

## **Medical Products Agency's Code of Statutes**

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**Medical Products Agency's guidelines on authorization to place natural remedies 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 natural remedies.**

### **1. 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.**

**A natural remedy denotes a medicinal product in which the active ingredient or ingredients derive from natural sources, have not been processed too highly and consist of part of a plant or animal, bacterial culture, mineral, salt or salt solution. Natural remedies may only be products which are suitable for self-medication in accordance with tested national tradition or tradition in countries close to Sweden with respect to drug usage.**

**Notes:**

**Ingredients which have been processed too highly are e.g. constituents produced in pure form or chemically modified. Active constituents which have been manufactured using biotechnical processing methods are not acceptable either.**

**Substances on the special list drawn up by the Medical Products Agency (list 1, Prescription Provisions) and substances classified according to hazard as lethal products or highly dangerous products according to Section 8 of the Chemical Products Latest amendment 1994:1532. Ordinance (1985:835) must not be included.**

**Substances for injection and homoeopathic preparations are not covered by the definition. With regard to homoeopathic preparations, the reader is referred instead to Provisions and Guidelines on Registration of Homoeopathic Preparations (LVFS 1995:23).**

**A new natural remedy 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 natural remedies. 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 and distinguishable name 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 natural remedies 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.**

## **2. 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 natural remedy can be made by the person who intends to sell the medicinal product, 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 natural remedy, 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 constituent parts. In the case of herbal drugs, the mother plant's Latin name as well as the authority/eponym and the Swedish name are to be stated. For other ingredients the current nomenclature is used 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., pINN, BAN, USAN Ph. Eur. = European Pharmacopoeia, pINN = preliminary International Nonproprietary Name, BAN = British Approved Name, USAN = United States Adopted Name etc. this should be stated. The nature of any ingredients which have been used in the manufacture, but which have been removed, must also be stated.**

**A 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 as well as information on any potential environmental risk which the medicinal product 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:**

**physical-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 ingredient or ingredients in the natural remedy 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 authorized to manufacture the medicinal product 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) as well as 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 made within the Community or in a third country, and the reasons for such decision.**

**This information is to be updated regularly.**

### **3. Fees**

**In accordance with the decision made by the government authorities, the regulation of medicinal products by the Medical Products Agency is financed completely by fees.**

**When submitting an application for marketing authorization for natural remedies, 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 1995:1017. The Ordinance states the conditions and amounts of the fees which the Government has fixed for the financial year concerned. The fee is to be paid to the Medical Products Agency's postgiro or bankgiro, stating the name of the sender, and the name of the natural remedy which the payment concerns. 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's 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 concerned (1993:595).**

### **4. 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 natural remedy. 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 use and dosage. No form is needed and no fee is charged at present.**

**Processed products, for example which contain active ingredients whose type and strength differ markedly from the starting material and/or the field of use for the product falls outside that which may be considered suitable for self-medication, cannot be defined as natural remedies.**

### **5. Documentation**

**When applying for authorization to market natural remedies, 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.

Supplementary information on the extent and structure of the documentation of the quality, safety, and efficacy of a natural remedy is given in Sections II-IV (see appendix 2-4).

For products which contain active ingredients which have been processed, but which are still considered to be natural remedies, bibliographical data alone are not always sufficient and supplementation with specific product-related studies may be required to substantiate the safety and efficacy of the product.

If the application indicates that the medicinal product is particularly suitable for a certain 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 in relation to the supporting documentation enclosed with the application should also be included.

The experts' reports are to provide a summary or 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 natural remedies, 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 documentation of quality 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. In view of the fact that the ingredients of natural remedies have special characteristics, guidelines for the documentation of the quality of these products have been compiled (Part II, (see appendix 2). These guidelines only deal with the quality requirements for ingredients which come from the plant kingdom (herbals), i.e. dried plants or parts of plants (crude drugs), extracts or tinctures from plants (crude drugs) or volatile (essential) or fatty oils from the plant kingdom which are unrefined.**

### **5.3 Safety**

**A natural remedy's safety should be discussed and assessed on the basis of 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.**

**If satisfactory proof of the safety of the product is not provided in the form of traditional use, then proof of the safety is to be established by means of clinical trials and/ or pharmacological and toxicological studies.**

**Even if the experience of long-term use of a natural remedy 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.**

**All new results of importance in the evaluation of a natural remedy 's safety which have become known after the application for marketing authorization must be communicated to the Medical Products Agency without delay.**

**For further details about the requirements relating to documentation of safety , please see Part III (see appendix 3).**

### **5.4 Efficacy**

**By definition, natural remedies may only be marketed as efficacious against diseases or symptoms of diseases which are temporary or mild in nature, i.e. for diseases or conditions which are suitable for self-medication. The fields of application which may be approved at a later date for natural remedies depend on the documentation which supports the application.**

**For well-documented ingredients or products for which there is adequate experience, reliable bibliographical data may be sufficient as documentation in support of the statements about a natural remedy's efficacy. However, the precondition is that the product's formulation, use and dosage etc., do not deviate from traditional ones. In the cases when the product's properties deviate from the traditional description, the application is to be supplemented with specific product-related documentation in accordance with what is stated in the Medical Products Agency's guidelines on the documentation of natural remedies, part IV, efficacy documentation (see appendix 4).**

**For further information about the requirements relating to clinical trials, please see the Medical Products Agency Provisions and Guidelines on Clinical Trial of Medicinal Products (LVFS 1990:25, new provisions and guidelines being drawn up).**

### **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 of herbal drugs included in a remedy provided that the documentation is satisfactory with respect to quality, safety and efficacy.

## **5.6 ATC Classification**

The application should contain the natural remedy's ATC classification. The ATC is a pharmacological code which stands for 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 to ATC Classification" and "Anatomical Therapeutic Chemical (ATC) classification index" as well as "Guidelines on ATC vet Classification" for human and veterinary medicinal products respectively.

## **6. 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 Product 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 PIC (Pharmaceutical Inspection Convention), an international convention for the mutual recognition of inspection work. For natural remedies, there is also a special appendix, number 8, in the "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 Product Agency's Provisions on Authorization 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 medicinal products and persons who have special permits for such import.

Retail trade of natural remedies signifies sale to persons who do not possess a licence for sale, e.g. sale to the individual consumer. As a result of an amendment (1992:1201) of the Law Concerning Retail Trade of Medicinal Products (1970:205), natural remedies may be sold in other premises than pharmacies, i.e. in the same way as under the earlier regulations which applied to natural preparations. However, exceptions do apply to natural remedies containing more than 1.8% alcohol which may only be supplied by pharmacies.

## **7. 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 natural remedy 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 supplementary data be submitted 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, for example, 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 Administrative Court of County. However, the appeal is to be sent to the Medical Products Agency.**

## **8. Variations**

**Variations which may affect the quality, safety and/or efficacy of a natural remedy may 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 appendices 5 and 6 in LVFS 1995:8 for further details).**

**Such modifications may include the following:**

**Change of manufacturer, site of manufacture, subcontractor, or change of supplier of active ingredient.**

**Composition with respect to type and quantity of inactive ingredients and minor changes in quantity of active ingredient.**

**Manufacturing method for active ingredient or product.**

**Quality norms (test control methods and requirements) for active and inactive ingredient and for the finished product.**

**New/ changed size of pack, packaging material, design of pack.**

**Storage period and period of use.**

**Storage instructions.**

**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 be made to the Medical Products Agency.**

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

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

## **9. 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**

**Natural remedies are to be labelled in Swedish in the same way as other medicinal products. The requirements are given in the Medical Products Agency's Provisions and Guidelines on the Packaging and Labelling of Medicinal Products (LVFS 1995:11). Proposals for the wording shall be submitted to the Medical Products Agency in conjunction with the application for approval.**

**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 Drugs Ordinance (1992:1752), the Medical Products Agency may grant exemptions from the requirement of complete declaration of the composition.**

**Furthermore, the labelling must make it clear that the preparation has been approved for sale as a natural remedy with the wording "Natural remedy" on the pack. The indications stated for natural remedies must contain the following wording: "Traditionally used..." or, when applicable, be labelled with other wording prescribed by the Medical Products Agency.**

**With regard to free-listed natural remedies, the regulations in force are still those which applied earlier as stated in the Medical Products Agency's Notice on the Notification of Substances in accordance with Section 1 paragraph 3 first subsection, part 2 (1 3 mom 1:a st. 2) of the Drugs Ordinance LVFS 1990:50 (SOSFS 1977:101) and the National Board for Consumer Policies Guidelines KOVFS 1993:4.**

## **9.2 Package leaflet**

**Detailed information for 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 stated in the Medical Products Agency Provisions and Guidelines on the Packaging and Labelling of Medicinal Products (LVFS 1995:11).**

**The proposal for information for 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 natural remedy. 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]. entry for medicinal products). The compilation of the information should be made according to the Medical Products Agency's Guidelines to Composing Product Summaries for 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 medicinal product shall be stated on the pack. This is done so that sales statistics on drug sales in Sweden can be recorded.

#### **Approval Number/Marketing Authorization Number**

The labelling provisions for medicinal products states that, when marketing authorization is granted, an authorization number must be printed on the medicine's pack. This number is assigned to the product when it is granted approval.

### **10. Marketing**

As with other medicinal products, the information given about natural remedies 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 should be to be up-to-date, factual and balanced. It must not be misleading. The Marketing Act (1975:1418) constitutes the basis for the current regulations.

For natural preparations for which temporary marketing authorization has been granted, so-called free-listed products, during the period of transition the Guidelines of Konsumentverket (the National Board for Consumer Policies) KOVFS 1993:4 apply. 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**

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### **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 contents, 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 for 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.**

- **Copy of previous authorization to market as natural preparation.**

#### **I B. Product information**

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

#### **I C. Experts' reports**

- **Experts' reports for each section (II-IV):  
chemical/pharmaceutical documentation, safety and efficacy  
documentation.**
  - **Appendices of tables, if applicable**
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### **Appendix 2**

#### **Documentation of Quality**

##### **II A. Composition**

***The name*** which the product is to be marketed under is to be stated.

**The *dosage form*** ( e.g. tablet) is to be stated. Use as far as possible the designation for dosage form given in the current *Läkemedelsstandard* [Pharmaceutical Standard] for Finland and Sweden (LS) .

**A complete declaration of the composition, stating the nature and amount of both active ingredients and other constituents are to be enclosed. Even constituents which are consumed in the manufacturing process are to be stated.**

***Each herbal drug must be defined by stating the Latin name of the mother plant as well as the authority (eponym) (e.g. Matricaria recutita L.) as well as the Swedish name.***

**If the herbal drug comes from a commercially grown, named variety, then this variety should also be given.**

**Preservatives and colourants included must also be stated with the type, amount and accepted name/and or E-code. It should be clear which ingredients are active and which are, for example, excipients and flavouring.**

##### ***1.1 Quantities***

- **Single herbal drug**

The total weight in the pack is given in grams, milligrams or micrograms and the volume in millilitres. It may also be necessary to state the quantity per unit dose.

- **Combination of several herbal drugs (e.g. herbal tea)**  
The percentage composition expressed as a weight/weight per cent (w/w%) and the total weight in the pack is given in grams, milligrams or micrograms and the volume in millilitres. It may also be necessary to state the quantity per unit dose.
- **Tablets and capsules**  
The quantity of each new ingredient is to be stated per divided dose, i.e. per tablet or capsule, in grams, milligrams, or micrograms. If the ingredient is an extract, the guidelines for extracts should be used.
- **Solutions**  
The quantity of each new ingredient is to be stated in grams, milligrams, or micrograms per millilitres. In some cases it may also be necessary to state the quantity per dose. If a ingredient is an extract or tincture, the guidelines for such should be followed to express its composition.
- **Tinctures and extracts**  
If the ingredient is described in an official monograph in the European Pharmacopoeia (Ph Eur) or other approved pharmacopoeia or national pharmaceutical standard, then the title of the official monograph is to be stated together with the date of publication if not given in the latest edition.

There may also be dosage forms other than those exemplified above, e.g. ointments.

*1.2 For Ingredients Which are not the Subject of an Official Monograph, the Following Rules Should be Applied :*

- **Tinctures**  
E.g. Tincture of herbal drug A (1:5 in 60% alcohol) in mg and/or ml. It must be stated clearly whether it concerns a dilution or concentration.
- **Extracts**  
E.g. Dry extract of herbal drug A (8:1 in 45% alcohol) in mg.  
A = *Cassia angustifolia*, folium,  
dry 45% ethanol extract (8:1) 125 mg  
or  
*Cassia angustifolia*, folium,  
dry 45% ethanol extract (8:1)\*  
(the range for the crude drug quantity used can also be stated)  
(8:1) or (7.5 - 8.5 : 1), 100 - 130 mg, equivalent to 25 mg  
anthraquinone glycosides, calculated as sennoside B.
- **Compound Extracts**  
E.g. Each 5 ml contains a 45 % alcohol extract (4:1) from each of  
crude drug A, x mg, crude drug B, y mg, crude drug C, z mg etc.  
E.g. Dry extract of crude drug A 20 % and crude drug B 80 % in

mg.

*Notes :*

- The nature of the ingredient must always be described, e.g. extract, tincture, ground drug.
- The vehicle or solvent and its strength must always be stated.
- The ratios represent the quantity of drug in relation to the quantity of extract : e.g. 5:1 extract means that 5 grams of crude drug have been used to produce 1 gram of extract.
- For compound tinctures and extracts, the total sum of the individual ingredients will amount to 100 %.
- Where extracts are used in tablets or capsules, it is required that the weight of the extract be stated. In cases where the method of preparation is standardized and the quantity of extract per quantity of original crude drug falls within defined quantities (may be an interval stated in the extract specification) the original quantity of the crude drug per tablet/capsule may be stated instead of the weight of the extract.

## *2. Containers*

A short description of the appearance of the pack, type of packaging material and size (e.g. number of tablets) is to be stated.

## *3. Pharmaceutical Form Used in Clinical Trials and/or in Bioavailability Studies*

## *4. Development Work*

*Information on technical development work is to be supplied, i.e. the effects of constituent preservatives, the effect of sterilization or decontamination processes and/or studies which are not done on every batch. With regard to tablets, results from dissolution studies may be presented in order to give evidence of the availability sic. Orig reads thus, This should probably read "bioavailability". Translator OP. of the medicine.*

## **II B. Manufacturing Methods**

**Manufacture should take place according to good manufacturing practice, i.e. comply with the current requirements in Good Manufacturing Practices (GMP) for medicinal products. The manufacturing process is to be described from the raw material to the finished product by, for example, the presentation of flow charts and written written manufacturing methods.**

**The following information is required:**

- 1. The batch size and quantity of all ingredients per batch.**
- 2. Manufacturing methods with details of all processes involved.**

- If the product contains dried herbs or parts of herbs, details are required of any drying, pulverization or comminution etc., including drying temperatures and methods for measuring the size of fragments and particles etc.
  - If the product is an extract or tincture, data are required on the solvent used for extraction, the time and temperatures of extraction, details of the concentration stages and the methods used, as well as details about the temperature/time cycle of drying where applicable.
  - If the product or the ingredients are sterilized or preserved etc., then full details of these methods are required.
  - In-process controls which takes place during the manufacturing process must be described and the limits stated where applicable.
3. Studies which show that the manufacturing process actually leads to the desired result (validation) must be presented. Presentation of the reproducibility of the manufacture is particularly important.

## **II C. Control of Starting Materials**

The starting materials must be of a well-defined quality. If there is a pharmacopoeial monograph then it should be followed, if not, then a detailed specification of the quality controls must be enclosed. This should be compiled in the same way as in the monographs in the Ph Eur. The quality specifications must contain all the requirements and testing methods which are used routinely for every batch. Physical properties, identity and purity as well as the levels of any micro-organisms, heavy metals, residues of solvents, biocides (i.e. pesticides, insecticides, etc.) disinfectants, radioactivity and any other pollutants must be stated in the specification where applicable.

### **1.1 Active Constituents**

#### *Herbal materials*

For all herbal materials which are used as the starting materials, the documentation of quality shall contain the following:

- The Latin name of the mother plant with the authority/eponym. Latin drug names, stating which part of the plant has been used. The quality codex (e.g. pharmacopoeial monograph) that is referred to and copy of this shall be enclosed.
- Detailed information on the place of origin of the drug including the country and region of production and whether it derives from a cultivated or wild plant. Furthermore, information is required about the time of harvest or collection and the conditions during drying and storage. If the drug derives from a cultivated plant then information about the supplier is required. Details must also

be given about the age of the drug when preparing it.

With regard to the following investigations, the methods used must also be described in detail. Quantitative methods of measurement shall be validated. Where applicable, reference to a pharmacopeal monograph or other equivalent codex may be accepted. The quality of the reference substances used should be documented.

- The herbal material shall be identified using macromorphological or micromorphological methods and thin-layer chromatography of a sample extracted using a suitable solvent. In the macromorphological and micromorphological identification, comparison must be made with authentic materials. The reference sample used for the chromatographic test must be an extract of an authentic drug prepared in the same way or a solution of one or several constituents of the drug which are either characteristic of the drug or important to its pharmacological effect.
- When possible, the results of measurements of contents, with appropriate limits, must be presented. The content of one, or several components, which are considered to be responsible for the pharmacological effect of the drug should be measured. If such are not known, then the measurement of another compound which is representative of the material may be accepted. The reason for the choice of compound whose content is measured should be given together with supporting references in the literature.

If the drug contains a volatile oil then quantitative measurement of this must be carried out. Limits for the content shall be stated.

- The following tests shall be carried out:
  - Tests for microbial contamination according to the European Pharmacopoeia. This test may be omitted if the drug is only to be used for the manufacture of extracts and if the manufacturing process consists of operations which kill micro-organisms.
  - Measurement of aflatoxin content stating the maximum permissible levels.
  - Measurement of pesticide content stating the maximum permissible levels.
  - Measurement of the levels of heavy metals (Pb, Hg, Cd) stating the maximum permissible levels.
  - Measurement of radioactive contamination stating the maximum permissible levels.
  - Tests to show the absence of residues from sterilisation procedures (e.g. sterilisation using ethylene oxide). Certificates which show that the drug has not been exposed to such procedures can be accepted.
  - Measurement of the drying loss, stating the maximum

limits.

- Measurement of the amounts of foreign materials, e.g. undesirable, foreign herbal materials, insect parts, excreta from rodents etc., stating the maximum limits.
- Measurement of the ash content and ash insoluble in acid content, stating the maximum permissible limits.

*In cases in which it can be shown that there is complete control over all stages of production of the drug, so that contamination by heavy metals, pesticides, aflatoxins, radioactivity and residues after sterilisation can be excluded, then tests for such contamination may be omitted.*

### *1.2 Other Constituents (inactive)*

*The quality specifications used for all other ingredients, including flavouring and colourants, must be presented either by reference to a approved pharmacopeia or as a list of the control methods used and requirements in the form of a monograph in Swedish or English.*

## **II D. Control Tests on Intermediate Products**

The analytical methods and specifications for intermediate products must be presented, particularly when the indices of quality cannot be measured or checked in the finished product or when the intermediate products are isolated or stored.

- The control test methods and requirements, with limits where applicable, for all tests which are carried out during manufacture, e.g. the measurement of particle size, humidity, alcohol content, pH, tablet weight, size etc.
- If the dosage form is a fluid which is produced by mixing two or several extracts or tinctures consisting of one or several components, it is important to check the identity and strength of these if the individual components cannot be identified or their content in the finished product measured .

## **II E. Control Tests on the Finished Product**

The object of control-testing the finished product is to ensure as far as possible the correct identity, reproducible composition and other properties of the product. An identity test must be included in the specification as well as a quantitative method of measurement, with limits, for representative or known pharmacologically active components. But, this may be difficult for certain drug mixtures. However, in the absence of a method of measurement this should be justified. The methods must refer to a recognised pharmacopeia or be described in such a manner that it will be possible for another, independent laboratory to conduct them.

A specification should contain the following (certificate of analysis

should be enclosed):

- For products containing only one active ingredient (a herbal drug or preparation of such) an identity test and, where appropriate, a suitable quantitative method of measurement are required.
- For products which contain more than one active ingredient (several herbal drugs or preparations of such) a test for proof of the presence of the ingredient in the product, e.g. thin-layer chromatography, and quantitative methods of measurement when possible.
- If the product contains significant quantities of a volatile oil then a method for measuring the content of the oil, with suitable limits, must be included.
- For tablets and capsules, tests and specifications of e.g. weight variation and disintegration are required. See current LS and Ph. Eur.
- For liquid preparations and creams which promote the growth of micro-organisms, contamination by micro-organisms must be controlled. If a preservative has been added, a method, with limits, for the analysis of this must be given.

## II F. Stability

The stability of a product is to be documented and should be measured using tests which indicate quality. Data which show the physical and microbiological stability of the product must also be included. Where applicable, the stability of the pharmacologically active ingredient or of a compound which is representative of the ingredient/product must be shown.

- The shelf-life stated must be based on data which have been collected during storage under defined conditions in the container (pack) in which the product is to be sold.
- Information on the physical stability of the product is to be included in the report (e.g. precipitation, change in colour, change in smell etc.). If an analytical method is described in the specification for the finished product, then this method may be used in the stability tests.
- The stability studies should include a suitable test, e.g. thin-layer chromatography to detect decomposition of the active ingredients in the product.
- For the finished product, it must be shown that there is no growth of micro-organisms. If a preservative is used, its stability should be shown.

## II Q. Special Details

## **Documentation of Safety**

### **General information on Safety Evaluation**

**The safety of a natural remedy is to be discussed and evaluated on the basis of all available relevant information. *First, consideration should be given to the experience gained from corresponding previous use of the product/ingredient concerned in the application for which harmful effects have not appeared or been suspected.* Corresponding use means that there are no substantial deviations in mode of administration, dosage or duration of use (short or long-term treatment) compared to earlier use.**

**For natural remedies whose ingredients are normally included in *foodstuffs* and which are generally considered not to entail any health risks, the safety assessment may be based on the knowledge that exists about the occurrence of the ingredients in foodstuffs. In such cases, it is the responsibility of the applicant to prove that the levels of these ingredients in the natural remedy do not deviate from the levels which normally occur in foodstuffs.**

**Even if experience from long-term use of a natural remedy does not indicate any harmful effects, it cannot always be considered proven that the substance is harmless. Harmful effects may have appeared but are not known about or have not been reported. It is therefore the responsibility of the applicant to critically assess the documentation which provides the basis for the evaluation of safety.**

### **Documentation in Support of an Acceptable Safety Level**

**The documentation of the safety for a natural remedy must contain an *up-to-date summary and assessment, so-called expert's report*, of all relevant, published information about the natural remedy and results from any clinical trials and/or pharmacological and toxicological investigations of the natural remedies.**

**1. It must be possible to substantiate any quoted reliable and adequate experience, as far as possible, by reference to the literature, as a history of documented use constitutes the basis for considering a substance by definition as a natural remedy. 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 natural remedy has been used**
- **in which countries the natural remedy 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 information is 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. For natural remedies whose safety has not been satisfactorily documented by reliable and adequate experience from long traditional use or, for which there exists doubt concerning their safety, their innocuousness must be shown by clinical trials and/or pharmacological and toxicological investigations of the natural remedies. The clinical trials which are quoted 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 natural remedy. 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 natural remedy is to be estimated and assessed.

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 Product Agency's Provisions and Guidelines on Clinical Trials of Medicinal Products (LVFS 1990:25).

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 natural remedy 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.

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#### Appendix 4 Documentation of efficacy

##### Indications

Traditionally, natural remedies have been used for self-medication in the

**field of folk medicine. The earlier Swedish guidelines for marketing natural preparations were also based on this principle. With time, approved self-medication indications may be changed, e.g. in connection with harmonisation with other OTC medicinal products.** Traditionally, natural remedies have been used for self-medication in the field of folk medicine. The earlier Swedish guidelines for marketing natural preparations were also based on this principle. With time, approved self-medication indications may be changed, e.g. in connection with harmonisation with other OTC medicinal products.

As a guide to which self-medication indications for a particular product may be accepted by the Medical Products Agency during a transition period, the National Board for Consumer Policies list (KOVFS 1993:4) may be used. A large number of the indications on this list have traditional ties in this country.

### **Documentation in Support of Efficacy**

As the basis for all assessment of natural remedies, there must be a *summary and assessment* of relevant data. This information is to be presented in a so-called *expert's report*, in separate sections:

**A.** A summary and assessment of *generally available documentation /information* on the medical background and traditional use of the active ingredients (herbal drugs or the equivalent). 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*. Here results of *relevant* clinical trials and pharmacological studies are to be presented. All such studies which have been carried out on 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 Appendix 5 and Medical Products Agency 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.

### **Proof of Efficacy for Different Types of Product**

The following norms for proving the efficacy of natural remedies take into consideration both Swedish/European folk medicine traditions and recent

developments in this field.

1. For traditionally used natural remedies with only one active ingredient, whose use/indication and dosage has been documented in approved handbooks, and which have been described according to point A above, no further documentation of efficacy needs to be submitted.
  2. For natural remedies according to 1. above, which, in addition, only contain *vitamins and/or minerals* in quantities which correspond to the recommended daily requirement (see e.g. Swedish Nutritional Recommendations), further documentation of efficacy does *not* need to be presented. However, it is a precondition that added vitamins/minerals are only marketed as dietary supplements.
  3. *Combination products containing several active ingredients* must be justified and documented according to A with data for each separate constituent included, *and for the mixture itself*, if there is one. Important note: each active component must contribute to the intended effect, and evidence of this must be given.
  4. For natural remedies whose active ingredients are based on long-term use as *foodstuffs*, their efficacy must be described either according to alternative A or B above depending on the indication proposed.
  5. For natural remedies which are a *further development* of products according to points 1-4, the applicant must present further documentation according to point B above. These substances deviate from traditional use in one or several ways: e.g. new dosage, new mode of administration, new dosage form, new mode of preparation of the active ingredient, new indication, long-term use.
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## **Appendix 5**

### **Specific Product Documentation**

The evidence that may be required to substantiate the efficacy of a natural remedy 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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