with various treatments where a randomised clinical trial is concerned;
- d) procedures and interventions in the course of the clinical trial, including all invasive interventions;
- e) responsibilities of the trial subject;
- f) emphasis on those elements of the clinical trial which are of a research nature;
- g) foreseeable risks or discomfort for the trial subject, including potential risk to foetus or breastfed infants;
- h) expected benefits; the trial subject shall be advised even if no clinical benefit is expected for trial subjects;
- i) alternative therapeutic procedures which may be applied for the treatment of the trial subject, their benefits and risks;
- j) the treatment and conditions of damage compensation provided to trial subjects in the event of an injury arising from the subject's participation in the clinical trial;
- k) expected amount of subject remuneration for the subject's participation in the clinical trial;
- l) expected expenditures of the subject associated with the subject's participation in the clinical trial;

- m) information to the effect that the subject's participation in the clinical trial is voluntary and that the subject may decline its participation or may withdraw from the clinical trial at any time, without any detriment or loss of benefits to which the subject is otherwise entitled;
- n) consent with the monitors, auditors, the concerned ethics committee and the Institute having direct access to the original clinical documentation for the purposes of verification of the conduct of the clinical trial or data, without the confidentiality of subject information being compromised, within the scope permitted by legal regulations, and information that by signing the informed consent the subject or its authorised guardian agree with this fact;
- o) consent with storing the records on the basis of which the trial subject may be identified as confidential and not being, in the extent guaranteed by legal regulations, made publicly available; if the results of the clinical trial are published, the identity of the subject shall not be disclosed;
- p) consent with the fact that the trial subject or its guardian shall be informed in time should any information that might be relevant to the subject's decision about continued participation in the clinical trial, arise;
- q) information about persons from whom it will be possible to obtain additional information concerning the clinical trial and trial subject rights and information about who should be contacted in the event of an injury associated with the clinical trial;
- r) foreseeable circumstances and reasons for which the participation of the subject in the clinical trial may be terminated;
- s) expected duration of the subject's participation in the clinical trial;
- t) approximate number of trial subjects participating in the clinical trial.

Annex 3

(Table – tbd)

Annex 4

Investigator's Brochure

The investigator's brochure shall contain at least the following data about the investigational medicinal product(s) in the below outlined structure. The Brochure shall have a title page showing the name of the sponsor, the name of the investigational medicinal product or its identification code, data of issue, and, where applicable, version number of the investigator's brochure.

1. Table of contents

2. Brief summary

It shall, on the maximum of two pages, provide basic information about physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical properties of the investigational medicinal product.

3. Introduction

It shall contain the chemical name of the investigational medicinal product and its international non-proprietary or commercial name, if it exists, the contents of active

substances, pharmacotherapeutic group and the position of the medicinal product within the group, rationale of the research, expected method of use, and indications.

4. Physical, chemical and pharmaceutical properties and composition

The description of the active substance(s) contained in the investigational product, including the chemical formula (rational as well as structural) and a brief description of their physical, chemical, and pharmaceutical properties shall be provided; moreover, the pharmaceutical form and composition shall be specified, including excipients and instructions for correct storage and handling of the investigational medicinal product. Structural similarities with other known pharmaceuticals shall be mentioned.

5. Non-clinical studies

The results of pharmacological, toxicological, pharmacokinetic and metabolic studies shall be provided in the form of a summary (preferably in tabular format). The applied methods of evaluation, results and interpretation of findings in relation to the investigational medicinal product and possible adverse reactions in man shall be mentioned as well as animal species used for non-clinical studies, numbers and gender of animals in each group, appropriately converted size of the administered dose (for example mg/kg, mg/m²), dosage intervals, method of administration, duration of administration, information about systemic distribution, duration of follow-up after the administration of the medicinal product has stopped.

Information about results shall include: the nature, frequency and severity or intensity of pharmacological and toxic effects, time of onset, reversibility and duration of effects and dose-dependency of response. This section shall specify the major findings from non-clinical studies and their relevancy to man. The identified effective and non-toxic doses in the same animal species (therapeutic index) and the relevancy of this information for the proposed human dosage shall be compared.

5.1 Preclinical pharmacology

It shall contain a summary of pharmacological properties of the investigational medicinal product and, if applicable, of its important metabolites monitored in animals. It shall include studies evaluating potential therapeutic effects (for example efficacy model, receptor binding and specificity) and studies evaluating safety (for example special studies to determine other pharmacological effects).

5.2 Pharmacokinetics and metabolism of the medicinal product in animals

A summary of pharmacokinetics, biological transformation, and distribution of the investigational pharmaceutical in all studied species shall be provided. Absorption, local and systemic bioavailability of the pharmaceutical and of its metabolites and relation to pharmacological and toxicological findings in animal species shall be evaluated.

5.3 Toxicology

A summary of toxicological effects in various animal species identified in toxicity studies after single and repeat administration, carcinogenicity studies, special studies (for example irritability or sensitisation), reproduction toxicity and genotoxicity (mutagenicity).

6. Effects in man

Known effects of the investigational medicinal product in man, including pharmacokinetics, metabolism, pharmacodynamics, dose-dependency of the response, safety, efficacy, and other pharmacological data shall be evaluated. A summary of all completed clinical trials and any

other possible experience in the use of the investigational medicinal product in practice shall be presented.

6.1 Pharmacokinetics and metabolism of the medicinal product in man

Summary of information about pharmacokinetics of the investigational medicinal product containing pharmacokinetics (including metabolism, absorption, plasma protein binding, distribution and elimination), bioavailability in the application of the concerned pharmaceutical form (absolute and/or relative), population groups (for example gender, age, organ dysfunction), interactions (for example interactions with other products and food) and other pharmacokinetic data.

6.2 Safety and efficacy

A summary of information obtained from previous clinical trials both in healthy volunteers and in patients in respect of the safety, pharmacodynamics, efficacy and dose-dependency of the response of the investigational medicinal product and, if applicable, its metabolites. In the case of a larger number of clinical trials a summary overview of efficacy and safety in individual trials by indications in various population groups and an overview of adverse reactions from all clinical trials may be provided. Significant differences in the nature and incidence of adverse reactions shall be stated for all indications or for population groups, as well as possible risks and adverse reactions which may be expected on the basis of previous experience with the investigational medicinal product or with related pharmaceuticals. Warnings or the need for special supervision in the use of the investigational medicinal product shall be specified.

6.3 Experience from the use of the investigational medicinal product in practice

Countries where the investigational medicinal product is authorised or where its marketing authorisation has been rejected or revoked shall be listed. Any significant information obtained from use in practice (including pharmaceutical form, dosage, method of administration, and adverse reactions) shall be summarised.

7. Conclusion

An overall evaluation of non-clinical and clinical data about the investigational medicinal product obtained from various sources the purpose of which is to provide the investigator with an interpretation of available data, including implications for future clinical trials. Published reports on related pharmaceuticals shall be evaluated in order to be able to foresee adverse reactions to the investigational medicinal product or other problems in the clinical trial.

Annex 5

Pharmaceutical data about investigational medicinal products submitted together with the application for clinical trial authorisation

(including all products used in the study, including placebo)

1. Products without marketing authorisation

- a) product name, pharmaceutical form(s), strength(s);
- b) full quantitative and qualitative composition of the product;
- c) name and address of all manufacturers involved in the manufacture of the given product, including, if applicable, the organisation performing sample blinding, specifying their functions in the manufacturing chain;

- d) name and address of the manufacturer performing final product release;
- e) certificate of compliance with the conditions of good manufacturing practice in the entire manufacturing or preparation process of the investigational medicinal product (for example a certificate evidencing compliance with the conditions of good manufacturing practice issued by the state control authority or a certificate of continuously conducted state inspections or an authorisation of manufacture of medicinal products for clinical trials specifying the authorised activities;
- f) information about active substance(s):
 - chemical name and formula,
 - name and address of all manufacturers specifying their functions in the manufacturing chain,
 - specifications of the active substance,
 - control analytical methods,
 - certificate of analysis for at least one batch of the active substance,
 - if the substance is not included in the European, American or Japanese pharmacopoeia or in a pharmacopoeia of any of the EU Member States, also:
 - evidence of identity and structure, characterisation of impurities,
 - scheme of synthesis specifying all starting materials, solvents and catalysts,
 - batch analysis results of batches used for preclinical studies and previous clinical studies,
 - batch analysis results of batches intended for use in the clinical study,
 - stability data in the form of stability study results;
- g) a brief description of the manufacture of the product (a general description of individual stages emphasising viral elimination or, if applicable, inactivation for products containing substances of biological origin, including the specification of blinding, where applicable);
- h) product specifications;
- i) control analytical methods for the product;
- j) certificates of analysis;
- k) description of immediate packaging;
- l) stability data for the product, proposed shelf-life, proposed storage conditions;
- m) documents of securing the product from the risk of BSE/TSE transmission.

The scope of submitted information shall be adopted to the degree of development of the medicinal product, whereas in initial stages of development emphasis shall be placed upon the identification and control of the active substance, while final specifications and complete data about the substance as well as the product are expected only at the end of the entire development; the fact whether a newly developed substance or a new product containing a known substance is concerned and trial subject exposure with a view to the scope, objectives, and expected study duration shall be taken into account.

2. Products authorised in the Czech Republic or in another country in the same pharmaceutical form, strength and pack size

- a) product name, pharmaceutical form(s), strength(s), pack size;
- b) name of the active substance(s), list of all excipients;
- c) where a product authorised in the Czech Republic is concerned, the name and address or registered office of the marketing authorisation holder or marketing authorisation number of the product in the Czech Republic;
- d) where a product authorised in another country is concerned, the name and address or registered office of the holder of marketing authorisation in the given country, specifying the year when the product has been authorised in this country, and the marketing authorisation number of the product.

Annex 6

Clinical trial progress report

A clinical trial progress report shall contain the following in the below outlined sequence:

- a) a description of the current status of the clinical trial, a brief description of the progress of the clinical trial to date, changes to investigators and trial sites in the Czech Republic, number of enrolled patients in the Czech Republic;
- b) information about newly identified properties of the investigational medicinal products, new findings about the investigational medicinal products in respect of their safety and efficacy;
- c) newly adopted measures in respect of the conduct of the clinical trial, for example interventions of ethics committees in the course of the clinical trial, interventions of foreign authorities, restrictive interventions of the sponsor in the course of the clinical trial, if applicable;
- d) information about performed audits.

Annex 7

Annual safety report

The annual safety report shall contain the following data in the below outlined structure:

1. Report on the safety of trial subjects in the concerned clinical trial

In this part, the sponsor shall provide a comprehensive safety analysis and risk-benefit evaluation. The evaluation should contain any newly known information relevant for the safety of the investigational medicinal product and its critical analysis with a view to potential impact upon the trial subjects enrolled in the clinical trial, i.e. information which is not provided in the investigator's brochure or in the summary of the product characteristics. In the evaluation, the following should be considered:

- a) dosage of the medicinal product, duration of effect, duration of treatment;
- b) reversibility of changes that have occurred;
- c) description of previously unreported toxicity in subjects;
- d) an increase in frequency, i.e. frequency of toxicity;
- e) whether changes due to overdosage or in the course of treatment have occurred;
- f) possible interactions or links to other risk factors;
- g) any specific information related to certain population groups, for example the elderly, children or otherwise defined risk groups;
- h) positive and negative findings related to pregnancy or breastfeeding;
- i) abuse of the medicinal product;
- j) risks associated with study or diagnostic procedures in the course of the clinical trial.

The report shall also provide significant/supporting results from non-clinical studies and other findings about the investigational medicinal product (for example spontaneous reports, literature sources), which may affect subject safety, including measures recommended to minimise risk. This section should be concluded with a detailed consideration with a justification why it is or why it is not necessary to adopt the following measures: amendment of the protocol, amendments or updates of patient information and informed consent form,

changes to package leaflet or to the investigator's brochure. The annual safety report does not substitute amendments to protocol.

2. A list of all suspected serious adverse reactions, including suspected serious unexpected adverse reactions in the given study

This part shall contain a special list of all reports of suspected serious adverse reactions, which have been reported in the course of the clinical trial. The list shall contain substantial information, but it shall not be necessary to report all details usually recorded for individual cases. Where several adverse reactions have occurred in a single subject for various reasons, it is necessary to record them as separate reports; a subject may hence appear in the list more than once. Individual reports shall be listed in the table separately by the standard organ system classification and shall show data as per the above specified recommendation. For each clinical trial a separate list shall be compiled; it may contain separate lists for individual investigational medicinal products (tested medicinal product, comparator, placebo) or even lists for various pharmaceutical forms, various indications, etc.

3. A summary table of suspected serious adverse reactions

The summary table of suspected serious adverse reactions should contain the numbers of all reports of individual signs, symptoms, or diagnoses for all trial subjects, separately for:

- a) each organ system the reports pertain to;
- b) individual types of adverse reactions;
- c) each treatment arm of the clinical trial (for example tested medicinal product, placebo, comparator). Unexpected adverse reactions shall be clearly highlighted in the table.

Annex 8

Information about completion, suspension or early termination of the clinical trial

The information about clinical trial completion shall contain data identical as those in the information about suspension or early termination, structured as follows:

- a) description of the completed clinical trial, list of trial sites and investigators in the Czech Republic, total number of trial subjects in the Czech Republic, a brief description and overall evaluation of the course of the study;
- b) information about preliminary conclusions from the clinical trial, information about the safety and monitored parameters of efficacy available before the final evaluation and drawing of the summary report on the clinical trial, including information about the site where the summary report will be available after it is completed;
- c) measures adopted in the course of the clinical trial, information about interventions of ethics committees in the course of the clinical trial, interventions of foreign control authorities and sponsor's interventions in the course of the clinical trial, if applicable;
- d) declaration of performed audits of the sponsor.

Where a clinical trial is suspended or early terminated, the information shall, furthermore, contain a rationale and a description of the method of execution, including the safeguarding of further treatment of trial subjects.

Annex 9

Summary report on the clinical trial

A summary report on the clinical trial shall contain the following data in the below specified structure.

1. Title page

This will show the name of the clinical trial, name or code of the investigational medicinal product, what indication the clinical trial has been focused on, a very brief characteristics of the clinical trial, if not obvious from the title, name of the sponsor, protocol number, phase of the clinical trial, date of commencement, date of early termination (if applicable), date of completion, name of the principal or coordinating investigator or responsible medical representative of the sponsor, name of the responsible representative of the sponsor and contact addresses for possible questions regarding the report, a declaration of compliance of the conduct of the clinical trial with the principles of good clinical practice and date of drawing the summary report.

2. Summary

The clinical trial shall be briefly described and its results presented.

3. Table of contents of the summary report

Page numbers of all parts of the report, including amendments and tables, shall be provided.

4. List of abbreviations and definitions of used terms

Abbreviations and terms essential for understanding the report shall be explained.

5. The ethics of the conduct of the clinical trial

5.1 Ethics committees: it shall be evidenced that the clinical trial, including any changes, has been conducted with the approval of ethics committees; a list of these committees shall be attached.

5.2 The course of the study compliant to ethical principles: it shall be confirmed that the study has been conducted in compliance with the ethical principles of the Helsinki Declaration.

5.3 Information for trial subjects and informed consent with participation in the study: it shall be specified how and when the informed consent of trial subjects has been obtained; written information for trial subjects and specimen of written informed consent form shall be attached.

6. The investigator and organisational background of the clinical trial

A brief description of distribution of individual functions and activities essential for the design, conduct, control and evaluation of the study shall be briefly described. A list of investigators at individual trial sites together with their CVs or data about their qualification shall be attached; furthermore, a similar list of persons who have been significantly involved in the conduct of the clinical trial shall be attached. Where extensive clinical trials are concerned, only the most essential data shall be presented.

7. Introduction

The position of the clinical trial in the overall context of the development of the medicinal product shall be briefly mentioned; basic characteristics of the clinical trial shall be presented (for example rationale, objectives, target population, primary evaluated parameters). Regulations or recommendations of control authorities taken into account in the drafting of the plan of the clinical trial shall be specified.

8. Objectives of the clinical trial

Objectives of the clinical trial shall be specified.

9. Research plan

9.1 Description of the study plan

9.2 Discussion on the study plan, including control group selection

9.3 Selection of population for the clinical trial

9.3.1 Inclusion criteria

9.3.2 Exclusion criteria

9.3.3 Withdrawal of patients from the treatment or trial

9.4 Medical care for trial subjects

9.4.1 Administered treatment

9.4.2 Identity of investigational medicinal products

9.4.3 Method of assigning patients to treatment groups

9.4.4 Selection of doses in the course of the study

9.4.5 Selection and timing of doses for each patient

9.4.6 Blinding

9.4.7 Previous and concurrent therapy

9.4.8 Compliance with treatment regimen

9.5 Variables characterising efficacy and safety

9.5.1 Determination of efficacy and safety, flowchart

9.5.2 Adequacy of measuring methods

9.5.3 Primary variables characterising efficacy

9.5.4 Measuring of concentration of the pharmaceutical

9.6 Data quality assurance

9.7 Statistical methods planned in the protocol and determination of sample size

9.7.1 Statistical and analytical plans

9.7.2 Determination of sample size

9.8 Changes to study process or to planned analysis

10. Patients included in the study

10.1 Patient logging

10.2 Deviations from the protocol

11. Evaluation of efficacy

11.1 Analysed data sets

11.2 Demographic and other essential characteristics

11.3 Measurements of treatment compliance

11.4 Results of evaluation of efficacy and patient data in tabular format

11.4.1 Analysis of efficacy

11.4.2 Statistical and analytical particulars

11.4.2.1 Covariable corrections

11.4.2.2 Procedures applied in the case of early termination of participation in the study and missing data

11.4.2.3 Progress analysis and data monitoring

11.4.2.4 Multicentric studies

11.4.2.5 Multiple comparisons (multiplicity)

11.4.2.6 Use of patient “efficacy subgroup”

11.4.2.7 Studies evidencing equality conducted in active control group

11.4.2.8 Analysis of subgroups

11.4.3 Tables for records of data from individual responses

11.4.4 Dosage of the medicine, concentration thereof and relations to response to treatment

11.4.5 Drug-drug and drug-disease interactions

11.4.6 Graphic representation of information obtained from individual patient data tables

11.4.7 Summary of efficacy of the medicinal product

12. Evaluation of safety

12.1 Duration of exposure to the investigational medicinal product

12.2 Adverse events

12.2.1 A brief summary of adverse events

12.2.2 Adverse event recording

12.2.3 Adverse event analysis

12.2.4 List of adverse events in patients

12.3 Death, other serious and other major adverse events

12.3.1 List of deaths and other serious and other major adverse events

12.3.1.1 Death

12.3.1.2 Other serious adverse events

12.3.1.3 Other major adverse events

12.3.2 Case studies – deaths, other serious and other major adverse events

12.3.3 Analysis of and discussion on deaths and other serious adverse events

12.4 Clinical laboratory assessment

12.4.1 Laboratory tests for individual patients (16.2.8) and all abnormal laboratory values (14.3.4)

12.4.2 Evaluation of all laboratory parameters

12.4.2.1 Laboratory values in the course of time

12.4.2.2 Changes to laboratory values in individual patients

12.4.2.3 Individual clinically significant abnormalities

12.5 Vital signs, physical findings and other observations associated with safety

12.6 Evaluation of safety

13. Discussion, general summary and conclusion

14. Tables and charts from the study but not contained in the text

14.1 Demographic data

14.2 Data about efficacy of the medicinal product

14.3 Safety data

14.3.1 Adverse event recording

14.3.2 List of deaths and other serious and major adverse events

14.3.3 Case reports – death and other serious and other major adverse events

14.3.4 List of abnormal laboratory values (for each patient)

15. List of used materials

16. Attachments

16.1 Information about the study

16.1.1 Protocol and amendments to protocol

16.1.2 Specimen case report form

16.1.3 List of ethics committees who have provided their opinion on the clinical trial, written patient information and text of the informed consent

16.1.4. List and description of investigators and other important participants of the study, including a brief CV or an equivalent overview of practical experience and expertise essential for the conduct of the study

16.1.5 Signatures of the principal or coordinating investigator

16.1.6 List of patients administered the medicinal product from specific batches, if more than one batch has been used

16.1.7 Randomisation scheme and codes allowing for the identification of the trial subject and of the relevant treatment

16.1.8 Certificates of audits

16.1.9 Documentation of statistical procedures

16.1.10 Documentation of laboratory standardisation methods and quality assurance procedures, if applied

16.1.11 Publications arising from the clinical trial

16.1.12 Important publications mentioned in the report

16.2. List of patients

- 16.2.1 Patients who have discontinued the clinical trial
- 16.2.2 Deviations from the protocol
- 16.2.3 Patients excluded from the analysis of efficacy
- 16.2.4 Demographic data
- 16.2.5 Compliance and/or data about concentration of the pharmaceutical, if available
- 16.2.6 Data about the effect of the medicinal product on individual patients
- 16.2.7 List of adverse events of each patient
- 16.2.8 A listing of individual laboratory results for each patient, if required by the control authority

16.3 Case Report Forms

- 16.3.1 Trial subject records about death, other serious adverse events and withdrawals due to an adverse event
- 16.3.2 Other submitted records for trial subjects

16.4 List of data for individual patients

Annex 10

Activities of monitors of clinical trials

1. A monitor shall examine the trial site prior to the commencement of the clinical trial, in its course and following its completion.
2. In compliance with the sponsor's requirements, the monitor shall ensure that the clinical trial is properly conducted and documented by means of the following activities in respect of the clinical trial and its site:
 - a) communication between the sponsor and the investigator;
 - b) verifies whether, in respect of the clinical trial in question:
 1. the investigator has adequate qualification and conditions for the conduct of the clinical trial,
 2. the facility, including laboratories, equipment and staffing, is adequate for safe and proper conduct of the clinical trial;
 - c) verifies, in respect of the investigational medicinal product, whether:
 1. storage times and conditions are acceptable and whether stock levels in the course of the trial are sufficient,
 2. investigational medicinal products are provided only to subjects for the administration to whom they are intended and in doses specified by the protocol,
 3. trial subjects have been properly instructed about the correct use, handling, storage, and returns of investigational medicinal products,
 4. the receipt, use, and return of investigational medicinal products at the trial site is adequately controlled and documented,
 5. the handling of unused investigational medicinal products at the trial site complies with the relevant legal regulations and sponsor's requirements;
 - d) verifies whether the investigator adheres to the approved protocol and, if applicable, to all of its approved amendments;
 - e) verifies whether the written informed consent has been obtained from the trial subject prior to the subject's inclusion in the clinical trial;

- f) ensures that the investigator gets the latest version of investigator's brochure, all documents and all particulars necessary for the conduct of the clinical trial properly and in compliance with legal regulations;
- g) ensures that the investigator and his/her staff are properly informed about the clinical trial;
- h) verifies whether the investigator and his/her staff carry out, within the scope of the clinical trial specified functions in compliance with the protocol or with the written agreement concluded by the sponsor and by the investigator/healthcare facility and whether they refrain from assigning these functions to unauthorised persons;
- j) verifies whether the investigator enrolls to the clinical trial only eligible subjects and monitors the recruitment of subjects for the trial;
- k) verifies whether source documents or other records from the clinical trial are correct, complete, up-to-date, and correctly stored;
- l) verifies whether the investigator provides all required reports, notifications, requests and source materials and whether these documents are correct, complete, readable, dated and identifiable by the clinical trial and whether they have been completed in time;
- m) controls and carries out cross-comparisons of the correctness and completeness of data in case report forms, source documents, and other records pertaining to the clinical trial.

3. A monitor shall verify, for example, whether:

- a) data required by the protocol are correctly recorded in the case report forms and whether they comply with source documents;
- b) all changes to dosage and/or treatment are properly documented for each trial subject;
- c) adverse events, add-on or concomitant therapy and concurrent diseases are recorded in the case report forms in compliance with the protocol;
- d) those control visits which the subject has not completed, tests which have not been performed and examinations which have not taken place are also recorded in the case report forms;
- e) all exclusions and withdrawals of enrolled subjects from the clinical trials are recorded and explained in the case report forms.

4. The monitor shall inform the investigator about any error, omission or corrupted readability of records in the case report forms and shall ensure that appropriate corrections, amendments or deletions of records are made, dated, explained, and signed by the investigator or by that person on his/her staff in the clinical trial who is authorised to make changes to case report forms on behalf of the investigator. This authorisation shall be documented.

5. The monitor shall verify whether all adverse events are properly reported in timelines required by good clinical practice, by the protocol, ethics committee, sponsor and relevant legal regulations.

6. The monitor shall check whether the investigator keeps essential documents.

7. The monitor shall inform the investigator about deviations from the protocol, from standard operating procedures, good clinical practice, and requirements of control authorities and shall adopt measures to prevent recurrence of the identified deviations.

8. The monitor shall proceed in compliance with the written operating procedures established by the sponsor for the monitoring of the clinical trial in question.

9. The monitor shall submit to the sponsor a written report on every visit to the trial site and on communication relevant for the concerned clinical trial, which shall contain:

a) the date, trial site, monitor's name and investigator's name, or if applicable, the names of other contacted persons;

b) a summary of what has been inspected by the monitor, and monitor's opinion regarding major findings, deviations and shortcomings, conclusions, measures which have been implemented or planned or measures recommended to ensure compliance.

10. The monitor's report shall be assessed by the sponsor and this assessment, as well as its consideration shall be documented by the sponsor.

Annex 3

I. Documents available prior to the commencement of the clinical trial

Number	Name of the document	Purpose of storage of the document	Stored with the investigator or in the healthcare facility	Stored with the sponsor
I/1.	Investigator's brochure	Documentation of the information about the investigational product provided to the investigator	X	X
I/2.	Clinical trial protocol, incl. any possible supplements signed by the investigator, sponsor, and administrator of the healthcare facility; and case report forms	Documentation of the investigator's and sponsor's approval of the protocol and of its amendments, if applicable	X	X
I/3.	Information provided to trial subjects: <ul style="list-style-type: none"> - written informed consent form; - instructions and any other information, if applicable; - materials for subject recruitment 	Documentation of the content of the written informed consent form; Documentation of the fact that trial subjects are provided with adequate information to be able to express a fully informed consent; Documentation of the fact that the method of subject recruitment is adequate and not coercive	X X X	X X
I/4.	Financial aspects of the clinical trial	Documentation of financial contract concluded by the investigator or healthcare facility, if applicable, and the sponsor	X	X

I/5.	Certificate of insurance for the sponsor and for the investigator covering compensation for trial subjects	Documentation of conditions under which and to what extent trial subjects will be compensated for possible injuries	X	X
I/6.	Signed contracts concluded by the stakeholders: <ul style="list-style-type: none"> - by the investigator/healthcare facility and the sponsor or contract research organisation; - by the sponsor and the contract research organization, if applicable 	Documentation of concluded contracts; containing e.g. the definition of responsibilities for individual activities, ensuring access to documentation, responsibility for the archival of documents, communication with the ethics committee, reporting and submission of reports	X X	X X
I/7.	Approval of the ethics committee (dated) of all data concerning the clinical trial notified thereto, and of all submitted documents	Evidence that the clinical trial has been assessed and approved by the ethics committee and identification of version numbers and dates of the documents	X	X
I/8.	Ethics committee membership	Evidence that the ethics committee has been established in compliance with the principles of good clinical practice	X	
I/9.	Authorisation issued by the Institute or certificate of notification	Documentation of the Institute's authorisation or of timely notification	X	X
I/10.	CVs and data about the qualification of the investigator(s) and any co-investigator(s), if applicable	Documentation of the qualification and competence for the conduct of the clinical trial	X	X
I/11.	Normal values/limits for results of tests included in the protocol	Documentation of normal values and/or limits for applied procedures	X	X
I/12.	Certificate of quality of conduct of laboratory	Documentation of the competence		X

	procedures/tests (certificate, accreditation, implemented quality control and/or external quality assessment or other validation)	of the facility conducting the required tests and of reliability of results		
I/13.	Specimen labelling of the investigational product	Documentation of compliance with the requirements governing labelling and of adequacy of the instructions for use for trial subjects		X
I/14.	Instructions for handling of investigational products and other materials	Documentation of instructions necessary to ensure proper storage, packaging, dispensing, and disposal of investigational products and other materials	X	X
I/15.	Records of supplies of investigational products and other materials	Documentation of dates of supplies, batch numbers, and method of supplying investigational products and other materials allowing for product batch traceability, control of transport conditions and accountability	X	X
I/16.	Certificates of supplied investigational products	Documentation of the identity, purity and contents of investigational products used in the study		X
I/17.	Decoding procedures for blinded studies	Documentation of how to disclose, if necessary, the identity of a blinded product without compromising the blinding of investigational products for other trial subjects	X	X
I/18.	Randomisation procedure	Documentation of the procedure		X

		used for the randomisation of trial subjects		
I/19.	Monitor's report before the commencement of the clinical trial	An evidence that the site is suitable for the clinical trial (may be merged with item 20)		X
I/20.	Monitor's report upon the commencement of the clinical trial	Documentation that the investigator and persons involved in the conduct of the clinical trial have been trained in respect of the conduct of the clinical trial	X	X

II. Documents available in the course of the clinical trial (other documents in addition to the documents listed in table I.)

Number	Name of the document	Purpose of storage of the document	Stored with the investigator or in the healthcare facility	Stored with the sponsor
II/1.	Amendments to investigator's brochure	Documentation of timely provision of new information to the investigator	X	X
II/2.	Any amendments to the protocol, and, if applicable, to any of its supplements, case report forms, written informed consent form, instructions and any other information and promotional materials	Documentation of changes made to the above mentioned documents associated with the clinical trial in the course of the trial	X	X
II/3.	Ethics committee approval (dated) of the supplements to the protocol, changes to the written informed consent form, instructions and any other information as the case may be, incl. promotional materials, and of any other submitted documents and protocol from the control of the conduct of the	Documentation that the supplements and changes have been assessed and approved by the ethics committee; identification of version numbers and dates of the documents	X	X

	clinical trial by the ethics committee			
II/4.	Notification of amendments to the protocol and changes to other documents to the Institute	Documentation of timely notification to the Institute	X	X
II/5.	CVs and data about the qualification of new investigator(s) and co-investigator(s)	Documentation of the qualification and competence for the conduct of the clinical trial and medical supervision	X	X
II/6.	Amendments and changes to normal values/limits of values for results of tests included in the protocol	Documentation of normal values and/or limits of procedures which have been changed in the course of the clinical trial	X	X
II/7.	Amendments and changes to the certificate of quality of conduct of laboratory procedures/tests (certificate, accreditation, implemented quality control and/or external quality assessment or other validation)	Documentation of maintaining the reliability of test results throughout the clinical trial		X
II/8.	Records of supplies of investigational products and other materials	Documentation of dates of supplies, batch numbers, and method of supplying investigational products and other materials allowing for product batch traceability, control of transport conditions and accountability	X	X
II/9.	Certificates of newly supplied batches of the investigational products	Documentation of the identity, purity and contents of investigational products used in the study		X
II/10.	Monitor's reports	Documentation of monitor's visits and findings at the trial site		X
II/11.	Communication in respect of the clinical trial, i.e. letters, minutes of meetings, logs from	Documentation of all agreements or substantial communication in	X	X

	telephone calls	respect of the clinical trial, non-compliance with the protocol, corrective action, study conduct, adverse event/reaction reporting		
II/12.	Signed written informed consent forms of trial subjects	Documentation evidencing that trial subject consents have been obtained in compliance with the principles of good clinical practice and with the protocol and that they are dated in advance of the subjects' inclusion in the clinical trial and that trial subjects do not object to providing access to the necessary data	X	
II/13.	Source documents	Documentation of subject existence, integrity of collected data, includes original documents relevant to the study, the to the treatment and to the medical history of trial subjects		X
II/14.	Case Report Forms – completed, signed, and dated	Documentation evidencing that the investigator or a person authorised thereby has correctly recorded and confirmed the observations	X copy	X original
II/15.	Documentation of corrections in Case Report Forms	Documentation of all changes, amendments or corrections made to CRFs after the information has been recorded	X copy	X original
II/16.	Reports of serious adverse events identified by the investigator and other information about the safety of the investigational medicinal products provided to the sponsor	Documentation of compliance with the provisions stipulated in Section 10 of this Decree	X	X

II/17.	Reports of serious unexpected adverse reactions by the sponsor to the Institute and to the Ethics Committee and other safety data	Documentation of compliance with the provisions stipulated in Section 58 of the Act		X
II/18.	Provision of safety information by the sponsor to the investigators	Documentation of compliance with the provisions stipulated in Section 56 of the Act	X	X
II/19.	Reports on the course of the clinical trial submitted to the ethics committee and to the Institute	Documentation of compliance with the provisions stipulated in Section 15 of this Decree		X
II/20.	The procedure of trial subjects inclusion in the primary selection	Documentation of identification of subjects included in the primary selection	X	X
II/21.	List of identification codes of trial subjects	Documentation evidencing that the investigator maintains a confidential list of names of all subjects with allocated trial subject identification codes which allows the investigator to establish the identity of any subject	X	
II/22.	The process of subjects inclusion in the clinical trial	Documentation of gradual inclusion of subjects by identification codes	X	
II/23.	Proof of accountability/registration of investigational products at the trial site	Documentation evidencing that the investigational products have been used in compliance with the protocol	X	X
II/24.	Specimen signatures	Documentation of signatures and initials of all persons authorised to record and/or correct data in case report forms	X	X
II/25.	Records of stored samples of body liquids and tissues, if stored	Documentation of the indication of stored samples and location of	X	X

		their storage for the purposes of potential need of repeated analysis		
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III. Documents stored after the completion of the clinical trial (other documents in addition to the documents listed in tables I and II)

Number	Name of the document	Purpose of storage of the document	Stored with the investigator or in the healthcare facility	Stored with the sponsor
III/1.	Documentation of accountability/registration of investigational products at the trial site	Documentation evidencing that the investigational products have been used in compliance with the protocol; of final accountability of investigational products supplied to the trial site, dispensed to subjects and returned to the sponsor	X	X
III/2.	Investigational products disposal documentation	Documentation evidencing the disposal of unused investigational products conducted by the sponsor or directly at the trial site	X (If disposal carried out at the trial site)	X
III/3.	A complete list of identification codes of trial subjects	A tool allowing for the identification of all subjects included in the study in the case that a follow-up is required; the list shall be maintained in a confidential manner for an agreed period of time	X	
III/4.	Certificate of performed audit	Documentation evidencing that an audit has been carried out		X
III/5.	Monitor's final report on the completion of the	Documentation evidencing that all		X

	clinical trial	activities required for the completion of the clinical trial have been carried out and that copies of essential documents are stored at relevant places		
III/6.	Identification of the method of treatment of individual trial subjects and decoding documentation	Documents returned to the sponsor to evidence any decoding performed		X
III/7.	Report on the completion of the clinical trial submitted by the sponsor to the ethics committee and to the Institute	Documentation of completion of the clinical trial and compliance with the provisions stipulated in Section 56 of the Act	X	
III/8.	Summary report on the clinical trial	Documentation of the results and interpretation of the clinical trial		X