Medical Products Agency's Code of Statutes

Medical Products Agency's provisions and guidelines on the clinical trials of medicinal products;

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Contents

Part 1  Scope and definitions etc.
Part 2  Procedure for applying for authorization
Part 3  Ethical examination
Part 4  Responsibility for how the trial is conducted
Part 5  Requirements to be met by the responsible investigator
Part 6  How the trial is to be designed and conducted
Part 7  Requirements to be met by the documentation
Part 8  Information and consent
Part 9  Insurance
Part 10  How the patients are to be cared for
Part 11  Information to staff
Part 12  The location for the trial
Part 13  Medicinal products
Part 14  Surveillance of medicinal products
Part 15  Quality control and quality assurance
Part 16  Handling of data
Part 17  Modification of a trial and additions to trial protocol
Part 18  How the trial is to be reported
Part 19  Archiving of data
Part 20  Handling of deviations from the regulations
Annex 1  Chemical and pharmaceutical documentation
Annex 2  Pharmacological and toxicological documentation
Annex 3  Clinical and pharmacokinetic documentation
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Pursuant to Section 17 of the Medicinal Products Ordinance (1992: 1752), following consultation with the National Board of Health and Welfare, the Medical Products Agency gives notice of the following provisions and guidelines on the clinical testing of medicinal products for human and veterinary use.

Provisions:

Part 1 Scope and definitions etc.

Section 1 The stipulations of these provisions shall also apply where applicable to radioactive medicinal products and medicinal products treated separately, i.e. natural remedies and certain medicinal products for external use.

Section 2 Clinical trials on medicinal products for human use shall be planned, conducted and reported in accordance with the latest versions of the Declaration of Helsinki and GCP.
Section 3 The expressions and designations used in the Medicinal Products Act (1992:859) have the same meaning in these provisions.

Section 4 The following terms are used in these provisions with the meaning indicated:

adverse drug reaction a response to a medicinal product which is noxious and unintended and which occurs at doses which are normally used for prophylaxis, diagnosis, therapy of diseases or for modification of physiological function; for medicinal products which do not have marketing authorization, adverse reaction means all noxious and unintended responses to a medicinal product related to any dose; the phrase responses to a medicinal product means that a causal link between a medicinal product and an adverse event may be suspected,

adverse event any untoward medical occurrence in a trial subject or patient administered a medicinal product whether it is related to these medicinal product in question or not,

audit a systematic and independent check to clarify firstly whether the trial is carried out in accordance with the trial protocol, sponsor's SOP, GCP and applicable stipulations and secondly whether the trial report correctly reflects procedures carried out and data collected,

blinding a procedure in which one or more participants in a trial do not know which treatment is being given; single blinding means that the patients or the investigator do not know the treatment, double blinding that the patients, the investigator, monitor and sometimes also the person analysing data from the trial do not know the treatment,

certain medicinal products for external use what are known as free medicinal products defined in accordance with the previously applicable Medicinal Products Ordinance (1962:701) containing medicinal products for external use for the treatment of simpler pathological conditions in humans or animals where the active ingredient or ingredients have a well-established medicinal use with a recognised effect and an acceptable safety margin.

clinical trial of medicinal products any systematic study of the effect of medicinal products on humans, both patients and volunteer subjects, with the purpose of discovering or confirming the efficacy of the medicinal product and/or of identifying any side-effects and/or studying its absorption, distribution, metabolism and excretion so that the efficacy and safety of the product can be guaranteed,

coordinator the responsible investigator or other competent person who has responsibility for the activity at the various centres taking part in a multi-centre trial being performed in a uniform manner,

CRF (Case Report Forms) a form for recording data from a patient,

CRO (Contract Research Organisation) a person, company or organisation which has been contracted by the sponsor to fulfil some of the sponsor's obligations,
**ethics committee** an independent committee consisting of both medical scientific expertise and laypeople whose responsibility is to ensure that the patient's rights, well-being, safety and integrity are respected and that the trial otherwise is appropriate and possible to conduct at a particular location,

**GCP** (Good Clinical Practice) an international, ethical and scientific standard to quality-assure and quality-control the conduct of a clinical trial and the data which emerges in the trial,

**ICH** the International Conference on Harmonization,

**inspection** the check made by the authority at the trial location, at the sponsor or at the CRO that the trial is conducted in accordance with applicable stipulations,

**investigator** registered physician, dentist or veterinarian who assists in a clinical trial and who, in addition to his or her medical care responsibility, is also under a duty to ensure that the trial is conducted correctly (cf. also responsible investigator and coordinator),

**monitor** the person appointed by the sponsor to monitor that a clinical trial is conducted in accordance with the trial protocol and applicable stipulations,

**monitoring** check that a clinical trial is conducted in accordance with the trial protocol and applicable stipulations,

**multi-centre trial** a clinical trial which is conducted at the same time in accordance with a trial protocol by more than one investigator at more than one trial site, sometimes also in different countries,

**natural remedy** medicinal product in which the active ingredient or ingredients is or are of natural origin, not excessively processed and constitute a plant or animal part, bacterial culture, mineral, salt or saline solution and which constitute products suitable for self-medication in accordance with well proven native tradition or tradition in countries which are similar to Sweden with regard to the use of medicinal products,

**patient code** a unique code which the investigator allocates to each patient who takes part in a trial and which is used instead of the patient's name and which makes it possible for data to be reported and analysed without the patient's identity being revealed; the code can be translated to a patient identification via a list, the patient identification list,

**patient/experimental subject** persons who in connection with the treatment of disease take part in a clinical trial are referred to as patients, persons who take part in a trial without any connection with the treatment of disease are referred to as trial subjects; where patients are referred to in these provisions, trial subjects are also meant where applicable,

**PMS (Post Marketing Surveillance) studies** are performed with the purpose of identifying previously unknown safety aspects (hypothesis generation), investigating possible risks
(hypothesis testing to verify a causal link) or confirming the expected safety profile of a medicinal product within current medical practice,

quality assurance (QA) all the planned and systematic measures drawn up to ensure that the trial is carried out and data are produced, documented and reported in accordance with GCP and applicable stipulations,

quality control (QC) the operational techniques and activities which all the participants in a trial perform within the quality assurance system to verify that the quality requirements for the trial have been fulfilled,

radioactive medicinal products medicinal products which emit ionizing radiation,

randomization procedure in which patients are divided between different treatment groups in a random manner,

responsible investigator the investigator who is responsible for a clinical medicinal product trial being conducted in accordance with applicable stipulations (cf. also investigator, coordinator and sponsor),

serious adverse drug reaction (human medicine) a side-effect which is fatal, life-threatening, disabling or results in malformation, the need for hospitalization or prolonged hospitalization; (veterinary medicine) an adverse reaction which is fatal, life-threatening, harmful or results in significant functional impairment or permanent or persistent symptoms in the treated animal,

serious unexpected adverse drug reaction an adverse reaction which is both serious and unexpected,

SOP (Standard Operating Procedure) detailed written instructions which are intended to ensure that a particular task or function is performed in a uniform manner,

source data original documents and printouts which are of significance for the results of the trial, e.g. laboratory printouts, the diary notes or checklists of patients, pharmacy stock records, printouts of results from automated measuring instruments, radiography films, patients' records and records and statements from pharmacies, laboratories etc.; in cases where measured results are directly noted down in CRFs and it is stated in the trial protocol that this must be done, CRFs are source data,

sponsor physical or legal person responsible for starting, organising and/or financing a clinical trial,

trial protocol a document which describes the background, motivation, aim, organisation, study population, methodology and statistical considerations for the trial,

unexpected adverse drug reaction an adverse reaction which is not mentioned in the relevant product information on the medicinal product, e.g. the Investigator's Brochure (IB), Summary of Product Characteristics (SPC) or Core Data Sheet (CDS).

Provisions:
Part 2 Procedure for applying for authorization

Section 1 Applications for authorization to conduct a clinical medicinal product trial shall be made by the responsible investigator. The application shall where applicable contain the information requested on the application form drawn up by the Medical Products Agency. The application shall be accompanied by a trial protocol as indicated in Part 6 and the documentation required by the stipulations in Part 7 of these provisions.

The application and trial protocol shall be submitted to the Medical Products Agency in three copies.

Section 2 A complete application shall be submitted to the Medical Products Agency for a multicentre trial. In addition, an application form shall be submitted for each individual trial centre. In cases where local deviations from the common trial protocol occur, this shall be indicated and a supplementary protocol sent in. Information shall be provided relating to which countries the trial is to be conducted in and how great a part of the trial is to be conducted abroad.

Guidelines relating to Part 2:

The Medical Products Agency has drawn up a special application form which should be used. No reference to an annex shall be made for the particulars which shall be included on the form. The form, which is also available on floppy disk, can be ordered from the Medical Products Agency.

An application for authorization shall be submitted to the Medical Products Agency for each prospective study on patients or trial subjects of a chemical or biological substance with the purpose of clarifying properties as a potential medicinal product. This also applies to the testing of a medicinal product with an approved indication, dosage and route of administration in order to shed further light on its efficacy and/or safety (phase IV trial) and what are referred to as PMS studies.

No application normally need be submitted to the Medical Products Agency for trials in which a substance or medicinal product is included without the purpose being to study its properties. Approval from an ethics committee is sufficient in these cases. This may be the case for example when utilising the known properties of a substance to bring about a physiological condition with the purpose of studying this condition or when the intention is to standardize concurrent pharmacological treatment in the study of a non-pharmacological treatment.

The Medical Products Agency should be consulted in the event of doubt as to whether authorization is required for a trial.

If there is a coordinator in a multi-centre trial who does not himself take part in the practical conduct of the trial, this can be indicated in connection with the application from a centre being sent in. If it is desirable for practical reasons, any correspondence from the Medical Products Agency can be sent direct to the coordinator. Contacts between the Medical Products Agency and the responsible investigator for the centre
from which the application has been sent in then take place in the same way as with the responsible investigator at the other centres.

Less detailed information may be sufficient in applications for authorization for a trial on patients which only relates to the usability of a pack or the testing of a flavouring additive. No application for authorization is required for testing an approved flavouring additive on healthy trial subjects.

If a medicinal product and a medical device are intended to be evaluated in the same clinical trial, an application for clinical medicinal product testing shall be submitted to the Medical Products Agency and notification of clinical testing of the medical device to the National Board of Health and Welfare. The examination of the two trials can be coordinated if the two authorities receive the necessary information for this to be done.

Provisions:

Part 3 Ethical examination

Section 1 To ensure that a clinical medicinal product trial is ethically justifiable, the responsible investigator shall apply for authorization of the trial from a regional ethics committee. A copy of the application to the ethics committee shall be attached to the application for authorization to conduct the trial which is submitted to the Medical Products Agency. The trial shall not be commenced before it has been approved by the ethics committee.

In the case of trials involving radioactive medicinal products, the ethics committee shall have access to an assessment by the local radiation protection committee.

In the case of trials with veterinary medicinal products, the stipulations of the Protection of Animals Act (1988:534) and the Protection of Animals Ordinance (1988:539) shall be complied with.

Section 2 If the decision of the ethics committee is not attached to the application to the Medical Products Agency, the responsible investigator shall submit a copy of the ethics committee’s decision to the Medical Products Agency immediately when it becomes available.

Guidelines relating to Part 3:

The ethics committees have an advisory function to the Medical Products Agency and have the task of examining the design of the trial before it is started. The examination shall in particular relate to the scientific feasibility of the project, the ethical problems which are thrown up, how the information to patients is formulated and how consent from the patients to take part in the trial is obtained. On the other hand, the committees do not have the task of monitoring the conduct of the trial thereafter.

A regional ethics committee may delegate the work of examining a trial to a local ethics committee.
An application form for human medicinal products which is common to all the ethics committees in Sweden has been drawn up.

Applications may be examined in parallel by the ethics committee and the Medical Products Agency. If the opinion of the committee is not available when the application for authorization for a trial is submitted to the Medical Products Agency, the Board may nevertheless complete its handling of the application and grant authorization which is subject to the condition that the trial must not start until it has been approved by the ethics committee.

It shall be apparent from the committee's decision on a matter concerning clinical testing what the decision has covered and which members attended the meeting and took part in reaching the decision.

The Swedish Medical Research Council in 1996 published a booklet entitled "Guidelines for the ethical evaluation of human medical research".

Provisions:

Part 4 Responsibility for how the trial is conducted

Section 1 The responsible investigator is responsible for continuous quality control being conducted at all stages of the trial and on the handling of data and is responsible for the contacts with and reporting inter alia to the Medical Products Agency and the ethics committee.

Section 2 If the responsible investigator hands over parts of his responsibility to another person, e.g. a sponsor, coordinator or monitor, this hand-over shall be made in writing. It shall be clearly indicated what is covered by the delegation.

Section 3 If the sponsor takes the initiative for a clinical trial, the sponsor is responsible for the selection of investigator and trial location being suitable and for there being competent personnel and the necessary resources.

The sponsor is additionally responsible for there being a functioning system for quality control and quality assurance in the form of SOPs.

The representative of the authority responsible for medical services, e.g. the chief medical officer in a particular unit, shall confirm by signing the application form that he has been informed about the trial.

Section 4 If the sponsor delegates all or parts of his obligations in a clinical trial to someone else, e.g. to a CRO, the sponsor is obliged to ensure that the trial is conducted to the standard required in accordance with these provisions. The delegation of tasks shall take place in writing, and it shall be clearly indicated what is covered by the delegation.

If additional information becomes available on the trial medicinal product, the sponsor shall ensure that it is forwarded to the investigators, e.g. through updating of the investigator's brochure.
Guidelines relating to Part 4:

A trial is often conducted for practical reasons in collaboration between several different investigators at the same location. However, it is always one of the investigators who is formally responsible for the trial and who has to sign the application papers and the trial protocol. Other investigators have their usual medical responsibilities and are responsible for the selection, treatment and monitoring of their patients and for the reliability of recorded data.

It is the task of the responsible investigator to ensure that there are adequate resources to enable the trial to be conducted in an acceptable manner. This applies both to equipment and access to it and to qualified personnel. The monitor shall also ensure before the trial begins that the necessary resources are available at the location and that these resources are available when the trial is conducted. The head of the medical unit also takes responsibility by signing the application form. The ethics committee should also take account of these factors.

The part of the duties of the responsible investigator relating for example to the application and reporting to an authority or the organization and quality control of the clinical trial may be transferred to a sponsor, who must then also sign the application form.

The obligations of the sponsor thus also include guaranteeing that the documentation sent in is correct and complete, making arrangements for the trial medicinal product to be available and marked in accordance with applicable provisions and ensuring that there is a system for monitoring and auditing the conduct of the trial. In addition, the sponsor, as well as the investigator, is responsible for data being handled and reported in a scientifically correct manner.

The person with medical and administrative responsibility in the medical unit where a trial is being conducted must monitor that it is carried out in accordance with the protocol and check that the trial is not adversely affected, e.g. by other trials in progress at the same location.

Provisions:

Part 5 Requirements to be met by the responsible investigator

Section 1 The responsible investigator shall have sufficient competence in the area which the trial covers and good knowledge of trial methodology and the stipulations which apply to the activity so that he can take responsibility for the trial being conducted in an acceptable manner.

While the trial is in progress, the investigator is under an obligation to follow developments in the area concerned by the trial. This also applies to information on the trial medicinal product from both clinical and preclinical reports.

Section 2 The responsible investigator has a duty to assist with auditing and monitoring.
Section 3 The responsible investigator may delegate tasks to competent colleagues. There shall be updated curricula vitae (CVs) for the responsible investigator and other colleagues who have more qualified work tasks within the trial. In addition there shall be a list containing the initials of the personnel concerned.

Guidelines relating to Part 5:

A trial may be conducted on humans only by a registered physician or registered dentist and on animals only by a registered veterinarian.

The responsible investigator should as a rule firstly have experience in carrying out clinical trials and secondly specialist competence and/or other suitable training in the area of medicine relevant to the trial. Knowledge is required on scientific methodology, the experimental medicinal product and on how to deal with patients in the relevant group intended to be included in the trial.

The investigator should have access to an investigator's brochure (IB) or a summary of product characteristics (SPC) for the trial medicinal product. These are as a rule supplied by the sponsor, and their scope depends on the medicinal product. An IB is generally required for non-marketed medicinal products or medicinal products with a new pharmaceutical form, new dosage or new indication. This must contain all relevant information on the trial medicinal product including chemical, pharmaceutical, toxicological, pharmacokinetic and pharmacodynamic data which are available from animal studies or studies on humans. The information should be so complete that it allows an opinion to be formed on the justification of the design and scope of the planned trial.

The other colleagues who take part in the trial should be thoroughly familiar with the trial protocol and have good knowledge in the medical area to which the trial relates and on the medicinal products involved in the trial.

Provisions:

Part 6 How the trial is to be designed and conducted

Section 1 The trial protocol shall provide a complete account of how the trial in all its parts is intended to be designed and conducted. The protocol shall where applicable contain the following information:

1. The title of the project.
2. The name, position and postal address of the responsible investigator.
3. The name and postal address of any sponsor.
4. The location of the trial.
5. The reasons for and objective of the trial. The objective is described in terms of primary and - where relevant - secondary intentions.
6. Schedule, i.e. calculated period for recruitment of patients and preliminary time when it is anticipated that a final report will be available.

7. Type of trial (controlled, non-controlled), experimental design (parallel groups, crossover etc.), masking (double blind, single blind) and masking methodology shall be stated. An account shall be given of the randomization procedure without revealing details which could affect the conduct of the trial.

8. Description of the study population and how patients will be recruited. An account shall be given of the inclusion and exclusion criteria. The representativeness of the selected group for the relevant patient population shall be discussed. The method for recording examined patients who have not been included should be stated.

9. Ethical considerations.

10. Information on the number of patients, total and in multi-centre studies for each trial site, as well as a statistical assessment of the possibility of answering primary questions for the trial, taking account of the consequences of any expected dropouts of patients.

11. Plan for discontinuing any previous treatment, requirement for periods free of treatment or introductory period with active treatment.

12. Motivation for the choice of route of administration, dose, dose interval and period of treatment with the experimental medicinal product. The methods for determining compliance with the medication. The reasons for adjusting the dose, how this is intended to be carried out and planned action in the event of temporary or permanent interruptions to the treatment.

13. The reasons for the selection of control treatment with presentation as in item 12.

14. Other permitted treatment which may be in progress concurrently. Treatment which is not permitted.

15. An account of how the patient code, patient identification lists and randomization are drawn up and how patient data will be recorded, e.g. in case report forms (CRFs) and how these will be kept. The patient identification lists shall permit rapid identification of the individual and be capable of forming the basis for the quality control of data.

16. Routines for how safe handling of medicinal products will be achieved and how this can be verified. This comprises the delivery, storage, labelling, dispensing and return of medicinal products.

17. Specification of primary and secondary evaluation variables. Description of statistical methods. Criteria for including or, where appropriate, excluding patients from various analyses.
18. Description of methods for efficacy and safety recording. Sample volumes and sampling times (where appropriate in relation to taking of medicinal product). The location where the analysis is performed shall be stated.

19. How suspected adverse drug reactions shall be recorded and reported and what action is planned in the case of complications. The reasons for the patient being withdrawn from the study or for breaking the randomization code shall be presented. It shall also be apparent where the randomization code is kept, who is allowed to break it and under what circumstances it may be broken.

20. The information for patients and the procedure for obtaining consent to take part.

21. A plan for how the trial will be monitored and how quality control and quality assurance will be carried out.

22. An account of how the patients are dealt with after the end of the trial (gradual reduction in dose, discontinuation of experimental medicinal product, change of treatment etc.). An account of how the treatment is planned for those patients for whom continued pharmacological treatment is medically justified.

23. The reasons for terminating the trial prematurely and any planned interim analyses.

24. Insurance and financial compensation or other benefits paid to the customers (attached where appropriate as separate contract/agreement).

25. An account of how the personnel affected will be informed.

26. The distribution of responsibility and/or the delegation of tasks within the trial to other employees. Reference shall be made to an annex.

27. The policy which shall be applied for the reporting and publication of the results.

28. Archiving of trial material, procedures, responsibilities and times.

29. List of the literature to which reference is made in the trial protocol.

Section 2 The trial protocol shall be identifiable and dated and signed by the responsible investigator and a representative of any sponsor.

Where trial protocols for multi-centre trials are sent in to the Medical Products Agency from a centre, this shall be signed by the responsible investigator at this centre or by the coordinator. There shall be a copy at all the centres signed by the investigator responsible at the location.

Guidelines relating to Part 6:

If it is intended that patients will be recruited by advertising, the draft formulation of the advertisement should be submitted to the Medical Products Agency in conjunction with the application.
A schedule which clarifies the times e.g. of the examinations and visits which take place during the trial should be attached.

There should be written documentation at the trial location on how the tasks are delegated to the various employees. The declaration should contain a list containing the initials of those who are entitled to enter data into different source documents, e.g. CRFs.

Provisions:

Part 7 Requirements to be met by the documentation

Section 1 Documentation shall be attached to the application concerning the chemical, pharmaceutical, pharmacological and toxicological properties of the medicinal product. Documentation relating to human pharmacological and clinical properties of significance to the trial shall be attached or referred to.

In the case of a radioactive medicinal product there shall be documentation on absorbed radiation doses to organs, effective doses and a detailed description of these.

Section 2 In cases where corresponding papers and documentation have previously been submitted to the Medical Products Agency, reference may be made to these papers.

Section 3 The requirements to be met by the documentation are stated in Annex 1 Chemical and pharmaceutical documentation, Annex 2 Pharmacological and toxicological documentation and Annex 3 Clinical and pharmacokinetic documentation to these provisions.

Guidelines relating to Part 7:

The requirements to be met by documentation on the trial medicinal product may vary depending on the nature of the trial and the character of the product. Reference may be made to documentation submitted to the Medical Products Agency previously in other contexts, which is still relevant. The Board's reference number should be stated. Complete reports may be requested.

In the case of the clinical testing of radioactive medicinal products, certain medicinal products for external use and natural remedies, certain departures may be made from the requirements applicable to the documentation for ordinary medicinal products. The requirements for preclinical documentation, for example, may be lower for older products which have a well established use.

Provisions:

Part 8 Information and consent

Section 1 Those patients whom the responsible investigator assesses as being capable of being included in a clinical drug trial shall receive such information on the trial that they can voluntarily decide whether they wish to take part or not. The information shall normally be given both verbally and in writing and be comprehensible to laypeople.
When a minor takes part in a trial, information shall be provided both to the minor and to the parents or guardians.

In the case of trials involving radioactive medicinal products, written information shall be provided on radiation doses and risks.

Section 2 For trials which are related to the treatment of disease, dated, written consent to participate shall be obtained from the patient, unless reasons exist for nevertheless undertaking the trial.

Section 3 Written consent to participate shall always be obtained for trials which are not related to the treatment of disease.

Section 4 Consent shall, where possible, be obtained from both the minor and in writing from the parents or guardians.

Section 5 In the case of trials on animals, the consent of the owner of the animal shall be obtained.

Section 6 The patients shall be informed and give written consent for particulars which relate to the trial and which within the medical services may become the object of secrecy to be examined by personnel from the sponsor and foreign authority for medicinal product control in connection with quality control and quality assurance. A proviso entailing that the particulars will not passed on shall be made.

Section 7 If new information of significance becomes available during the course of the trial or major changes are made in the experimental design which are of significance to the patient, the patient shall be informed accordingly and give consent again for continued participation in the trial.

Section 8 An account shall be given in the trial protocol of when, how and by whom it is intended that the information will be supplied and consent obtained and how it is intended that this will be documented.

Section 9 A copy of the information which is intended to be handed over to the patient shall be attached to the application made to the Medical Products Agency.

Section 10 The patient has the right to discontinue his participation in the trial at any time and without stating reasons, without this affecting his continued care.

Guidelines relating to Part 8:

The principles contained in the latest version of the Declaration of Helsinki shall serve as a guide.

It should be apparent from the information for patients that it is a research product, what the purpose of the project is and what the possible benefits and drawbacks or inconveniences associated with taking part are. The patients should be given reasonable time to consider whether they wish to take part.
Despite the right of the patient to withdraw from a clinical trial prematurely without stating reasons, the investigator may make attempts to find out the reason for the patient's decision to the extent that is compatible with full respect for the patient's rights. This may be of significance for the safety assessment in the trial.

In the event that the patient is unable to give his informed consent, the patient may nevertheless be included in a trial which is linked to the treatment of illness, if the ethics committee has given its approval in principle and the investigator judges that it may be of benefit to the patient. This may apply for example to patients who are demented, psychotic or unconscious. Relatives should receive written information in such cases.

A confidential link must be established between those who check the quality and safety of data in the trial and the person who is responsible for the case records in the health service.

The National Board of Health and Welfare has drawn up guidelines on confidentiality in the health service (1991:4).

Provisions:

Part 9 Insurance

Section 1 The sponsor is responsible for the patients being guaranteed satisfactory financial protection through insurance or in some other way if harm should arise in connection with the trial. If a sponsor does not take part in the trial, this obligation instead falls on the responsible investigator.

Guidelines relating to section 9:

With effect from 1 January 1997, compensation for harm to patients and volunteer trial subjects which arises in connection with medical research is paid in accordance with the stipulations of the Harm to Patients Act (1996:799). Compensation may be paid for harm due to medicinal products if the harm has arisen as a result of the product having been prescribed incorrectly or handled by health service personnel contrary to applicable instructions. On the other hand, compensation is not paid for harm due to properties of the medicinal product or deficiencies in the description of how it is to be used.

Medicinal product insurance only covers medicinal products intended for humans. However, the insurance does not cover natural remedies or certain medicinal products for external use.

Provisions:

Part 10: How the patients are to be cared for

Section 1 The responsible investigator must ensure that the patients have access to necessary medical care during the period when they are included in the trial for the illness concerned and any adverse reactions.
Section 2 When a patient interrupts or terminates the trial, the responsible investigator shall ensure that the patient receives the care and follow-up which is necessary.

Guidelines relating to Part 10:

When a patient is cared for within the framework of a clinical medicinal product trial, patient records or the equivalent shall be kept in the usual way in accordance with the Patient Records Act (1985:562) and the National Board of Health and Welfare provisions and guidelines pursuant to this Act. The fact that the patient is taking part in a clinical trial and what the trial entails in the form of treatment, doses and periods of treatment must be apparent. An account must be given of tests of significance for the care of the patient.

In the case of blind trials, the same particulars as are shown on the labelling of the medicinal products may be stated to avoid the risk of the blinding being jeopardised. If the patient is allocated a code number in the trial, this should be stated in the case record so that the code can be quickly broken if required. This can be done directly through the code envelope and without the need to go via the code list. If the code is broken, it should be stated in the case record which medicinal product treatment the patient has received.

If the patients gives permission, it is appropriate for the investigator to inform the patient's general practitioner that the patient is taking part in a clinical trial.

During the period when the patient is included in a trial, the patient for safety reasons should be provided with and recommended to carry on him a card containing information about the trial. It must be apparent from the card that the patient is taking part in a clinical medicinal product trial, what medicinal products are involved, who can be contacted to provide further information about the trial and how this person can be reached.

Provisions:

Part 11 Information to staff

Section 1 The responsible investigator shall continuously supply relevant information which is significant for the conduct of the trial to all personnel who are affected by the trial, including pharmacy and laboratory personnel. When the trial starts, the information shall cover the intention of the trial and how it is intended to be conducted.

Information shall also be provided when the trial is modified in any major respect, discontinued prematurely or terminated.

Section 2 The responsible investigator shall document how and when information has been given.

Guidelines relating to Part 11:

The nature and scope of the information may vary in consideration of the work tasks of the personnel in the trial. It is of great importance that information is provided to
affected groups of personnel on the procedure followed for any randomization and on where the trial code for the individual patients is kept and who is allowed to break it. Protective information is also given if necessary to the personnel who handle the trial medicinal product.

Provisions:

Part 12 The location for the trial

Section 1 The location for the trial shall be sufficiently well equipped for it to be possible for the trial to be conducted in an acceptable manner. Where radioactive medicinal products are used, the location must be suitable from the point of view of radiation protection.

Guidelines relating to Part 12:

The nature and scope of the trial and imaginable risks to the patients are circumstances which affect the selection of location. The guiding principle must be that the greatest possible safety is achieved for the patients.

Trials which involve the supply of medicinal products to patients for the first time and studies involving parenteral administration should as a rule take place where medical emergency situations can be dealt with. As it is essential for a medicinal product to be tested in a clinical situation which corresponds to that in which the medicinal product is primarily intended to be used, trials must often be conducted within different levels of care, e.g. in outpatient care.

Provisions:

Part 13 Medicinal products

Section 1 The sponsor is under an obligation to ensure that trial medicinal products including placebos are available and that updated documentation on the medicinal products which are to be used is presented to the Medical Products Agency. If there is no sponsor, this obligation instead rests on the responsible investigator.

Section 2 All handling of medicinal products shall be well documented. Documentation and reference samples from each manufacturing batch shall be kept by the manufacturer for at least two years after the clinical trial has been terminated, or for at least one year after the final expiry date has passed if this occurs at a later date.

Section 3 The labelling of the medicinal product pack, including placebo, shall comprise the following:

- the words "For clinical trial", if it is not an authorized medicinal product in its original pack which is used in a trial in outpatient care which is not blinded,
- the name or code designation, quantity, dosage and route of administration of the medicinal product,
- batch number or other method of identification,
- where appropriate, technical instructions and/or directions for use,
• storage instructions,
• the name of the manufacturer and investigator,
• the name and address of the sponsor,
• expiry date in accordance with ISO standard,
• warning to keep out of the reach of children, if the medicinal product is not to be used solely in hospitals.

The labelling of medicinal products for veterinary use shall additionally contain the words "For animals" and information on the withdrawal period for food-producing animals.

Radioactive medicines shall be labelled with information on radiation dose. The labelling shall additionally include the words “Contains radioactive substance”.

Section 4 When the manufacturer/agent is involved in the trial, it is responsible for the labelling being applied.

Section 5 All handling of medicinal products shall in general take place via a pharmacy. If reasons exist for doing so, the Medical Products Agency may grant exceptions to this requirement in individual cases.

When a trial has been terminated or discontinued, remaining medicinal product and placebo shall be returned to the manufacturer via the pharmacy or be destroyed by agreement with the sponsor or investigator. A list of destroyed medicinal products shall be drawn up.

Guidelines relating to Part 13:

The requirements for the manufacturing of medicinal products for clinical testing are specified more closely in the Medical Products Agency's provisions (LVFS 1995:3) on authorization for the manufacturing of medicinal products and in the Medical Products Agency's provisions (LVFS 1996:2) on Good Manufacturing Practice for medicinal products.

The labelling must be adapted according to the design of the trial. In the case of double-blind studies, the batch number or expiry date, for example, must not be stated in such a way that they can reveal the identity of the contents. The "name" in comparative blind trials becomes for example "x/y" or "x/placebo". In early phases, "x" may be constituted by the code designation the substance has. When a dosage cannot be indicated on the pack, separate dosage instructions should be supplied. A suitable pack size for the medicinal product must be used.

In cases where there is outer packaging with smaller units inside, the smaller units must be labelled in such a way that it is possible to identify the contents of the units. This can be done by stating as above the name or code designation and batch number of the medicinal product and that it is intended for clinical trial.

If there is not space for all the text on the label, it can be stated in a separate instruction for patient.
When the manufacturer takes part in a trial and makes medicinal products available, the authorization of the Medical Products Agency for the trial and authorization for the dispensing of medicinal products apply, see Section 10 of the Medical Products Agency’s provisions and guidelines (LVFS 1995:7) on authorization for the sale of non-authorized medicinal products (licensing provisions). If the manufacturer does not take part as sponsor, applications for licence to dispense trial medicinal products must be submitted in certain cases to the Medical Products Agency.

In the normal case (when the trial is not carried out at the manufacturer), medicinal products are requisitioned from the pharmacy which in consultation with the investigator is responsible for the storage and distribution of medicinal product and placebo. The name of the pharmacy is printed on the prescription or requisition.

Reference samples must be saved to allow the quality of the medicinal products which have been used in a clinical trial to be checked. They must be labelled in such a way that at least their identity and batch number are apparent. They must be stored under the best possible storage conditions. The quantity must allow a check to be made as to whether the product satisfies the given quality standards and any repetition of limited studies such as dissolution and/or bioavailability tests.

Provisions:

Part 14 Surveillance of medicinal products

Section 1 The responsible investigator shall in the manner indicated in Sections 5 - 10 of this Part record adverse drug reactions and adverse events which occur during administration of a medicinal product in connection with clinical trials and report them to the Medical Products Agency and the sponsor.

The sponsor shall also report adverse drug reactions and adverse events to the Medical Products Agency in the manner indicated in Sections 11 - 15 of this Part.

Section 2 All reporting shall take place within the time limits stated below and be accompanied by an assessment firstly of a causal relationship with the administration of the medicinal product and secondly of how the relevant trial is affected. The report shall as far as possible be supplemented by information on diagnosis/symptoms, medicinal product and further data which make it possible to assess any causal relationship with the medicinal product. The relationship with the start of treatment and the latest dose taken of the medicinal product shall be stated on the report.

Section 3 The duration of exposure to the trial medicinal product shall be considered when stating the frequency of adverse drug reactions and adverse events and in the statistical analysis. Information shall also be provided on previous experience with the same or similar medicinal products and an assessment of the significance of the adverse reaction for the use of the medicinal product.

Section 4 If it is not assessed as being possible to comply with the reporting of adverse drug reactions or adverse events for practical or methodological reasons in the planning of the trial in accordance with these provisions, a proposal on how it is intended that the
reporting will be dealt with shall be attached to an application for authorization for a clinical trial.

Section 5 The responsible investigator shall report in writing to the Medical Products Agency adverse drug reactions which are both unexpected and serious. This shall be done as soon as possible, but no later than fifteen calendar days after the first knowledge by the investigator.

Section 6 Unexpected adverse drug reactions which are fatal or life-threatening shall be reported by telephone, fax or in some other way as soon as possible and at the latest within seven calendar days from the first knowledge by the investigator to the Medical Products Agency. The report shall thereafter as soon as possible, but at the latest within a further eight calendar days, as far as possible be supplemented by information which makes possible an assessment of any causal relationship with the medicinal product.

Section 7 The responsible investigator shall report in writing to the Medical Products Agency adverse drug reactions which are both unexpected and serious. This shall be done as soon as possible, but no later than fifteen calendar days after the first knowledge by the investigator.

Section 6 Unexpected adverse drug reactions which are fatal or life-threatening shall be reported by telephone, fax or in some other way as soon as possible and at the latest within seven calendar days from the first knowledge by the investigator to the Medical Products Agency. The report shall thereafter as soon as possible, but at the latest within a further eight calendar days, as far as possible be supplemented by information which makes possible an assessment of any causal relationship with the medicinal product.

Section 7 The report of the responsible investigator to the Medical Products Agency on an adverse drug reaction shall contain information on the patient's identity, the code number the patient has in the trial, which trial the patient is included in and the Medical Products Agency's reference number for this trial.

The report of the responsible investigator to the sponsor shall not contain information on the patient's identity but only the code number the patient has received in the trial, which trial the patient is included in and the Medical Products Agency's reference number for this trial.

Section 8 In addition to individual reports on adverse drug reactions as above, the responsible investigator shall also report as soon as possible observations of suspected increased incidence and/or severity of adverse reactions or adverse events which may affect the formulation of the protocol or the conduct of the trial. These reports shall be sent to the Medical Products Agency and the sponsor.

Section 9 The reporting by the investigator to the sponsor shall cover all serious adverse events and early discontinuations of the trial medicinal product and their cause.

Section 10 All adverse drug reactions and early discontinuations of the trial medicinal product and their shall be presented and evaluated in the responsible investigator's final report.

Section 11 The sponsor shall report to the Medical Products Agency in writing adverse drug reactions which are both unexpected and serious. This shall be done as soon as possible and at the latest within fifteen calendar days after information has been received.

Where possible, the sponsor shall mention whether the investigator has previously reported the adverse reaction to the Medical Products Agency.

Section 12 The sponsor shall report unexpected adverse drug reactions which are fatal or life-threatening as soon as possible by telephone, fax or in some other way, but at latest within seven calendar days after the first knowledge by the sponsor that a case qualifies. The report shall thereafter be confirmed in writing by the sponsor as soon as
possible and at the latest within a further eight days and as far as possible be supplemented by information which makes possible an assessment of any causal relationship with the medicinal product.

Section 13 In addition to individual reports on adverse drug reactions as above, the sponsor shall also report as soon as possible observations of suspected increased incidence and/or severity of adverse reactions or adverse events which may affect the formulation of the protocol or the conduct of the trial. These reports shall be sent to the Medical Products Agency and the investigators.

Section 14 The sponsor shall present a report of serious adverse drug reactions and adverse reactions or adverse events which have led to discontinuation of the trial medicinal product at least once per year and in the final report.

Section 15 The sponsor is obliged to report as soon as possible to the Medical Products Agency that a trial has been discontinued in another country or that approval for the sale of a medicinal product has been revoked in another country as a result of adverse reactions or other safety problems.

Guidelines relating to Part 14:

It is apparent from Part 4 Section 2 that the responsible investigator can delegate parts of his responsibility to the sponsor among others. This delegation may for example relate to the reporting to the Medical Products Agency in accordance with this Part. The delegation must be made in writing.

The reporting of adverse drug reactions and adverse events also covers those suspected as being linked to an active comparator.

It is important in reporting by the investigator and sponsor to the Medical Products Agency that reports which relate to the same patient can be identified, linked together and recorded as one. In addition to the patient code, it is essential that the Medical Products Agency's reference number and the number of the trial protocol are also stated.

The sponsor is considered to have received information on a adverse reaction when a report arrives which at least contains the following: the information can be related to a particular patient/trial subject, a suspected medicinal product, an adverse reaction diagnosis/finding, a known rapporteur or other individual source of the report (e.g. a known medical journal) and the time of occurrence. The sponsor shall report adverse reactions irrespective of source.

Other types of safety problems which affect the assessment of the appropriateness of the medicinal product should also be reported as soon as possible and at the latest within fifteen calendar days to the Medical Products Agency by the sponsor. This category includes an increase in the incidence of known serious adverse reactions, inadequate efficacy in life-threatening diseases or findings in various safety studies.

Provisions:
Part 15 Quality control and quality assurance

Section 1 A continuous check shall be made during the course of the trial on the methods used and the quality of the data which are collected. The principles underlying this check shall be stated in the trial protocol or in an SOP.

Section 2 The persons who are responsible for quality control (monitor) and quality assurance (auditor) shall be sufficiently qualified for their tasks. SOP shall be drawn up for their work.

Section 3 An account shall be given of the monitor's contacts with the trial site and the action which the monitor has taken as a result of these contacts. The monitor shall draw up a report on his activity for his principal.

Section 4 The quality assurance system shall be independent of those who are involved in the practical conduct of the trial.

Guidelines relating to Part 15:

The quality control should be carried out by one or more monitors, depending on how extensive the trial is. The type and design of the trial determines what competence is required in the monitor and how frequent the contacts with the investigator should be.

The report which the monitor draws up normally need not be available at the time of the inspection. On the other hand, there should be a list of the monitor's visits. This should be counter-signed by the investigator or a colleague. In addition, the actions which the monitor has proposed should be documented, e.g. through a letter to the investigator.

The Medical Products Agency may carry out inspections at the location of the trial. The responsible investigator is responsible for documentation and other material being available, for it being possible for premises, laboratories and equipment to be checked and for it being possible to meet the staff who are involved in quality control and quality assurance.

The Medical Products Agency may also carry out inspections at the sponsor.

Supervision by the Medical Products Agency also comprises a check that the trial medicinal products have been manufactured in accordance with Good Manufacturing Practice (GMP) and that the preclinical safety documentation complies with the requirements of Good Laboratory Practice (GLP).

If the trial has been audited, this can be documented with a certificate. The auditor's report is normally a matter solely for the principal and need not be presented to the investigator or the authority.

Provisions:

Part 16 Handling of data
Section 1 The responsible investigator is responsible for findings and observations made within the framework of the trial being noted down and reported correctly and in full.

Section 2 At each trial site the investigator shall draw up a patient identification list which allows the code numbers used for the patients who are included in the trial and the patient's identity to be translated.

Section 3 A list shall be made of those persons who have access to data and any authority they have to make changes.

Section 4 All corrections of data shall be made in such a way that the original information is not made invisible. The correction shall be dated and initialled by the person who has made it. If the reason for the change is not obvious, it shall be stated.

Section 5 When information on individuals is recorded using automatic data processing, the Data Protection Act (1973:289) becomes applicable and the security provisions of the Data Inspection Board shall be observed.

Guidelines relating to Part 16:

It is of particular importance that the blinding is kept intact until all the data has been examined and assessed as being capable of being evaluated without additional supplements. It must be possible in blind studies to state who knows or know the code and at what time the code is broken.

In those cases where information on individuals is recorded using automatic data processing and the information is not completely anonymized, the Data Protection Act (1973:289) becomes applicable. This means that permission for the recording of personal data needs to be sought in most cases from the Data Inspection Board. Such permission must be obtained before recording begins.

Provisions:

Part 17 Modification of a trial and addition to the trial protocol

Section 1 Major modifications to the trial and/or additions to the trial protocol shall be notified as soon as possible to the Medical Products Agency. They shall be approved by the Medical Products Agency before they may be implemented.

Modifications and/or additions relating to the integrity and safety of the patients and the evaluability of the trial shall also be sent to the ethics committee for its comment and approval.

Changes of sponsor shall be notified as soon as possible to the Medical Products Agency.

Guidelines relating to Part 17:

Major modifications to the trial means modifications which affect the safety of patients and/or possibilities to evaluate the trial. This applies to modifications for example to evaluation (primary efficacy analysis), inclusion/exclusion criteria, sampling routines,
dosage, treatment groups and numbers of patients and the duration of treatment. It also applies in the case of changes of manufacturer and modifications to the manufacturing procedure, composition, packaging and labelling of the medicinal product.

Reference should be made to the reference number for the trial at the Medical Products Agency. It should be clearly apparent what modifications are planned. The reason for and consequence of the modification should be indicated as well as how the evaluation of any results which have already been obtained will be affected.

The requirement of approval from the Medical Products Agency before a modification may be implemented only applies to the modifications which will be carried out systematically in the trial. Emergency modifications which the investigator has to make and which are necessary to guarantee good care for the individual patient are part of the medical responsibilities of the investigator. Such measures are not encompassed by the requirement of approval in advance.

A change of responsible investigator requires new authorization from the Medical Products Agency and a new application must be submitted.

Provisions:

Part 18 How the trial is to be reported

Section 1 If a trial is not started, the responsible investigator shall notify the Medical Products Agency accordingly at once and state the reason.

Section 2 When a trial is in progress for more than one year, the responsible investigator shall send to the Medical Products Agency brief annual reports.

Section 3 When a trial is discontinued or terminated prematurely, the responsible investigator or coordinator shall as soon as possible submit a dated and signed report to the Medical Products Agency. Such a report may be less detailed. In cases in which a sponsor has taken part in the trial, a representative of the sponsor shall also sign the report.

Section 4 The final report shall be dated and signed and contain a detailed account of the trial and its results. In cases in which a sponsor has taken part in the trial, a representative of the sponsor shall also sign the report.

When several investigators take part in a trial, signing the final report may be delegated for example to the main investigator. This person shall always obtain the views of the other investigators.

Guidelines relating to Part 18:

The annual report should contain a brief account of whether the recruitment of patients is going according to plan, whether the timetable can be kept to, the occurrence of adverse reactions and whether anything of significance to the conduct of the trial has happened. In the case of a multi-centre trial, an annual report common to the whole
The final report is usually drawn up in collaboration between the responsible investigator and sponsor.

If a coordinator or a specially appointed committee compiles and signs the final report in a multi-centre trial, this should not be done until the other investigators have had an opportunity to examine and influence the contents of the report. There should be a list of signatures from the responsible investigators who have taken part.

Provisions:

Part 19 Archiving of data

Section 1 Both the responsible investigator and the sponsor are obliged to keep the papers from the clinical trial which are necessary so that the trial can be reconstructed when an inspection is carried out.

Section 2 The papers shall be kept in such a way that the responsible investigator or sponsor has full control over them. The location shall be appropriate and it shall be possible to guarantee the integrity of data.

Guidelines relating to Part 19:

All-embracing stipulations on archiving are contained in the Archives Act (1990:782) and the Archives Ordinance (1991:446). The National Archives have issued provisions pursuant to this legislation.

With regard to information registered on computer media, guidance is given in the National Archives provisions and guidelines (RA-FS 1994:2) on recordings for automatic data processing (ADP recordings).

The archiving period must be adapted to applicable rules and should not be less than fifteen years after the trial has been terminated.

If the investigator himself cannot take responsibility for archiving, this may be delegated. If this is the case, the sponsor must be informed about how archiving is done.

In cases where the responsible investigator is unable to guarantee safe storage of the patient identification lists, these can be sent to the Medical Products Agency for storage at the same time as the investigator sends in a final report on the trial.

Provisions:

Part 20: Handling of deviations from the regulations

Section 1 If it emerges from quality control or quality assurance or in some other way that significant departures from applicable stipulations have taken place, the responsible investigator or sponsor shall immediately take appropriate action.
Section 2 There shall be SOP for how deviations from the regulations shall be handled and how information on action taken shall be supplied to the Medical Products Agency, the ethics committee and other parties concerned.

Section 3 The Medical Products Agency may grant exceptions (exemptions) from the stipulations of these provisions.

Annex 1. Chemical and pharmaceutical documentation

Chemical and pharmaceutical documentation shall in principle be of the same kind as that required in applications for marketing authorization for medicinal products. However, it may be adapted to the relevant trial phase and be preliminary and less complete than in the case of applications for authorization. It may become necessary to supply further information at the transition between one phase and another. Special emphasis should be put on documentation which guarantees reproducible biopharmaceutical properties and quality features which are significant for the results of the trial and the validity of the toxicological studies.

If the chemical or pharmaceutical properties are changed in comparison with those which applied in the case of pharmacological and toxicological studies or previous clinical trials, this shall be reported and commented on.

Changes of a chemical or pharmaceutical nature which are carried out while a trial is in progress shall be notified to the Medical Products Agency at once. Changes to the composition of products often require investigations relating to the biopharmaceutical properties of the medicinal product, e.g. its bioavailability.

In the case of an extension of the shelf life for the trial medicinal product or comparison product, a request for this to be done shall be submitted to the Medical Products Agency. Stability data or analytical certificates from renewed analysis of the batch concerned shall be attached. Relabelling of the product packs resulting from an approved extension of the shelf life shall be carried out by a responsible person at the manufacturer or in the pharmacy and shall be logged.

Production conditions

The requirements for the manufacturing of medicinal products are specified in more detail in the Medical Products Agency's provisions (LVFS 1995:3) on authorization for the manufacturing of medicinal products and in the Medical Products Agency's provisions (LVFS 1996:2) on Good Manufacturing Practice for medicinal products. In addition, the document entitled “EU GMP Annex on Manufacture of Investigational Medicinal Products” and the guidelines stated in the Medicinal Products Standard for Finland and Sweden (LS) shall be complied with.

Manufacturers of medicinal products for clinical testing shall document that they follow GMP rules in some generally accepted form.

Any subcontracting manufacturer shall be stated.

Complete composition
The complete quantitative composition of the preparation shall be stated. The name and/or code designation and the pharmaceutical form and strength are stated for the product.

Active substance

The structural formula, empirical formula, chemical name and generic name and any internal name and laboratory code are stated where possible for the active substance.

The method of synthesis and/or isolating procedure shall be briefly stated. A more detailed description of the method of production and requirements to be met by the starting material are required for products of biological origin.

Proof of structure shall be provided if possible; the active principle shall if possible be characterized for biological substances.

The description of the substance shall be as complete as possible. Information on physico-chemical properties such as solubility and other properties of significance to bioavailability is particularly important.

Information on impurities may be adapted to the trial phase concerned. In phase III, the investigation of impurities shall have been mostly completed. Particular attention shall be paid to the occurrence of any active impurities in biological substances.

Quality standards shall exist and be stated. They may be preliminary and be replaced in phase I and phase II studies by results from single batches or small numbers of batches.

Stability studies shall be reported if they are essential for an assessment of the shelf life of the finished medicinal product.

Other constituents

Information shall be provided which shows that other ingredients are of reproducible quality. The same information as is required for marketing authorization shall be provided for new or unusual substances which have a great impact on the efficacy of the finished medicinal product.

The finished medicinal product (preparation)

The method of production shall be briefly described, unless it is entirely obvious. Information shall always be provided for medicinal products prepared in a sterile or aseptic manner.

Galenic properties such as disintegration time, dissolution profile, viscosity, crystal shape and particle size should be briefly stated and if necessary reasoned.

Quality standards shall always be provided and cover at least identification, assaying and checking of essential galenic properties. The information may be preliminary and in certain cases (phase I and II) be replaced by the results of single or small numbers of batches.
Stability tests should normally have been started and it should be possible for a preliminary idea of shelf life to be given. Information on the set storage period and storage instructions should also be provided.

Information on whether the trial medicinal product or comparison product have marketing authorization in other countries should be provided.

Packaging material

Design and function should be described in the testing of technically more advanced or completely new forms of packaging. The nature and quality of the packaging material should be stated for products for injection, rinsing liquids and eye products.

Comparison products

If a placebo or other comparison product is included in the trial, its complete qualitative composition, quality standards or analytical certificate, appearance and taste should be stated. It should be apparent how differences in appearance, taste or odour between the products are masked. Information on the method of production shall always be provided for medicinal products produced in a sterile or aseptic manner. Information on quality standards and method of preparation may be omitted if the product is authorized and marketed in EU countries or North America.

If a product which has been authorized for marketing in Sweden is modified or processed in some way and this product is to be used either as a trial medicinal product or as a comparison product, this shall be reported and any effect the modification may have shall be elucidated, particularly with regard to the biopharmaceutical properties.

Annex 2 Pharmacological and toxicological documentation

Introduction

Documentation concerning the pharmacodynamic, pharmacokinetic and toxicological properties of the medicinal product shall be presented. It shall exist in the form of a summary, accompanied by a reference list of studies referred to and other literature.

The complete reports on which the summary is based shall be readily available so that they can be sent in on request. The summary must be sufficiently detailed for the reader to be able to form an idea of the design, quality and conduct of the studies carried out and the results obtained. Information is thus required for example on the number of animals per dose group, doses given, route of administration etc. This can be presented in table form. Toxicokinetic data shall be presented for pivotal toxicological studies.

In cases where they constitute the basis for the assessment of safety, the studies should be carried out in accordance with Good Laboratory Practice (GLP). An account of the GLP status of the studies shall be given, preferably in table form. The Medical Products Agency has issued provisions on Good Manufacturing Practice for medicinal products (LVFS 1996:2).
In addition to completed studies, it is desirable that an overview account should be given of studies which are in progress or planned to date.

The scope of the documentation shall be in reasonable proportion to the nature and scope of the clinical trial.

Comparisons with other well-known substances in the same pharmacological group may be of value.

If the medicinal product is constituted by a mixture of stereoisomers, information shall be supplied on the pharmacological properties of the isomers contained in the mixture.

**Pharmacodynamics**

The studies shall be carried out using appropriate animal experimentation methods. Both qualitative and quantitative aspects should be considered. More important observations should be studied on more than one type of animal. Any occurrence of active metabolites should be documented.

Studies relating to the primary effects of the product, i.e. such effects as constitute the basis for its proposed use, shall be presented with special emphasis on the mode of action of the substance.

Studies relating to the other effects of the substance on essential functions and organs shall also be presented.

Consideration should be given to the possibilities of interaction with other medicinal products which may be used together with the trial medicinal product in the relevant pathological situation.

**Pharmacokinetics**

Information should be provided which elucidates the systemic exposure attained for the active substance in the toxicological studies with the aim of facilitating interpretation of these in connection with safety assessment for the clinical trial on the medicinal product. The systemic exposure for active metabolites should also be documented.

**Toxicology**

Information shall normally be provided on the toxicity of the medicinal product in both single-dose administration and repeated administration to at least two types of animal. The substance should be administered in a similar way as in the trial, unless there are special reasons why a different route of administration is more suitable.

The length of the toxicity studies should be adapted to the period of treatment in the clinical trial.

The following table can serve as a guide:

| Duration of the trial | Period of administration in the toxicity studies |
Interruption of treatment may affect the formulation of the toxicity studies. This must be the object of assessment in connection with each clinical trial.

The results of studies relating to any genotoxic effect shall be provided for all new substances, including new excipients, which are not included in medicinal products previously authorized in Sweden.

All substances must be evaluated with respect to any carcinogenic effect.

Reproduction toxicology studies are required in those cases in which fertile women do not constitute an exclusion criterion. Effects on male fertility should also be considered.

Studies relating to special toxic effects (e.g. local irritant or sensitizing effect) may be required in certain cases.

Safety evaluation

A summary assessment and safety evaluation shall be provided ahead of proposed clinical trials against the background of the scope of and results from the pharmacological and toxicological studies performed. Insofar as results from clinical studies are available, this should also be considered in the safety evaluation.

Annex 3 Clinical and pharmacokinetic documentation

Existing documentation relating to the pharmacokinetic and clinical properties of the medicinal product on humans shall be presented. The requirements vary according to the phase in the development of the experimental medicinal product in which the planned trial takes place. It is essential that the information makes possible a satisfactory benefit/risk assessment for the study concerned.

The documentation should exist in the form of a summary accompanied by a reference list of documentation referred to. The complete reports which form the basis for the summary should be readily available so that they be sent in on request. The summary shall be sufficiently detailed for the reader to be able to form an idea of the quality, design and conduct of the studies carried out and results of significance for the trial concerned. Summary tables may be of value.

Information on the number of trial subjects and patients who have received the product should be stated as well as doses given and the duration of the studies. It shall also be apparent what types of patients have been included in studies. Sex and age should be stated. It is of value if not just studies which have already been completed are presented.
but also those which are in progress and planned to date. The scope of the documentation shall be in reasonable proportion to the nature and scope of the trial.

Essential pharmacokinetic basic data on humans shall be described. It shall be apparent whether the product is a racemate, whether there are active metabolites and whether there is a risk of accumulation of the parent compound or metabolite. For early studies on humans, the expected systemic exposure in trial subjects may be set in relation to equivalent data on animals. The question of known or expected interactions with other medicinal products should be discussed in certain cases, as should the effect of food. Major pharmacodynamic findings on humans shall also be described.

Data obtained on clinical efficacy or any major "surrogate-end point" and any other effects shall be described. Experience from use on another indication may be of value.

The documentation concerning the adverse reactions of the medicinal product shall be presented. In addition to descriptions of adverse reactions which have occurred in completed studies or spontaneous reports, unexpected serious events which have occurred in studies which are in progress should be presented. Known or possible risk factors or population(s) at risk shall be presented. Risks relevant to humans which can be predicted on the basis of pharmacological and toxicological documentation shall be stated. It may sometimes be necessary to state certain precautions or requirements for special monitoring which are relevant.

There shall be a summary benefit/risk assessment for the study concerned against the background of the scope of the results from experience presented. It is also of value to obtain information on how it is planned that further investigations will be made on suspected risks of the medicinal product.

Reasons shall be given for the selected dose and period of treatment in the study concerned.

This statutory instrument comes into effect on 1 February 1997.

The following are repealed on the entry into force of this statutory instrument:

1. The Medical Products Agency's provisions and guidelines LVFS 1990:25 (SOSFS 1984:9) on the clinical testing of medicinal products,


Transitional provisions

These provisions shall be applied to applications for authorization for clinical medicinal product testing which are submitted to the Medical Products Agency after 1 May 1997.

The Medical Products Agency

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