

The Medical Product Agency's provisions and guidelines on clinical trials of medicinal products for human use

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Pursuant to 17 § of the Pharmaceutical Products Ordinance (1992:1752), the Medical Products Agency issues the following provisions and guidelines relating to clinical trials of medicinal products for human use¹.

¹ Cf. Parliament's and the Council Directive 2001/20/EC of 4 April 2001 concerning the harmonisation of the laws and other ordinances of Member States concerning good clinical practises in clinical testing of medicinal products for human use (EGT no. L 121, 1.5.2001, p.34, Celex, 32001L0020).

Chapter 1. Field of application and definitions

1 § These provisions are applicable to all clinical trials of medicinal products for human use, including studies of bioavailability and bioequivalence. These provisions do not cover non-interventional studies.

Guidelines to 1 §

The regulations in these provisions should be applied in relevant parts, also on radioactive medicinal products as well as natural remedies, homeopathic products, certain external remedies and products manufactured using gene technology.

Each prospective study of a chemical or biological substance conducted on trial subjects or patients with the aim of elucidating its characteristics as a possible medicinal product requires an application for authorisation to be submitted to the Medical Products Agency. This is also required when testing medicinal products with an approved indication, with approved dosage and with an approved mode of administration where the intention is to further elucidate the effect and/or safety. In the case of trials where a substance or a medicinal product is used without an intention to study its characteristics as a medicinal product an application need not be submitted to the Medical Products Agency. In such a case, it is sufficient with a positive opinion from an Ethics Committee. An example of testing of this kind is when known characteristics of a substance are used to achieve a physiological condition in order to study this condition or, in studies of non-pharmacological treatment, when it is desired to standardise a physiological condition through simultaneous pharmacological treatment.

In case of doubt whether approval is needed for a clinical trial, the Medical Products Agency should be consulted.

2 § The expressions used in the Medicinal Products Act (1992:859) have the same meaning in these provisions.

3 § In these provisions, the terms listed below have the same meaning as in Directive 2001/20/EC:

(a) '*Clinical trial*': any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy; This includes clinical trials carried out in either one site or multiple sites, whether in one or more than one Member State.

(b) '*Multi-centre clinical trial*': a clinical trial conducted according to a single protocol but at more than one site, and therefore by more than one investigator, in which the trial sites may be located in a single Member State, in a number of Member States and/or in Member States and third countries;

(c) '*Non-interventional trial*': a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data;

(d) '*Investigational medicinal product*': a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form;

- (e) '*Sponsor*': an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial;
- (f) '*Investigator*': a physician or a person following a profession agreed in the Member State for investigations because of the scientific background and the experience in patient care it requires. The investigator is responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the leader responsible for the team and may be called the principal investigator;
- (g) '*Investigator's brochure*': a compilation of the clinical and non-clinical data on the investigational medicinal product or products which are relevant to the study of the product or products in human subjects;
- (h) '*Protocol*': a document that describes the objective(s), design, methodology, statistical considerations and organisation of a trial. The term protocol refers to the protocol, successive versions of the protocol and protocol amendments;
- (i) '*Subject patient*': an individual who participates in a clinical trial as either a recipient of the investigational medicinal product or a control;
- (j) '*Informed consent*': decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative; if the person concerned is capable of giving consent but unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation.
- (k) '*Ethics committee*': an independent body in a Member State, consisting of healthcare professionals and nonmedical members, whose responsibility it is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent;
- (l) '*Inspection*': the act by a competent authority of conducting an official review of documents, facilities, records, quality assurance arrangements, and any other resources that are deemed by the competent authority to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organisation's facilities, or at other establishments which the competent authority sees fit to inspect;
- (m) '*Adverse event*': any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment;
- (n) '*Adverse reaction*': all untoward and unintended responses to an investigational medicinal product related to any dose administered;

(o) *'Serious adverse event or serious adverse reaction'*: any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect;

(p) *'Unexpected adverse reaction'*: an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product).

The definition of other terms given in the guidelines CPMP/ICH/135/95², CPMP/ICH/377/95³ and CPMP/ICH/287/95 modified⁴ apply also with regard to these provisions.

Chapter 2. Scope of the provisions and guidelines

1 § Clinical trials of medicinal products shall be designed, conducted, recorded and reported in compliance with internationally accepted requirements on ethical and scientific standards in order to provide assurance that the rights, safety and well-being for those participating in a trial on an investigational medicinal product as trial subject(s) or patient(s) are protected and that the data recorded are credible.

2 § The principles of Good Clinical Practice, GCP, and the Declaration of Helsinki shall be applied.

Guidelines to 2 §

The Commission guidelines on GCP when conducting clinical trials⁵ provides the principles for GCP. A more detailed description of the system is given in the guidelines CPMP/ICH/135/95.

The guidelines prepared by the Commission will be published on the Commission homepage www.eudra.org.

3 § The conditions for commencing a clinical trial are that an authorisation is granted by the Medical Products Agency and that the Ethics Committee issues a favourable opinion.

Guidelines to 3 §

Guidance relating to the application for authorisation and other contacts with the Medical Products Agency in connection with a clinical trial is also provided in the Commission guidelines to Directive 2001/20/EC.

- [Commission's guidelines 2001/20/EC](#)

Contacts with the Medical Products Agency should be made in compliance with the Commission guidance on the request for authorisation of a clinical trial⁶.

Guidance on the application to the Ethics Committee is given in the guidelines issued by the Commission on the application for an Ethics Committee opinion⁷.

If the applicant to the Medical Products Agency for authorisation to conduct a clinical trial has not been informed within sixty days from the time a valid application has been received by the Agency that there are objections to the trial, authorisation is considered to have been granted and the trial may be commenced, see further in Chapter 5.

4 § The investigational medicinal product used in clinical trials shall be manufactured and handled in accordance with the principles of Good Manufacturing Practice, GMP.

Guidelines to 4 §

Information on the requirements for the investigational medicinal product used in clinical trials is found in the Commission guidance on the request for authorisation of a clinical trial; see also below in Ch. 4. Requirements on manufacturing of medicinal products in the Medical Products Agency provisions LVFS 1995:3 and LVFS 1962:2 also apply to medicinal products for use in clinical trials.

Chapter 3. Distribution of responsibilities in the clinical trial

1 § The person responsible for the conduct of the clinical trial at the site shall be appropriately qualified, be suitable for the task, have access to the necessary resources throughout the entire time the trial is ongoing, and be responsible for the necessary contacts in accordance with the requirements laid out in Chapters 5, 6 and 7 below.

Guidelines to 1 §

The principal investigator should be a qualified physician and have specialist competence or corresponding competence, or when applicable be a qualified dentist, and be trained within the medical field relevant for the trial in question. Additional requirements are documented experience in participating in clinical trials of medicinal products, knowledge of scientific methods and principles for GCP, good knowledge of the investigational medicinal product(s) and experience of the medical care of persons planned to participate in the trial. If a principal investigator lacks practical experience of participating in a clinical trial, exemption from the requirements may be granted under the condition that special assistance and special monitoring is provided.

In multicentre trials the contacts required between the Medical Products Agency, the sponsor and the principal investigator at the participating trial sites could be made through an investigator who has been appointed to co-ordinate the work at the different sites, i.e., the co-ordinating investigator. The same requirements for competence that apply to the principal

investigator must also apply to the co-ordinating investigator even if the co-ordinating investigator is not personally responsible for a trial site.

All persons participating in a trial must be qualified for their duties. There must not be circumstances that could cast doubt upon a person's impartial participation in the trial, e.g., economic links that might imply economic profit.

It is the duty of the principal investigator to check that there is access to suitable and competent personnel, that sufficient resources are available, and that the members of the trial team receive relevant information about the trial. Assessment that these requirements have been fulfilled is the responsibility of the Ethics Committee.

2 § If the investigator intends to include patients or trial subjects who cannot themselves decide on whether or not to participate particularly high requirements are placed on the reporting of reasons for nonetheless wishing to conduct the trial with the inclusion of these patients or trial subjects, as well as the account of benefits, discomfort and risks associated with participation. A decisive factor will be that the trial is essential for confirmation of data obtained from clinical trials on persons who are able to give informed consent, or from trials using other scientific methods, and also that the trial must have a direct relationship to the clinical condition of the patient, or that it can only be conducted on these patients or test subjects.

Guidelines to 2 §

Information on the requirements for clinical trials on vulnerable groups, e.g., children, is published in guidelines prepared by CPMP⁸ and available on the EMEA⁸ website, www.emea.eu.int.

3 § The investigator shall ensure that the patients or trial subjects included in a trial have full protection for their rights, their integrity and their welfare and that they receive the information required for reaching a decision on whether or not to participate. The persons asked shall give informed written consent voluntarily. If the persons asked cannot themselves give written consent, the reasons for nevertheless including them in the trial shall be stated and the procedure to be used shall be described in detail.

Guidelines to 3 §

In the Commission guidelines regarding the application for an Ethics Committee opinion it is stated what the information to patients and trial subjects should include. In clinical trials on children and persons incapable of giving consent, special requirements apply. Further information can be obtained from the regulations governing the work of the Ethics Committee.

The Ethics Committee will examine the patient information and the procedure for obtaining informed consent. The Medical Products Agency will examine certain aspects of the patient information, e.g., information on risks involved in participation.

Personal data that are handled within the scope of clinical trials of medicinal products must be treated in compliance with the regulations established in the Personal Data Act (*Personuppgiftslagen*, 1998:204). This implies that the treatment of such personal data as a rule should be notified to the Swedish Data Inspection Board. In the Personal Data Ordinance (*Personuppgiftsförordningen*, 1998:1191) there is also the requirement that the processing of certain integrity-sensitive personal data must be notified to the Data Inspection Board for control in advance. This concerns treatment of personal data regarding genetic predisposition that appear in a genetic study. If such personal data are handled within the scope of a clinical trial a notification must be made to the Data Inspection Board for control in advance regardless of whether the Ethics Committee has reviewed and given a positive opinion of the study, and regardless of whether the persons participating in the trial have given their informed consent.

4 § The principal investigator shall ensure that the persons included in a trial as trial subjects or patients have access to the medical care required during the trial for the condition being studied as well as for any adverse events that may occur. The investigator shall also ensure that the patients and trial subjects receive the care and follow-up required after participation in the trial has been ended and that is required in addition to what their condition might otherwise require.

Guidelines to 4 §

When a patient is included in a clinical trial of medicinal products the regulatory requirements applicable to health care must be applied. This implies that, for example, patient hospital files or corresponding records must be kept in the customary manner in accordance with the

Patient Records Act (*Patientjournalagen*, 1985:562) and the Swedish National Board of Health and Welfare's provisions and guidelines. The hospital files must state that the patient is participating in a clinical trial and explain what the trial involves regarding form of treatment, dosage and time of treatment. Examinations of importance for the care of the patient must be described. In blinded trials the medicinal treatment can be described with the same information as printed on the labelling of the medicinal product in order to avoid the blinding being broken. If the patient is given a code number in the trial this should be stated in the hospital files in order that, if so required, the code can rapidly be broken without access to the code list. Details of where the code envelopes are kept should also be stated in the patient's hospital file.

When the code is broken, information of the treatment given to the patient should be stated in the hospital files.

If the patient consents, it is preferable that the investigator informs the patient's usual physician that the patient is participating in a clinical trial.

For reasons of safety, during the time the patient is participating in a trial he/she should be given, and recommended to carry, a card containing information on the trial. The card should state that the patient is participating in a clinical trial, giving the investigational medicinal products (as shown on the labelling of the medicinal product) and also the name of the person

who can be contacted for further information on the trial, and how this person can be contacted.

In the context of clinical trials, trial subjects are equal to patients, and the same system must be used also for healthy trial subjects.

Treatment that may be required for patients or trial subjects after the clinical trial has ended need not be provided at the site where the trial was conducted, or by the investigator, but it is the responsibility of the investigator to ensure that the patient or test subject is cared for in a satisfactory manner.

5 § The principal investigator is obliged to ensure that the trial is conducted and reported in the prescribed manner. If the principal investigator delegates parts of his work in the trial to somebody else, this shall be done in writing. The extent of the delegating must be stated.

Guidelines to 5 §

When conducting a trial, divergences must not be made from the requirements stated in the protocol, or in the conditions established when authorisation was granted, unless exceptional circumstances arise, see Ch. 6.

Duties may be delegated to members of the trial team at the site. Duties delegated to another organisation, e.g., a Contract Research Organisation (CRO), may be for example recruiting and advertising for patients/trial subjects, or analyses of samples, or examination of recorded results. Delegated tasks must be identified in writing and the document must be available at the trial site when requested and in the event of an inspection.

6 § The principal investigator, or co-ordinating investigator, shall provide the sponsor, the concerned Ethics Committee and the Medical Products Agency with all the supplementary information that is requested.

Guidelines to 6 §

Supplementary information may be requested in connection with the application for authorisation, in connection with the reports the principal investigator is obliged to submit, or in connection with controls of how the trial is being conducted.

7 § The person(s) with the medical responsibility for, and administrative leadership of, the trial site (e.g., the regional director or director of the unit participating in the trial) shall confirm in a certificate or by other means that he/she has been informed about the trial, that the principal investigator is suitable, and shall be responsible for the necessary resources being available throughout the entire period of the trial.

Guidelines to 7 §

For all trials of medicinal products there must be a medically responsible person at the site of the trial. This also applies when the investigational medicinal product is given for the first time to healthy trial subjects (phase 1). The suitability of each trial site as well as of the

principal investigator for the conduct of the trial must be confirmed. This can be done, for example, by means of a certificate from the person responsible for the medical care.

The person responsible for the administrative leadership at the site where the trial is planned to be conducted is responsible for the trial not being affected negatively by e.g. other trials that are ongoing or planned to start during the same period of time.

If several clinics are involved and/or participate, the person responsible for the administration should ensure that the other clinics concerned are not prevented from participating and that resources are available for the co-operation.

Certificates must be available upon request and for inspection at the trial site and must be annexed to the application submitted to the Ethics Committee, which will assess the resources of the trial site and the suitability of the principal investigator.

8 § The sponsor is responsible for obtaining the necessary authorisations for a medicinal product trial, and is responsible for contacts with the principal or co-ordinating investigator, and with the Medical Products Agency both before, during and after the trial, as well as being responsible for ensuring that the necessary positive opinion(s) from the Ethics Committee has been forwarded to the Medical Products Agency.

Guidelines to 8 §

The sponsor is the person who has accepted the responsibility to fulfil the duties that fall upon the sponsor in accordance with these provisions.

In cases where the duties of the sponsor and the principal or co-ordinating investigator fall upon the same person, "sponsor-investigator" (according to the guidelines CPMP/ICH/135/95) this must be made clear on the application form to the Medical Products Agency.

9 § It is the sponsor's responsibility that persons working with the trial in the sponsor's organisation have sufficient qualifications for their duties, and that there are written instructions for the work and that they are complied with. The sponsor is responsible for continuous quality control (monitoring) and quality assurance (auditing) of the methods used and of the data collected.

The sponsor's personnel is responsible for submitting the information requested by the Medical Products Agency and for participating in the controls that the Medical Products Agency conduct in fulfilling its supervisory function.

Guidelines to 9 §

The Medical Products Agency may require information from the sponsor, for example in connection with suspicions that conditions of importance for the trial have been changed, that the requirements for the conduct of the trial have not been fulfilled, or that the safety and/or the scientific value of the study may be questioned. In connection with the reporting of

adverse events or reactions the Agency may require supplementary information upon which to base its decision.

10 § The sponsor is responsible for ensuring that the documents referred to as the basis for assessment of a clinical trial of an investigational medicinal product, as well as later protocol changes, amendments and reports, are complete and correct, and that, when required, there is continual updating of submitted information.

11 § The investigational medicinal product shall be provided by the sponsor without cost unless special exemption from this requirement has been granted by the Medical Products Agency.

Guidelines to 11 §

It is the responsibility of the sponsor to ensure that all investigational medicinal products are available and that updated information on these products is reported to the Medical Products Agency.

It is also the responsibility of the sponsor to ensure that the labelling is correct. Provisions on labelling requirements regarding investigational medicinal products can be found in Annex 13 to Vol. 4 of the rules governing medicinal products in the European Union¹⁰, see further Ch. 4, 4 §.

The handling of medicinal products must be done through a pharmacy unless special exemption from this requirement has been granted by the Medical Products Agency. The pharmacy may dispense investigational medicinal products when authorisation from the Medical Products Agency for the trial has been obtained, see 10 § of the Medical Products Agency's provisions and guidelines for permission to retail unauthorised medicinal products (LVFS 1995:7). The pharmacy may also dispense investigational medicinal products in cases where written authorisation is not required (cf. Ch.5, 4 §) if no grounds for non acceptance of the trial have been given by the Medical Products Agency within the deadlines stated in Ch. 5.

For certain types of trials, exemption may be granted from the requirement to provide the investigational medicinal product free of charge. Application for exemption should be submitted to the Medical Products Agency at the same time as the application for authorisation of the trial. Exemption may be granted, for example, in trials where the investigational medicinal product is used in accordance with the market authorisation, or when the investigational medicinal product is an orphan drug with a small estimated retailing volume.

12 § If the sponsor delegates all or part of his/her duties to another party this shall be documented in writing, clearly stating the duties that are encompassed and the person(s) who will perform these duties.

Guidelines to 12 §

When a sponsor delegates duties to another party, e.g., to a CRO, the written documentation establishing this must be available upon request and at inspections. The sponsor retains

responsibility for the trial being conducted in accordance with the conditions stated when the trial was given authorisation to start. The application form must include information on the duties that have been delegated, together with the name(s) of the person(s) to whom these duties have been delegated.

13 § The sponsor is responsible for all persons included in the trial as patients or trial subjects being insured or by other means guaranteed full economic protection if injuries should occur in connection with the trial.

Guidelines to 13 §

Injuries occurring during a clinical trial may be covered by patient insurance according to the Patient Injury Act (*Patientsskadelagen*, 1996:799) and/or by the medicinal product insurance.

Chapter 4. Application procedure

1 § For all clinical trials of medicinal products an application for authorisation shall be submitted by the sponsor or by the sponsor's representative to the Medical Products Agency. The form prescribed by the Medical Products Agency must be used.

Guidelines to 1 §

The procedure for applying for an authorisation, for the conduct, reporting and quality control of clinical trials must fulfil the requirements established by the European Commission that are common to all Member States.

The application form prescribed by the Medical Products Agency is common to all Member States. The form can be obtained electronically through the Medical Products Agency homepage, www.mpa.se, or from the Commission or EMEA homepage.

An application to the Ethics Committee consists of two parts. One part consists of the form that is common to all Member States and that is used for the application to the Medical Products Agency. The second part, which will provide detailed information on the trial, may differ between Member States; see further the Commission guidance on the request for authorisation of a clinical trial or the Commission guidance on the application for an ethics committee opinion on a clinical trial.

Medicinal products integrated in a medical device

If a medical device contains as an integrated part a substance regarded as a medicinal product when used separately, the product may under certain circumstances be regarded as a medicinal product. If the medicinal product has no marketing authorisation for the intended use an application for authorisation of a clinical trial of an investigational medicinal product must be made. For the definition of a medical device and a medicinal product, see 2 § of the

Medical-technical Products Act (*Lagen om medicintekniska producter*, 1993:584) and 1§ of the Medicinal Products Act (*Läkemedelslagen*, 1992:859).

In the Commission guidelines MEDDEV 2.1/3 rev 2¹¹, guidance is given on matters relating to the demarcation between, e.g., medicinal products and medical devices.

Requirements concerning clinical trials of medical-technical products are published in LVFS 2001:6 and LVFS 2001:5. The evaluation of performance of *in vitro* diagnostic products in connection with clinical trials of medicinal products is regulated in LVFS 2001:7.

2 § The application form submitted to the Medical Products Agency shall have a unique number for the trial, a Eudract number, that is obtained from the European clinical trials database.

Guidelines to 2 §

The trial number can be obtained electronically by the sponsor from EMEA's Eudract database. The number is unique for the trial protocol and must be stated in all contacts with authorities concerning clinical trials that are conducted in accordance with that protocol. The protocol has the same Eudract number regardless of the number of trial sites or participating Member States within the EEA area. Further information on how the number is obtained, and the data that must be available concerning the planned trial, is given in the Commission guidelines on the European database¹². The Medical Products Agency homepage has a link to the EMEA Eudract database where the number can be obtained.

3 § The application form shall be submitted electronically to the Medical Products Agency. The application form shall also be submitted in writing in one original and five copies.

Guidelines to 3 §

A database containing information on clinical trials on medicinal products will be available at the EMEA. The application form should be submitted electronically on account of it containing data that the Medical Products Agency, after verification, transfers electronically to the Eudract clinical trials database. Certain information on the form is specific for each Member State. In the Commission guidelines on the European database there is information on the system and the purpose of the database.

4 § The documentation relating to the application shall be submitted in writing to the Medical Products Agency in six copies. In special cases the Agency may require fewer copies.

Guidelines to 4 §

Details on format and content of the application and the documentation that should be annexed can be found in the Commission guidelines on the request for authorisation of clinical trials and on the Medical Products Agency's homepage. If the application diverges from the stated requirements on documentation, the divergencies must be justified.

With regard to the handling of the application by the Medical Products Agency, it is sufficient that, for example, the Investigator's brochure, a summary of details on the investigational medicinal product, the proposed labelling, the written information on the trial and the form for informed consent are submitted in three copies (the number of copies required will be specified on the Medical Products Agency's homepage).

The part of the documentation that contains technical and scientific data may be submitted in English. The information to be handed out to trial subjects and patients must be available in a Swedish version.

Under certain circumstances, a less comprehensive documentation can be submitted, as detailed in the Commission guidelines on the request for authorisation of clinical trials. If the same documentation has been sent to the Medical Products Agency at an earlier occasion, it is sufficient to provide clear references to when and in which context it was submitted.

All documentation must be presented in accordance with the requirements stated in the Commission guidelines on the request for authorisation of clinical trials.

Additional requirements as regards documentation for trials on medicinal products that consist of, or contain, genetically modified organisms, are provided in the Ordinance (2002:1086) on the release into the environment of genetically modified organisms.

When genetically modified organisms are included in a clinical trial, this Ordinance (2002:1086) represents the Swedish implementation of Directive 2001/18/EC¹³.

The Medical Products Agency has published provisions on clinical trials of medicinal products that contain or consist of genetically modified organisms.

5 § The application shall include a proposal on labelling in Swedish of packages containing the investigational medicinal product. The labelling shall be adapted to the trial design and to the size of the package. The labelling shall include the following information:

- a. name, address and telephone number of the sponsor or the sponsor's representative.
- b. the name or code of the medicinal product, its strength, dosage form, means of administration and quantity.
- c. batch number or other means of identification.
- d. reference code for the trial
- e. the patient's code number in the trial and, if necessary, the visit number.
- f. the name of the principal investigator.
- g. dosage and, when relevant, technical instructions and/or instructions for use (reference to a separate document may be made).
- h. "For clinical trial".
- i. details of storage requirements.
- j. expiry date according to ISO standard.
- k. "Stored out of sight and reach of children" (can be omitted if the medicinal product is only for use in hospitals).

Radioactive medicinal products shall be labelled with details of radiation dose and the text "contains radioactive substance".

In double-blinded trials the name of the medicinal product can be stated as "x/y" or "x/placebo".

Batch number and expiry date shall be given in such a manner that the identity of the contents of the package is not revealed.

When using medicinal products authorised for marketing in Sweden which are supplied specifically for the trial, an additional labelling containing (a), (d) and (e)-(h) shall be attached to the package.

Guidelines to 5 §

In (a) on the labelling, the telephone number and address can be omitted if the patient receives a patient card containing these data and where the patient is instructed always to carry the card.

Consequently, in the additional labelling of medicinal products that have a marketing authorisation, the following data shall be included:

- (a) sponsor (if other than the manufacturer or principal investigator).
- (d) reference code of the trial.
- (e) the patient's code number in the trial/identity and, if necessary, the number of the visit.
- (f) name of the principal investigator.
- (g) dosage
- (h) "For clinical trial".

Additional labelling may be done by manufacturers authorised for such manufacturing procedures, or by a pharmacy.

Regulations on the labelling of medicinal product packages in the Medical Products Agency's provisions on the prescription of medicinal products (LVFS 1997:10) must be complied with when relevant.

Annex 13 lists the specific GMP requirements that apply to investigational medicinal products.

6 § In multicentre trials a complete application shall be submitted. For each trial site intended to participate, the name, position and the address of the principal investigator shall be given on the form.

Guidelines to 6 §

In multicentre trials the sponsor and the co-ordinating investigator must sign the trial protocol that is submitted together with the application. At each trial site there must be a protocol signed by the principal investigator. The assessment made by the Medical Products Agency refers to the project as a whole.

All trial sites that are reported as participating in Sweden must be listed on the application form. Each trial site is identified subsequently by the suffix allotted to it in the application by the Medical Products Agency and which is only used internally within the Medical Products Agency. A "trial site" refers to a clinical unit. This implies that several trial sites may exist within the same hospital in a situation where several clinics participate.

The Ethics Committee's review of the application includes an assessment for each trial site of the principal investigator's qualifications and the suitability of the trial site.

The sponsor will submit information to the Medical Products Agency concerning which trial sites and principal investigators that have received a positive opinion by the Ethics Committee. The review of the application by the Medical Products Agency and the Ethics Committee may occur successively or in parallel.

The handling of an application concerning the addition of trial sites after the start of the trial is regulated in Chapter 6, 1 and 3 §§.

Chapter 5. Evaluation before the start of the trial

1 § The Medical Products Agency's review is started when examination of the application shows that it is valid. That the application is valid implies that it contains, as applicable, the required information and documentation listed on the application form.

Guidelines to 1 §

Initially, the Medical Products Agency goes through the submitted documents in order to verify that the application is valid. This is an administrative verification that all documents stated on the application form have been submitted. If a document has been omitted, this must be specifically justified. This verification procedure is expected to take three to five days following receipt of the application by the Medical Products Agency. If deficiencies are identified the Medical Products Agency will inform the sponsor as to what is missing and allow a period, usually thirty days, within which the missing documents must be received by the Agency. When the application is valid, the sponsor will be informed that the Medical Products Agency will start the review, i.e., the clock is started for the review times listed below. If the requested documentation is not received within the stated time period, the application is dismissed.

The Commission guidelines on the request for authorisation of clinical trials give the conditions under which an abbreviated application can be submitted and what distinguishes such an application..

2 § The trial may start if a positive opinion by the Ethics Committee has been obtained and if the Medical Products Agency has not informed the sponsor of grounds for not accepting the application within sixty days after the application has been declared valid. With regard to trials of certain types of medicinal products there are specific requirements, see 4 and 5 §§.

Guidelines to 2 §

When the application has been declared valid the review is normally expected to be completed within thirty days. When the review has been completed the Medical Products Agency will report the result in writing. If the sponsor has not received a reply within sixty days following notification that the application has been declared valid, it may be assumed that the Medical Products Agency has no objections and that the trial may be started providing that the Ethics Committee has given a positive opinion. For some types of trials there are requirements for written authorisation and other deadlines for review, see below.

3 § The sponsor has the opportunity to submit supplementary information on one single occasion to remedy the deficiencies stated as reasons for not accepting the application. This shall be done within the deadline stated by the Medical Products Agency. If the required information has not been received within the stated deadline, the application will be rejected.

Guidelines to 3 §

During the primary review period of thirty days any deficiencies in the application are identified. The Medical Products Agency will inform the sponsor of the reasons for the trial not being able to start and will give the sponsor the opportunity to provide supplementary documentation on a single occasion, within ten days, in order to remedy the deficiency. This deadline is justified by the fact that the Medical Products Agency is not allowed to "stop the clock" and that the evaluation at the Medical Products Agency is not allowed to exceed sixty days. Within the total period of sixty days allowed for the evaluation the Medical Products Agency must reach a decision on the supplementary documentation. In exceptional cases the Medical Products Agency may allow a longer time period than ten days if special reasons are given. However, the supplementary documentation must always be available to the Medical Products Agency in time for the Agency to be able to make an assessment within sixty days after the clock has been started. If the identified deficiencies cannot be remedied and/or the supplementary material does not reach the Medical Products Agency within the stated time limit, the application will be rejected.

Examples of such deficiencies are important weaknesses in documentation, deficient pharmaceutical quality of the investigational medicinal product, toxic effects leading to a safety risk, serious deficiencies in the planning of the trial and/or in co-ordination between the different phases in the plan to document the medicinal product, or an unscientific trial design.

4 § Written authorisation from the Medical Products Agency and a positive opinion by the Ethics Committee must be obtained before trials involving medicinal products with specific

characteristics can be conducted. This group includes medicinal products that contain active ingredient(s) or component(s) that are biological products and/or biological products of human or animal origin, or where such products are required in the manufacturing process.

Guidelines to 4 §

This regulation implies that the sponsor cannot start the trial if the Medical Products Agency has not issued a written authorisation. In other respects, 2 and 3 §§ apply in the same way as for other medicinal products.

5 § The review of trials of medicinal products for gene therapy or somatic cell therapy, as well as all therapy where genetically modified organisms are included, are subject to special regulation. In these cases the Medical Products Agency may extend the evaluation period by thirty days in addition to the previously stated sixty days. In some cases there may be a need for an extension of the evaluation period by an additional ninety days, making a total of one hundred and eighty days. Written authorisation from the Medical Products Agency is required for these trials.

Guidelines to 5 §

An extension of the evaluation period for the Medical Products Agency may be needed when, for example, the review requires extensive consultation with external experts. Information about an extension of the evaluation period will be provided within approximately thirty days after the beginning of the evaluation period.

A longer time period than ten days for submitting required documentation may be granted.

6 § In the case of trials on xenogenous cell therapy there is no time limit to the Medical Product Agency's review period. Before such a trial is started, written authorisation is required from the Agency.

7§ The sponsor is responsible for ensuring that the data and the documentation included in the request for authorisation by the Medical Products Agency is identical to the data and documentation which has formed, or will form the basis for the Ethics Committee evaluation.

Guidelines to 7 §

In multicentre trials the principle is that a positive opinion on the project shall be given by one Ethics Committee. In addition to the part of the application form used for the application to both the Medical Products Agency and to the Ethics Committee, a specific form must be used in the application to the Ethics Committee. Information on the work of the Ethics Committees can be obtained from the Research Council (*Vetenskapsrådet*), www.vr.se. A link to the description of the procedures for handling applications used by the Ethics Committees will also be found on the Medical Products Agency's homepage, www.mpa.se.

The data and the documentation to be included in an application to the Ethics Committee are described in the Commission guidelines on the application for an Ethics Committee opinion.

If the Ethics Committee, in its evaluation, lays down conditions for a positive opinion that lead to modifications to the documentation that has already been submitted to the Medical Products Agency, the sponsor must ensure that the Medical Products Agency is informed of the modifications. The Medical Products Agency will then decide whether the modifications are of such importance that the decision already made must be reassessed.

8 § It is the responsibility of the sponsor to ensure that a copy of the Ethics Committee's justified opinion reaches the Medical Products Agency within fifteen days after being received by the sponsor.

Guidelines to 8 §

The evaluation by the Ethics Committee may be done before, after or in parallel with the evaluation done by the Medical Products Agency. If the opinion of the Ethics Committee is not enclosed with the application to the Medical Products Agency the sponsor is responsible for ensuring that it is received by the Agency. The opinion of the Ethics Committee must include the trial's Eudract number and identify the trial sites as well as the principal investigators approved as participants in a multicentre trial.

Chapter 6. Contacts during the conduct of a trial

1 § If the sponsor wishes to make substantial amendments to the protocol after the start of the trial, or to the documentation that has previously been submitted, a new authorisation is required from the Medical Products Agency. A request for authorisation shall be sent electronically to the Medical Products Agency on the prescribed form. The application form and the documentation shall also be submitted in writing in six copies, or in a smaller number as required by the Agency. Reference may be made to material previously submitted.

Guidelines to 1 §

An explanation of what is meant by "substantial amendment" and the requirements regarding the documentation that must be submitted is given in the Commission guidelines on the request for authorisation of a clinical trial. The form to be used is the same for all Member States and can be obtained from the Medical Product Agency's homepage.

The submitted documentation must clearly indicate what the amendment involves and the reasons for the amendment. Information on amendments that only require an opinion by the Ethics Committee must be sent to the Medical Products Agency for information, see 3 §.

Non-substantial amendments, that do not require authorisation, must be recorded and archived by the sponsor and by the principal investigator. The documentation must be made available to the Medical Products Agency on request and at inspections. It is the responsibility of the sponsor to assess whether an amendment is substantial or non-substantial.

2 § A proposed substantial amendment can be introduced if the Medical Products Agency has not raised justified grounds for non-acceptance and on the condition that the Ethics Committee has given a positive opinion. If the Medical Products Agency has raised justified grounds for non-acceptance of an application for an amendment, the sponsor shall consider the objections made by the Agency and either adapt the proposal accordingly or abstain from making the amendment.

Guidelines to 2 §

The Ethics Committee must give an opinion on an application for a substantial amendment within thirty-five days from the day the application was received. No deadline is given in Directive 2001/20/EC for the evaluation by the competent authority. The Commission guidelines on the request for authorisation of a clinical trial give the recommendation that the competent authority should inform the applicant of any objections to the proposed amendment within thirty-five days. The Medical Products Agency will give an answer in writing within thirty-five days after having received the application for the amendment.

3§ Details of substantial amendments the evaluation of which is the responsibility of the Ethics Committee must be communicated to the Medical Products Agency for information. An example of a substantial amendment may be that additional principal investigators or trial sites will be included as participating in a clinical trial of a medicinal product for which the Medical Products Agency has granted authorisation. The sponsor is responsible for information about changes being submitted to the Medical Products Agency within fifteen days after the sponsor has received the Ethics Committee's positive opinion on the amendment.

Guidelines to 3 §

As explained in the Commission guidance on the request for authorisation of a clinical trial and the guidance on the application for an Ethics Committee opinion on a clinical trial, either the Ethics Committee or the Medical Products Agency may be responsible for the evaluation of certain documentation, whereas, in accordance with the requirements decided nationally, both examine other documentation. This implies that not all documentation must be sent to both; see the Commission guidelines mentioned above. If a substantial amendment is made in documentation that only has to be sent to, and evaluated by, the Ethics Committee, the Medical Products Agency must be informed about this, and vice versa.

That the Medical Products Agency receives information on the result of the Ethics Committee's evaluation can be assured, for example, by the sponsor making sure that the Ethics Committee has forwarded its opinion to the Medical Products Agency.

Information on additional trial site(s) and name(s) of principal investigator(s) must be sent to the Medical Products Agency in order for the Agency to be able to fulfil its role as supervisory authority. This requires that the Agency has knowledge of all sites where the trial is being conducted and the time when the trial is started. This requirement is fulfilled if the sponsor ensures that the Agency has received a copy of the Ethics Committee opinion.

4 § The investigator is obliged to take immediate action to introduce the measures necessary to relieve acute danger or risk to the trial subjects or patients in a trial. The sponsor shall without delay inform the Medical Products Agency and Ethics Committee of the measures taken.

Guidelines to 4 §

When information is submitted to the Medical Products Agency, the application form for substantial amendment must be used. The procedure for contacts with the Medical Products Agency is explained in the Commission guidelines on the request for authorisation of a clinical trial.

5 § The sponsor must inform the Medical Products Agency immediately about changes in the conditions that applied when the trial received authorisation and if there is reason to question either the safety of the persons included in the trial or the scientific value of the trial.

Guidelines to 5 §

This provision refers to, e.g., safety problems that are identified, or new data on the investigational medicinal product that give rise to a different interpretation of previously submitted documentation, or quality problems in the conduct of the trial.

6 § The Medical Products Agency can request information or explanations from the sponsor regarding changed conditions in accordance with 5 § if there is no immediate risk to the trial subjects or patients included in the trial. The sponsor and/or principal investigator shall provide the required information within one week.

If there is an immediate risk the trial shall be terminated unless another measure is considered sufficient.

Guidelines to 6 §

The sponsor and the Investigator have the opportunity to influence and/or comment on the Medical Products Agency's decision to terminate a trial in advance only if time permits.

The Medical Products Agency may receive knowledge of changed circumstances or conditions for the trial e.g. through information from the sponsor or investigator, from other sources or through inspections carried out by the Agency.

7 § If the sponsor terminates an ongoing trial the Medical Products Agency shall be informed without delay, but within fifteen days at the latest. The reason for the termination shall be given as well as the consequences for the patients or trial subjects participating or those that have previously participated in the trial, together with the measures planned.

Guidelines to 7 §

Further information is available in the Commission guidelines on the request for authorisation of a clinical trial. A new authorisation must be obtained from the Medical Products Agency before the trial can be recommenced.

8 § If the Medical Products Agency is informed of circumstances implying that trial subjects or patients are exposed to risk, or that the quality of the conduct of the trial can be questioned, the Medical Products Agency may either temporarily or permanently stop the trial. The Agency will inform the sponsor, the principal investigator and/or the co-ordinating investigator about its decision.

Guidelines to 8 §

The Medical Products Agency will also inform the Ethics Committee and the competent authorities in the other Member States that have authorised the trial, as well as the EMEA and the Commission.

The sponsor can apply for authorisation to continue the trial and the Medical Products Agency will then consider whether the deficiencies have been corrected and whether the measures taken are sufficient.

9 § The sponsor shall inform the Medical Products Agency if the trial has not started at any of the trial sites that have received authorisation. This information shall be communicated without delay and within fifteen days after the sponsor has reached a decision in this matter. Reasons for the decision shall be given.

10 § If there are special reasons, the Medical Products Agency may require a report on the progress of the trial.

Guidelines to 10 §

A report can be requested, for example, in connection with the Medical Products Agency granting authorisation for the trial to start, when authorisation is granted for substantial amendment to be made, if there are changed conditions for the conduct of the trial, or after reports of adverse reactions.

In studies that are early in the development of an investigational medicinal product, phase 1 trials, reports may be requested during the ongoing trial. The protocol, for example, may include conditions that must be fulfilled before the next step in the trial plan can be accomplished. This may involve, for example, a dose increase or a change in pharmaceutical form. Authorisation can then be granted by the Medical Products Agency on condition that the result of certain steps in the trial plan must be reported before the next step may be commenced.

11 § The investigator is responsible for monitoring the safety of trial subjects and patients participating in the trial. The investigator shall immediately report all serious adverse reactions to the sponsor, unless the protocol or the investigator's brochure clearly states that immediate reporting is not required. Subsequently, the investigator must without delay submit

detailed written report(s). The report(s) shall include the unique code number given to the patient or test subject participating in the trial.

Guidelines to 11 §

The reporting of adverse reactions should be done in accordance with the Commission guidelines on the collection, verification and presentation of reports on adverse reactions in clinical trials¹⁴ and the European database on serious adverse events in clinical trials¹⁵.

12 § Adverse reactions and/or abnormal laboratory values that are stated in the protocol as being critical for the monitoring of safety in the trial shall be reported by the investigator to the sponsor in accordance with the requirements and within the deadlines established in the protocol.

13 § If a trial subject or patient participating in a trial dies, the investigator shall report this event to the sponsor and give the sponsor and the Ethics Committee all the additional information requested.

14 § The sponsor shall document in detail all adverse reactions reported by the investigator(s). When a trial or part of a trial is conducted in Sweden the documentation must, if requested, be sent to the Medical Products Agency.

15 § The sponsor is responsible for ensuring that all relevant information on suspected unexpected serious adverse reactions that lead to death, or are life-threatening, are registered and reported to the Medical Products Agency and other relevant competent authorities in the Member States, as well as to the Ethics Committee, as soon as possible and no later than seven days after the event has become known to the sponsor. Relevant follow-up data shall thereafter be sent within an additional eight days. Reporting to the Medical Products Agency shall be done electronically on the prescribed form.

Guidelines to 15 §

Provisions on the procedures that apply for reporting adverse reactions can be found in the Commission guidelines on the collection, verification and presentation of reports on adverse reactions in clinical trials and the European database of serious adverse reactions in clinical trials.

16 § The sponsor shall report all other suspected unexpected serious adverse reactions to the Medical Products Agency and to the concerned Ethics Committee within a maximum of fifteen days after these events have become known to the sponsor.

Guidelines to 16 §

See further the Commission guidelines on the collection, verification and presentation of adverse reaction reports in clinical trials.

17 § The sponsor is responsible for informing all investigators about the suspected, unexpected serious adverse reactions that occur or are reported.

Guidelines to 17 §

Guidance on the procedures to be followed when reporting suspected unexpected serious adverse reactions (SUSAR) can be found in the Commission guidelines on the collection, verification and presentation of adverse reaction reports in clinical trials.

18 § Once annually during the period the trial is ongoing in Sweden the sponsor shall submit a list to the Medical Products Agency and the Ethics Committee of all suspected unexpected serious adverse reactions that have occurred during the period, together with an assessment of the safety of the persons participating in the trial as trial subjects or patients.

Guidelines to 18 §

Guidance on the presentation of such lists and the time for their submission can be found in the Commission guidelines on the collection, verification and presentation of adverse reaction reports in clinical trials.

Chapter 7. Contacts in connection with the end of the trial

1§ It is the responsibility of the sponsor to report within ninety days to the Medical Products Agency, using the prescribed form, that a trial has been concluded in Sweden if this has occurred in compliance with the definition in the protocol.

Guidelines to 1 §

Information on the procedure can be found in the Commission guidelines on the request for authorisation of a clinical trial. The form to be used is the same for all Member States and can be obtained from the Medical Products Agency's homepage.

2 § When a trial is terminated in advance in accordance with the decision of the sponsor the sponsor shall, within fifteen days, report this to the Medical Products Agency on the prescribed form. The reasons for this shall be given.

Guidelines to 2 §

The Commission's guidance on the request for authorisation of a clinical trial provides guidance on the procedure for reporting. The form to be used is the same as mentioned in 1§.

3 § A summary report on the trial shall be submitted to the Medical Products Agency within twelve months after the conclusion of the entire study.

Guidelines to 3 §

In international multicentre trials the time for submitting the report is calculated from the time the trial was concluded, or terminated at the last trial site, regardless of the country in which this occurs.

Chapter 8. Quality control and quality assurance

1 § The investigator is responsible for ensuring that all work and all data that are registered in the trial are of good quality. The investigators and the members of the trial team are obliged to participate in the quality control (monitoring) and quality assurance (auditing) that the sponsor shall conduct.

Guidelines to 1 §

The quality requirements to be fulfilled must comply with the principles set out in the guidelines CPMP/ICH/135/95. The sponsor is obliged to continuously monitor the quality of the management of the trial and of the recording and reporting of data, see 2 §.

The principal investigator shall ensure that the regulations on the protection of patient data are complied with at these quality controls. There must be, among other things, a confidentiality undertaking formulated in due order that is signed by all persons having access to confidential information during the examination of data.

2 § The sponsor shall ensure that there are written, functioning, procedures for quality control (monitoring) and quality assurance (auditing), that these are complied with, and that the necessary measures are taken within the framework of these procedures and that they are documented.

Guidelines to 2 §

The requirements to be fulfilled by the sponsor's system for control of the conduct of the trial, i.e., monitoring and auditing, can be found in the Commission guidelines on GCP when conducting clinical trials and in the CPMP/ICH/135/95 guidelines.

3 § Investigators and sponsors are obliged to draw up and archive the documents that are required in order to verify the conditions and the data registered in connection with the trial. The data shall be made available in readable form if requested by the Medical Products Agency and during the Agency's inspections.

Guidelines to 3 §

Guidelines on which documents that must be retained, requirements regarding quality and where the original documents and copies may be archived can be found in the Commission guidelines "Trial Master File and Archiving"¹⁶ and in the CPMP/ICH/135/95 guidelines.

Comprehensive regulations on archiving can be found in the Archives Act (*Arkivlagen* 1990:782) and the Archives Ordinance (*Arkivförordningen* 1991:446). The Swedish National Archive has issued provisions in conjunction with this legislation.

As regards data registered on ADP, guidelines are given in the National Archives Provisions and Guidelines (RA-FS 1994:2) concerning recording for automatic data processing (ADP recording).

The archiving period must be adapted to regulations in force and should not be shorter than ten years after the termination of the trial and the presentation of the final report.

If the principal investigator and/or sponsor cannot themselves make provisions for archiving their documentation, this task can be delegated. In such cases, the sponsor or the principal investigator, respectively, must be informed how this has been arranged.

4 § Investigators and sponsors are obliged to participate to the extent required in the inspections that the Medical Products Agency carries out at the trial site(s) the manufacturing site of the investigational medicinal product, any laboratory used for analyses in the clinical trial, and/or on the sponsor's premises or at other sites that the Agency finds essential to inspect in order to verify how the trial has been conducted.

Guidelines to 4 §

The Medical Products Agency may conduct both GCP and GMP inspections on account of a clinical trial. The inspections may be performed in accordance with a national programme or at the request of the commission and in co-operation with other competent authorities in the Member States. The Commission guidelines for GCP and GMP inspections contain the requirements as regards the qualifications of the inspectors^{17 18} and the procedure for the accomplishment of inspections^{19 20} conducted together with other competent authorities.

Chapter 9. Exchange of information

1 § Investigators and sponsors shall submit to the Medical Products Agency any information required for the Agency to perform its supervision of clinical trials and for the Agency to be able to enter data in the common EU databases.

Guidelines to 1 §

Within the EU common databases have been established in order to ensure good surveillance of the trials that have received authorisation and to improve the safety of the persons included as patients or trial subjects. The two databases concerned, the EUDRACT database and the database for reports of adverse reactions in clinical trials, are described in the guidelines mentioned in Chapter 6, guidelines to 15 §. The databases are available only to the competent authorities, the Commission and the EMEA.

2 § The sponsor is obliged to inform the Medical Products Agency about the changes made to documents and/or procedures that the Ethics Committee requires, and which form a condition for a positive opinion.

Guidelines to 2 §

Since the Ethics Committee and the Medical Products Agency work independently of each other, and the work of both may lead to demands for changes, a system has been prepared for the exchange of information between the relevant Ethics Committee and the Agency.

3 § The Medical Products Agency shall ensure that all suspected unexpected serious adverse reactions which occur when an investigational medicinal product is used in accordance with the marketing authorisation and which are made known to the Medical Products Agency from sources other than the sponsor, are registered and made available to the marketing authorisation holder if this person is the sponsor.

4§ The Medical Products Agency shall provide relevant information to the parties concerned with consideration to confidentiality legislation in force.

Guidelines to 4 §

As an example, it can be mentioned that entire or relevant parts of the reports from the inspections conducted by the Medical Products Agency are sent to, e.g., the sponsor, the principal investigator, and in some cases also to the pharmacy and the Ethics Committee.

5§ The Medical Products Agency shall participate with inspectors and other assistance in the international teams requested for inspection of, e.g., trial sites, laboratories, technical units and/or sponsors and/or CROs in trials that are conducted in Sweden, in other Member States, or in a third country.

Guidelines to 5 §

Information on the systems that have been established for co-operation between the inspectorates of the competent authorities can be found in, for example, the Commission guidelines on procedures for GCP inspections.

6§ The Medical Products Agency may grant exemption from clauses in these provisions.

These provisions come into force on 1 May 2004

Transitional regulations

These provisions shall apply to applications for authorisation to conduct clinical trials that are submitted to the Medical Products Agency after the 1st of May 2004.

Medical Products Agency
Gunnar Alvan
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Notes

1. Cf. Parliament's and the Council Directive 2001/20/EC of 4 April 2001 concerning the harmonisation of the laws and other ordinances of Member States concerning good clinical practices in clinical testing of medicinal products for human use (EGT no. L 121, 1.5.2001, p.34, Celex, 32001L0020).
2. Note for Guidance on Good Clinical Practice, CPMP/ICH/135/95
3. Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95).
4. Note for Guidance on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports (CPMP/ICH/287/95 modification)
5. Guideline on good clinical practice in the conduct of clinical trials on medicinal products for human use.
6. Detailed guidance on the submission to competent authorities of a request for authorisation of a clinical trial on a medicinal product for human use.
7. Detailed guidance on the application format and documentation to be submitted in an application for an ethics committee opinion on a clinical trial on a medicinal product for human use.
8. The Committee for Proprietary Medicinal Products.
9. The European Agency of Evaluation of Medicinal Products
10. Revised Annex 13, Manufacture of investigated medicinal products, Vol. 4 of the rules governing medicinal products in the European Union.
11. MEDDEV 2.1/3 rev 2 July 2001: Demarcation between: Directive 90/385/EEC on implantable medical devices, Directive 93/42 on medical devices and Directive 65/65/EEC relating to medicinal products.
12. Detailed guidance on the European clinical trial database.
13. Directive 2001/18/EC of the European Parliament and Council (12 March 2001) concerning the deliberate release into the environment of genetically modified organisms and rescinding of Council Directive 90/220/EEC (EGT no. L 106, 17.4.2001, p.1, Celex 32001L0018).
14. Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use.
15. Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions.
16. Detailed guidance on the Trial Master File and archiving.
17. Detailed guidelines on the qualifications of inspectors who should verify compliance in clinical trials with the provisions of good clinical practice.
18. Detailed guidance on the qualifications of GMP inspectors.
19. Detailed guidelines on the inspection procedures for the verification of GCP compliance.
20. Detailed guidance on the inspection procedures for the verification of GMP compliance.

