Medical Products Agency's guidelines on authorization to place certain medicinal products for external use on the market;
resolved on 2 October 1995.

The purpose of these guidelines is to provide a comprehensive outline of the current requirements and regulations for obtaining authorization to market certain medicinal products for external use.

Definitions etc.

- **Medicinal products** are products which are intended for administration to human beings or animals in order to prevent, detect, palliate or cure disease or symptoms of disease or to be used for a similar purpose.

- **Certain medicinal products for external use** refer to so-called free medicinal products as defined in the Drugs Ordinance which applied earlier (1962:701).

Notes:

- The definition covers medicinal products for external use for the treatment of mild diseases in man or animals in which the active ingredient or ingredients have a well established medical use with a recognised effect and an acceptable safety margin.

- Active ingredients which will be the subject of an abridged application procedure are those which have been included in products which have been sold in accordance with earlier regulations, such as so-called free medicinal products in Sweden, from the establishment of the Regulations Concerning Pharmaceutical Commodities [Apoteksvärustadgan] in 1913 up until the coming into force of the new Medicinal Products Act, i.e. until 1 July 1993.

- These products must not contain:
  1. Substances which are classified as lethal or highly dangerous products according to section 8 of the Ordinance concerning Chemical Products. Latest amendment 1994:1532. (1985:835), with amendments.

- With regard to the products and substances below, the following conditions apply:
  1. The maximum permissible boric acid content is 3%.
2. Preparations for warts may contain silver nitrate in the solid form.

A certain medicinal product for external use may only be sold when marketing authorization has been granted by the Medical Products Agency. Such authorization is valid for five years and can be renewed for further five-year periods.

The fundamental requirements placed on medicinal products in Section 4 of the Medicinal Products Act (1992:859) also apply to certain medicinal products for external use. A medicinal product must be of high quality, efficacious for its purpose and, in normal usage, not have harmful effects which are disproportionate to the effect intended. The medicinal product must have a complete declaration (of its contents), have an acceptable name which distinguishes it and be clearly labelled. Its manufacture is to be carried out in accordance with Good Manufacturing Practice for Medicinal products (GMP).

Under certain conditions an abridged application for certain medicinal products for external use may be approved. In the case of preparations whose use has become well established, full documentation of the results of pharmacological and toxicological investigations or clinical trials may be replaced by data from published scientific literature.

Application

The application is made in writing for each dosage form and strength on one of the forms provided by the Medical Products Agency (LV 246 - 93-09/eng + sv/ or LV 246S - 93.11/sv/). Application for authorization to market a certain medicine for external use can be made by the person who intends to sell the medicine, i.e. the manufacturer or representative if this person has special authorization from the manufacturer to do so.

One copy of the application is to be sent to Medical Products Agency.

The application should contain the following information:

- The applicant's name or company and postal address, and where applicable, corresponding information about the manufacturer. Two copies of a current certificate of incorporation from the National Swedish Patent and Registration Office are to be enclosed (applies only to Swedish applicants). Foreign applicants are to state their VAT number instead.

- The name of the medicine, its dosage form and strength, where applicable. Use as far as possible the designation for dosage forms given in the current Läkemedelsstandard (LS) (pharmaceutical standard).

- Information about the composition of the product, stating the nature, amount and function of all the ingredients included in the medicine using the current nomenclature and stating the international generic names which are recommended by the World Health Organization (WHO) if such names exist. If another nomenclature is used, e.g. Ph. Eur., INN, BAN, USAN. Ph. Eur. = Europena Pharmacopoeia, pINN = preliminary International Nonproprietary Name, BAN = British Approved name, USAN = United States Adopted Name etc., this should be stated. For herbal drugs, the mother plant's Latin name as well as the authority/eponym and the Swedish name are to be stated. The nature of products
which have been used in the manufacture, but which have been removed, must also be stated.

- Brief description of the method of manufacturing the product with emphasis on the factors which are important in guaranteeing reproducibility.
- Therapeutic indications, information on contra-indications and side-effects.
- Dosage, mode of use and route of administration. Where applicable, reasons should be given for any precautions and safety measures which must be taken when storing the medicine and discarding waste products and information on any potential environmental risk which the medicine may produce.
- Information on the manufacturing stages, the site of manufacture and description of the control methods used by the manufacturer (qualitative and quantitative analysis of the ingredients and of the finished product, particularly investigations, such as test controls carried out during the manufacturing process, tests to detect pyrogens and heavy metals, studies of stability and toxicity and biological investigations) as well as expected stability. Results of:
  - physico-chemical, biological or microbiological investigations,
  - pharmacological and toxicological investigations,
  - clinical trials.

Exemptions from the requirement of complete documentation containing results from pharmacological and toxicological investigations or the results of clinical trials can be granted if the active substances/constituents in a certain medicine for external use can be shown, by reference to exhaustive work published in the scientific literature, to have well-established medical use with a recognized effect, and an acceptable safety margin and fulfil the other conditions.

- A summary of the product's more important properties - the Summary of Product Characteristics (SPC)—together with a package leaflet. A sample pack as well as other pack size if the material differs or it differs in some other way.
- Documents which show that the manufacturer is authorised to manufacture the medicine concerned in his plant (manufacturing licence).
- Copies of any certificates of marketing authorization which have been granted in other member states or in a third country (e.g. Norway, USA, Canada, Switzerland or Australia) and a list of the member states which are scrutinising an application for marketing authorization. Copies of the summary of product characteristics which the applicant has proposed or which the authorities responsible in the member states have approved. Copies of the package leaflet which has been proposed or which has been approved by the authorities responsible in the Member states. Details of any decision to reject the application for authorization which has been within the Community or in a third country, and the reasons for such decisions.

This information is to be updated regularly.

Fees

In accordance with the decision by the government authorities, the regulation of medicinal products by the Medical Products Agency is financed completely by fees. In conjunction with the submission of the application for marketing authorization for medicinal products, an application fee is to be paid as stated in the Ordinance.
(1993:595) on Fees for the State Control of Medicinal Products, latest amendment in 1995:1017. The Ordinance states the conditions and amount of the fees which the Government has fixed for the financial year concerned. The fee is paid to the Medical Products Agency's postgiro or bankgiro, stating the name of the sender, and the name of the medicinal product which the payment refers to. In addition, there is an annual fee for the remedy which is charged from the month after which the remedy has been approved. Further regulations concerning this can be found in the Medical Products Agency Provisions and Guidelines Concerning the Payment of Application and Annual Fees for Medicinal Products (LVFS 1995:12).

For information about other fees, e.g. for clinical trials, please see the Ordinance (1993:595).

Classification

As fees are not refunded if an application is rejected, it is recommended that, if uncertainty exists, a classification is carried out by the Medical Products Agency before the application is submitted. The purpose of this is to make a general investigation of whether the product can be defined as a certain medicinal product for external use. Such queries are sent in together with a list giving the type and number of the ingredients, as well as a description of the field of application and dosage. No form is needed and no fee is charged at present.

Documentation

When applying for authorization to market a certain medicine for external use, the documentation should be compiled according to the guidelines which have been drawn up for medicinal products, i.e. according to the EC Notice to Applicants, Volume II A, latest amendment. The application is introduced with a summary containing administrative information, Part I (see appendix 1).

Pursuant to Section 8 of the Medicinal Products Act, the documentation enclosed with the application must have been prepared by a person with sufficient knowledge and control of the contents of the documentation.

The application with accompanying documentation, including experts' reports or other summaries, may be in Swedish or English.

If the application indicates that the medicinal product is particularly suitable for a specific group, e.g. pregnant women or children, the applicant must be able to give evidence that the remedy is of special benefit to this group, e.g. for the pregnant woman, and that the foetus will not be harmed.

5.1 Experts' reports

The reports of experts shall contain information on the experience available from testing the constituents or the product itself. The reason why published references are used in support of statements on safety and efficacy, i.e. justification for why an abridged application is applicable, is to be given. If further studies, product-specific ones, are enclosed, these shall be summarised and assessed in a special section. A discussion of the
statements made in the proposed Summary of Product Characteristics (SPC) in relation to the supporting documentation enclosed with the application should also be included.

The experts' reports are to provide a summary and a critical evaluation of the documentation on each respective section (quality, safety and efficacy). These should be drawn up according to the EC guidelines in "Notice to applicants" which include information on the content and extent. The summary of results from inter alia product-specific studies can be made in the form of tables. Three copies of the experts' reports on each respective section are to be enclosed with the application.

With regard to abridged applications for certain medicinal products for external use, at present no formal requirements are placed on the expert, except that he or she should have sufficient special knowledge of the field concerned in the report and the application. The report must be signed with the date and accompanied by a list of qualifications and must be written in Swedish or English.

An expert's report of a high standard contributes to effective processing of the application.

5.2 Quality

Complete quality documentation is to be submitted. It includes chemical, microbiological and pharmaceutical-technical data, and its purpose is to describe and ensure satisfactory product quality. In order to achieve this requires, e.g. that the raw materials are of a high and uniform quality. Furthermore, the documentation should describe adequately that the manufacturing process is conducted in compliance with the guidelines for Good Manufacturing Practice (GMP). Control of these factors helps to ensure that the product has a reproducible composition and other characteristics, which in turn means that the final consumer receives a product of uniform quality.

The documentation of quality must contain the corresponding information which applies to other medicinal products. If herbal drugs are included as active constituents, further details concerning the documentation requirements can be found in the Medical Products Agency's Guidelines on Authorization to Place Natural Remedies on the Market, Part II (LVFS 1995:18).

5.3 Safety

5.3.1 Evaluation of safety
The safety of a certain medicinal products for external use should be discussed and evaluated after considering all the available relevant information. In this context, consideration should be given primarily to the experience of corresponding earlier use of the product/constituent concerned in the application in which no harmful effects have arisen or been suspected. Corresponding earlier use denotes use in which there were no marked differences in mode of administration, dosage or duration of use (short-term or long-term use) compared to previous use.

Even if the experience of long-term use of a certain medicinal products for external use does not indicate that it has any harmful effects, this cannot always be assumed to be proof of the safety of using the remedy. Harmful effects may have occurred but not
become known or reported. It is therefore the responsibility of the applicant to critically evaluate the documentation which constitutes the basis of the safety assessment.

5.3.2 Documentation in support of an acceptable safety level

The documentation of the safety of a certain medicinal products for external use must contain a current summary and evaluation, so called experts report, of all relevant, published information about the medicinal product and of any results from clinical trials and/or pharmacological and toxicological investigations of the medicinal product.

1. It must be possible to substantiate any quoted reliable and adequate experience, as far as possible, by reference to the literature, as earlier documented use constitutes the basis for an abridged application. Copies of works referred to (scientific original articles/outline articles, excerpts from official monographs and handbooks) are to be enclosed with the application.

Information which is of great importance is:

- earlier recommended dosage
- earlier method of administration
- earlier method of manufacturing active ingredient
- which diseases/symptoms have been treated
- how far back in time the medicinal product has been used
- in which countries the medicinal product has been used
- estimated number of users (where applicable).

The first four items are used to compare earlier use with the currently recommended use of the product. All the data are used to give evidence that there has been reliable and adequate experience/acceptable safety levels for the recommended use of the product. If the information above is missing in the application, it is required that the applicant discusses the significance of this.

2. If the safety has not been satisfactorily documented according to the above, then the safety of the medicinal product must be proven by means of clinical trials and/or pharmacological and toxicological investigations of the medicinal product. The clinical trials which are referred to must be designed so that they include an active follow-up of any undesirable effects.

This section should elucidate, if possible, different types of risk that may be associated with use of the medicinal product. These risks include undesirable pharmacological effects, general toxicological, local irritant, allergy-inducing, genotoxic and carcinogenic effects as well as effects on reproduction. If a risk is detected then the margin between harmful and recommended doses of the medicinal product is to be estimated and evaluated.

If the applicant has done his own clinical trials and/or pharmacological or toxicological investigations then it must be stated whether these have been done according to internationally accepted scientific standards (e.g. OECD's principles of Good Laboratory Practice, and the Nordic Council on Medicine Good Clinical Trial Practice). See also the Medical Products Agency's Provisions and
Guidelines Concerning Clinical Trials of Medicinal Products (LVFS 1990:25, new directives and guidelines are being drawn up).

3. On the basis of presentations 1. and 2. above, an assessment of the safety of the product concerned is to be made. Both deviations from traditional use (e.g. dosage and method of manufacture) as well as information on any side-effects and interactions should always be discussed and assessed.

All new findings of significance for the safety assessment of a certain medicinal products for external use which have become known after application for marketing authorization must be communicated to the Medical Products Agency without delay. This supplementary information must also be accompanied by a summary and assessment according to the above.

5.4 Efficacy

According to the definition, certain medicinal products for external use may only be marketed as active against diseases or symptoms of disease which are temporary or mild, i.e. for conditions which are suitable for self-medication. The fields of application which may be accepted for certain medicinal products for external use are listed below. Synonymous wording may also be accepted.

The following applies to products for human use:

<table>
<thead>
<tr>
<th>Type of product:</th>
<th>Indications:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ointments for wounds</td>
<td>Treatment of minor, uninfected wounds, such as blisters,</td>
</tr>
<tr>
<td></td>
<td>scratches and scrapes, small, superficial burns and mild skin irritations.</td>
</tr>
<tr>
<td></td>
<td>The treatment of mild forms of acne and external haemorrhoids.</td>
</tr>
<tr>
<td>Antiseptic agents</td>
<td>Treatment of minor, uninfected wounds, such as blisters,</td>
</tr>
<tr>
<td></td>
<td>scratches and scrapes, and small, superficial burns. The treatment</td>
</tr>
<tr>
<td></td>
<td>of mild forms of acne. Rinsing the mouth and throat when treating mild sore</td>
</tr>
<tr>
<td>Liniments and impregnated plasters</td>
<td>Local increase of the blood circulation to relieve temporary</td>
</tr>
<tr>
<td>Products for inhalation*</td>
<td>Temporary irritation in the upper respiratory tract.</td>
</tr>
<tr>
<td>Preparations for corns</td>
<td>Treatment of corns.</td>
</tr>
<tr>
<td>Preparations for warts</td>
<td>Treatment of warts on hands, feet, knees and elbows.</td>
</tr>
<tr>
<td>Eye-baths</td>
<td>Rinsing and bathing when treating mild eye irritation or dry eyes.</td>
</tr>
</tbody>
</table>

* Also include nose drops to treat colds (containing physiological saline).

The following applies to certain medicinal products for external use for animals:

<table>
<thead>
<tr>
<th>Type of product:</th>
<th>Indications:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ointments for wounds</td>
<td>Treatment of minor, uninfected wounds, such as blisters,</td>
</tr>
<tr>
<td></td>
<td>scratches and scrapes, small, superficial burns and mild skin</td>
</tr>
</tbody>
</table>
irritations.

Antiseptic agents  Treatment of minor, uninfected wounds, such as blisters, scratches and scrapes, and small, superficial burns. Rinsing the mouth and throat when treating mild sore throats.

Liniments and impregnated plasters  Local increase of the blood circulation to relieve temporary muscle pains.

Products for inhalation  Temporary irritation in the upper respiratory tract.

Eye-baths  Rinsing and bathing when treating mild eye irritation or dry eyes.

Cooling clays and ointments  For the relief of temporary muscle, tendon, or joint pains.

For well-documented constituents or products for which there is reliable and adequate experience, dependable bibliographical data may be sufficient to support the statements concerning the efficacy of a certain medicinal products for external use. However, the precondition is that the form, use, dosage etc of the product do not deviate from that which has been described and what has actually been the case for a long time. In cases when the properties of the product deviate from those described, the application shall be supplemented with specific product documentation.

5.4.1 Documentation in support of efficacy

As the basis for all assessment of certain medicinal products for external use, there must be a presentation, a so-called expert's report, of relevant data. This presentation shall be given in separate sections:

A. A summary and evaluation of generally available documentation/information concerning the medical use of the active ingredients. It must also be possible to substantiate any tested experience mentioned by reference to approved handbooks. As an Appendix to A, copies from relevant literature are to be enclosed (a number of references must be presented) as well as the other references (outline articles etc.) which are referred to.

B. A summary and assessment of documentation specifically on the product, where appropriate. Here results of relevant clinical trials and pharmacological studies are to be presented. All such studies which have been carried out with the product are to be presented, including criteria for patient selection, randomization, the composition of the placebo preparation and which variables have been chosen for clinical assessment. It is desirable that results from several independent studies are described. It must be possible to show that the preparation that has been used in the studies is identical with that referred to in the application. See also the Medical Products Agency's Provisions and Guidelines Concerning Clinical Trial of Medicinal products (LVFS 1990:25).

C. Based on presentations A. and B. above, the applicant is to state the indication and dosage for the product in question. If there is any information on the interactions with the product then this should also be discussed and evaluated.

For further information concerning product-specific documentation see appendix 2.

5.5 Combination Products
For combination products containing several active ingredients, special explanatory statements should be included in the application. However, a fundamental precondition for the approval of combination products is that each active ingredient contributes to the overall effect for the indication submitted in the application. No restriction has been placed on the number active ingredients included in a remedy provided that the documentation is satisfactory with respect to quality, safety and efficacy.

5.6 ATC Classification

The ATC classification is to be stated in the application. The ATC is a pharmacological code which stands for the Anatomical Therapeutic Chemical classification system. The system is divided into groups according to where or how a medication acts. The code is used by the WHO, among others, in conjunction with international reporting of side-effects. More detailed information about the ATC classification can be found in "Guidelines on ATC classification" and "Anatomical Therapeutic Chemical (ATC) classification index" as well as "Guidelines on ATC vet Classification" for human and veterinary medicinal products respectively.

1. Manufacture and Trade

Here Manufacture means the production, packaging or repackaging of medicinal products. The commercial manufacture of medicinal products requires a licence from the Medical Products Agency according to the Medical Products Agency's Provisions on Authorization for the Manufacturing of Medicinal Products (LVFS 1995:3). Manufacture should comply with the requirements of Good Manufacturing Practice, GMP. A qualified person with sufficient knowledge and influence must ensure that the requirements for the quality and safety of the medicinal products are met.

Guidelines giving specified manufacturing standards have been drawn up by the PIC (Pharmaceutical Inspection Convention), an international convention for the mutual recognition of inspections. For medicinal products containing herbal constituents, there is also a special appendix, number 8, to these guidelines: "Manufacture of Herbal Pharmaceutical Products".

Wholesale trade of medicinal products may only be conducted by those who are licensed to do so by the Medical Products Agency according to the Medical Products Agency's Provisions on Authorisation for the Wholesale Distribution of Medicinal Products (LVFS 1995:4). Wholesale trade denotes all other sale than retail trade. Trade with medicinal products is to be conducted in such manner that the medicinal products do not harm people, property or the environment and that the quality of the medicinal products does not deteriorate.

Medicinal products may be imported by persons licensed to manufacture or trade with medicinal products and the persons who hold special permits for such import.

Retail trade of medicinal products signifies sale to persons who do not possess a licence for sale, e.g. sale to the individual consumer. As a result of amendment (1992:1201) of the Act on Retail Trade Of Medicinal products (1970:205), certain
medicinal products for external use may be sold in other premises than pharmacies, i.e. in the same way as under earlier regulations for free preparations. There are, however, exceptions for certain medicinal products for external use which contain more than 1.8% alcohol which may only be supplied by pharmacies.

2. Processing of Applications

The Medical Products Agency's assessment of the documentation submitted leads to a decision of approval or refusal of marketing authorization for the medicinal product and the Medical Products Agency's reply is communicated in writing. Provided that the application is complete, the active processing time at the MPA is a maximum of 210 days. This applies during the period in which the free-listed products are examined. Later, the effective processing time will be a maximum of 120 days. The processing time is counted from the moment when both the application documents and the application fee are received by the Agency. If the application is incomplete, the Medical Products Agency can request that the application be supplemented by a certain date. The period given can vary from six weeks to three months.

The Medical Products Agency may decide that marketing authorization is to be withdrawn. The reasons for this may be that the remedy no longer meets the requirements for approval.

Appeal against individual decisions communicated by the Medical Products Agency may be made to the County Administrative Court. However, the appeal is to be sent to the Medical Products Agency.

3. Variations

Variations which may affect the quality of a medicinal products only be made after approval by the Medical Products Agency. The application is to state clearly which variations are included in the application and is to be accompanied by the necessary documentation including validations, corresponding in extent to that which is required when applying for marketing authorization (see appendix 5 and 6 in LVFS 1995:8 for further details).

Such variations may include the following:

1. Change of manufacturer, site of manufacture, subcontractor, or change of supplier of active ingredient.
2. Composition with respect to type and quantity of inactive ingredients and minor changes in quantity of active ingredient.
3. Manufacturing method for active ingredient or product.
4. Quality norms (test control methods and requirements) for active and inactive ingredient and for the finished product.
5. New/changed size of pack, packaging material, design of pack.
6. Storage period and period of use.
7. Storage instructions.
8. Labelling including package leaflet.
If there is a change in the type or a substantial change in the quantity of active ingredient a new application for marketing authorization is to made to the Medical Products Agency.

Any change in the Summary of Product Characteristics (SPC, see point 9.3) is to be approved by the Medical Products Agency.

Transfer of authorization and any change of representative may be only be made after a permission from the Medical Products Agency. If the person who holds the marketing authorization for a certain medicinal product for external use wishes to withdraw approval for the product, this should be communicated in writing to the Medical Products Agency.

4. **Product Information**

Pursuant to Section 21 paragraph 1 of the Medicinal Products Act, information about a medicinal product which is of particular significance for preventing injury or for promoting expedient use of the medicine must be stated in writing when a medicinal product is supplied to the consumer.

9.1 Labelling

Medicinal products are to be labelled in Swedish. The requirements are given in the Medical Products Agency's Provisons and Guidelines Concerning the Packaging and Labelling of Medicinal Products (LVFS 1995:11). Proposals for the wording shall be submitted to the Medical Products Agency when applying for authorization.

Pursuant to Section 4 paragraph 2 of the Medicinal Products Act a medicinal product must have a complete declaration of its composition, have an *acceptable and distinguishable name* and be clearly labelled. Pursuant to Section 4 of the Medicinal Products Ordinance (1992:1752), the Medical Products Agency may grant exemptions from the requirement for complete declaration of composition.

With regard to *free-listed medicinal products for external use*, the regulations in force are still those which applied earlier concerning labelling in the Medical Products Agency's Provisions Concerning Certain Exemptions from the Application of the Drugs Ordinance (LVFS 1990:21 earlier SOSFS 1981:105)

9.2 Package leaflet

Detailed information to users (cf. current consumer FASS entry for medicinal products) is to be enclosed with medicinal products in the form of a separate package leaflet or, if there is room, as a text on the pack. However, in the latter case, the text must not obscure the legibility of the other information that is to be given on the pack.

The requirements are given in the Medical Products Agency's Provisons and Guidelines Concerning the Packaging and Labelling of Medicinal Products (LVFS 1995:11).

The proposal for information to users must be written in Swedish and enclosed with the application.
9.3 Summary of Product Characteristics (SPC)

A proposal for the summary of the product's more important properties, primarily in Swedish, is to be enclosed with the application. This summary will be assessed and considered for approval by the Medical Products Agency in conjunction with the assessment of the medicinal product. The Summary of Product Characteristics can be used as the basis for written information about the product (cf. current FASS [Swedish equivalent of BNF or PDR]. Translator entry for medicinal products). The compilation of the information should be made according to the Medical Products Agency's Provisions to Composing Summaries of Products Characteristics of Natural Remedies and Certain Medicinal Products for External Use (LVFS 1995:14).

9.4 Identity Number

The EAN code or other number (e.g. commodity number) which identifies each individual pack of an approved medicine shall be stated on the pack. This is done so that sales statistics of drug sales in Sweden can be recorded.

Approval Number/Marketing Authorization Number

The labelling directives for medicinal products states that, when marketing authorization is granted, the medicinal product must have an authorization number printed on the pack. This is assigned to the product when it is approved.

Marketing

As with other medicinal products, the information given about certain medicinal products for external use is also required to be reliable. In accordance with Section 21 paragraph two of the Medicinal Products Act, the information which is given in the marketing of a medicine is to be up-to-date, factual and balanced. It must not be misleading.

The Marketing Act (1975:1418) constitutes the foundation for the current regulations.

The authority responsible for these matters is the National Board for Consumer Policies, Stockholm.

These guidelines enter into force on 1 November 1995.

The Medical Products Agency

KJELL STRANDBERG
Bengt Sjöberg

Appendix 1

Outline of the Contents of the Application
The information in the application should be drawn up according to the directions below. In order to clarify the extent and structure of the information enclosed, a table of contents with page references should also be included for each section (I-IV).

I. Synopsis - summary of the content of the application

I A. Administrative data

- Application form containing administrative information.
- Copy of receipt of paid application fee together with name of the product.
- Copy of the manufacturing/wholesale trader's licence.
- Copy of marketing authorization for the product granted in other countries.

I B. Product Information

- Proposal for Summary of Product Characteristics (SPC).
- Proposal for wording of package label
- Proposal for package leaflet.
- Sample packages.
- Summaries of Product Characteristics which have been approved earlier.

I C. Experts' reports

- Experts' reports for each section (II-IV): chemical/pharmaceutical documentation, safety and efficacy documentation.
- Appendices with tables, if applicable.

II. Documentation of Quality

III. Documentation of Safety

IV. Documentation of Efficacy

Appendix 2

Specific Product Documentation

The evidence that may be required to substantiate the efficacy of a medicinal product in a specific field of use must be judged from case to case. The studies which are presented in support of the use should refer to the substance concerned, administered in the dose and manner which the applicant recommends.

The effect or effects should be substantiated with reliable clinical investigations which may, in part, be replaced by reliable pharmacological studies.

Reliable clinical investigations may be, for example, studies which compare the study preparation with an inactive preparation (placebo) and/or a preparation, including medicinal products, whose effect in the same field of use is already known. The patients
are to be randomly allocated to the two groups and the investigation is to be carried out double-blind, i.e. neither the patient nor the investigator is allowed to know who receives which preparation. A sufficiently large number of patients must be included in the investigation to make statistical processing of the results possible. It must be stated whether the study has been carried out in compliance with the guidelines for Good Clinical Trial Practice (NLN 28, 1989).

In cases when the results of efficacious treatment can be recorded objectively and spontaneous fluctuations in the course of the disease do not appear, an alternative trial design may be chosen.

The investigations should be published in well-known scientific periodicals (with a referee system). However, complete reports of the studies are to be enclosed as well. Unpublished investigations may only be accepted if they are signed with the date and come from clinics/hospitals or laboratories of good repute.

Patients' certificates and equivalent statements or reports from individuals are not acceptable documentation.

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