The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

EMEA/HMPWP/25/99

REPORT FROM THE

AD HOC WORKING GROUP ON

HERBAL MEDICINAL PRODUCTS

1997/1998

The views presented in this document are those of the HMPWP, which has been created as a forum for exchange of experience in the field of herbal medicinal products. This document is released for the purposes of transparency and has no legal force with respect to Directive 2001/83/EC.

Report to the Management Board
10 February 1999

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 75 23 70 51
E-mail: mail@emea.eu.int http://www.emea.eu.int

Foreword

by Fernand Sauer, Executive Director

The use of herbal medicinal products in Europe has gradually changed during the present century with the advances made in medicine and the progress of pharmaceutical research. Not all National Competent Authorities in the European Union fully recognise products of herbal origin as medicinal products. Study methods used in bibliographical references for herbal medicinal products are not always presented in terms accepted by the scientific community. However, these products constitute a valuable heritage in therapy, as many active substances have originated from plants.

It is sometimes assumed that the European Agency for the Evaluation of Medicinal Products should only focus its activity on innovative and biotechnology/biological products and would not consider herbal medicinal products in the remit of its core responsibilities. However, in keeping with its mission statement to contribute to the protection and promotion of public health in Europe, the Agency has endeavoured to prevent possible conflicts in the Mutual Recognition of national authorisations, which are referred to the Committee for Proprietary Medicinal Products (CPMP) for arbitration. It should be highlighted that the creation of an ad hoc Working Group on Herbal Medicinal Products at the EMEA was agreed by the EMEA Management Board with the primary objective to pre-empt arbitrations in the Mutual Recognition of marketing authorisations for herbal medicinal products.

I would like to acknowledge the considerable work achieved by the working group during its mandate in 1997 and 1998. This work resulted in the preparation of proposals for revised and new guidance and requirements in the field of quality, safety and efficacy of herbal medicinal products, which should prove useful in the future evaluation of such products. In agreement with the Management Board, continuation of the work is supported by the EMEA in the framework of a permanent EMEA working party.

This report gives an overview of the current status of the proposals from the EMEA working group, either draft or final documents. Some suggestions will require further discussion within the CPMP. Draft proposals are currently under consultation with Interested Parties and are expected to be finalised in the course of the year. It was considered important to make public the work achieved so far by the group. More work will be needed to reach agreement on the proposals at the EU level and within the Member States.

Introduction

by Konstantin Keller, Chairman

Herbal medicinal products are available in all Member States of the European Union. Industrially prepared, finished herbal medicinal products fall within the scope of Council Directive 65/65/EEC. They have access to the decentralised marketing authorisation procedure. Major differences in the assessment of quality, safety and efficacy may represent a risk to consumers and would hinder free circulation of herbal medicinal products in the EU. Upon the initiative of the European Parliament, the European Commission and the EMEA Executive Director, supported by the EMEA Management Board, an ad hoc Working Group on Herbal Medicinal Products was established at the European Medicines Evaluation Agency in May 1997. The main thrust of the working group since 1997 has been the protection of public health by preparing guidance intended for successful mutual recognition of marketing authorisations in the field of herbal medicinal products and hopefully restricting arbitration to a minimum.

The complexity of herbal drug preparations and the very difficult interpretation of bibliographic data on safety and efficacy that reflect the experience gathered during long-term use, require specific expertise and experience. In most cases the safety and efficacy of preparations of herbal origin cannot be attributed to one single chemical constituent. Various pharmaceutical particulars, including the production or collection of the starting material and the manufacture of extracts, need to be assessed. In 1997 there were only very few European guidelines addressing the specific quality aspects of herbal medicinal products. In the area of safety and efficacy there is a lack of interpretation of open terms in the European legislation, especially for bibliographic applications. Such interpretation is particularly relevant for herbal medicinal products because they have been used for a long time, sometimes over centuries, and a wealth of literature is available. It is desirable that this documented knowledge is exploited in order to avoid unnecessary tests in animals or clinical trials. The European Parliament expressed the hope of many Europeans for an open-minded approach to the use and scientific evaluation of the traditional knowledge. Thanks to the active support of all Member States and observers, the group had all the regulatory, pharmaceutical, pharmacological/toxicological and clinical expertise required for their work.

Over six meetings and in accordance with its original mandate the group reviewed the criteria set out in European legislation and guidelines for the demonstration of pharmaceutical quality, pre-clinical safety, and clinical efficacy in applications for marketing authorisation of herbal medicinal products. Changes were found necessary in order to adapt the texts to the specific situation of herbal preparations. Draft proposals were published by the EMEA and the group received constructive comments from European and non-European organisations. Interested parties were invited to hearings to present their positions. Following implementation of proposals, the documents were finalised and made available by the EMEA. The report presented here gives a comprehensive overview of the activities of the group concerning proposals to review and to interpret European legislation on medicinal products and scientific guidelines. New scientific guidelines are presented, where adequate guidance was not available until now. The report includes draft recommendations, where input from the public is still needed, as well as final proposals.

The group acts as a forum for the Member States to exchange experience in the field of herbal medicinal products. It promotes the development of a common interpretation of existing legislation in this specific area and provides guidance for competent authorities and applicants.
It is evident that final recommendations will require continuous updating in the light of new scientific data and developments. Future guidelines on quality, safety and efficacy have to be discussed and specifically adapted to herbal medicinal products where necessary. More detailed guidance is still needed in the field of efficacy. In this area, the assessment of the monographs presented by ESCOP and WHO and the drafting of core SPCs are important tools to improve consumer protection and to promote free circulation of products within the European Union.

The high public interest in the matter, on the side of regulatory agencies, the industry, scientific organisations as well as individuals from Europe, the United States, Canada, Australia and Asian countries, demonstrates the need for criteria and guidance to the assessment of herbal medicinal products. The continuous support of our work by the European Parliament and the European Commission has been a great encouragement for us. The Heads of Agencies made the participation of delegates and numerous experts from all Member States possible. This support was the basis of our scientific work. On behalf of the members of the group, it is a pleasure for me to thank the EMEA for holding the meetings and for the support they have given us. We are particularly grateful for the active and constructive participation of Professor Bass in preparing the proposals. Our successful work and the present report could not have been achieved without the efficient and committed support from the EMEA Secretariat.

Berlin and London
1 February 1999

CONTENTS

1. REGULATORY ASPECTS

1.1. Final comments for revision of Notice to Applicants Volume 2A Part 1.4.2 Bibliographical applications - (EMEA/HMPWG/6/99)

The working group suggests including a paragraph on scientific monographs into the Notice to Applicants Volume 2A
In Chapter I – 'Marketing Authorisations'
Section 4 – 'Stand Alone Applications for a Marketing Authorisation'.

4.2 BIBLIOGRAPHICAL APPLICATIONS

1. Where the constituent or constituents of the medicinal product have a well established medicinal use, with recognised efficacy and an acceptable level of safety, demonstrated by detailed references to published literature presented in accordance with second paragraph of Article 1 of Directive 75/318/EEC, an application (so called "bibliographical") for marketing authorisation may be submitted in accordance with Directive 65/65/EEC, article 4.8.(a)ii.

2. An applicant wishing to use Article 4.8 (a)ii) of Directive 65/65/EEC must fully satisfy all the requirements of Article 1 of Directive 75/318/EEC as well as those of Directives 65/65/EEC and 75/319/EEC as amended, in effect, submit a "complete" application.

3. Directive 75/318/EEC Article 1 states that "where pursuant to point 8(a) of Article 4, second paragraph, of Directive 65/65/EEC, references to published data are submitted, the provisions of this Directive (i.e. Directive 75/318/EEC) shall apply in like manner." In such cases, the full article or reference should be supplied, with necessary translations. Moreover, the Expert Reports must clearly state the grounds for using published references under the conditions set out in Directive 75/318/EEC. This would include the completion of all of the tabular formats provided in "The rules governing medicinal products in the European Union, Volume 2B Notice to Applicants: Presentation and content of applications' where relevant, unless there is a justification that the study is no relevant for the medicinal product. The impurity/related substances profile and the decomposition products arising during storage must be clearly indicated in order to allow assessment of appropriate efficacy and safety.

4. In the event that neither detailed reference to published literature, nor appropriate justification is available to cover all the requirements, the applicant must supplement the missing data with appropriate additional studies.

Scientific monographs on certain substances (e.g. those drafted by the European Scientific Co-operative on Phytotherapy (ESCOP) and the World Health Organisation (WHO) for herbal drugs) offer a valuable and updated overview on published scientific literature, which together may be used in support of the demonstration of the safety and efficacy of a medicinal product in a bibliographical application in accordance with Article 4.8 (a)ii. These monographs may help to avoid duplication of work and bring about gradual harmonisation in the evaluation of medicinal products, e.g. herbal medicinal products. Therefore the Commission and Member States recommend that both applicants and competent authorities should make use of these monographs. The use of these monographs should not preclude the future development or implementation of results of new clinical trials.

5. It should be noted that summary assessment reports such as the EPAR for Community marketing authorisations or evaluation reports on Maximum Residue Limits which are made publicly available by competent authorities for reasons of transparency would generally not be considered to supply sufficient information to meet the requirements of Directive 75/318/EEC.

1.2. Draft Comments on the Commission Regulation (EC) No. 541/95 of 10 March 1995 concerning the examination of variations to the terms of a marketing authorisation granted by a competent authority of a Member State as amended by Commission Regulation (EC) No. 1146/98 - (EMEA/HMPWG/20/99)

The working group suggests amending Annex I and Annex II to the Commission Regulation (EC) No. 541/95 on variations in order to encompass herbal medicinal products in the scope of the Regulation.

Annex I

The working group suggests replacing "no change in dissolution profile" by "no change in ***disintegration time or*** in dissolution profile" in sections B.4., B.5., B.7., B.33. of Annex I.

The working group suggests replacing "The specifications, synthetic route and quality control procedures are the same as those already approved or ...submitted" by "The specifications, synthetic route or ***manufacturing route, geographical source and production of the herbal drug (in the case of herbal medicinal products)***, and quality control procedures are the same as those already approved or ...submitted" in sections B.11. and B.11b.

Annex II

The working group suggests adding a paragraph in section 1.

"***(viii) in the case of herbal drug preparations***

- ***change of the herbal drug (e.g. different species, different part of the plant)***
- ***change of the extraction solvent or relevant change in the concentration of the extraction solvent***
- ***relevant change in the ratio of the herbal drug to the herbal drug preparation or the ratio of the herbal drug to the extraction solvent***
- ***change to the physical state (e.g. soft extract to dry extract)***"

1.3. Draft Comments on the European Commission Guideline on dossier requirements for Type I variations - (EMEA/HMPWG/22/99)

The working group suggests amending the guideline on dossier requirements for Type I variations (Notice to Applicants Volume 2A, Chapter 5) in order to encompass herbal medicinal products in the scope of the European Commission guideline.

The following changes are proposed and appear in bold italic:

- for changes no 4, 7 and 33 in part 'Conditions/remarks'
  replace "dissolution profile" by "***disintegration time or*** dissolution profile"

- for changes no 4, 7 and 33 in part 'Documentation to be supplied'
  replace "Comparative dissolution profile data" by "Comparative ***disintegration data or*** dissolution profile data"

- for change no 11 and 11b in parts 'Conditions/remarks' and 'Documentation to be supplied'
  replace "synthetic route and quality control procedures" by "synthetic route ***or manufacturing route***, ***geographical source and production of the herbal drug (in the case of herbal medicinal products)*** and quality control procedures"

- for changes no 12a., 14, 15a, 17 and 19 in part 'Documentation to be supplied'
  replace "Comparative dissolution profile data" by "Comparative ***disintegration data or*** dissolution profile data"

- for change no 15 in part 'Documentation to be supplied'
  replace "dissolution profile data" by "***disintegration data or*** dissolution profile data".

1.4. Comments on the Report "Herbal medicinal products in the European Union" following the study carried out by AESGP on behalf of the European Commission

The working group took note of the report "Herbal medicinal products in the European Union" presented by the representative of the European Commission. The group acknowledged the efforts of AESGP and European Commission to prepare a comprehensive overview of the situation of herbal medicinal products on the European market. The recommendations of the report are in principle endorsed by the group. Some members, however, expressed concerns about the recommendation to create a specific category of traditional herbal medicinal products for which no evidence on efficacy is available at all. They reported that this might be misleading and create a risk to Public Health because the labelling 'traditional' will be perceived as a positive enforcement of the use rather than to make the deficiencies evident. The group reiterated that there should be no minor requirements related to quality and safety and that the deficiencies in establishing efficacy should be clearly labelled, if such category would be established. The group pointed out that 'traditional use' might differ between Member States. It appeared questionable to the group whether such products could have access to Mutual Recognition.

2. QUALITY OF HERBAL MEDICINAL PRODUCTS

2.1. Draft Comments on the draft directive on the Good Manufacturing Practice (G.M.P) guide for starting materials of medicinal products and inspection of manufacturers - (EMEA/HMPWG/17/99)

The working group reviewed the draft directive. The group was of the general view that the concept of Good Manufacturing Practice should apply to herbal starting materials. Therefore herbal starting materials should not be excluded from the new directive.

The group made reference to the general aspects expressed in the final comments on GMP (EMEA/HMPWP/7/99) including GAP guidelines. Recent examples of adulteration of herbal drugs with toxic plants demonstrate the urgent need to establish GMP for herbal starting materials.

The working group had no specific comments on draft 2 of the G.M.P guide but expressed the wish to review the further versions of the document when available.

2.2. Draft Comments on the document Good Agricultural Practice (G.A.P) from the European Herbs Growers and Producers Association (Europam) of 5 August 1998 - (EMEA/HMPWG/18/99)

The working group considered the document on G.A.P prepared by the European Herbs Growers and Producers Association and agreed to endorse it without any amendment. The group proposed that a timeframe for the implementation of the requirements be defined. The group was of the view that a period of 5 years should be sufficient to allow producers to implement the requirements described in the document (see Annex 3).

2.3. Final Comments for revision of Good Manufacturing Practice (G.M.P) provisions - (EMEA/HMPWG/7/99)

The working group reviewed existing provisions in the Good Manufacturing Practice guide, in particular Annex 7 on the Manufacture of Herbal Medicinal Products. It confirmed the appropriateness of this guidance, though a few minor changes are suggested as follows:

Principle

- The working group indicated that a consistent quality of herbal drugs may need more detailed definitions of aspects of agricultural production. The selection of seeds, conditions of cultivation and harvesting represent an important aspect in producing a reproducible quality of herbal drugs. Ongoing discussions on Good Agricultural Practice (G.A.P) for medicinal plants should be monitored and cross-references should be included as soon as a consensus on G.A.P is obtained (see comments from the working group on the G.A.P document from Europam).

Documentation

- The working group indicated that "starting material" could be a medicinal plant, a herbal drug or a herbal drug preparation. A clear distinction should be made between these starting materials. In the case where, for example, a herbal drug preparation is the starting material, there is a need to go back to the source material and to obtain the data on the source of the plant. In those cases where such data are lacking the applicant has to justify why these data cannot be obtained. It was indicated that in those cases additional specifications on possible contamination are required. Some Member States' representatives reported on the difficulties they encounter in obtaining information on the origin of plants and production conditions.

- The working group agreed that ***water content*** should be included in the list of specifications to be provided for products such as medicinal plants and herbal drugs. Such a specification is not necessary for essential oils, fatty oils and resins.

- It was suggested to amend the seventh indent of the specifications for medicinal crude plants as follows: "assay of constituents of known therapeutic activity ***if identified***, or ***where appropriate*** of markers" (instead of "assay, where appropriate, of constituents of known therapeutic activity or of markers").

- The working group examined the issue of pesticide contamination and the European Pharmacopoeia representative reminded participants of the general method to test pesticide residues which provides a list of pesticides and their maximum limits and information on the methods of testing. Therefore it was suggested to add in the text "***in accordance with European Pharmacopoeia methods***" after "methods suitable to determine possible pesticide contamination and limits accepted" (eighth indent). The group underlined the need for a general monograph on herbal drugs in the European Pharmacopoeia because harmonised criteria for limits for toxic metals and mycotoxins are still lacking.

Sampling

- It was indicated that a reference sample of the plant material will be necessary in those cases where the plant is not well known in Europe, for example, herbal drugs coming from Asia. Samples of plant material are particular necessary if powders are used.

2.4. Final Comments for revision of Notice to Applicants Volume 2B Part IC1 "Tabular formats specific to herbal medicinal products" - (EMEA/HMPWG/16/99)

The working group suggests the following tabular formats specific to herbal medicinal products to be used in Part I C 1.

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Format 2B101A/HERBAL

Name of Company : **Name of Finished Herbal Medicinal Product :** **Name of Active substance(s) :**	**Tabular format Referring to Part of the Dossier**	**(For National Authority Use Only)**
PART II A : COMPOSITION		
Product Description : Volume Page(s)		**(For National Authority Use Only) COMMENTS**
Complete Composition : Volume Page(s)		
Unit and/or Percentage Formula **Active substance(s)** **Excipient(s)**		
Container (brief description) : Volume Page(s)		
Clinical trial formula(e) : Volume Page(s) **or formulae used in bibliographical application**		
Unit and/or Percentage Formula **Active substance(s)** **Excipient(s)**		

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Format 2B102A/HERBAL

Name of Company : **Name of Finished Herbal Medicinal Product :** **Name of Active substance(s) :**	**Tabular format Referring to Part of the Dossier**	**(For National Authority Use only)**
PART II A: DOSAGE FORM - DEVELOPMENT PHARMACEUTICS		
Product Development Studies Summary[1] : Volume Page(s)		**(For National Authority Use Only) COMMENTS**
Explanation of choice of the composition : Volume Page(s)		
Explanation of optimisation of concentrations of the additives in the composition : Volume Page(s)		
Summary of studies on compatibility data with other products (if necessary) : Volume Page(s)		

[1] The phytochemical overview is included in Format 2B110A and 2B111A

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Format 2B103A/HERBAL

Name of Company : **Name of Finished Herbal Medicinal Product :** **Name of Active substance(s) :**	**Tabular format Referring to Part of the Dossier**	**(For National Authority Use only)**
PART II A : DOSAGE FORM - DEVELOPMENT PHARMACEUTICS		
Summary of studies on compatibility with the container/ closure : **Volume Page(s)**		**(For National Authority Use only) COMMENTS**
Summary of in vivo bioavailability/bioequivalence studies : **Volume Page(s)**		
In vitro dissolution data on products used in the in vivo bioavailability studies : **Volume Page(s)**		

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Format 2B104A/HERBAL

Name of Company : **Name of Finished Herbal Medicinal Product :** **Name of Active substance(s) :**	**Tabular format Referring to Part of the Dossier**	**(For National Authority Use only)**
PART II B : METHOD OF PREPARATION		
Manufacturing formula : Volume Page(s)		**(For National Authority Use only) COMMENTS**
Batch size : **Formula :**		
Manufacturing process (including in process control and assembly) : Volume Page(s)		

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Format 2B105A/HERBAL

Name of Company : **Name of Finished Herbal Medicinal Product :** **Name of Active substance(s) :**	**Tabular format Referring to Part of the Dossier**	**(For National Authority Use only)**
PART II B : METHOD OF PREPARATION - PROCESS VALIDATION		
Summary of experimental studies : Volume Page(s)		**(For National Authority Use only) COMMENTS**

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Format 2B106Ai/HERBAL

Name of Company : **Name of Finished Herbal Medicinal Product :** **Name of Active substance(s) :**	**Tabular format Referring to Part of the Dossier**	**(For National Authority Use only)**

PART II C : CONTROL OF STARTING MATERIALS - ACTIVE SUBSTANCE(S) : HERBAL DRUG PREPARATION[2]	
Specifications and routine tests : Volume Page(s)	**(For National Authority Use only) COMMENTS**
Summary of specifications and Routine Tests - Characteristics : Volume Page(s)	
Identification tests : Volume Page(s)	
Purity tests : Volume Page(s)	
Potential contamination: Loss on drying/Dry residue: Residual solvents: Relative density:	
Other tests : Volume Page(s)	
Assay/Other evaluation of potency : Volume Page(s)	
Constituents with known therapeutic activity: or Markers: or other justified determination: Compliance with Pharmacopoeia[1]:..... ☐	

[1] Reference to the Pharmacopoeia used should be given; see CD 75/318 Annex Part 2 C.1.1

[2] If no monograph for the herbal drug exists, neither in the European Pharmacopoeia nor in the pharmacopoeia of a Member State, a comprehensive specification of the herbal drug has to be presented (see Format 2B106Aii).

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Format 2B106Aii/HERBAL

Name of Company : **Name of Finished Herbal Medicinal Product :** **Name of Active substance(s) :**	**Tabular format Referring to Part of the Dossier**	**(For National Authority Use only)**

PART II C : CONTROL OF STARTING MATERIALS - ACTIVE SUBSTANCE(S) : HERBAL DRUG	
Specifications and routine tests : Volume Page(s)	**(For National Authority Use only) COMMENTS**
Summary of specifications and Routine Tests - Characteristics : Volume Page(s)	
Identification tests : Volume Page(s)	
Purity tests : Volume Page(s)	
Foreign matter: Pharmacopoeia[1].....☐ Loss on drying/Water: Pharmacopoeia[1].....☐ Total ash/Ash insoluble in hydrochloric acid: Pharmacopoeia[1].....☐ Microbial contamination: Pharmacopoeia[1].....☐ Other potential contamination:	
Other tests : Volume Page(s)	
Assay/Other evaluation of potency : Volume Page(s)	
Constituents with known therapeutic activity: or Markers: or other justified determination: Compliance with Pharmacopoeia[1]:..... ☐	

[1] Reference to the Pharmacopoeia used should be given; see CD 75/318 Annex Part 2 C.1.1

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Format 2B107A/HERBAL

<table>
<tr><td colspan="2">Name of Company :

Name of Finished Herbal Medicinal Product :

Name of Active substance(s) :</td><td>Tabular format Referring to Part of the Dossier</td><td>(For National Authority Use only)</td></tr>
<tr><td colspan="4">PART II C : CONTROL OF STARTING MATERIALS - ACTIVE SUBSTANCE(S): HERBAL DRUG/HERBAL DRUG PREPARATION - SCIENTIFIC DATA</td></tr>
<tr><td colspan="3">1. Nomenclature : Volume Page(s)</td><td>(For National Authority Use only) COMMENTS</td></tr>
<tr><td colspan="3">Scientific name of the plant, with the name of the authority, variety and chemotype (where applicable):

Parts of the plant :

Definition of herbal drug/herbal drug preparation :

Ratio of the herbal drug to the herbal drug preparation :

Extraction solvent(s) :

Other name :

Laboratory code :</td><td rowspan="5"></td></tr>
<tr><td colspan="3">2. Description : Volume Page(s)</td></tr>
<tr><td colspan="3">Physical form :</td></tr>
<tr><td>Constituents with known therapeutic activity:</td><td colspan="2">Justification of the appropriateness of the choice of markers:</td></tr>
<tr><td colspan="3">Other substance(s):</td></tr>
</table>

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Format 2B108A/HERBAL

Name of Company : **Name of Finished Herbal Medicinal Product :** **Name of Active substance(s) :**	**Tabular format Referring to Part of the Dossier**	**(For National Authority Use Only)**
PART II C : CONTROL OF STARTING MATERIALS - ACTIVE SUBSTANCE(S): HERBAL DRUG/HERBAL DRUG PREPARATION - SCIENTIFIC DATA		
3. Manufacture : **Volume** **Page(s)**		**(For National Authority Use Only) COMMENTS**
Definition of a production batch : **Volume** **Page(s)**		
(a) Herbal drug: (b) Herbal drug preparation(s):		
Plant Production / Plant Collection: **Volume** **Page(s)**		
Geographical source : Name(s) and address(es) of the grower(s) and/or the supplier(s) of the drug : Cultivation/Collection from wild sources : Pre-harvest chemical treatment : Harvest : Drying : Cutting and milling : Other processes :		
Name(s) and address(es) of the manufacturer of the preparation : **Volume** **Page(s)**		
Manufacturing route : **Volume** **Page(s)**		

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Format 2B109A/HERBAL

Name of Company : **Name of Finished Herbal Medicinal Product :** **Name of Active substance(s) :**	**Tabular format Referring to Part of the Dossier**	**(For National Authority Use only)**

PART II C : CONTROL OF STARTING MATERIALS - ACTIVE SUBSTANCE(S) : HERBAL DRUG/HERBAL DRUG PREPARATION - SCIENTIFIC DATA	
Description of process : Volume Page(s)	**(For National Authority Use Only) COMMENTS**
Extraction solvents, reagents : Volume Page(s)	
Purification stages : Volume Page(s)	
Standardisation (adjusted to a defined content of constituents with known therapeutic activity): Volume Page(s)	
Range of the inert material or herbal drug preparation added:.....-.....%	
4. Quality control during manufacture : Volume Page(s)	
Starting materials : Volume Page(s)	
Control tests on intermediate products : Volume Page(s)	

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Format 2B110A/HERBAL

Name of Company : **Name of Finished Herbal Medicinal Product :** **Name of Active substance(s) :**	**Tabular format Referring to Part of the Dossier**	**(For National Authority Use only)**
PART II C : CONTROL OF STARTING MATERIALS - ACTIVE SUBSTANCE(S) : (DEVELOPMENT) HERBAL DRUG - SCIENTIFIC DATA		
Description of the herbal drug: **Volume** **Page(s)**		**(For National Authority Use Only) COMMENTS**
Macroscopic description: Pharmacopoeia[1].....☐ Microscopic description: Pharmacopoeia[1].....☐ Additional tests: Pharmacopoeia[1].....☐ (e.g. thin-layer chromatography):		
Composition and analytical research for constituents and physical characteristics: **Volume** **Page(s)**		
Tests for adulterants and for known toxic constituents: **Volume** **Page(s)**		
Summary of Analytical Development and Validation Studies: **Volume** **Page(s)**		

[1] Reference to the Pharmacopoeia used should be given; see CD 75/318 Annex Part 2 C.1.1

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Format 2B111A/HERBAL

Name of Company : **Name of Finished Herbal Medicinal Product :** **Name of Active substance(s) :**	**Tabular format Referring to Part of the Dossier**	**(For National Authority Use only)**
PART II C : CONTROL OF STARTING MATERIALS - ACTIVE SUBSTANCE(S) : (DEVELOPMENT) HERBAL DRUG PREPARATION - SCIENTIFIC DATA		
Herbal drug preparations such as extracts		**(For National Authority Use Only) COMMENTS**
Analytical chemical profile: Volume Page(s)		
Detection of known toxic constituents/adulterants: Volume Page(s)		
Summary of Analytical Development and Validation Studies: Volume Page(s)		

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Format 2B112A/HERBAL

Name of Company : **Name of Finished Medicinal Product :** **Name of Active substance(s) :**	**Tabular format Referring to Part of the Dossier**	**(For National Authority Use only)**

PART II C : CONTROL OF STARTING MATERIALS - ACTIVE SUBSTANCE(S) : (IMPURITIES) HERBAL DRUG/HERBAL DRUG PREPARATION - SCIENTIFIC DATA	
Potential impurities originating from cultivation harvesting/collection, storage: Page(s) :	**Test procedures and their limits of detection or limits of quantitation :**
Microbial contamination:	Pharmacopoeia[1].....☐
Pesticide residues:	Pharmacopoeia[1].....☐
Heavy metals/other toxic elements:	Pharmacopoeia[1].....☐
Mycotoxins:	Pharmacopoeia[1].....☐
Fumigation agents:	
Radioactivity:	
Potential impurities arising during the production and purification : Page(s) :	**Test procedures and their limits of detection or limits of quantitation :**
Residual solvents:	Pharmacopoeia[1].....☐
Other substance(s):	
Potential impurities/contaminants in herbal drug preparations :	**Test procedures and their limits of detection or limits of quantitation :**
Microbiological quality :	Pharmacopoeia[1].....☐
Other Substance(s) :	
Potential substitution and adulterants:	**Test procedures and their limits of detection or limits of quantitation :**

COMMENTS : (For National Authorities Use Only)

[1] Reference to the Pharmacopoeia used should be given; see CD 75/318 Annex Part 2 C.1.1

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Format 2B113Ai/HERBAL

Name of Company : **Name of Finished Herbal Medicinal Product :** **Name of Active substance(s) :**	**Tabular format Referring to Part of the Dossier**	**(For National Authority Use only)**

PART II C : CONTROL OF STARTING MATERIALS - ACTIVE SUBSTANCE(S) : (BATCH ANALYSIS) - HERBAL DRUG PREPARATION[1]		
Batches tested :	**Volume Page(s)**	**(For National Authority Use Only) COMMENTS**
Date(s) of manufacture : Place(s) of manufacture : Batch size : Batch (Lot) number : Use of batches (incl.: preclinical & clinical testing) :		
Results of tests :	**Volume Page(s)**	
Batch Nos :		
Characteristics : Identification tests : Purity tests : Potential contaminants : Other tests : Assay(s) / potency :		
Reference standard (analytical results) :	**Volume Page(s)**	
Origin/supplier Characteristics : Identification tests : Purity tests : Potential contaminants : Other tests : Assay(s) / potency :		

[1] The batch analysis of the herbal drug has to be presented (see Format 2B113Aii)

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Format 2B113Aii/HERBAL

Name of Company : **Name of Finished Herbal Medicinal Product :** **Name of Active substance(s) :**	**Tabular format Referring to Part of the Dossier**	**(For National Authority Use only)**

PART II C : CONTROL OF STARTING MATERIALS - ACTIVE SUBSTANCE(S): (BATCH ANALYSIS) - HERBAL DRUG			
Batches tested :		**Volume Page(s)**	**(For National Authority Use Only) COMMENTS**
Date(s) of manufacture : Place(s) of manufacture : Batch size : Batch (Lot) number : Use of batches (incl. : preclinical & clinical testing)			
Results of tests :		**Volume Page(s)**	
Batch Nos :			
Characteristics : Identification tests : Purity tests : Potential contaminants : Other tests : Assay(s) / potency :			
Reference standard (analytical results) :		**Volume Page(s)**	
Origin/supplier : Characteristics : Identification tests : Purity tests : Potential contaminants : Other tests : Assay(s) / potency :			

Pharmaceutical Expert Report

Format 2B114A/HERBAL

Name of Company : **Name of Finished Herbal Medicinal Product :** **Name of Active substance(s) :**	**Tabular format Referring to Part of the Dossier**	**(For National Authority Use only)**
PART II C : CONTROL OF STARTING MATERIALS - EXCIPIENT(S) : SPECIFICATIONS AND ROUTINE TESTS		
1. Excipient(s) described in a pharmacopoeia[1]: **Volume Page(s)**		**(For National Authority Use Only) COMMENTS**
2. Excipient(s) not described in a pharmacopoeia : **Volume Page(s)**		
Characteristics : Identification tests : Purity tests : - Physical - Chemical - Biological / Immunological Other tests : Assay(s) and/or evaluations:		

[1] Reference to the Pharmacopoeia used should be given; see CD 75/318 Annex Part 2 C.1.1

Pharmaceutical Expert Report

Format 2B115A/HERBAL

Name of Company : **Name of Finished Herbal Medicinal Product :** **Name of Active substance(s) :**	**Tabular format Referring to Part of the Dossier**	**(For National Authority Use only)**
PART II C : CONTROL OF STARTING MATERIALS - EXCIPIENT(S) : SCIENTIFIC DATA		
Summary of studies : Volume Page(s)		**(For National Authority Use Only) COMMENTS**

Pharmaceutical Expert Report

Format 2B116A/HERBAL

Name of Company : **Name of Finished Herbal Medicinal Product :** **Name of Active substance(s) :**	**Tabular format Referring to Part of the Dossier**	**(For National Authority Use only)**
PART II C : CONTROL OF STARTING MATERIALS - PACKAGING MATERIAL (IMMEDIATE PACKAGING)		
Specifications and routine tests : Volume Page(s)		**(For National Authority Use Only) COMMENTS**
Type of material : Construction : Quality specifications (routine tests and summary of control methods) :		
Scientific data : Volume Page(s)		
Summary of development studies on packaging materials : Batch analysis (analytical results) :		

Pharmaceutical Expert Report

Format 2B117A/HERBAL

Name of Company : **Name of Finished Herbal Medicinal Product :** **Name of Active substance(s) :**	**Tabular format Referring to Part of the Dossier**	**(For National Authority Use only)**
PART II D : CONTROL TESTS ON INTERMEDIATE PRODUCTS **Volume Page(s)**		**(For National Authority Use Only) COMMENTS**
PART II E : CONTROL TESTS ON THE FINISHED PRODUCT : **Volume Page(s)**		
Product specifications and tests for release at time of manufacture :		
General product characteristics : Identification tests : Quantitative determination of herbal drug/herbal drug preparations : - in case of constituents with known therapeutic activity - in case of markers Or other justified determination : Purity tests : Pharmaceutical tests :		
Identification and determination of excipient(s) : Volume Page(s)		
Approved colouring materials : Determination of preservative agents (e.g. antimicrobial or chemical preservatives) : Other additives :		

Pharmaceutical Expert Report

Format 2B118A/HERBAL

Name of Company : **Name of Finished Herbal Medicinal Product :** **Name of Active substance(s) :**	**Tabular format Referring to Part of the Dossier**	**(For National Authority Use only)**

PART II E : CONTROL TESTS ON THE FINISHED PRODUCT - SCIENTIFIC DATA

Summary of analytical development and validation studies : **Volume Page(s)**	**(For National Authority Use Only) COMMENTS**
Batch Analysis: **Volume Page(s)**	
Batches tested : Batch (Lot) number : Date(s) of manufacture : Place(s) of manufacture : Batch size : Use of batches :	
Results of Batch Analysis : **Volume Page(s)**	
Batch Nos :	
Tests :	
Reference standard : **Volume Page(s)**	

Pharmaceutical Expert Report

Format 2B119A/HERBAL

Name of Company : **Name of Finished Herbal Medicinal Product :** **Name of Active substance(s) :**	**Tabular format Referring to Part of the Dossier**	**(For National Authority Use only)**
PART II F : STABILITY - STABILITY TESTS ON ACTIVE SUBSTANCE(S)		
Batches tested : **Volume** **Page(s)**		
Batch Nos :		
General test methodology : **Volume** **Page(s)**		
Accelerated test conditions (temperature ° C, % RH, light) : Normal test conditions (temperature ° C, % RH, light) :		
Analytical test procedures : **Volume** **Page(s)**		
Assay techniques : Determination of degradation products/chromatographic profile :		
Validation of all test procedures including limits of detection (including initial results): **Volume** **Page(s)**		
Results of tests : **Volume** **Page(s)**		
Proposed storage conditions and Duration of Storage to be permitted before re-testing : **Volume** **Page(s)**		
COMMENTS (For National Authorities Use Only)		

Pharmaceutical Expert Report

Format 2B120A/HERBAL

Name of Company : **Name of Finished Herbal Medicinal Product :** **Name of Active substance(s) :**	**Tabular format Referring to Part of the Dossier**	**(For National Authority Use only)**

PART II F : STABILITY - STABILITY TESTS ON THE FINISHED PRODUCT

Batches tested and packaging used :	**Volume**	**Page(s)**
Stability study methods :	**Volume**	**Page(s)**
Real time studies (temperature °C, % RH, light) : Studies under other conditions :		
Characteristics studied :	**Volume**	**Page(s)**
Physical characteristics : Microbiological characteristics : Chemical characteristics : Chromatographic characteristics : Packaging characteristics :		
Evaluation methods and validation :	**Volume**	**Page(s)**
Results of tests :	**Volume**	**Page(s)**
Interpretation of results :	**Volume**	**Page(s)**
Proposed shelf-life and storage conditions (incl. after reconstitution or after first opening if appropriate) :	**Volume**	**Page(s)**
Ongoing stability studies :	**Volume**	**Page(s)**
COMMENTS : (For National Authorities Use Only)		

Pharmaceutical Expert Report

Format 2B121A/HERBAL

Name of Company : **Name of Finished Herbal Medicinal Product :** **Name of Active substance(s) :**	**Tabular format Referring to Part of the Dossier**	**(For National Authority Use only)**
PART II G : BIOAVAILABILITY/BIOEQUIVALENCE **Volume** **Page(s)**		
Give reference to relevant sections in Part IV.		
PART II Q : OTHER INFORMATION		
Summary of analytical test procedures used in metabolism and bioavailability studies, and validation studies : **Volume** **Page(s)**		
Summary of synthesis of radiolabelled active substance(s) used in metabolic and/or pharmacokinetic studies : **Volume** **Page(s)**		
COMMENTS (For National Authority Use Only)		

2.5. Final Comments for revision of Notice to Applicants Volume 2B Part II: Concerning chemical, pharmaceutical and biological documentation for vegetable medicinal products - (EMEA/HMPWG/8/99)

The working group suggests amending the text as follows. Changes are in bold italic.

Part II: Concerning Chemical, Pharmaceutical and Biological Documentation for *Herbal* Medicinal Products

The principle of GMP and the detailed guidelines are applicable to all operations, which require the authorisation referred to in **Article 16 of Directive 75/319/EEC** as modified. They are also relevant for all other large-scale pharmaceutical manufacturing processes, such as that undertaken in hospitals, for the preparations of products for use in clinical trials, and for wholesaling, where applicable.

All analytical test procedures described in the various sections of the Part II chemical, pharmaceutical and biological documentation must be described in sufficient detail to enable the procedures to be repeated if necessary (e.g. by an official laboratory). All procedures need to be validated and the results of the validation studies must be provided.

PART II A: COMPOSITION

1. COMPOSITION OF THE MEDICINAL PRODUCT

NAMES OF INGREDIENTS	UNIT AND/OR PERCENTAGE FORMULA	FUNCTION	REFERENCE TO STANDARDS
Active substance(s)			
Excipient(s)			

2. CONTAINER (BRIEF DESCRIPTION)

Nature of container materials; qualitative composition; method of closure; method of opening.

3. CLINICAL TRIAL FORMULA(E)

4. *DOSAGE FORM* - DEVELOPMENT PHARMACEUTICS

Explanation with regard to the choice of formulation, composition, ingredients and container, supported, if necessary, by data on development pharmaceutics. The overage, with justification thereof, should be stated. Tests carried out during pharmaceutical development must be described in detail, e. g. in vitro dissolution studies for solid pharmaceutical forms.

PART II B: METHOD OF PREPARATION

1. MANUFACTURING FORMULA (including details of batch size)

2. MANUFACTURING PROCESS (including in-process control and the pharmaceutical assembly process)

If ***herbal drug*** preparations are the starting material, the description of their manufacturing process and their control belong to section C.
A flow-chart of the manufacturing process should be given.

3. VALIDATION OF THE PROCESS

Validation of the process should be carried out when a non-standard method of manufacture is used or for steps of the manufacturing process which are critical for the product described in the finished product specifications (experimental data showing that the manufacturing process, using materials of the stated quality and the types of manufacturing equipment specified, is a suitable one and will consistently yield a product of the desired quality).

PART II C: CONTROL OF STARTING MATERIALS

1. ACTIVE SUBSTANCE(S) ***(HERBAL DRUG(S)/(HERBAL DRUG PREPARATION(S))***

1.1. Specifications and routine tests

1.1.1 Active substance(s) described in a pharmacopoeia
For herbal drug preparations additional specifications as set out in 1.1.2 may be required.

1.1.2 Active substance(s) not described in a pharmacopoeia

- Characteristics
- Identification tests
- ***Purity tests***
  * Potential contamination by micro-organisms, products of micro-organisms, pesticides, toxic metals, radioactivity, fumigants, etc.
  * Physical
  * Chemical
- Other tests
- Assay(s) of ***constituents*** with known therapeutic activity ***or of markers, or other justified determination***.

In the case of a herbal drug preparation, a monograph on the herbal drug has to be presented. If no monograph for the herbal drug exists, neither in the European Pharmacopoeia nor in the pharmacopoeia of a Member State, a comprehensive specification of the herbal drug has to be presented.

1.2. Scientific Data

1.2.1 Nomenclature

- Scientific name of plant, with the name of the authority, variety and chemotype ***(where applicable)***
- ***Parts of the plant***
- ***Definition of the herbal drug/herbal drug preparation***
- ***Ratio of the herbal drug to the herbal drug preparation***
- ***Extraction solvent(s)***
- Other name
- Laboratory code

1.2.2 Description

- Physical form
- ***Constituents with known therapeutic activity or markers***
  - Structural formula (including conformational data for macromolecules)
  - Molecular formula
  - Relative molecular mass
  - Chirality
- ***Other substance(s)***

1.2.3 Manufacture

- ***Definition of a production batch***
- ***Plant production/Plant collection***
- Geographical source of active substance ***of herbal origin***
- Name(s) and address(es) of the ***manufacturer of the preparation***
- ***Manufacturing route***
- Description of process
- Solvents, reagents
- Purification stages
- ***Standardisation***

1.2.4 Quality control during manufacture

- Starting materials
- Control tests on intermediate products (where appropriate)

1.2.5 Development (for active substance(s) of ***herbal*** origin)

1.2.5.1 ***Herbal drugs, herbal drug preparations such as powders***

- Description of the ***herbal drug or of the herbal drug preparation***
  - macroscopic
  - microscopic
  - ***Additional tests***
- Composition and analytical research for ***constituents*** and physical characteristics
- ***Tests for adulterants and for known toxic constituents***
- ***Summary of*** analytical development and validation ***studies***, commentary on the choice of routine tests and specifications

1.2.5.2 ***Herbal drug preparations such as extracts***

- Analytical chemical profile (qualitative and quantitative)
- Detection of ***known*** toxic ***constituents (e.g. pyrrolizidine alkaloids, ginkgolic acids, estragole, thujone, ...)*** /adulterants
- ***Summary of*** analytical development and validation ***studies***, commentary on the choice of routine tests and specifications.

1.2.6 Impurities

- Potential impurities originating from the ***cultivation, harvesting/collection, storage***
- Potential impurities arising during the production and purification, ***residual solvents***
- Methods detecting potential contamination of the active substance(s) ***of herbal origin*** by micro-organisms and products of micro-organisms, pesticides, fumigation agents, toxic metals, radioactivity etc.
- Potential ***substitution and adulterants***

1.2.7 Batch analysis

- Batches tested (date of manufacture, place of manufacture, batch size, and use of batches including batches used in preclinical and clinical testing)
- Results of tests
- Reference ***standard*** (analytical results), primary and others

2. EXCIPIENT(S)

2.1. Specifications and routine tests

2.1.1 Excipient(s) described in a pharmacopoeia

2.1.2 Excipient(s) not described in a pharmacopoeia

- Characteristics
- Identification tests
- Purity tests (including limits for named, total, other single, unidentified single and unidentified total impurities)
  - physical
  - chemical
  - ***biological/immunological***
- Other tests
- Assay(s) and/or evaluations (where necessary)

2.2. Scientific data

Data, where necessary, for example on excipient(s) used for the first time in medicinal products (see II C.1.2).

3. PACKAGING MATERIAL (IMMEDIATE PACKAGING)

3.1 Specifications and routine tests

- Type of material
- Construction
- Quality specifications (routine tests and ***summary of control methods***)

3.2 Scientific data

- Development studies on packaging materials
- Batch analysis, analytical results

PART II D: CONTROL TESTS ON INTERMEDIATE PRODUCTS (IF NECESSARY)

A distinction should be made between in-process controls (Part II B) and control tests on intermediate products.

PART II E: CONTROL TESTS ON THE FINISHED PRODUCT

1. SPECIFICATIONS AND ROUTINE TESTS

1.1 Product specifications and tests for release at time of manufacture (general characteristics, specific standards)

1.2 Control Methods

1.2.1 Test procedures for identification and quantitative determination ***of herbal drugs/herbal drug preparations.***

It must be described in detail (including biological and micro-biological methods where relevant), together with other tests which include those in the appropriate general monograph for the type of dosage form in the European Pharmacopoeia:

- Identification tests
- Quantitative determination of active substance(s); and additionally for ***herbal drugs*** and ***herbal drug preparations***, quantitative determination of ***constituents*** with known therapeutic activity ***or of markers, or other justified determination***
- Purity tests
- Pharmaceutical tests (e.g. dissolution)

1.2.2 Identification and determination of excipient(s)

- Identification tests for approved colouring materials
- Determination of ***preservative agents, e.g.*** antimicrobial or chemical preservatives (with limits)
- ***Other additives***

2. SCIENTIFIC DATA

2.1 Analytical validation of methods and comments on the choice of routine tests and standards (e.g. working standards)

2.2 Batch analysis

- Batches tested (date of manufacture, place of manufacture, batch size and use of batches)
- Results of ***batch analysis***
- Reference ***standard*** (analytical results), primary and others

PART II F: STABILITY

1. STABILITY TESTS ON ACTIVE SUBSTANCE(S)

- Batches tested
- General test methodology
  - accelerated test conditions
  - normal test conditions
- Analytical test procedures
  - assay ***techniques***
  - determination of degradation products/***chromatographic profile***
- Validation of all test procedures including limits of detection (including initial results)
- Results of tests
- Conclusions

Data on stability tests on active substances may not be required if justified by the applicant, provided that the finished product is manufactured immediately after production of the active substance(s).

2. STABILITY TESTS ON THE FINISHED PRODUCT

- Quality specification for the proposed shelf-life
- Batches tested and packaging
- ***Stability*** study methods
  - real time studies
  - studies under other conditions
- Characteristics studied
  - physical characteristics
  - microbiological characteristics
  - chemical characteristics
  - chromatographic characteristics
  - characteristics of the packaging (container/closure interaction with the product)
- Evaluation test procedures
  - description of test procedures
  - validation of test procedures
- Results of tests (including initials and reference to degradation products)
- Conclusions
  - shelf-life and storage conditions
  - shelf-life after reconstitution or first opening of the product
- Ongoing stability studies

PART II G: BIOAVAILABILITY/ BIOEQUIVALENCE

Give reference to relevant sections in Part IV.

PART II Q: OTHER INFORMATION

This part is intended for information not covered by any of the previous parts, e.g. the analytical tests used for the pharmaceutical development of the product, studies concerning metabolism and bioavailability, etc.

2.6. Final Proposals for revision of the Note for guidance on quality of herbal remedies - (EMEA/HMPWG/9/99)

The working group suggests amending the Note for guidance "quality of herbal remedies" (November 1988) as follows. Changes are in bold italic.

Note for guidance on quality of herbal ***medicinal products*** (July 1998)

Table of Contents

Introduction

Note for guidance concerning the application of Part ***2*** of the Annex to Directive 75/318/EEC, as amended. The special problems of herbal ***medicinal products*** and the differences between medicinal products containing chemically defined active ***substances*** are described in this Note for guidance [(*)].

This Note for guidance should be read in conjunction with the Annex 7 "Manufacture of Herbal Medicinal Products" of Good Manufacturing Practice (GMP) for medicinal products; GMP recommendations should be respected.

Consistent quality for products of ***herbal*** origin can only be assured if the starting materials are defined in a rigorous and detailed manner including especially the specific botanical identification of the plant material used. It is also important to know the geographical source and the conditions under which the ***herbal*** drug is obtained to ensure material of consistent quality.

Reference substances used in the control of all stages of the manufacturing process should be ***specified***.

A. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE ***ACTIVE SUBSTANCE(S) OF A HERBAL MEDICINAL PRODUCT***

1) In the case of a ***herbal*** drug ***or of a herbal drug preparation consisting of reduced, comminuted or powdered herbal drugs***

either (i) the ***native*** quantity of a ***herbal*** drug ***or of a herbal drug preparation shall*** be stated ***if constituents with known therapeutic activity are unknown***

or (ii) the ***native*** quantity of a ***herbal*** drug ***or of a herbal drug preparation shall*** be given as a range corresponding to a defined quantity of constituents with known therapeutic activity.

EXAMPLE

i) Active ***substance***

Name	Quantity [(**)]
Valerianae radix	900 mg

Other substance(s)
Name
...

ii) Active ***substance***

Name	Quantity
Sennae folium	415-500 mg, corresponding to 12.5 mg of hydroxyanthracene glycosides, calculated as Sennoside B.

Other ***substance(s)***
Name
...

(*) In this Note for guidance, the sequence used is designed to relate directly to Part ***2*** of the Annex to Directive 75/318/EEC, as amended.

(**) ***The quantity indicated refers to the specifications provided in the documentation***.

2) In the case of a ***herbal*** drug preparation ***produced by steps which exceed comminution and reduction, the nature and concentration of the solvent and the physical state of the extract have to be given. Furthermore the following has to be indicated:***

either (i) the equivalent quantity ***x - y*** [(*)], or the ratio ***a - b: 1***[(*)] of the ***herbal*** drug to the ***herbal*** drug preparation ***shall*** be stated ***if constituents with known therapeutic activity are unknown*** (this does not apply to fatty or essential oils).

or (ii) ***if the constituents with known therapeutic activity are known***, the quantity of the ***herbal*** drug preparation may be given as a range corresponding to a defined quantity of ***these*** constituents (see example).

The composition of any solvent or solvent mixture and the physical state of the extract must be indicated.
If any other substance is added during the manufacture of the ***herbal*** drug preparation to adjust the ***herbal*** drug preparation to a ***defined content*** of constituents with known therapeutic activity, or for any other purpose, the added substance must be mentioned as an "other ***substance***" and the genuine extract as the "active ***substance***".

EXAMPLE

i) Active ***substance***

Name	Quantity
Valerianae radix	125 mg
dry extract ethanolic 60% ***(V/V)***	
(a - b : 1)	
or	
Valerianae radix	125 mg
dry extract ethanolic 60% ***(V/V)***	***equivalent to x - y mg Valeriane radix***

Other substance(s)
Name
...

or

ii) Active ***substance***

Name	Quantity
Sennae folium	50-65 mg, corresponding to 12.5 mg of
dry extract ethanolic 60% ***(V/V)***	hydroxyanthracene glycosides, calculated as
(a - b: 1)	Sennoside B

Other ***substance(s)***
Name
...

B. DESCRIPTION OF THE METHOD OF PREPARATION

The manufacturing process within the meaning of this section is the preparation of the finished product from ***herbal drug(s) or herbal drug preparation(s)***. The description should include details of ***the process together with the controls exercised***. ***This section should be in accordance with the "Note for Guidance on Manufacture of the finished dosage form" (CPMP/QWP/486/95).*** If ***herbal*** drug preparations are the starting material, the manufacture of the ***herbal*** drug preparations and their controls do not belong under this section but under section C.

(*) ***'a' and 'b' or 'x' and 'y' have to be justified by the applicant***

C. CONTROL OF STARTING MATERIALS

1) Control of the ***herbal*** drug ***and of herbal drug preparations***

- ***Control of the herbal drug***

A ***comprehensive specification*** for each ***herbal*** drug must be submitted, even if the starting material is a ***herbal*** drug preparation. This also applies if the applicant is not the manufacturer of the preparation. In the case of fatty or essential oils ***used as active substances of herbal medicinal products,*** a ***specification*** for the ***herbal*** drug is ***required unless fully justified***. The scientific name of the parent plant and its part(s) have to be stated.

If no monograph for the ***herbal*** drug is given in a Pharmacopoeia referred to in Directive 75/318/EEC, Annex 1, a ***comprehensive specification*** on the ***herbal*** drug must be supplied and should be set out in the same way where practicable, as the monographs on ***herbal*** drugs in the European Pharmacopoeia. This should include the botanical name and authority and the common name if used for labelling purposes. Information on the site of collection, the time of harvesting and stage of growth, treatment during growth with pesticides etc., and drying and storage conditions should be included if possible. The ***comprehensive specification*** should be established on the basis of recent scientific data. In the case of ***herbal*** drugs with constituents of known therapeutic activity, assays of their content (with test procedure) are required. The content must be included as a range, so as to ensure reproducibility of the quality of the finished product. ***In the case of herbal drugs where constituents of known therapeutic activity are not known, assays of marker substances (with test procedure) are required. The choice of markers should be justified.***

As a general rule, ***herbal*** drugs must be tested for microbiological quality and for residues of pesticides and fumigation agents, toxic metals, likely contaminants and adulterants, etc., unless otherwise justified. ***Radioactivity should be tested if there are reasons for concerns.*** Specifications and descriptions of the analytical procedures must be submitted, together with the limits applied. ***Analytical procedures not given in a Pharmacopoeia should be validated in accordance with the ICH guideline "Validation of analytical procedures: methodology" (CPMP/ICH/281/95).***

Reference samples of the ***herbal*** drugs must be available for use in comparative tests e.g. macro and microscopic examination, chromatography etc.

- ***Control of herbal drug preparations***

If the herbal ***medicinal product*** contains not the ***herbal*** drug itself but a preparation, the ***comprehensive specification*** on the ***herbal*** drug must be followed by a description and validation of the manufacturing process for the ***herbal*** drug preparation. ***The information may be supplied either as part of the marketing authorisation application or using the European Drug Master File procedure. If the latter is chosen the documentation should be submitted in accordance with the Note for Guidance "European Drug Master File Procedure for Active Substances" (Eudra/Q/93/014).***

For each ***herbal*** drug preparation, a ***comprehensive specification*** must be submitted. This must be established on the basis of recent scientific data and must give particulars of the characteristics, identification tests and purity tests. This has to be done e.g. by different appropriate chromatographic methods. If deemed necessary by the results of the analysis of the starting material, tests on microbiological quality, residues of pesticides, fumigation agents, solvents and toxic metals have to be carried out. ***Radioactivity should be tested if there are reasons for concerns***. Quantitative determination (assay) of ***markers or of substances with known therapeutic activity*** is required. The content must be indicated with the lowest possible tolerance. The test methods must be described in detail.

If preparations from ***herbal*** drugs with constituents of known therapeutic activity are standardised (i.e. adjusted to a ***defined content*** of constituents with known therapeutic activity) it must be stated how such standardisation is achieved. If another ***substance*** is used for this purpose, it is necessary to specify as a range the quantity that can be added.

2) Control of excipients

Excipients including those added during the manufacture of the herbal drug preparations should be described according to the "Note for guidance on Excipients in the dossier for application for marketing authorisation of a medicinal product" (Eudra/Q/91/015).

D. CONTROL TESTS CARRIED OUT AT AN INTERMEDIATE STAGE OF THE MANUFACTURING PROCESS OF THE FINISHED PRODUCT

Details of all control tests with details of test procedures and limits applied at any intermediate stages of the manufacturing processes are required, especially if these tests cannot be done in the finished product.

E. CONTROL TESTS ON THE FINISHED PRODUCT

This section should be in accordance with the "Note for guidance on Specifications and control tests on the finished product" (Eudra/Q/91/020) and the analytical procedures should be validated according to the ICH guideline "Validation of analytical procedures: methodology" (CPMP/ICH/281/95).

The control tests on the finished product must be such as to allow the qualitative and quantitative determination of the composition of the active ***substances*** and a specification has to be given which may be done by using markers if constituents with known therapeutic activity are unknown. In the case of ***herbal*** drugs or ***herbal*** drug preparations with constituents of known therapeutic activity, these constituents must also be specified and quantitatively determined.

If a herbal ***medicinal product*** contains several ***herbal*** drugs or preparations of several ***herbal*** drugs and if it is not possible to perform a quantitative determination of each active ***substance***, the determination may be carried out jointly for several active ***substances***. The need for this procedure must be justified.

The criteria given by the European Pharmacopoeia to ensure the microbiological quality should be applied unless justified.

F. STABILITY TESTS

This section should be in accordance with the "Note for guidance on Stability testing of new active substances and medicinal products" (Eudra/Q/92/021) and the "Note for guidance on stability testing of existing active substances and related finished products" (CPMP/QWP/556/96).
Since the ***herbal*** drug or ***herbal*** drug preparation in its entirety is regarded as the active ***substance***, a mere determination of the stability of the constituents with known therapeutic activity will not suffice. It must also be shown, as far as possible e.g. by means of appropriate fingerprint chromatograms, that other substances present in the ***herbal*** drug or in the ***herbal*** drug preparation are likewise stable and that their proportional content remains constant.

If a herbal ***medicinal product*** contains several ***herbal*** drugs or preparations of several ***herbal*** drugs and if it is not possible to determine the stability of each active ***substance***, the stability of the medicinal product should be determined by appropriate fingerprint chromatograms, appropriate overall methods of assay and physical and sensory tests or other appropriate tests. ***The appropriateness of the tests shall be justified by the applicant.***

In the case of herbal drug preparations containing constituents with known therapeutic activity, the limit should be ± 5% of the initial assay value unless justified. In the case of constituents without known therapeutic activity, a limit of ±10% of the initial assay value can be accepted if justified by the applicant. These criteria shall apply to the stability testing of active substances in like manner.

ANNEX

GLOSSARY

Herbal ***medicinal products*** are medicinal products containing as active ***substances*** exclusively ***herbal drugs*** or ***herbal*** drug preparations.

Herbal drugs are ***plants***(*) ***or part of plants in an unprocessed state, which are*** used for a medicinal ***or pharmaceutical*** purpose. A ***herbal*** drug or a preparation thereof is regarded as one active ***substance*** in its entirety whether or not the constituents with therapeutic activity are known.

Herbal drug preparations are comminuted or powdered ***herbal*** drugs, extracts, tinctures, fatty or essential oils, expressed juices, ***processed resins or gums***, etc...prepared from ***herbal*** drugs, and preparations whose production involves a fractionation, purification or concentration process. However, chemically defined isolated constituents or their mixture are not ***herbal*** drug preparations. Other ***components*** such as solvents, diluents, preservatives may form part of ***herbal*** drug preparations. These ***components*** must be ***declared***.

Constituents with known therapeutic activity are chemically defined substances or groups of substances which are ***generally accepted*** to contribute ***substantially*** to the therapeutic activity of a ***herbal*** drug or of a preparation.

Markers are chemically defined constituents of a ***herbal*** drug which are of interest for control purposes ***independent of whether they have any therapeutic activity or not***. Markers may serve to calculate the quantity of ***herbal*** drug or preparation in the finished product if that marker has been quantitatively determined in the ***herbal*** drug or preparation when the starting materials were tested.

Standardisation(**) ***means adjusting the herbal drug preparation to a defined content of a constituent or a group of substances with known therapeutic activity respectively by adding excipients or by mixing herbal drugs or herbal drug preparations (e.g. standardised extract from the European Pharmacopoeia).***

(*) ***Thallophytes, especially lichens, higher fungi and algae, are included in like manner***

(**) ***In some Member States the expression "standardisation" is used on a national level to describe all measures which are taken during the manufacturing process and quality control leading to a reproducible quality***

2.7. Draft Note for guidance on specifications: test procedures and acceptance criteria for herbal drug preparations (herbal drugs) and herbal medicinal products - (EMEA/HMPWG/19/99)

The working group presents the following draft Note for guidance on specifications.

Note for guidance on specifications: test procedures and acceptance criteria for herbal drug preparation (herbal drug)s and herbal medicinal products (January 1999)

Table of Contents

1. INTRODUCTION

1.1 Specifications

A specification is defined as a list of tests, references to analytical and biological procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a herbal drug preparation (herbal drug) or herbal medicinal product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the herbal drug preparation (herbal drug) and herbal medicinal product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are legally binding quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities.

Specifications are one part of a total control strategy for the herbal drug preparation (herbal drug) and herbal medicinal product designed to ensure product quality and consistency. Other parts of this strategy include thorough product characterisation during development, upon which specifications are based, adherence to Good Agriculture Practice and Good Manufacturing Practice, and a validated manufacturing process, e.g., raw material testing, in-process testing, stability testing, etc.

In the case of herbal medicinal products, specifications are generally applied to the starting plant material (herbal drug), to the herbal drug preparation and to the finished herbal medicinal product. .Specifications are primarily intended to define the quality of the herbal drug preparation (herbal drug) and herbal medicinal product rather than to establish full characterisation, and should focus on those characteristics found to be useful in ensuring the safety and efficacy of the herbal drug preparation (herbal drug) and herbal medicinal product.

1.2 Objective of the Guideline

This guidance document provides general principles on the setting and justification, to the extent possible, of a uniform set of specifications for herbal drug preparations (herbal drugs) and herbal medicinal products to support applications for marketing authorisations and should be read in conjunction with the Note for guidance on quality of herbal medicinal products (EMEA/HMPWG/9/99).

1.3 Scope of the Guideline

The quality of herbal drug preparations (herbal drugs) and herbal medicinal products is determined by the quality of the starting plant material, development, in- process controls, GMP controls, and process validation, and by specifications applied to them throughout development and manufacture. This guideline addresses specifications, i.e., those tests, procedures, and acceptance criteria used to assure the quality of the herbal drug preparations (herbal drug) and herbal medicinal products at release and during the shelf life. Specifications are an important component of quality assurance, but are not its only component. All of the considerations listed above are necessary to ensure consistent production of herbal drug preparations (herbal drugs) and herbal medicinal products of high quality.
This guideline addresses only the marketing approval of herbal medicinal products (including fixed combinations); it does not address herbal drug preparations (herbal drugs) or herbal medicinal products during the clinical research stages of drug development but should be viewed as useful points for considerations.

Guidance is provided with regard to acceptance criteria which should be established for all herbal drug preparations (herbal drugs) and herbal medicinal products, i.e. universal acceptance criteria, and those which are considered specific to individual herbal drug preparations (herbal drugs) and / or dosage forms. This guideline reflects the current state of the art at the time it has been written, and should not be considered all-encompassing. New analytical technology, and modifications to existing technology, are continuously being developed. Such technologies should be used when justifiable.

2. GENERAL CONCEPTS

The following concepts are important in the development and setting of specifications. They are not universally applicable, but each should be considered in particular circumstances. This guideline presents a brief definition of each concept and an indication of the circumstances under which it may be applicable. Generally, proposals to implement these concepts should be justified by the applicant and approved by the appropriate regulatory authority before being put into effect.

2.1 Characterisation

Consistent quality for products of herbal origin can only be assured if the starting plant materials are defined in a rigorous and detailed manner. Characterisation of a herbal drug preparation (herbal drug) or herbal medicinal product (which includes a detailed evaluation of the botanical and phytochemical aspects of the plant, manufacture of the preparation and the finished product) is therefore essential to allow specifications to be established, which are both comprehensive and relevant.
Acceptance criteria should primarily be established and justified based on information from batches used in preclinical/clinical studies. However, data from batches used to demonstrate manufacturing consistency, relevant development data, such as those arising from analytical procedures and stability studies. as well as historical batch data may need to be taken into account.
Extensive characterisation usually is performed only in the development phase and where necessary following significant process changes. If necessary, at the time of submission, the manufacturer should have established appropriately characterised in-house reference materials (primary and working) which will serve for identification and determination of content of production batches.

2.1.1 Macroscopical/microscopical characterisation
Includes characterisation of potential adulterants and substitutes.

2.1.2 Phytochemical characterisation
Analytical research of constituents including active constituents as well as compounds suitable as marker substances. Includes chromatographic fingerprinting.

2.1.3 Potential Impurities/Contaminants/Degradation Products

2.1.4 Biological variation
Includes historical batch data and published information concerning biological variation.

2.2 Design and Development Considerations

The experience and data accumulated during the development of a herbal drug preparation (herbal drug) or herbal medicinal product should form the basis for the setting of specifications. In general, it should be necessary to test the herbal medicinal product for quality attributes uniquely associated with the herbal drug preparation (herbal drug). For example: It may be possible to propose excluding or replacing certain tests on this basis. Some examples are:

- reduced testing for pesticide residues where a herbal drug is grown under strict organic cultivation without pesticides etc and potential contamination from adjacent plantations has been eliminated,

- excluding or reducing tests for microbial limits in herbal extracts or tinctures depending on the ethanol content.

2.3 Pharmacopoeial Tests and Acceptance Criteria

The European Pharmacopoeia contains important requirements pertaining to certain analytical procedures and acceptance criteria which are relevant to herbal drugs, herbal drug preparations and their finished products. Wherever they are appropriate, pharmacopoeial methods should be utilised.

2.4 Periodic / Skip Testing

Periodic or skip testing is the performance of specified tests at release on pre-selected batches and / or at predetermined intervals, rather than on a batch-to-batch basis. This represents a less than full schedule of testing and should therefore be justified and presented to the regulatory authority prior to implementation. This concept may be applicable to, for example, dissolution, residual solvents, and microbiological testing, e.g., for solid oral dosage forms. This concept may therefore sometimes be implemented post-approval in accordance with GMP.

2.5 Release versus Shelf-life Acceptance Criteria

The concept of different acceptance criteria for release versus shelf-life specifications applies to herbal medicinal products only; it pertains to the establishment of more restrictive criteria for the release of a herbal medicinal product than are applied to the shelf-life. Examples where this may be applicable include assay and impurity (degradation product) levels.

2.6 In-process Tests

In-process tests are tests, which may be performed during the manufacture of either the herbal drug preparation (herbal drug) or herbal medicinal product, rather than as part of the formal battery of tests which are conducted prior to release. In-process tests, which are used for the purpose of adjusting process parameters within an operating range, e.g., hardness and friability of tablet cores, which will be coated, are not included in the specification. Certain tests conducted during the manufacturing process, where the acceptance criterion is identical to or tighter than the release requirement, (e.g., pH of a solution) may be used to satisfy specification requirements when the test is included in the specification.

2.7 Alternative Procedures

Alternative procedures are those which may be used to measure an attribute when such procedures control the quality of the herbal drug preparation (herbal drug) or herbal medicinal product to an extent which is comparable or superior to the official procedure. Example: for tablets that have been shown not to degrade during manufacture, it may be permissible to use a spectrophotometric procedure for release as opposed to the official procedure, which is chromatographic. However, the chromatographic procedure should still be used to demonstrate compliance with the acceptance criteria during the shelf- life of the product.

2.8. Evolving Technologies

New analytical technology, and modifications to existing technology, are continuously being developed. Such technologies should be used when they are considered to offer additional assurance of quality, or are otherwise justifiable.

2.9 Reference Standard

A reference standard, or reference material, is a substance prepared for use as the standard in an assay, identification, or purity test. In the case of herbal medicinal products, the reference standard may be a

botanical sample of the herbal drug, a sample of the herbal drug preparation e.g. extract or tincture or a chemically defined substance e.g. a known active constituent, a marker substance or a known impurity. The reference standard has a quality appropriate to its use. For herbal drug preparation (herbal drug) reference standards intended for use in assays, the impurities should be adequately identified and / or controlled, and purity should be measured by quantitative procedure and validated.

- Herbarium samples

  If the herbal drug is not described in the European Pharmacopoeia or in an other Pharmacopoeia of a Member State, a herbarium sample of the whole plant or part of the plant, if the whole plant is a tree etc., is necessary.

2.10 Statistical Concepts

Appropriate statistical analysis should be applied, when necessary, to quantitative data reported. The methods of analysis, including justification and rationale, should be described fully. These descriptions should be sufficiently clear to permit independent calculation of the results presented.

3. GUIDELINES

3.1 Specifications: Definition and Justification

3.1.1. Definition of Specifications

A specification is defined as a list of tests, references to analytical or biological procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a herbal drug preparation (herbal drug) or herbal medicinal product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the herbal drug preparation (herbal drug) and / or herbal medicinal product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are legally binding quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities.

It is possible that, in addition to release tests, a specification may list in-process tests, periodic (skip) tests, and other tests, which are not always conducted on a batch-by-batch basis. In such cases the applicant should specify which tests are routinely conducted batch-by-batch, and which tests are not, with an indication and justification of the actual testing frequency. In this situation, the herbal drug preparation (herbal drug) and / or herbal medicinal product should meet the acceptance criteria if tested.

It should be noted that changes in the specification after approval of the application may need prior approval by the regulatory authority.

3.1.2. Justification of Specifications

The setting of specifications for a herbal drug preparation (herbal drug) and herbal medicinal product is part of an overall control strategy which includes control of raw materials and excipients, in-process testing, process evaluation/validation, stability testing and testing for consistency of batches. When combined in total, these elements provide assurance that the appropriate quality of the product will be maintained. Since specifications are chosen to confirm the quality rather than to characterize the product, the manufacturer should provide the rationale and justification for including and/or excluding testing for specific quality attributes. The following points should be taken into consideration when establishing scientifically justifiable specifications.

- Specifications for Herbal Drugs are linked to:
  botanical characteristics of the plant part
  phytochemical characteristics of the plant part - known therapeutic constituents, toxic constituents (identity, assay, limit tests)
  biological /geographical variation
  cultivation/harvesting/drying conditions (microbial levels, aflatoxins, heavy metals etc)
  pre-/post-harvest chemical treatments (pesticides, fumigants)
  stability of the constituents

- Specifications for Herbal Drug Preparations are linked to:
  quality of the herbal drug (as above)
  method of preparation from the herbal drug
  drying conditions (e.g. microbial levels, residual solvents in extracts)
  stability of the constituents
  microbial stability
  batches used in pre-clinical/clinical testing (safety and efficacy considerations)

- Specifications for Herbal Medicinal Products are linked to:
  quality of the herbal drug preparation
  manufacturing process (temperature effects, residual solvents)
  stability of the active constituents/ formulation in packaging
  batches used in pre-clinical/clinical testing (safety and efficacy considerations)

Specifications should be based on data obtained from lots used to demonstrate manufacturing consistency. Linking specifications to a manufacturing process is important, especially for product-related substances, product-related impurities and process-related impurities. Process changes and degradation products produced during storage may result in heterogeneity patterns, which differ from that observed in the material used during pre-clinical and clinical development. The significance of these alterations should be evaluated.

Due to the inherent complexity of herbal products there is no single stability- indicating assay or parameter that profiles the stability characteristics. Consequently the manufacturer should propose a stability-indicating profile. The result of this stability-indicating profile will then provide assurance that changes in the quality of the product will be detected. The determination of which tests should be included will be product-specific. The manufacturer is referred to the Note for guidance on Stability Testing of existing Active Substances and Related Finished Products (CPMP/QWP/556/96).

3.2 Universal Tests / Criteria

Implementation of the recommendations in the following section should take into account the ICH Guidelines „Text on Validation of Analytical Procedures“ and „Validation of Analytical Procedures: Methodology“.

3.2.1. Herbal drugs

Herbal drugs are a diverse range of botanical materials including leaves, herbs, roots, flowers, seeds, bark etc. A comprehensive specification must be developed for each herbal drug even if the starting material is a herbal drug preparation. In the case of fatty or essential oils used as active substances of herbal medicinal products a specification for the herbal drug is required unless fully justified. The specification should be established on the basis of recent scientific data and should be set out in the same way as the European Pharmacopoeia monographs.
The following tests and acceptance criteria are considered generally applicable to all herbal drug preparations (herbal drugs).

a) Definition: a qualitative statement about the state (e.g. whole, reduced, powdered, fresh, dry) of the herbal drug. It is also important to know the geographical source and the conditions under which the herbal drug is obtained.

b) Characters: a qualitative statement about the organoleptic character and the macroscopic and microscopic botanical characters of the herbal drug. If any of these characteristics change during storage, this change should be investigated and appropriate action taken.

c) Identification: identification testing should optimally be able to discriminate between related species or potential adulterants/substitutes, which are likely to be present. Identification tests should be specific for the herbal drug and are usually a combination of three or more of the following:

Macroscopical characters
Microscopical characters
Thin layer chromatography
Chemical reactions

d) Tests:

- Total Ash
- Ash Insoluble in hydrochloric acid
- Foreign matter
- Water soluble extractive
- Extractable matter
- Particle size: For some herbal drugs intended for use in Herbal teas or solid herbal medicinal products, particle size can have a significant effect on dissolution rates, bioavailability, and / or stability. In such instances, testing for particle size distribution should be carried out using an appropriate procedure, and acceptance criteria should be provided.

- Water content: This test is important as where the herbal drugs are known to be hygroscopic. The acceptance criteria may be justified with data on the effects of moisture absorption. A Loss on Drying procedure may be adequate; however, in some cases (essential-oil containing plants), a detection procedure that is specific for water is required.

- Inorganic impurities, toxic metals: The need for inclusion of tests and acceptance criteria for inorganic impurities should be studied during development and based on knowledge of the plant species, its cultivation and the manufacturing process. Acceptance criteria will ultimately depend on safety considerations. Where justified, procedures and acceptance criteria for sulfated ash / residue on ignition should follow pharmacopoeial precedents; other inorganic impurities may be determined by other appropriate procedures, e.g., atomic absorption spectroscopy.

- Microbial limits: There may be a need to specify the total count of aerobic micro-organisms, the total count of yeasts and moulds, and the absence of specific objectionable bacteria (e.g., *Staphylococcus aureus, Escherichia coli, Salmonella, Pseudomonas aeruginosa*). These should be suitably determined using pharmacopoeial procedures. The European Pharmacopoeia gives guidance on acceptance criteria.

- Mycotoxins: The potential for mycotoxins contamination should be fully considered. Where necessary suitable validated methods should be used to control potential mycotoxins and the acceptance criteria should be justified.

- Pesticides, Fumigation agents, etc.: The potential for residues of pesticides, fumigation agents etc. should be fully considered. Where necessary suitable validated methods should be used to control potential residues and the acceptance criteria should be justified. In the case of pesticide residues the method and acceptance criteria of the European Pharmacopoeia should be applied unless fully justified.

e) Assay:
In the case of herbal drugs with constituents of known therapeutic activity, assays of their content are required with details of the analytical procedure. Where possible, a specific, stability-indicating procedure should be included to determine the content of the herbal drug. In cases where use of a non-specific assay is justified, other supporting analytical procedures should be used to achieve overall specificity. For example, where determination of essential oils is adopted to assay the herbal drug, the combination of the assay and a suitable test for identification (e.g. fingerprint chromatography) can be used.
In the case of herbal drugs where the constituents responsible for the therapeutic activity are unknown assays of marker substances or other justified determinations are required. The choice of marker substance should be justified.

3.2.2. Herbal drug preparations

Herbal drug preparations are also diverse in character ranging from simple, comminuted plant material to extracts, tinctures, oils and resins. A comprehensive specification must be developed for each herbal drug preparation based on recent scientific data.

The following tests and acceptance criteria are considered generally applicable to all herbal drug preparations.

a) Definition: a qualitative statement about the state (e.g. solid, liquid) of the herbal drug preparation. The ratio of the herbal drug to the herbal drug preparation must be stated. If any of these characteristics change during storage, this change should be investigated and appropriate action taken.

b) Characters: a qualitative statement about the organoleptic character of the herbal drug preparation. If any of these characteristics change during storage, this change should be investigated and appropriate action taken.

c) Identification: identification testing should optimally be able to discriminate between related preparations, which are likely to be present. Identification tests should be specific for the herbal drug preparation. Identification solely by chromatographic retention time, for example, is not regarded as being specific; however, a combination of chromatographic tests (e.g. HPLC and TLC-densitometry) or a combination of tests into a single procedure, such as HPLC/UV-diode array, HPLC/MS, or GC/MS may be acceptable.

d) Tests:

- Residual solvents: Refer to the European Pharmacopoeia Monograph *Residual Solvents* for detailed information.

- Water content: This test is important as where the herbal drug preparations are known to be hygroscopic. The acceptance criteria may be justified with data on the effects of hydration or moisture absorption. A Loss on Drying procedure may be adequate; however, in some cases (essential-oil containing preparations), a detection procedure that is specific for water is required.

- Inorganic impurities, toxic metals: The need for inclusion of tests and acceptance criteria for inorganic impurities should be studied during development and based on knowledge of the plant species, its cultivation and the manufacturing process. The potential for manufacturing process to concentrate toxic residues should be fully addressed. Acceptance criteria will ultimately depend on safety considerations. Where justified, procedures and acceptance criteria for sulfated ash / residue on ignition should follow pharmacopoeial precedents; other inorganic impurities may be determined by other appropriate procedures, e.g., atomic absorption spectroscopy.

- Microbial limits: There may be a need to specify the total count of aerobic micro-organisms, the total count of yeasts and moulds, and the absence of specific objectionable bacteria (e.g., *Staphylococcus aureus, Escherichia coli, Salmonella, Pseudomonas aeruginosa*). These limits should comply with the European Pharmacopoeia.

- Mycotoxins: The potential for mycotoxins contamination should be fully considered. Where necessary suitable validated methods should be used to control potential mycotoxins and the acceptance criteria should be justified.

- Pesticides, Fumigation agents, etc.: The potential for residues of pesticides, fumigation agents etc. should be fully considered. Where necessary suitable validated methods should be used to control potential residues and the acceptance criteria should be justified. In the case of pesticide residues the method and acceptance criteria of the European Pharmacopoeia should be applied unless fully justified.

e) Assay:
In the case of herbal drug preparations with constituents of known therapeutic activity, assays of their content are required with details of the analytical procedure. Where possible, a specific, stability-indicating procedure should be included to determine the content of the herbal drug in the herbal drug preparation. In cases where use of a non-specific assay is justified, other supporting analytical procedures should be used to achieve overall specificity. For example, where a visible UV spectrophotometric assay is used e.g. with anthraquinone glycosides a combination of the assay and a suitable test for identification (e.g. fingerprint chromatography) can be used

In the case of herbal drug preparations where the constituents responsible for the therapeutic activity are unknown, assays of marker substances or other justified determinations are required. The appropriateness of the choice of marker substance should be justified.

3.2.3. Herbal medicinal products

The following tests and acceptance criteria are considered generally applicable to all herbal medicinal products:

a) Description: A qualitative description of the dosage form should be provided (e.g., size, shape, colour). If any of these characteristics change during manufacture or storage, this change should be investigated and appropriate action taken. The acceptance criteria should include the final acceptable appearance. If colour changes during storage, a quantitative procedure may be appropriate.

b) Identification: Identification testing should establish the identity of the herbal drug preparation(s) (herbal drug(s)) in the herbal medicinal product and should be able to discriminate between closely related preparations which are likely to be present. Identity tests should be specific for the herbal drug preparation (herbal drug). Identification solely by chromatographic retention time, for example, is not regarded as being specific; however, a combination of chromatographic tests (e.g. HPLC and TLC-densitometry) or a combination of tests into a single procedure, such as HPLC/UV-diode array, HPLC/MS, or GC/MS may be acceptable.

c) Assay:
In the case of herbal drug preparations with constituents of known therapeutic activity, assays of their content are required with details of the analytical procedure. Where possible, a specific, stability-indicating procedure should be included to determine the content of the herbal drug preparation in the finished product. In cases where use of a non-specific assay is justified, other supporting analytical procedures should be used to achieve overall specificity. For example, where a visible UV spectrophotometric assay is used e.g. with anthraquinone glycosides a combination of the assay and a suitable test for identification (e.g. fingerprint chromatography) can be used

In the case of herbal drug preparations where the constituents responsible for the therapeutic activity are unknown, assays of marker substances or other justified determinations are required. The appropriateness of the choice of marker substance should be justified.

d) Impurities:
Organic and inorganic impurities and residual solvents are included in this category. Refer to the ICH Guidelines Impurities in New Drug Products and the European Pharmacopoeia Monograph Residual Solvents for detailed information.

- Impurities arising from the herbal drug preparation (herbal drug) e.g. contaminants such as pesticide/fumigant residues, heavy metals, are normally controlled during the testing of the herbal drug preparation (herbal drug) and it is not necessary to test for these in the herbal medicinal product.

- Similarly, residual solvent arising from the manufacture of the herbal drug preparation (e.g. an extract) need not be controlled in the finished herbal medicinal product provided it is appropriately controlled in the extract specification. However, solvents used for example in tablet coating will need to be controlled in the dosage form.

- Impurities arising from degradation of the herbal drug preparation (herbal drug) should be monitored in the herbal medicinal product. Acceptance limits should be stated for individual specified degradation products, which may include both identified and unidentified degradation products as appropriate, and total degradation products.

  When it has been conclusively demonstrated via appropriate analytical methodology with a significant body of data, that the herbal drug preparation (herbal drug) does not degrade in the specific formulation and under the specific storage conditions proposed in the marketing authorisation, degradation product testing may be reduced or eliminated upon approval by the regulatory authorities.

- Microbial limits: There may be a need to specify the total count of aerobic micro-organisms, the total count of yeasts and moulds, and the absence of specific objectionable bacteria (e.g., *Staphylococcus aureus, Escherichia coli, Salmonella, Pseudomonas aeruginosa*). These limits should be comply with the European Pharmacopoeia.

3.3 Specific Tests / Criteria

In addition to the universal tests listed above, the following tests may be considered on a case by case basis herbal medicinal products. Individual tests/criteria should be included in the specification when the tests have an impact on the quality of the herbal medicinal product for batch control. Tests other than those listed below may be needed in particular situations or as new information becomes available.

3.3.1. Herbal medicinal products

Additional tests and acceptance criteria generally should be included for particular herbal medicinal products. The following selection presents a representative sample of both the herbal medicinal products and the types of tests and acceptance criteria, which may be appropriate. The specific dosage forms addressed include solid oral herbal medicinal products, and liquid oral herbal medicinal products. Application of the concepts in this guideline to other dosage forms is encouraged.

3.3.1.1 The following tests are applicable to tablets (coated and uncoated) and hard capsules.

One or more of these tests may also be applicable to soft capsules and granules.

a) Dissolution / disintegration:

In the case of rapid release herbal medicinal products and without constituents with known therapeutic activity, the test for in-vitro active ingredient release can be omitted.

For rapidly dissolving products containing herbal drug preparations, which are highly soluble throughout the physiological pH range, disintegration testing may sometimes be sufficient. Disintegration testing is most appropriate when a relationship to dissolution has been established or when disintegration is shown to be more discriminating than dissolution. In such cases dissolution testing may not always be necessary, or may be proposed as a skip test. It is expected that development information will be provided to support the robustness of the formulation and manufacturing process with respect to the selection of dissolution vs. disintegration testing.

Single-point measurements are normally considered to be suitable for immediate-release dosage forms. For modified-release dosage forms, appropriate test conditions and sampling procedures should be established. For example, multiple-time-point sampling should be performed for extended-release dosage forms, and two-stage testing (using different media in succession or in parallel, as appropriate) may be appropriate for delayed-release dosage forms. In these cases it is important to consider the populations of individuals who will be taking the herbal medicinal product (e.g., achlorhydric elderly) when designing the tests and acceptance criteria.

Where multiple-point acceptance criteria are necessary, in vitro / in vivo correlation may be used to establish these criteria when human bioavailability data are available for formulations exhibiting different release rates. Where such data are not available, and drug release cannot be shown to be independent of in vitro test conditions, then acceptance criteria must be established on the basis of available batch data. Normally, the permitted variability in release rate at any given time point should not exceed a total numerical difference of +/-10% of the labelled content of herbal drug preparation (herbal drug) (i.e., a total variability of 20%: a requirement of 50 +/- 10% thus means an acceptable range from 40% to 60%), unless a wider range is supported by a bioequivalency study.

b) Hardness/friability: It is normally appropriate to perform hardness and/or friability testing as an in-process control. Under these circumstances, it is normally not necessary to include these attributes in the specification. If the characteristics of hardness and friability have a critical impact on herbal medicinal product quality (e.g., chewable tablets), acceptance criteria should be included in the specification.

c) Uniformity of dosage units: This term includes both uniformity of content and uniformity of mass; a pharmacopoeial procedure should be used. If appropriate, these tests may be performed as in-process controls; the acceptance criteria should be included in the specification.

d) Water content: A test for water content should be included when appropriate. The acceptance criteria may be justified with data on the effects of or water absorption on the herbal medicinal product. In some cases, a Loss on Drying procedure may be adequate; however, a detection procedure which is specific for water (e.g., Karl Fischer titration) is required.

e) Microbial limits: Microbial limit testing is seen as an attribute of Good Manufacturing Practice, as well as of quality assurance. In general, it is advisable to test the herbal medicinal product unless its components are tested before manufacture and the manufacturing process is known, through validation studies, not to carry a significant risk of microbial contamination. It should

be noted that, whereas this guideline does not directly address excipients elsewhere, the principles discussed here may be applicable to excipients as well as to herbal medicinal products. Skip testing may be an appropriate approach in both cases.

Acceptance criteria should be set for the total count of aerobic micro-organisms, the total count of yeasts and moulds, and the absence of specific objectionable bacteria (e.g., *Staphylococcus aureus, Escherichia coli, Salmonella, Pseudomonas*). These should be determined by suitable procedures, using pharmacopoeial procedures, and at a sampling frequency or time point in manufacture which is justified by data and experience. With acceptable scientific justification, it may be possible to propose no microbial limit testing for solid oral dosage forms.

3.3.1.2. Oral liquids

One or more of the following specific tests will normally be applicable to oral liquids and to powders intended for reconstitution as oral liquids.

a) Uniformity of dosage units: This term includes both uniformity of content and uniformity of mass. Generally, acceptance criteria should be set for weight variation, fill volume, and/or uniformity of fill. Pharmacopoeial procedures should be used.

If appropriate, tests may be performed as in-process controls; however, the acceptance criteria should be included in the specification. This concept may be applied to both single-dose and multiple-dose packages.

The dosage unit is considered to be the typical dose taken by the patient. If the actual unit dose, as taken by the patient, is controlled, it may either be measured directly or calculated, based on the total measured weight or volume of drug, divided by the total number of doses expected. If dispensing equipment (such as medicine droppers or dropper tips for bottles) is an integral part of the packaging, this equipment should be used to measure the dose. Otherwise, a standard volume measure should be used. The dispensing equipment to be used is normally determined during development.

For powders for reconstitution, uniformity of mass testing is generally considered acceptable.

b) pH: Acceptance criteria for pH should be provided where applicable and the proposed range justified.

c) Microbial limits: Microbial limit testing is seen as an attribute of Good Manufacturing Practice, as well as of quality assurance. In general, it is advisable to test the herbal medicinal product unless its components are tested before manufacture and the manufacturing process is known, through validation studies, not to carry a significant risk of microbial contamination. It should be noted that, whereas this guideline does not directly address excipients elsewhere, the principles discussed here may be applicable to excipients as well as to herbal medicinal products. Skip testing may be an appropriate approach in both cases. With acceptable scientific justification, it may be possible to propose no microbial limit testing for powders intended for reconstitution as oral liquids.

Acceptance criteria should be set for the total count of aerobic micro-organisms, total count of yeasts and moulds, and the absence of specific objectionable bacteria (e.g., *Staphylococcus aureus, Escherichia coli, Salmonella, Pseudomonas*). These should be determined by suitable procedures, using pharmacopoeial procedures, and at a sampling frequency or time point in manufacture which is justified by data and experience.

d) Antimicrobial preservative content: For oral liquids needing an antimicrobial preservative, acceptance criteria for preservative content may be appropriate. These criteria should be based

on the levels necessary to maintain microbiological product quality throughout the shelf-life. The lowest specified concentration of antimicrobial preservative should be demonstrated to be effective in controlling micro-organisms by using a pharmacopoeial antimicrobial preservative effectiveness test.

Release testing for antimicrobial preservative content should normally be performed. Under certain circumstances, in-process testing may suffice in lieu of release testing. When antimicrobial preservative content testing is performed as an in-process test, the acceptance criteria should remain part of the specification.

Antimicrobial preservative effectiveness should be demonstrated during development, during scaleup, and throughout the shelf-life (e.g., in stability testing: see the Note for guidance on Stability Testing of existing Active Substances and Related Finished Products (CPMP/QWP/556/96), although chemical testing for preservative content is the attribute normally included in the specification.

e) Antioxidant preservative content. Release testing for antioxidant content should normally be performed. Under certain circumstances, where justified by developmental and stability data, shelf-life testing may be unnecessary, and in-process testing may suffice in lieu of release testing. When antioxidant content testing is performed as an in-process test, the acceptance criteria should remain part of the specification. If only release testing is performed, this decision should be reinvestigated whenever either the manufacturing procedure or the container/closure system changes.

f) Extractables: Generally, where development and stability data show no significant evidence of extractables, elimination of this test may be proposed. This should be reinvestigated if the container/closure system changes.

Where data demonstrate the need, tests and acceptance criteria for extractables from the container- closure system components (e.g., rubber stopper, cap liner, plastic bottle, etc.) are considered appropriate for oral solutions packaged in non-glass systems, or in glass containers with non-glass closures. The container/closure components should be listed, and data collected for these components as early in the development process as possible.

g) Alcohol content: Where it is declared quantitatively on the label in accordance with pertinent regulations, the alcohol content should be specified. It may be assayed or calculated.

h) Dissolution: In addition to the attributes recommended immediately above, it may be appropriate (e.g., insoluble herbal drug preparation (herbal drug)) to include dissolution testing and acceptance criteria for oral suspensions and dry powder products for resuspension. The testing apparatus, media, and conditions should be pharmacopoeial, if possible, or otherwise justified. Dissolution procedures using either pharmacopoeial or non-pharmacopoeial apparatus and conditions should be validated.

Single-point measurements are normally considered suitable for immediate-release dosage forms. Multiple-point sampling, at appropriate intervals, should be performed for modified-release dosage forms. Acceptance criteria should be set based on the observed range of variation, and should take into account the dissolution profiles of the batches that showed acceptable performance in vivo. Developmental data should be considered when determining the need for either a dissolution procedure or a particle size distribution procedure.

Dissolution testing may be performed as an in-process test, or as a release test, depending on its relevance to product performance. The discussion of dissolution for solid oral dosage forms (above), and of particle size distribution (immediately following), should also be considered here.

i) Particle size distribution: Quantitative acceptance criteria and a procedure for determination of particle size distribution may be appropriate for oral suspensions. Developmental data should be considered when determining the need for either a dissolution procedure or a particle size distribution procedure for these formulations.
Particle size distribution testing may be performed as an in-process test or as a release test, depending on its relevance to product performance. If these products have been demonstrated during development to have consistently rapid drug release characteristics, exclusion of a particle size distribution test from the specification may be proposed.

Particle size distribution testing may also be proposed in place of dissolution testing; justification should be provided. The acceptance criteria should include acceptable particle size distribution in terms of the percent of total particles in given size ranges. The mean, upper, and / or lower particle size limits should be well defined.

Acceptance criteria should be set based on the observed range of variation, and should take into account the dissolution profiles of the batches that showed acceptable performance in vivo, as well as the intended use of the product. The potential for particle growth should be investigated during product development; the acceptance criteria should take the results of these studies into account.

j) Redispersibility: For oral suspensions, which settle on storage (produce sediment) acceptance criteria for redispersibility may be appropriate. Shaking may be an appropriate test. The procedure (mechanical or manual) should be indicated. Time required to achieve resuspension by the indicated procedure should be clearly defined. Data generated during product development may be sufficient to justify skip lot testing, or elimination of this attribute from the specification.

k) Rheological properties: For relatively viscous solutions or suspensions, it may be appropriate to include rheological properties (viscosity) in the specification. The test and acceptance criteria should be stated. Data generated during product development may be sufficient to justify skip lot testing, or elimination of this attribute from the specification.

l) Specific gravity: For oral suspensions, or relatively viscous or non-aqueous solutions, acceptance criteria for specific gravity may be appropriate. Testing may be performed as an in-process control.

m) Reconstitution time: Acceptance criteria for reconstitution time should be provided for dry powder products, which require reconstitution. The choice of diluent should be justified. Data generated during product development may be sufficient to justify skip lot testing or elimination of this attribute from the specification.

n) Water content: For oral products requiring reconstitution, a test and acceptance criterion for water content should be proposed when appropriate. Loss on drying is generally considered sufficient if the effect of absorbed moisture vs. water of hydration has been adequately characterised during the development of the product. In certain cases (e.g. essential-oil containing preparations) a more specific procedure (e.g., Karl Fischer titration) is required.

4. GLOSSARY

Herbal medicinal products: See Note for guidance on quality of herbal medicinal products (EMEA/HMPWP/9/99).

Herbal drugs: See Note for guidance on quality of herbal medicinal products (EMEA/HMPWP/9/99).

Herbal drug preparations: See Note for guidance on quality of herbal medicinal products (EMEA/HMPWP/9/99).

Acceptance criteria: Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures.

Fixed Combination: A herbal medicinal product which contains more than one herbal drug preparation or herbal drug.

Degradation product: Degradation products are molecular variants resulting from changes in the desired product or product-related substances brought about over time and/or by the action of, e.g., light, temperature, pH, water, or by reaction with an excipient and/or the immediate container/closure system. Such changes may occur as a result of processing and/or storage (e.g. deamidation, oxidation, aggregation, proteolysis). Degradation products may be either product-related substances or product-related impurities.

Impurity: (1) Any component of the herbal drug preparation (herbal drug) which is not the entity defined as the herbal drug preparation (herbal drug). (2) Any component of the herbal medicinal product that is not the entity defined as the herbal drug preparation (herbal drug) or an excipient in the herbal medicinal product.

Identified impurity: An impurity for which a structural characterisation has been achieved.

Quality: The suitability of either a herbal drug preparation (herbal drug) or herbal medicinal product for its intended use. This term includes such attributes as the identity, strength, and purity of the article.

Reagent: A substance other than a starting material or solvent, which is used in the manufacture of a herbal drug preparation (herbal drug).

Solvent: An inorganic or an organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of a herbal drug preparation (herbal drug) or the manufacture of a herbal medicinal product.

Specification: A list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a herbal drug preparation (herbal drug) or herbal medicinal product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the herbal drug preparation (herbal drug) and / or herbal medicinal product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are binding quality standards that are agreed to between the appropriate governmental regulatory agency and the applicant.

Specific test: A test which is considered to be applicable to particular herbal drug preparation (herbal drug)s or particular herbal medicinal products depending on their specific properties and/or intended use.

Specified impurity: An identified or unidentified impurity that is selected for inclusion in the herbal drug preparation (herbal drug) or herbal medicinal product specification and is individually listed and

limited in order to assure the quality of the herbal drug preparation (herbal drug) or herbal medicinal product.

Unidentified impurity: An impurity which is defined solely by qualitative analytical properties, (e.g., chromatographic retention time).

Universal test: A test which is considered to be potentially applicable to all herbal drug preparation (herbal drug)s, or all herbal medicinal products; e.g., appearance, identification, assay, and impurity tests.

2.8. Draft Comments on the CPMP Note for guidance on stability testing for a Type II variation to a marketing authorisation - (EMEA/HMPWG/21/99)

The working group suggests amending the CPMP Note for guidance on stability testing for a Type II variation to a marketing authorisation (CPMP/SWP/576/96) in order to encompass herbal medicinal products in the scope of the guideline.

The following changes are proposed and appear in bold italic:

Preamble

Fifth paragraph
It is suggested adding "herbal drug preparations" so as to read "This guideline is applicable ***to herbal drug preparations***, chemical active substances and related finished products and not to...biotechnology".

Section 1.a)
First paragraph
It is suggested adding "***route of manufacturing***" after "route of synthesis".

Fifth paragraph
It is suggested adding another example in the text so as to read "In the case of variations of the final step of the manufacturing process of the active substance (e.g. new solvent, ***conditions of drying***, conditions of crystallisation), additional stability data on the finished product...impact on stability".

Section 1.b)
First paragraph
It is suggested adding "***route of manufacturing***" after "route of synthesis".

Second paragraph
It is suggested adding "***route of manufacturing***" after "route of synthesis".

Third paragraph
It is suggested adding "***manufacturing***" after "synthesis" and adding "level of micro-organisms" in the text so as to read "(e.g. physical characteristics, increase of the level ***of micro-organisms or*** of degradation products)".

3. SAFETY OF HERBAL MEDICINAL PRODUCTS

3.1. Final Comments on Notice to Applicants Volume 2B Part IC2 "Expert report on toxico-pharmacological documentation" and Part III "Toxico-pharmacological documentation" - (EMEA/HMPWG/10/99)

- **NTA 2B, Part I C 2: Expert Report on toxico-pharmacological documentation**
  NTA 2B, Part III "Toxico-pharmacological Documentation"

These parts are found adequate for herbal medicinal products. It was confirmed that the Expert Report has to address all aspects of Part 3 of the Annex to Council Directive 75/318/EEC of 20 May 1975 'Toxicological and pharmacological tests'.

3.2. Proposal for a Note for guidance on non-clinical testing of herbal drug preparations with long-term marketing experience - guidance to facilitate mutual recognition and use of bibliographic data - (EMEA/HMPWG/11/99)

The working group finalised the following proposal for a Note for guidance on non-clinical testing of herbal drug preparations with long term marketing experience. The group acknowledged the need to update this document taking into account comments expected from the CPMP Safety Working Party, and in view of the anticipated finalisation of the CPMP Note for guidance on non-clinical testing of substances with long-term marketing experience -old substances- (CPMP/SWP/799/95).

INTRODUCTION

Article 4 point 8 a) ii) of Council Directive 65/65/EEC makes it clear that the applicant shall not be required to provide the results of pharmacological and toxicological tests if he can demonstrate by detailed reference to published scientific literature presented in accordance with the second paragraph of Article 1 of Council Directive 75/318/EEC that the constituent(s) of the medicinal product have a well-established medicinal use, with recognised efficacy and an acceptable level of safety. This regulation in no way relaxes the requirements of proof of safety set out by the Annex to Council Directive 75/318/EEC. All aspects must be covered by appropriate bibliographic data and the expert report.
Published non-clinical tests for well-established herbal drug preparations are often incomplete or not in accordance with today's state of the art. Well-presented clinical experience (with regard to the time and extent of use in humans) as well as post-marketing experience gained by wide spread use in humans contribute to the avoidance of unnecessary tests in animals. Protection of animals should be taken into consideration when requesting non-clinical testing of well-established herbal drug preparations (86/609/EEC). Studies that do not agree with the current state of the art (e.g. GLP-conformity), should be judged for credibility; subsequent demands that could lead to a "blind" repetition of animal experiments should be avoided. In particular, it should be assessed whether the observed effects in animals studies would modify the benefit/risk assessment and would lead to a negative decision for the granting of a Marketing Authorisation.

In cases of reasonable suspicion, additional appropriate non-clinical tests can be requested.

NON-CLINICAL TESTING

Where there is sufficient experience available in humans, single dose and repeated dose toxicity, immunotoxicity as well as local tolerance testing of well-established herbal drug preparations is not necessary. Likewise, pharmacological tests including safety pharmacology and pharmacokinetics are not necessary. The expert report must address these aspects and give the grounds why the documented medical experience justifies a safe use of the herbal drug preparation.

Non-clinical testing of well-established herbal drug preparations should be directed towards the study of effects that are difficult, even impossible to detect clinically. These effects would include toxicity to reproduction, genotoxicity and carcinogenicity.

Reproductive toxicological investigations regarding fertility are generally not necessary, insofar as there are no grounds for suspicion that would necessitate testing.

The reproductive toxicological potential with regard to embryo-foetal and peri-post-natal development is to be clarified. Reproductive toxicity data are available for many old substances, however, these data are often not reliable. A repetition of the tests is only justified in cases in which the significance of the results is not clear and there are grounds for suspicion. Reproductive toxicological tests in animals are not necessary if one of the following criteria is fulfilled:

- Results from epidemiological data of adequate power or post-marketing safety studies are available.
- Results from investigations in pregnant women and neonates are present.
- The medicinal product is not intended to be used in women of child-bearing age or during pregnancy and lactation.

The clinical Expert Report should justify the distinction made between women of child-bearing age and pregnancy.

The genotoxic potential of herbal drug preparations should be clarified.

A repetition of the studies is only required in cases in which the significance of the results is unclear or they yield grounds for suspicion. Positive findings for one herbal drug preparation or for substances from one chemical class can frequently be extrapolated to another herbal drug preparation without necessitating further testing.

It is recommended to first perform *in vitro* tests for substances in which the genotoxicity tests are insufficient. Substances with negative results *in vitro* also exhibit negative results *in vivo* in the majority of cases. In cases in which positive results in vitro are present, these are to be clarified by way of appropriate investigations, mainly *in vivo*. (CPMP Note for guidance on genotoxicity: a standard battery for genotoxicity testing of pharmaceuticals (CPMP/ICH/174/95), CPMP Note for guidance on genotoxicity: guidance on specific aspects of regulatory genotoxicity tests for pharmaceuticals (CPMP/ICH/141/95) and OECD 1995).

It is appropriate to assess genotoxicity initially in a bacterial reverse mutation test using a test battery of different bacterial strains and metabolic activation (s. CPMP/ICH and OECD Guidelines). This test has been shown to detect relevant genetic changes and the majority of genotoxic rodent carcinogens. If positive results can not be clearly attributed to specific constituents with a well-established safety-profile (e.g. Quercetin) additional *in vitro* and, if necessary, *in vivo* studies should be performed. A co-operative approach is encouraged to investigate herbal drug preparations with the same specification.

Carcinogenicity studies are not needed in cases where there is no suspicion for a carcinogenic potential (Council Directive 75/318/EEC of 20 May 1975, Part 3, IIE. Carcinogenic Potential; CPMP Note for guidance on the need for carcinogenicity studies of pharmaceuticals (CPMP/ICH/140/95), CPMP Note for guidance on carcinogenicity: testing for carcinogenicity of pharmaceuticals (CPMP/ICH/299/95), Addendum to Note for guidance on dose selection for carcinogenicity studies of pharmaceuticals: addition of a limit dose and related notes (CPMP/ICH/366/96)).

Even a positive suspicion of a carcinogenic effect of an well-established herbal drug preparation does not necessarily require a study to be performed. The following considerations should be included in the assessment:

- Is the suspicion based on positive results of genotoxicity studies and can it be clarified in further genotoxicity studies, mainly *in vivo?*
- Is there sufficient epidemiological experience in humans that could refute the suspicion?

EXPERT REPORT

The expert is obliged to point out the necessity or not of non-clinical testing for the herbal drug preparation. Plausible presentation of the facts contributes to the acceptance of the application for marketing authorisation and facilitates the evaluation performed by the authorities.
The expert should discuss available published toxicological data on closely related herbal drug preparations, different parts of the plant, data on related species of the same genus or plant family. If there are toxicological data on well-defined constituents of a herbal drugs preparation, the expert should discuss the relevance of these data for the safety-assessment of the herbal drug preparation.

4. EFFICACY OF HERBAL MEDICINAL PRODUCTS

4.1. Final Comments on Notice to Applicants Volume 2B, Part I B 1: Summary of Product Characteristics - (EMEA/HMPWG/12/99)

- **NTA 2B, Part I B 1: Summary of Product Characteristics**

The requirements are found adequate for herbal medicinal products. It was clarified that marker substances will not be declared in section 2 of the SPC, Qualitative and Quantitative Composition.

The working group provided in July 1998 the CPMP QWP with comments on the draft guidance for revision of the SPC sections 2, 3 and 6, as part of the update of the guidance on SPCs undergone by the CPMP.

4.2. Final Comments and proposals for revision of Part 4 of Annex to Council Directive 75/318/EEC of 20 May 1975 "Clinical documentation" - (EMEA/HMPWG/13/99)

The working group offers the following comments, including some suggestions for amendment.

The group found the terminology not well adapted to bibliographic applications. The group discussed the issue of the broader definition of a clinical trial as provided in the text with comparison to the definitions laid down in the Good Clinical Practice (GCP) Directive for "clinical trials" and "non-interventional studies". The group wondered whether epidemiological studies would be covered by the proposed definition. To clarify this matter, the group agreed to suggest the introduction of a new paragraph stating:
"***Documentation on experience in the form of epidemiological studies can be taken into account in bibliographical applications for well-established medicinal products***".

Section A. General requirements
It is suggested to modify the last sentence of the first paragraph as follows: "***Consequently, an essential requirement is that all clinical data should be communicated, both favourable and unfavourable***".

Section C. Presentation of results
In section C.1., the group agreed to introduce ***a statement on the need for identity or essential similarity between the product tested in the clinical trials and the product intended for marketing***. The precise composition and specification of the product investigated must be provided. For compounds with well-known therapeutic activity, the Expert Report must explain the relevance of any data submitted which concern a product different from the product intended for marketing. It is indeed up to the Expert to judge that the differences are small enough to consider that the product studied is similar to the product which will be granted a marketing authorisation.

In section C.2., the group also felt the need for ***a paragraph in the text which clearly mentions that the Expert Report must pay particular attention to any missing information in a bibliographical application*** for a well-established product. Justification must be given why demonstration of efficacy can be supported although some studies are lacking.

The group recognised that, beside the fact that there are mandatory requirements, which are to be met in principle, it is known that some of the data required are not available from bibliographic sources. It was stated that in the case of well-established herbal medicinal products the need for new clinical studies should not only derive from formal criteria. The expected benefit of additional studies for the safeguard of public health should be considered in each particular case. The group highlighted that this issue is linked to the claimed indication(s) and that more severe criteria for the acceptability of clinical data presented/missing data would be used in the case of "modern" indication, e.g. hypercholesterolemia.

Section D.1. Pharmacodynamics
The group reviewed this section and considered that the paragraph stating that "the demonstration of pharmacodynamic effects in human beings shall not in itself be sufficient to justify conclusions regarding any particular potential therapeutic effect" is an essential remark. This statement fully applies to herbal medicinal products. In some circumstances, where a well-established use is adequately documented, pharmacodynamic data may contribute to an acceptance of bibliographic applications for herbal medicinal products.
It was recognised that the demonstration of the mode of action of an herbal medicinal product often cannot be clarified by the applicant and that the documentation of efficacy, in those cases, should be a priority.

Section D.2. Pharmacokinetics

The issue of the request for pharmacokinetic data for herbal medicinal products, and in particular for complex mixtures with constituents of unknown therapeutic activity was discussed. *Ginkgo biloba* extract was mentioned as a relevant example of a complex active substances mixture in which case pharmacokinetic data should not be required. Requirements for pharmacokinetic data should always be realistic and relate to the Public Health and safety risks associated with the product. When there are safety concerns (example of photosensitisation in the case of Hypericum) pharmacokinetic data are useful to provide safety margins.

The group concluded its discussion on pharmacokinetic by stating that, for well-established medicinal products where the efficacy is based on bibliographical documentation, pharmacokinetic data would not be required unless there are ground for safety concerns from the presence of one or several constituents. If there is a constituent with known therapeutic activity and a narrow therapeutic range, pharmacokinetic data will be required. The Expert Report should carefully address all these issues.

Section E. Bioavailability/bioequivalence

The same principle as defined above for pharmacokinetic data shall apply for bioavailability/bioequivalence data. The group would also recommend the introduction of ***a statement on the need to provide bioavailability data for galenic preparations with modified release***, in view of the difficulty to use bibliographical data in such case.

Section F. Clinical efficacy and safety

The group reported some elements, which make it difficult for applicants to conduct proper comparative clinical trials. The blinding feature of a clinical trial cannot always be respected, for example in the case of essential oils with strong smell.

Section F.5 on vaccines and serums was considered irrelevant for herbal medicinal products. The group indicated that the principles of points 6 to 9 (safe use) apply to bibliographical applications and that these points should be underlined in the Expert Report for each individual product.

Section G. Documentation for applications in exceptional circumstances

This section was considered to be not relevant to well-established herbal medicinal products.

Section H. Post-marketing experience

This section was, on the contrary, felt to be of particular importance for herbal medicinal products.
The group indicated that applicants should put a special emphasis to this issue for individual products and for all related products originating from the same herbal drug.

As a conclusion, the group recognised the validity of the framework provided by this document. The basic concepts and general rules should apply to bibliographical data, but taking into account the specific comments made by the group.

4.3. Final Note for guidance on fixed combinations of herbal medicinal products with long-term marketing experience - guidance to facilitate mutual recognition and use of bibliographic data - (EMEA/HMPWG/15/99)

The working group prepared the following Note for guidance on fixed-combinations.

Note for guidance on fixed combinations of herbal medicinal products with long-term marketing experience - guidance to facilitate mutual recognition and use of bibliographic data

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INTRODUCTION

Fixed combinations of herbal medicinal products are in widespread use in Phytotherapy. This Note for guidance is intended to contribute to a rational assessment of the safety and efficacy of such fixed combinations, therefore guaranteeing the availability of such rational fixed combinations to consumers and medical doctors.

Note for guidance concerning the application of section C.6 Part 4 of the Annex to Directive 91/507/EEC as amended, with a view to the submission of an application for a marketing authorisation for a well-established herbal medicinal product. This guideline should be read in conjunction with current EU guidelines.

1. JUSTIFICATION

Applicants will be required to justify the particular combination of active substances (herbal drugs/herbal drug preparations) proposed. Fixed combination products will only be considered acceptable if the proposed combination is based on valid therapeutic principles.

For any individual fixed combination it is necessary to assess the potential advantages in the therapeutic situation against possible disadvantages, in order to determine whether the product meets the requirements with respect to efficacy and safety.

1.1 Potential advantages of fixed combinations include one of the following:

a) an improvement of the benefit/risk assessment due to:

i. the addition or potentiation of therapeutic activities of their substances, which results in:

- a level of efficacy similar to the one achievable by each active substance used alone at higher doses than in combination, but associated with a better safety profile

or

- a level of efficacy above the one achievable by a single substance with an acceptable safety profile.

ii. the counteracting by one substance of an adverse reaction produced by another one.

b) a simplification of therapy

A fixed combination of active substances is acceptable if it achieves a similar level of efficacy to the one achievable by each active substance used alone at higher doses than in combination but improves patient compliance (e.g. simplification of posology, improvement of organoleptic properties).

1.2 Possible disadvantages of fixed combinations include:

i. the fact that even a combination which meets the needs of the average patient is unlikely to be ideally adjusted for the needs of each individual patient;

ii. the addition of the different adverse reactions specific to each substance.

1.3 General rules

Combinations, in principle, may not be considered rational if the duration of action of the substances differ significantly. This may not necessarily apply where it can be shown that the combination is clinically valid despite differences in this respect, e.g. if one substance is intended to enhance absorption of the other or where the substances are intended to exert their effects successively.

Each substance of the fixed combination must have documented contribution within the combination.

The inclusion of a substance to counteract an adverse reaction of another substance may be considered justified, but only if the adverse reaction is a commonly occurring one.

The inclusion of a substance intended to produce unpleasant adverse effects as a means of preventing abuse is undesirable.

Substances having a critical dosage range or a narrow therapeutic index are unlikely to be suitable for inclusion in fixed combinations.

2. INDICATIONS

The indications claimed for a fixed-combination medicinal product should be such that the presence of each active substance makes a contribution to the claimed effect. The product should be formulated so that the dose and proportion of each substance present is appropriate for the intended use.

An indication must be a well-recognised disease state, modification of a physiological state, dysfunctional state, syndrome or pathological entity. The individual substances of a fixed combination may be intended to relieve simultaneously different symptoms of such a disease state. In this case, it should be a prerequisite that these symptoms regularly occur simultaneously in a clinically relevant intensity and for a relevant period of time. It will not be proper to regard each individual symptom as an indication for the fixed combination, since it may also occur in other diseases and for treating this symptom alone the other substances may be irrelevant.

3. PHARMACODYNAMIC AND PHARMACOKINETIC DATA

The possibility of interactions between the active substances should always be considered and discussed in the expert report. When data on interactions are available, they have to be submitted with the dossier and discussed by the expert.

3.1 Pharmacodynamic data

The expert report should address the question of the addition or the potentiation of the pharmacodynamic effects of the various active substances (herbal drug/herbal drug preparation) as far as data are available.

3.2 Pharmacokinetic data

The expert report should address the question of the various pharmacokinetic parameters of each active substance (herbal drug/herbal drug preparation) as far as data are available.

4. SAFETY AND EFFICACY

It is permissible to distinguish between the extent of the studies required in the case of those fixed combinations which correspond closely to combinations which are already in widespread use[1], provided these are thoroughly and reliably documented, and those studies required in the case of those combinations which are essentially new :

a) When the fixed combination corresponds closely to combinations that are already in widespread use a well founded bibliographical data analysis should be submitted. Provided that the respective bibliographic data on the fixed combination and on its ingredients are thoroughly and reliably documented, this analysis may be helpful in reducing the amount of clinical trials to be performed[2] and could facilitate the selection of doses for each substance and the proposed dose range of the fixed combination.

[1] Even if the quantitative composition of usually combined substances (herbal drug or herbal drug preparations) has been adjusted to reflect the current scientific knowledge, the combination itself still may be classified as well known.

[2] In some cases this analysis may be sufficient for the justification of the efficacy and safety of the fixed combination of the herbal medicinal products.

b) When the fixed combination is essentially new (active substances not usually combined, unusual quantitative composition of usually combined substances or one substance entirely new), the data needed are similar to a new chemical entity in the situation where the fixed combination is to be proposed. Existing experience with the substances should be taken into account.

4.1 Safety aspects

Where there are grounds to expect that a fixed-combination product may be substantially more harmful or give rise to much more frequent adverse effects than any individual active substances given alone, the applicant should provide evidence that this does not occur in therapeutic use, or that the advantages of the combination e.g. increased efficacy, outweigh such disadvantages.

This should be read in conjunction with the draft Note for guidance on non-clinical testing of herbal drug preparations with long-term marketing experience - guidance to facilitate mutual recognition and use of bibliographic data (EMEA/HMPWG/11/99).

4.2 Therapeutic data

The efficacy and the safety of use of the fixed combination must be evident from clinical trials or bibliographic data submitted by the applicant.

This should be read in conjunction with the draft Points to consider on the evidence of safety and efficacy required for well-established herbal medicinal products in bibliographic applications (EMEA/HMPWG/23/99).

4.3 Composition and dosage regimen

The proposed dosage regimen must be justified in the clinical expert report.

The dosage of each active substance within the fixed combination must be such as the combination is safe and effective for a significant population subgroup and the benefit/risk assessment of the fixed combination is equal or exceeds the one of each of its active substances taken alone.

Where active substances are intended to relieve simultaneously different symptoms or to prevent different diseases, selected doses of each active substance are often those commonly used for the treatment of each symptom or the prevention of each disease.

4.4. Draft Points to consider on the evidence of safety and efficacy required for well-established herbal medicinal products in bibliographic applications - (EMEA/HMPWG/23/99)

The working group prepared the following Points to consider.

Points to consider on the evidence of safety and efficacy required for well-established herbal medicinal products in bibliographic applications

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1. Legal background

Volume 2A of the Notice to Applicants clarifies the legal background of bibliographic applications as follows:

1.1. Where the constituent or constituents of the medicinal product have a ***well established medicinal use***, with ***recognised efficacy*** and an ***acceptable level of safety***, demonstrated by detailed references to **published literature** presented in accordance with second paragraph of Article 1 of Directive 75/318/EEC, an application (so called "bibliographical") for marketing authorisation may be submitted in accordance with Directive 65/65/EEC, article 4.8.(a)ii.

1.2. An applicant wishing to use Article 4.8 (a)ii) of Directive 65/65/EEC must fully satisfy all the ***requirements*** of Article 1 of Directive 75/318/EEC as well as those of Directives 65/65/EEC and 75/319/EEC as amended, in effect, submit a "***complete" application***.

1.3. Directive 75/318/EEC Article 1 states that „where pursuant to point 8(a) of Article 4, second paragraph, of Directive 65/65/EEC, references to published data are submitted, the provisions of this Directive (i.e. Directive 75/318/EEC) shall ***apply in like manner***." In such cases, the full article or reference should be supplied, with necessary translations. Moreover, the Expert Reports must clearly state the grounds for using published references under the conditions set out in Directive 75/318/EEC. This would include the completion of all of the tabular formats provided in „The rules governing medicinal products in the European Union, Volume 2B Notice to Applicants: Presentation and content of applications" where relevant, unless there is a justification that the study is not relevant for the medicinal product. The impurity/related substances profile and the decomposition products arising during storage must be clearly indicated in order to allow assessment of appropriate efficacy and safety.

1.4. In the event that neither detailed reference to published literature, nor appropriate justification is available to cover all the requirements, the applicant must supplement the missing data with ***appropriate additional studies***.
Scientific monographs on certain substances (e.g. those drafted by the European Scientific Co-operative on Phytotherapy (ESCOP) and the World Health Organisation (WHO) for herbal drugs) offer a valuable and updated overview on published scientific literature, which together may be used in support of the demonstration of the safety and efficacy of a medicinal product in a bibliographical application in accordance with Article 4.8 (a)ii. These monographs may help to avoid duplication of work and bring about gradual harmonisation in the evaluation of medicinal products, e.g. herbal medicinal products. Therefore the Commission and Member States recommend that both applicants and competent authorities should make use of these monographs.

1.5. It should be noted that summary assessment reports such as the EPAR for Community marketing authorisations or evaluation reports on Maximum Residue Limits which are made publicly available by competent authorities for reasons of transparency would generally not be considered to supply sufficient information to meet the requirements of Directive 75/318/EEC.

2. Points to be considered and recommendations for implementation of the legal requirements in marketing authorisations for well-established herbal medicinal products

The interpretation of open terms such as "well established medicinal use", "recognised efficacy" (Council Directive 65/65/EEC, Art. 4.8a) ii) and "in like manner" have lead to conflicting interpretation within the Community. Herbal medicinal products present several particularities that are relevant for the interpretation of these open terms:

2.1. Many herbal medicinal products have been used as medicinal products for several decennies or even hundreds of years. This long-term use has created a comprehensive body of experience laid down in published literature. Systematic use of published literature will be a contribution to avoid animal experiments in preclinical testing and reduce the number of clinical trials in humans.

2.2. Herbal drug preparations are complex biological mixtures and the therapeutic effect can, in most cases, not be related to one single constituent. A statement on the safe use of a herbal drug preparation is not possible without detailed information on quality aspects including production.

2.3. Herbal medicinal products are often used in the OTC treatment of minor illness. Most of these medicinal products are available without medical prescription. In some Member States, however, herbal drug preparations are widely prescribed by medical doctors whereas in others they are practically non-existent in medical prescription.

2.4. Whereas a considerable part of the citizens of the European Union has a preference for using herbal medicinal products because they are of natural origin and are believed to have fewer undesirable effects there is a more sceptical attitude towards them in modern medicine and clinical pharmacology. These differences in perspective have to be balanced in a scientific assessment.

2.5. In some Member States herbal preparations had a legal status different from medicinal products. Most of the herbal drugs have access to the market in the form of crude botanical drugs without being subject to CD 65/65/EEC. These uses appear to have generated information on the safety and efficacy of herbal medicinal products that should be used in assessment.

The ad hoc Working Group on Herbal Medicinal Products has prepared guidance and proposals for modifications of existing legislation. Reference is made to these texts for interpretation of the Annex to Council Directive 75/318/EEC.

In the interpretation of the open terms in Council Directive 65/65/EEC and Article 1 of Council Directive 75/318/EEC and in the preparation of new legislation on well-established herbal medicinal products the following aspects should be considered:

3. Well-established use

3.1. According to WHO, a "*long history of medical use*" may be defined, depending on the history of a given country [or community], as not less than several decades. The particular context of the medical, historical, spiritual, ethnological/cultural backgrounds of the given community have to be respected in this classification.
Well-established use implies that a sufficient number of patients were treated by the concerned product or by a product essentially similar to the concerned product.

3.2. Herbal drug preparations that have a long history of medical use are expected to have useful bibliographic data and information published in official pharmacopoeias and scientific reference textbooks. The inclusion of a herbal drug in official pharmacopoeias of different Member States or the inclusion in scientific reference textbooks may contribute to substantiate a well-established medicinal use.

3.3. In abridged applications, a well-established medicinal use can be accepted if a herbal medicinal product is essentially similar to one authorised as a medicinal product in the European Community for more than 6/10 years. Essential similarity requires the same qualitative and quantitative composition in terms of active substance(s) and the same pharmaceutical form. The concept also applies to different oral forms for immediate release. Appropriate data on bioavailability may be required, if necessary. In bibliographic applications these criteria may be useful in order to decide if published literature on one herbal medicinal product can be used in the assessment of another herbal medicinal products. Because complex biological mixtures, e.g. herbal extracts produced by different manufacturers, are never identical the following aspects must be considered: Herbal drug preparations used as active substance can be considered as sufficiently identical if the specification is the same and no relevant differences in the manufacturing process exists. The identity of specification and manufacturing process is particularly important in those cases

where bibliographic data on highly purified extracts are presented or where a new method of preparation of an extract is used. In the case of "classical" herbal drug preparations such as tinctures and extracts described in pharmacopoeias and used for long time, a "comprehensive" specification will not be available from published literature in most cases. For these preparations the starting material, the extraction solvent and the drug/extract ratio must be identical. Reference is made to the Note for guidance on quality of herbal medicinal products (EMEA/HMPWG/9/99), Chapter A 1 and A 2. If there are reasons to expect a different pharmacological or toxicological profile, additional data and an update of the specification and/or appropriate data on bioavailability may be necessary.

3.4. It should be taken into account that herbal medicinal products had a different legal status in some Member states. Herbal drugs may have a widespread use over a long time without being finished medicinal products. In those cases, the expression "medicinal use" in a) and b) should include information on such parallel uses as well.

4. Recognised efficacy

The "entry-point" to bibliographic applications, i.e. the possibility to use Art. 4.8 (a) ii of Council Directive 65/65/EEC, and the assessment of the data presented in the application must be differentiated. The term "recognised efficacy" should not be confused with "accepted efficacy" in the marketing authorisation procedure.

It is important that in the case of well-established herbal medicinal products the requirements for proof of efficacy and the documentation required to support the indicated claims should depend on the nature and the level of the indication(s). For treatment of minor disorders a lower level of evidence may be adequate, especially when the extent of long-term use, the experience with that particular herbal medicinal product and supportive pharmacological data are taken into account. The level of evidence and the grading of recommendations must correspond to the nature of the disease that is to be treated. The therapeutic alternatives available, the risks of a delayed or insufficient treatment and the risks of the herbal drug preparation have to be taken into account.

In the assessment of well-established herbal medicinal products all bibliographic documents should be taken into consideration. Old reports should be judged for their credibility. The following type of documents could be used: controlled clinical trials, other clinical trials, cohort or longitudinal studies, observational (non-interventional) studies, case-control-studies, other collections of single cases allowing a scientific evaluation, scientifically documented medical experience, for example scientific literature and expertise from scientific medical associations. These bibliographic data must be assessed in order to establish if they can demonstrate a sufficient level of safety and efficacy. When studying clinical safety and efficacy by using bibliographic references, the following aspects should be evaluated: the number of patients, specific diagnosis, preparation used (see point 1.3), dosage, duration of administration, criteria for evaluation (e.g. improvement of symptoms), and applicable statistical analysis. The following factors will increase the relevance and credibility of published data[1]:

a) if there are multiple studies conducted by different investigators and/or independent literature reports where the findings across studies / reports are consistent;
b) if there is a high level of detail in the published reports, including clear and adequate descriptions of statistical plans, analytic methods (prospectively determined), and study endpoints, and a full accounting of all enrolled patients;
c) if there are clearly appropriate endpoints that can be objectively assessed and are not dependent on investigator judgement (e.g., overall mortality, blood pressure, or microbial eradication). Such endpoints are more readily interpreted than more subjective endpoints such as relief of symptoms.
d) if there are robust results achieved by protocol-specified analyses that yield a consistent conclusion of efficacy and do not require selected post hoc analyses such as covariate

[1] based on FDA May 1998: Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products

adjustment, subsetting, or reduced data sets (e.g., analysis of only responders or compliant patients, or of an "eligible" or “evaluable” subset).

e) if there is a conduct of studies by groups with properly documented operatingprocedures and a history of implementing such procedures effectively.

A review of the literature should identify the current level of evidence of the safe and effective use of a herbal medicinal product. The definitions of the types of evidence and the grading of recommendations set out in the following tables originate from the US Agency for Health Care Policy and Research (AHCPR) and WHO. They may be considered as guidance:

Levels of evidence

Level	*Type of evidence*[2]
Ia	*Evidence obtained from meta-analysis of randomized controlled trials*
Ib	*Evidence obtained from at least one randomized controlled trial*
IIa	*Evidence obtained from at least one well-designed controlled study without randomization*
IIb	*Evidence obtained from at least one other type of well- designed quasi-experimental study*
III	*Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies*
IV	*Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities*

Grading of recommendations

Grade	*Recommendation*[3]
A *(Evidence levels quality Ia, Ib)*	*Requires at least one randomized controlled trial as part of the body of literature of overall good and consistency addressing the specific recommendation.*
B *(Evidence levels IIa, IIb, III)*	*Requires availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation.*
C *(Evidence level IV)*	*Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality.*

[2] based on WHO and AHCPR 1994
[3] based on WHO and AHCPR 1994

An indication may be accepted, if the documented long-term safe use in a well-defined indication is made plausible by supportive experimental data. Such an approach is, however, limited to minor indications (e.g. symptomatic treatment of self-limiting conditions). Description of traditional use without any supportive clinical or experimental data is not sufficient to establish a sufficient level of evidence of efficacy.

5. Acceptable level of safety

The level of safety must correspond to the indication claimed for the product. Reference is made to the Note for guidance on non-clinical testing of well-established herbal medicinal products (EMEA/HMPWG/11/99).

6. Requirements to be satisfied

An applicant wishing to use Article 4.8 (a) ii) of Directive 65/65/EEC must fully satisfy all the requirements of Article 1 of Directive 75/318/EEC as well as those of Directives 65/65/EEC and 75/319/EEC as amended, in effect, submit a „complete“ application. Directive 75/318/EEC Article 1 states that „where pursuant to point 8(a) of Article 4, second paragraph, of Directive 65/65/EEC, references to published data are submitted, the provisions of this Directive (i.e. Directive 75/318/EEC) shall apply in like manner.“ It should be kept in mind that the main goal of the European pharmaceutical legislation is protection of public health. The information necessary for the acceptance of safe use is mainly laid down in the Annex to Directive 75/318/EEC. For new drugs this information can only be extracted from new preclinical tests and clinical studies. For well-established herbal medicinal products the information may be extracted from bibliographic data and other evidence available. In order to avoid unnecessary experiments in animals and unnecessary involvement of patients in clinical trials the existing body of evidence has to be checked. The pharmacological/toxicological and the clinical expert report must discuss in detail that all information addressed in part 3 and 4 of the annex to Directive 75/318/EEC is covered by sufficient evidence. If information is lacking, the expert should discuss to which extent this particular lack of evidence will influence the overall assessment of risks and benefits of the herbal drug preparation.

7. Appropriate additional study

In the case that information addressed in the requirements of the annex to Directive 75/318/EEC is lacking, appropriate additional studies may be necessary to establish sufficient evidence of safe and effective use. Reference is made to the comments of the ad hoc Working Group on Herbal Medicinal Products on Part 4 of Annex to Council Directive 75/318/EEC (EMEA/HMPWG/13/99).

8. Sufficient information, complete application

A documentation will be considered as sufficient basis for an application for marketing authorisation if all relevant questions derived from the headings of the Annex to Directive 75/318/EEC are addressed by the experts in a competent way and if the relevant bibliographic information is submitted. If a European harmonisation in the form of core-SPCs was achieved by the working group, on the basis of ESCOP or WHO monographs, reference to the bibliographic data mentioned in these monographs may be accepted. Because these bibliographies may not be present in all Member States, the applicant should clarify in each case if copies of the bibliographic data have to be submitted to the reference and/or concerned Member States.

4.5. Final Proposal for a core-SPC for *Valerianae radix* - (EMEA/HMPWG/14/99)

The working group proposes the following core-SPC for *Valeriane radix*[1] (July 1998)

1. NAME OF THE MEDICINAL PRODUCT

To be specified for the individual finished product.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION[2]

Valerian root
Extract prepared with water, ethanol/water (max 70%)
Tinctures (1:5, ethanol max 70% V/V)

3. PHARMACEUTICAL FORM

Herbal drug or herbal drug preparation in solid or liquid dosage forms (to be labelled according to the standard terms published by the European Pharmacopoeia)

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Herbal medicinal product for the relief of temporary mild nervous tension and temporary difficulty in falling asleep (see Section 4.4 Special warnings and special precautions for use).

4.2. Posology and method of administration

For oral use

Adults and children over 12 years
Single dose:
2 to 3 g of the drug (e.g. as herbal tea).
1 to 3 ml of tincture (1:5, ethanol max 70% V/V).
Extracts with water, ethanol/water (max 70%) equivalent to 2 to 3 g of the drug.
For nervous tension up to 3 time daily.
As an aid to sleep, a single dose half to one hour before bedtime with an earlier dose during the evening if necessary.

Elderly: As for adults.

4.3. Contra-indications

Because there is no experience available, the use is not recommended in children younger than 12 years of age.

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1 The herbal drug complies with the European Pharmacopoeia

2 The declaration of all active substances should be done in accordance to the Note for guidance on quality of herbal medicinal products (type A.1.i or type A.2.i.) as revised by the ad hoc Working Group on Herbal Medicinal Products

4.4. Special warnings and special precautions for use

Please note that the Patient Leaflet invites the patient to seek medical advice if symptoms persist for more than 2 weeks or worsen.

4.5. Interaction with other medicinal products and other forms of interaction

None reported.
If the patient is on other medication he/she is invited to seek medical advice.

4.6. Use during pregnancy and lactation

Because data on the use during pregnancy and lactation are not available, the use is not recommended as a general precaution. No adverse effects have been reported from the common use of Valerian roots as a medicinal product but experimental data are lacking.

4.7. Effects on ability to drive and use machines

Intake of valerian preparations immediately (up to two hours) before driving a car or operating machinery is not recommended. The effect of valerian preparations may be enhanced by consumption of alcohol.

4.8. Undesirable effects

No adverse effect known to date under the recommended conditions of short term use.

4.9. Overdose

Valerian root at a dose of approximately 20 g caused benign symptoms (fatigue, abdominal cramp, chest tightness, lightheadedness, hand tremor and mydriasis) which disappeared within 24 hours. If symptoms arise, treatment should be supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Hypnotics and sedatives, ATC code: N05C M09

The sedative effects of preparations of Valerian roots such as tea-infusions or tincture have long been recognised empirically but cannot be attributed with certainty to any known constituents. Orally administered dry extracts of valerian root prepared with water have been shown to improve sleep latency and sleep quality in man, although the statistical significance in these studies was more apparent from subjective evaluations than from objective measures of sleep.

5.2. Pharmacokinetic properties

No pharmacokinetic data available.

5.3. Preclinical safety data[3]

Extracts with ethanol and the essential oil of Valerian root have shown low toxicity in rodents during acute test and from repeated dose toxicity over periods of 4-8 weeks.

[3] In case of Valerian root used as powder, the total exposure to valepotriates should not exceed the maximum exposure with herbal tea. Alkylating and cytotoxic properties of valepotriates are not relevant for finished products. This is because valepotriates decompose rapidly and only traces of valepotriates or their degradation products (in part, baldrinals) are found.

4.6. Draft Proposal for a core-SPC for *Ispaghula husk* - (EMEA/HMPWG/24/99)

The working group proposes the following core-SPC for *Ispaghula husk*[1] (January 1999).

1. NAME OF THE MEDICINAL PRODUCT

To be specified for the individual finished product.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION[2]

Ispaghula husk

3. PHARMACEUTICAL FORM

Herbal drug or herbal drug preparation in solid dosage forms such as granules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Herbal medicinal product for the treatment of habitual constipation; conditions in which easy defecation with soft stools is desirable, e.g. in cases of anal fissures, haemorrhoids, after rectal or anal surgery as well as in pregnancy; adjuvant symptomatic therapy in cases of diarrhoea from various causes; conditions which need an increased daily fibre intake e.g. irritable bowel syndrome.

4.2 Posology and method and duration of administration

Unless otherwise prescribed:
Daily dose:
Adults, elderly, children over 12 years of age: 4 - 20 g in 1 - 3 doses.

Method of administration: Mix approx. 5 g with 150 ml cool water, stir briskly and swallow as quickly as possible: then maintain adequate fluid intake. The product should be taken during the day at least ½ to 1 hour before and after intake of food or other medicines.

Warning: not to be taken immediately prior to retiring.

Duration of administration: Medical advice should be sought if the symptoms persist more than 3 days in order to make a definitive diagnosis as to the cause of constipation.

[1] The herbal drug complies with the European Pharmacopoeia
[2] The declaration of all active substances should be done in accordance to the Note for guidance on quality of herbal medicinal products (type A.1.i or type A.2.i.) as revised by the ad hoc Working Group on Herbal Medicinal Products

4.3 Contra-indications

Ispaghula husk is not to be used by patients with faecal impaction and undiagnosed abdominal symptoms , abdominal pain, nausea and vomiting unless advised by a doctor, a sudden change in bowel habit that persists for more than 2 weeks, rectal bleeding and failure to defecate following the use of a laxative. Ispaghula husk is also not to be used by patients suffering from abnormal constrictions in the gastro-intestinal tract, with diseases of the esophagus and cardia, potential or existing intestinal blockage (ileus), or megacolon, diabetes mellitus which is difficult to regulate; by patients with known hypersensitivity to ispaghula or any of the other constituents of the product, children aged less than 12.

4.4 Special warnings and precautions for use

A sufficient amount of liquid should always be taken e. g. 150 ml of water per 5 g of drug.
Warning: Take this product with at least 150 ml of water or other fluid. Taking this product without adequate fluid may cause it to swell and block your throat or esophagus and may cause choking. Intestinal obstruction may occur should an adequate fluid intake not be maintained. Do not take this product if you have ever had difficulty in swallowing or have any throat problems. If you experience chest pain, vomiting, or difficulty in swallowing or breathing after taking this product, seek immediate medical attention. The treatment of elderly and the debilitated patient requires medical supervision.

4.5 Interaction with other medicaments and other form of interaction

Enteral absorption of concomitantly administered medicines such as minerals (e. g. calcium, iron, lithium, zinc), vitamins (B12), cardiac glycosides and coumarin derivatives may be delayed. For this reason the product should not be taken 0,5 to 1 hour before and after intake of food or other drugs.
In the case of insulin dependent diabetics it may be necessary to reduce the insulin dose.

4.6 Use in pregnancy and lactation

No restriction for use in pregnancy and lactation.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Flatulence may occur with the absorption of the product, which generally disappears in the course of the treatment. Abdominal distension and risk of intestinal or oesophageal obstruction and faecal impaction, particularly if swallowed with insufficient fluid.
Due to occupational exposure, risk of allergic reaction possible through inhalation of the powder. Due to the allergic potential of Ispaghula, patients must be aware of reactions of hypersensitivity including anaphylaxis-like reactions in single cases.

4.9 Overdose

Overdose with Ispaghula husk may cause abdominal discomfort and flatulence and even intestinal obstruction. An adequate fluid intake should be maintained and management should be symptomatic.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

The active ingredient Ispaghula husk consists of the epidermis and adjacent layers of the dried, ripe seeds of Plantago ovata FORSK. Ispaghula husk seed is particularly rich in alimentary fibres and mucilages; with it's content of mucilage being higher than other Plantago species, absorbency of water is more than 40 times its weight. Psyllium fibers are partly fermentable (72 % unfermentable residue) and act by hydration in the bowel. The pharmacological effects, gut motility and transit rate can be modified by Ispaghula husk through mechanical stimulation of the gut wall depending on the increase in intestinal bulk by water and in viscosity of the luminal contents or by contact with rough fiber particles. When taken with a sufficient amount of liquid - at least 150 mL per 5 g of drug - Ispaghula husk produces an increased volume of intestinal contents due to it's highly bulking properties and hence a stretch stimulus which triggers defecation; at the same time the swollen mass of mucilage forms a lubricating layer which makes the transit of intestinal contents easier.

5.2 Pharmacokinetic properties

No experimental data available.

Absorption: mucilage swells without being dissolved. About 10 % of the mucilage gets hydrolysed in the stomach; mainly free arabinose is well absorbed.

Progress of action: action sets in 12 to 24 hours after single administration. Sometimes the maximum effect is not reached until 2 or 3 days.

Elimination: human intestinal flora in the large intestine degrades the polysaccharides.

5.3 Preclinical safety data

No new experimental data available.
No data are available in the literature on mutagenicity and carcinogenicity.
Data are based on scientific literature about Plantaginis ovatae testa; there are no preclinical concerns based on extensive human experience.

5. PROPOSED ACTIVITIES IN 1999

5.1. Finalisation of ongoing activities/draft documents

5.1.1 Amendment of the Note for guidance on non-clinical testing of herbal medicinal products with long-term marketing experience - guidance to facilitate mutual recognition and use of bibliographical data (EMEA/HMPWG/11/99)

5.1.2. Finalisation of draft proposals currently under consultation with interested parties.

- Draft Comments on the Commission Regulation (EC) No. 541/95 of 10 March 1995 concerning the examination of variations to the terms of a marketing authorisation granted by a competent authority of a Member State as amended by Commission Regulation (EC) No. 1146/98 - (EMEA/HMPWG/20/99)
- Draft Comments on the European Commission Guideline on dossier requirements for Type I variations - (EMEA/HMPWG/22/99)
- Draft Comments on the draft Directive on Good Manufacturing Practice (G.M.P) guide for starting materials of medicinal products and inspection of manufacturers - (EMEA/HMPWG/17/99)
- Draft Comments on the document Good Agricultural Practice (G.A.P) from the European Herbs Growers and Producers Associations (Europam) of 5 August 1998 - (EMEA/HMPWG/18/99)
- Draft Note for guidance on specifications: test procedures and acceptance criteria for herbal drug preparations (herbal drugs) and herbal medicinal products - (EMEA/HMPWG/19/99)
- Draft Comments on the CPMP Note for guidance on stability testing after Type II variations to a marketing authorisation - (EMEA/HMPWG/21/99)
- Draft Points to consider on the evidence of safety and efficacy required for well-established herbal medicinal products in bibliographic applications -(EMEA/HMPWG/23/99)
- Draft Proposal for a core-SPC for *Ispaghula husk* - (EMEA/HMPWG/24/99)

5.2. Adaptation of EU guidelines to herbal medicinal products

5.3. Assessment of scientific monographs prepared by ESCOP and WHO

Priority by indication	Assessment prepared by / date
Aloe capensis	Netherlands 10/99
Frangulae cortex	CPMP core SPC (update by NL if necessary)
Rhamni purshiani cortex	Netherlands 10/99
Sennae folium	CPMP core SPC (update by NL if necessary)
Sennae fructus acutifoliae	CPMP core SPC (update by NL if necessary)
Sennae fructus angustifoliae	CPMP core SPC (update by NL if necessary)
Valerianae radix	HMPWG draft core-SPC (July 1998)
Althaeae radix	
Lupuli flos	Sweden 05/99
Anisi fructus	Italy 10/99
Passiflorae herba	Sweden 05/99
Calendulae flos	Austria 05/99
Menthae piperitae folium	Portugal 10/99

Plantaginis ovatae semen	HMPWG draft core-SPC (January 1999)
Psyllii semen	Germany 05/99
Orthosiphonis folium	France 10/99
Foeniculi fructus	Italy 10/99
Gentianae radix	Italy 10/99
Solidaginis virgaureae herba	France 10/99
Urticae radix	
Betulae folium	
Menthae piperitae aetheroleum	Portugal 10/99
Urticae folium/herba	
Uvae ursi folium	
Zingiberis rhizoma	Denmark 10/99
Harpagophyti radix	France 05/99
Absinthii herba	
Arnicae flos	
Boldo folium	UK 10/99
Melissae fol	Sweden 05/99
Polygalae radix	
Lini semen	
Ononidis radix	
Primulae radix	
Thymi herba	
Lichen islandicus	
Salicis cortex	
Hamamelidis folium	
Juniperi fructus	
Melitoti herba	
Plantaginis ovatae testa	Germany 05/99
Taraxaci radix	
Rosmarini folium cum flore	Portugal 10/99
Tanaceti parthenii herba/folium	
Carvi fructus	
Hyperici herba	Portugal 05/99
Salviae folium	
Taraxaci folium	
Allii sativi bulbus	UK 10/99
Ribis nigri folium	

ANNEXES

Annex 1

London, 10 June 1997
EMEA/adhocHMPWP/497/97

AD HOC WORKING GROUP ON HERBAL MEDICINAL PRODUCTS

Mandate

Introduction

An ad hoc working group on herbal medicinal products has been created within the EMEA with a limited mandate of 3 meetings in 1997, upon the initiative of the European Commission and the EMEA Executive Director, which constitutes a pragmatic and useful approach to address the issue of quality, safety and efficacy of these products. The group will gather the experience of Member States in the field of herbal medicinal products, in liaison with the CPMP, and integrate industry's expertise in the development and manufacturing of such products.

Points for discussion

The discussion within the working group should serve the following purposes:

- provide guidance for applicants to Marketing Authorisations for herbal medicinal products
- provide guidance for competent authorities for the assessment of herbal medicinal products

The following points should be addressed :

- establishment of a common understanding of **existing legislation and guidelines**.
  In particular the group should discuss the need
  - to revise existing Quality guidelines[1]
  - to update existing provisions in the Good Manufacturing Practice of herbal medicinal products[2]
  - to develop European Pharmacopoeia monographs in collaboration with other bodies and authorities who have initiated activities in this area;

- development of **guidance and common criteria for assessment to sufficiently prove quality, safety and efficacy** of herbal medicinal products, with particular reference to scientific literature, WHO and ESCOP monographs where they exist; reviewing the usefulness of tabulated formats of the Notice to Applicants (NTA II B of January 1997);

- advice to the European Commission on the **ongoing study on herbal medicinal products** and on possible legislative measures to be envisaged after finalisation of the study and discussion of its results;

- discussion as to whether specific action is needed to ease the **access to relevant information** for both applicants and authorities.

Outcome of discussion

The ad hoc working group should prepare a report with proposals for initiatives which will highlight, for the different actions, their respective timeframe and required resources, for recommendation to the EMEA/CPMP and to the European Commission, respectively.

[1]In Particular the Note for Guidance "Quality of Herbal Remedies" (Vol. III Part I of the Rules governing Medicinal Products in the European Community)
[2]Annex 7 "Manufacture of Herbal Medicinal Products" of Good Manufacturing Practice for medicinal products (Vol. IV of the Rules governing Medicinal Products in the European Community)

London, 18 March 1998
EMEA/adhocHMPWP/497/97 Rev.1

AD HOC WORKING GROUP ON HERBAL MEDICINAL PRODUCTS

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Annex 2

AD HOC WORKING GROUP ON HERBAL MEDICINAL PRODUCTS
List of former and actual Members

Chairman
Konstantin KELLER

Austria
Alexander JENTZSCH (actual member)
Brigitte KOPP (expert)
Wolfgang KUBELKA (actual member)
Renate VITEK (expert)

Belgium
Claudine ELOY (former member)
Gert LAEKEMAN (expert)
Pascale POUKENS (actual member)
Arnold VLIETINK (actual member)

Denmark
Steffen BAGER (actual member)
Kirsten BRØNNUM-HANSEN (actual member)

Finland
Sari EKHOLM (expert)
Anna-Liisa ENKOVAARA (actual member)
Sari KOSKI (actual member)
Tiina KUMMALA (expert)

France
Karen BENMAOR (actual member)
Arielle NORTH (former member)

Germany
Klaus REH (actual member)
Ulrike WISSINGER-GRÄFENHAHN (actual member)

Greece
Skevos PHILIANOS (actual member)

Italy
Marisa DELBÒ (actual member)
Franco Francesco VINCIERI (actual member)

Ireland
Frank HALLINAN (actual member)
John G. KELLY (former member)
Christtl KLOOS (expert)
T. McGUINN (actual member)

Luxemburg
Mariette BACKES-LIES (actual member)
Jacqueline GENOUX-HAMES (actual member)

The Netherlands
Burt KROES (expert)
Carla RUTGERS (former member)
Mr Willem K. SCHOLTEN (actual member)
Emiel VAN GALEN (actual member)

Portugal
Maria DO CEU COSTA (expert)
Elsa GOMES (actual member)
Ana CORRÊA-NUNES (expert)
Beatriz SILVA-LIMA (actual member)

Spain
Nohelly ARRIETA (former member)
Julia MARTINEZ DE AÑO (actual member)
Gonzalo SAIZ (actual member)

Sweden
Barbro GERDÉN (actual member)
Bengt GUSTAVSSON (expert)
Maria SZIRMAI (actual member)
Cecilia ULLERYD (expert)

United Kingdom
Roy ALDER (former member)
Linda ANDERSON (actual member)
Paul RAPTOPOULOS (expert)
Richard WOODFIELD (actual member)

European Commission
Fabian LUTZ

European Parliament
Gianmatino BENZI
Dietrich HENSCHLER

European Pharmacopoeia (Observer)
Marie-Hélène LOULERGUE
Sylvie THOLOMIER

EMEA Secretariat
Rolf BASS
Estelle COQUILLETTE

Guidelines for Good Agricultural Practice (G.A.P.) of Medicinal and Aromatic Plants

5 August 1998

Final Europam Version

General Part

INTRODUCTION

0.1. Scope. The guidelines for the Good Agricultural Practice of Medicinal and Aromatic (Culinary) herbs is intended to apply to the growing and primary processing of all such plants traded and used in the European Union. Hence it applies to the production of all plant materials used in the food, feed, medicinal, flavouring and perfume industries. It also applies to all methods of production including organic production in accordance with the European regulations.

0.2. The Environment. Growers involved in the production of herbs must ensure that they avoid damage to existing wildlife habitats, and that they make efforts to maintain and to enhance the biodiversity of their farms. Wild crafting might be regulated by a specific guideline.

0.3. The present Good Agricultural Practice Guidelines provide additional standards for the production and processing of raw materials insofar as they mainly focus on identifying those critical production steps (measures) that are needed to comply with good quality. In this respect, it will be attempt to minimize insufficient quality by prevention.

0.4. A main aim is to ensure that the plant raw material meets the demands of the consumer and as such the standards of the highest quality. Especially important aspects are that they:

- are produced hygienically, in order to reduce microbiological load to a minimum,

- are produced with care, so that the negative impacts affecting plants during cultivation, processing and storage can be limited,

As in the course of the production process medicinal and aromatic plants and their products are exposed to a large number of both microbiological and other contaminants, the main aim of present guidelines is to provide guidance for producers to reduce plant (raw material) contamination to the greatest extent.

0.5. All participants of the production process (from primary producers to traders) are required to comply with these guidelines voluntarily and to elaborate practical measures in order to realize them.

Producers, traders and processors of medicinal and aromatic plants, especially of tea-like products and herbal medicinal products, should comply with the GAP Guidelines, document this, by a Way Bill (batch documentation) and demand that their partners also meet these requirements.

Principles and Guidelines for Good Agricultural Practice (G.A.P.)

1. Seeds and propagation material

1.1. Seeding materials are to be identified botanically, indicating plant variety, cultivar, chemotype and origin[4]. The material used should be 100% traceable. The same applies to vegetatively propagated starting material. Starting material used in organic production has to be certified organic.

1.2. Starting material should meet the requirements/standards concerning purity and germination (wherever available: certified seed/propagation material should be used). The starting material should be as free as possible of pests and diseases in order to guarantee healthy plant growth. When resistant or tolerant species or origins are available, they should be preferred.

1.3. The occurrence of not species/variety-identical plants and parts of plants has to be controlled in the course of the entire production process (cultivation, harvest, drying, packaging). Such impurities have to be eliminated promptly. Plants material or seeds derived from or comprising Genetically Modified Organisms have to be in accordance with national and European regulations.

2. Cultivation

2.1. Depending on the mode of cultivation e.g. conventional or organic, growers should be allowed to follow different Standard Operating Procedures for cultivation (to be elaborated). In general, care should be taken to avoid environmental disturbances. The principles of good crop husbandry must be followed including an appropriate rotation of crops.

2.2. Soil and Fertilization

2.2.1. Medicinal and aromatic plants cannot be grown in soils that are contaminated by sludge. Soils should furthermore not be contaminated by heavy metals, residues of plant protection products and other not naturally occurring chemicals, etc. For this reason, minimum effective chemical input should be achieved.

2.2.2. The manure applied should be void of human feces and prior to application should be thoroughly composted.

2.2.3. All other fertilizing agents should be applied sparingly and in accordance with the demands of the plant and the particular species (including application between harvests). The use of fertilizers should be in accordance with efforts to minimise leaching.

2.3. Irrigation

2.3.1. Irrigation should be minimized as much as possible and applied according to the needs of the plant.

2.3.2. Irrigation-water should be in accordance with national and potential European quality standards and should be as free as possible of contaminants, such as faeces, heavy metals, pesticides, herbicides and toxicologically hazardous substances.

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[4] These specifications can vary, as follows:
a) Species: Chamomilla recutita Rauschert: cultivar: Bodegold: chemotype: bisabololoxide A/Chamazulene. Origin: Seed Company, 1996. Charge No 4711
b) Species: Chamomilla recutita Rauschert: self-collected seed from the area in front of the ranch: Delightful Herbs. No.5. Harvester Str. 91222 Chamomille Town. California. On 26.6.1991.: since that time propagated

2.4. Crop maintenance and plant protection

2.4.1 Tillage should be adapted to plant growth and requirements.

2.4.2. Pesticide and herbicide application should be avoided as far as possible. When necessary they should be carried out using the minimum effective rates of approved plant protection products. Products for chemical plant protection have to conform with the European Union's maximum residue limits (European Pharmacopoeia, European Directives, Codex Alimentarius). Application and storage of plant protection products has to be in accordance with the recommendations of manufacturers and the authorities.

The application should be carried out only by qualified staff using approved equipment. Application should precede the harvest by a period either defined by the buyer or indicated by the producer of the plant protection product.

The use of pesticides and herbicides has to be documented.

2.4.3. All measures regarding nutrient supply and chemical plant protection should secure the marketability of the product. It is obligatory that the buyer of the batch be informed of the brand, quantity and date of pesticide use in a written form.

3. Harvest

3.1. The harvest should take place when the plants are of the best possible quality according to the different utilizations.

3.2. Harvest should preferably take place under the best possible conditions (wet soils, dew, rain or exceptionally high air humidity can be unfavourable). If harvest is performed under wet conditions, extra care should be taken in order to avoid the unfavourable influence of moisture.

3.3. Equipment should be in both a clean and technically perfect working order. Those machine parts including their housings that have a direct contact with the harvested crop, should be regularly and kept free of oil and contamination (including plant left-overs).

3.4. Cutting devices of harvesters must be adjusted so that the collection of soil particles can be reduced to a minimum.

3.5. In the course of harvest, care should be taken to ensure that no toxic weeds can mix with the harvested crop.

3.6. Damaged and perished plant parts must be promptly eliminated.

3.7. All containers used in the harvest must be clean and must be kept free of the remnants of previous crops; containers out of use, must also be preserved in a dry condition, free of pests and inaccessible for mice/rodents as well as livestock and domestic animals.

3.8. The harvested crop should not be exposed to direct contact with the soil. It must be promptly collected and under dry, clean conditions (e.g. sacks, baskets, trailers and containers, etc) submitted to transport.

3.9. Mechanical damage and compacting of the crop that would result in undesirable quality changes must be avoided. In this respect, attention must be paid to
- avoiding the overfilling of the sacks,
- the stacking up of sacks should not result in thickening of the crop,
- the harvested crop should be transported and kept in containers or bags in such way that the occurrence of heating is prevented.

3.10. Delivery of freshly harvested plant material must occur as quickly as possible to the processing facility in order to prevent heating.

3.11. The harvested crop must be protected from pests, mice/rodents and domestic animals. Pest control measures should be documented.

4. Primary processing

Primary processing includes steps of processing such as washing, freezing, distilling, drying, etc.. all these processes whether for food or medicinal use must conform to European and national regulations.

4.1. Arriving at the processing facility the harvested crop has to be promptly unloaded and unpacked. Prior to processing the material should not be exposed directly to the sun (except in case there is a specific need e.g. for distillation) and it must be protected from rainfall.

4.2. Buildings used in the processing of harvested crops must be clean, as well as thoroughly aerated and must never be used for housing livestock.

4.3. Buildings must be constructed so as to provide protection for the harvested crop against birds, insects, rodents as well as domestic animals. In all storage (including packaging stores) and processing areas suitable pest control measures such as baits and electric insect killing machines must be operated and maintained by professionally qualified staff or contractors.

4.4. Processing equipment must be maintained clean and must be regularly serviced.

4.5. In the case of natural open air drying, the crop must be spread out in a thin layer. In order to secure unlimited air circulation, the drying frames must be located at a sufficient distance form the ground. Attempts must be made to achieve uniform drying of the crop and as a consequence to avoid mould formation.

When drying wit oil, the exhaust fumes should not be reused for drying. Direct drying should not be allowed except with butane, propane, or natural gas.

4.6. Except in the case of natural open air drying, the conditions (e.g. temperature, duration, etc.) must be selected taking into consideration the type (e.g. root, leaf or flower) and active substance content (e.g. essential oils and others) of the crude drug to be produced.

Drying conditions should be documented.

4.7. Drying directly on the ground or under direct exposure to the sun-light should be avoided unless it is required for a particular plant.

4.8. All material must be inspected or sieved in order to eliminate sub-standard products and foreign bodies. Sieves must be maintained in a clean state and should be serviced regularly.

4.9. Clearly marked waste-bins should be kept ready, emptied daily and cleaned.

4.10. In order to protect it and to reduce the risk of pest attacks, the product should be promptly packaged.

5. Packaging

5.1. After the repeated control and eventual elimination of low-quality materials and foreign bodies, the product should be packaged in clean and dry, preferably new sacks, bags or cases. The label must be clear, permanently fixed and made from non-toxic material. Information must conform with the European and national labelling regulations.

5.2. Packaging materials should be stored in a clean and dry place that has to be free of pests and inaccessible for livestock and domestic animals. It must be guaranteed that no contamination of the product takes place by the use of packaging material, particularly in the case of fibre bags.

5.3. Reusable packaging materials should be well cleaned and perfectly dried prior to their usage. It must be guaranteed that no contamination takes place be reusing bags.

6. Storage and Transport

6.1. Packaged dried materials and essential oils should be stored in a dry, well-aerated building, in which the daily temperature fluctuations are limited and good aeration is given. Fresh products (except Basil) should be stored between 1°C and 5°C while frozen products should be stored below -18°C (or below -20°C for longer-term storage). Essential oil storage must conform to the appropriate chemical storage standards.

6.2. As a protection against pests, birds, rodents and domestic animals, the window and door openings are to be protected, e.g. by wire netting

6.3. It is recommended that the packaged dry cop will be stored:
- in buildings with concrete or similar easy to clean floors,
- on pallets,
- with a sufficient distance to the wall,
- thoroughly separated from other crops to avoid cross-contamination.
  Organic products must be stored separately.

6.4. In the case of bulk transport, it is important to secure dry conditions and furthermore, in order to reduce the risk of mould formation or fermentation, it is extremely advisable to use aerated containers. As a substitute, the use of sufficiently aerated transport vehicles and other aerated facilities is recommended. Essential oil transport must conform to appropriate regulations. National and European regulations on transport have to be respected.

6.5. Fumigation against pest attack should be carried out only in the case of necessity and it must be carried out exclusively by licensed personnel. Only registered chemicals must be used. Any fumigation against pest attack should be reported in the documentation.

6.6. For fumigation of warehouses, only permitted substances should be used, according to European or national regulations.

6.7. When frozen storage or saturated steam is used for pest control, humidity of the material must be controlled after treatment.

7. Equipment

7.1. Equipment used in plant cultivation and processing should be easy to clean, in order to eliminate the risk of contamination.

7.2. All machinery should be mounted in an easily accessible way. They must be well serviced and regularly cleaned. Fertilizer and pesticide application machinery must be regularly calibrated.

7.3. Preferably non-wooden equipment should be used unless tradition demands wooden material. When wooden equipment (such as e.g. pallets, hoppers, etc.) is used, it should not come into direct contact with chemicals and contaminated/infected material, so that infection of the plant material can be prevented.

8. Personnel and Facilities

8.1. Personnel should receive adequate botanical education before performing tasks that require this knowledge.

8.2. All processing procedures should fully conform with both EU-Guidelines on Food Hygiene and the General Principles for food hygiene of Codex Alimentarius as well as the European Directive on Good Manufacturing Practice.

8.3. Personnel entrusted with the plant material should be required to have a high degree of personal hygiene (including personnel working in the fields) and have received adequate training regarding their hygiene responsibilities.

The buildings where the plant processing is carried out, have to be provided with changing facilities as well as toilets including hand washing facilities, according to the respective regulations

8.4. Persons suffering from known infectious diseases transmittable via food, including diarrhoea, or being transmitters of such diseases, must be suspended from areas where they are in contact with the plant material, according to the respective regulations.

8.5. Persons with open wounds, inflammations and skin-infections should be suspended from the areas where plant processing takes place, or have to wear appropriate protecting clothing or gloves, until their complete recuperation.

8.6. Personnel should be protected from contact with toxic or potentially allergenic plant materials by means of adequate protective clothing.

8.7. The welfare of all staff involved in the growing and processing shall be ensured.

9. Documentation

9.1. All starting materials and processing steps have to be documented including the location of cultivation. Field records showing previous cropping and inputs should be maintained by all growers.

9.2. All batches from coherent areas should be unambiguously and unmistakably labelled (e.g. by the application of a batch number). This should take place as early as possible.

9.3. Batches from differing areas shall be mixed only if it is guaranteed that the mixture in itself will be homogenous. Such mixing procedures should also be documented.

9.4. It is essential to document the type, quantity and the date of harvest of the crop, as well as the chemicals and other substances (e.g. fertilizers, pesticides and herbicides, growth regulators, etc.) used during production.

9.5. The application of the fumigation agents such as phosphin must be entered into batch documentation.

9.6. All processes and procedures that could bear an impact on the quality of the product must be entered into the batch documentation.

9.7. All agreements (production guidelines, contracts, etc.) between producer and buyer should be fixed in a written form.

It should be documented in a Way Bill (batch documentation) that cultivation, harvesting and production have been performed in accordance with the GAP Guideline. Minimum information included in the Way Bill should cover geographical definition of growth place, country of origin and responsible producer.

9.8. The results of audits should be documented in an Audit Report (copies of all documents, Schlagkartei, Audit Reports, Analyse Reports) to be stored for a minimum of 10 years.

9.9. Special circumstances during the growth period, which may influence the chemical composition like extreme weather conditions, pests – particularly in the harvest period – must be documented.

10. Education

It is extremely advisable to educate all personnel dealing with the crop or those engaged in the direction of the production regarding production techniques and the appropriate use of herbicides and pesticides.

11. Quality Assurance

Agreements between producers and buyers of medicinal and aromatic plants, with regard to quality questions, e.g. active principles and other characteristic ingredients, optical and sensoric properties, limit values of germ numbers, plant protection chemical residues and heavy metals, must be based on internationally recognized or national specifications and should be laid down in written form.