HOMEOPATHIC MEDICINAL PRODUCT WORKING GROUP (HMPWG)

GUIDANCE ON MODULE 3 OF THE HOMEOPATHIC MEDICINAL PRODUCTS DOSSIER

DISCUSSION IN THE HMPWG	2003- 2005
RELEASE FOR CONSULTATION	December 2005
DEADLINE FOR COMMENTS	February 2006
DISCUSSION IN THE HMPWG	June/November2006
ADOPTION BY THE HMPWG	November 2006
ADOPTION BY THE HMA	November 2007

SPECIFIC GUIDANCE ON MODULE 3 OF THE HOMEOPATHIC MEDICINAL PRODUCTS DOSSIER

Introduction

With the implementation of Directive 2001/83/EC as amended all Member States of the European Union (EU) will have a system for licensing or authorizing homeopathics as medicinal products on their market. In the absence of a specific EU dossier template, the EU-Notice To Applicants (NTA) format is mandatory for homeopathic medicinal products.
Aim of this document is to provide guidance on the use of the NTA format when compiling an application dossier for homeopathic medicinal products. Moreover it is an attempt to harmonize the dossier template for homeopathic medicinal products to facilitate mutual recognition as laid down in the 2004/27/EC.
This document was drafted by the Homeopathic Medicinal Products Working Group of the Head of Agencies Group. Therefore this document is also applicable if a mutual recognition procedure for homeopathic medicinal products is considered. However, to determine the applicability of this format for a particular type of product, applicants should consult with the appropriate regulatory authorities

Scope

In homeopathy, the active substances can be either the stock or its dilutions, whereas the stock could be processed as well as unprocessed raw material. Homeopathic medicinal products may contain large numbers of active homeopathic substances or a combination of active substances of biological, chemical and herbal origin. In addition, the finished medicinal product could be the (packed) homeopathic active substance itself or a further processed stock/dilution.
Due to these particularities the use of NTA template to compile a dossier for homeopathic medicinal products may be problematic.
This document is intended to provide clarification on the use of the NTA template. Guidance given is appropriate for registration under the simplified procedure (article 14) as well as for authorization of homeopathic medicinal products (article 16), if implemented in national legislation. The information provided is based on the specific provisions that are laid down for homeopathic medicinal products in Directive 2003/63/EC. In accordance with this Directive under Drug substance (Module **3.2.S**) information on the starting material, including raw materials, homeopathic stock(s), and intermediates up to the final dilution(s) (or triturations) to be incorporated into the finished product should be provided. Information on the finished homeopathic medicinal should be provided in Module **3.2.P**.
The text following the section titles is intended to be explanatory and illustrative only. It is not all-inclusive and additional national requirements may apply. The content of the sections should include relevant information described in HMPC or CHMP-/ICH guidelines. The applicant should refer to CHMP/HMPC guidelines and Directive 2003/63/EC for further guidance.
Specific guidance for Homeopathic medicinal products is given, where relevant.
The information provided in this document does not replace the texts of the NTA, it merely provides some clarification. Hence, this document should be read in conjunction with the NTA. If no specific information is provided the text of the NTA applies.

References to guidelines are inserted to assist applicants. However, it remains the applicant's responsibility to ensure that all relevant legislation and guidelines are taken into account in the preparation of each part of the dossier. The guidelines referenced in each section provide useful information on the content expected in that section. This list should not be regarded as

comprehensive. Furthermore, in absence of specific CHMP/HMPC guidelines for homeopathic products of botanical origin, the CHMP/HMPC guidelines for herbal drugs, herbal drug preparations and herbal medicinal products, should be considered.
Wherever relevant, the requirements of the European Pharmacopoeias apply (specific monographs, general monographs and general chapters) or, in absence thereof, an official Pharmacopoeia of a Member State.

All analytical test procedures described in the various sections of the 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.
The principle of GMP and the detailed guidelines are applicable to all operations which require the authorization referred to in Article 40 of Directive 2001/83/EC as amended

CPMP/QWP/2820/00 Note for guidance on specifications: Test Procedures and Acceptance Criteria for Herbal Drugs, Herbal Drug Preparations and Herbal Medicinal Products"
CPMP/QWP/2819/00 Note for guidance on specifications on Quality of Herbal Medicinal Products
European Pharmacopoeia and/or an official Pharmacopoeia of a Member State of the European Union

3.2.S. DRUG SUBSTANCE[1] (NAME[2], MANUFACTURER)

3.2.S.1 General information (name, manufacturer)

3.2.S.1.1. Nomenclature (name, manufacturer)

Also a definition of the homeopathic stock(s) and the homeopathic name (s) should be provided. For homeopathic stocks of herbal origin for example:

- Binominal scientific name of plant (genus, species, variety and author) and chemotype (where applicable)
- State (fresh or dried) and part(s) of the plant
- Other names (synonyms)/ homeopathic names /latin names
- Reference of the homeopathic manufacturing procedure
- Description of vehicles used

3.2.S.1.2. Structure (name, manufacturer)

3.2.S.1.3 General Properties (name, manufacturer)

3.2.S.2 Manufacture (name and manufacturer)

3.2.S.2.1 Manufacturer(s) (name and manufacturer)

The name, address, and responsibility of each manufacturer, including manufacturer of stock, dilutions and/or triturations as well as, contractors, and each proposed production site or facility involved in manufacturing/collection and testing should be provided.

3.2.S.2.2 Description of Manufacturing Process and Process Controls (name and manufacturer)

The description of the homeopathic stock(s), intermediate dilutions and/or triturations and final dilution manufacturing process represents the applicant's commitment for the manufacture of the homeopathic stock(s) and final dilution. Information should be provided to adequately describe the manufacturing process and process controls. For example:

A sequential procedural narrative of the manufacturing process should be submitted. The narrative should include, for example, quantities of raw materials, solvents/vehicles, reagents (if applicable), critical steps and the controls that are intended to result in the routine and consistent production of material(s) of appropriate quality. A flow chart of the manufacturing process should be included. For homeopathic stock(s) and final dilution reference should be made to the appropriate section of a European

[1] For homeopathic medicinal products in part S information on raw material(s), stock(s), intermediate dilutions and/or triturations and final dilutions should be provided.

[2] For a drug product containing more than one drug substance, the information requested for part “S” should be provided in its entirety for each drug substance

Pharmacopoeia, or in absence thereof, to a homeopathic manufacturing procedure described in an official Pharmacopoeia of a Member State of the European Union. The different stages of the preparation of the homeopathic stock(s) and final dilution or any preliminary treatment or transformation operation must be sufficiently described to allow the assessment of the consistency of the quality. The material, processes and specific precautions (light, moisture, miscellaneous contamination, and temperatures) must be described.

Reference guidelines: "Chemistry of Active Substances", " Note for guidance on specifications on quality of Herbal Medical Products", " Note for guidance on specifications: Test Procedures and Acceptance Criteria for Herbal Drugs, Herbal Drug Preparations and Herbal Medicinal Products", Points to consider on good agricultural and collection practice for starting material of herbal origin.
CPMP-ICH Guideline: Note for guidance on specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products"
European Pharmacopoeia or an official Pharmacopoeia of a Member State of the European Union

3.2.S.2.3 Control of Materials (name, manufacture)

The information on the raw material(s) and the solvents/reagents or vehicles used for the Homeopathic Stock(s) and final dilution preparation should be presented

Nomenclature of the raw materials

For raw materials of botanical origin, the scientific name -genus, species, variety, chemo type-, part employed and other names should be provided.
For raw materials of biological origin, the scientific name (e.g., animal), -genus, species- tissue(s), fluid(s), parts of organ(s) or organ(s) used and other names should be provided.
For minerals or chemicals, the international non-proprietary name (I.N.N), chemical and other names should be provided.

Description of the raw materials

For raw materials of botanical origin, the state (e.g. fresh, dried) of the material used and, where applicable, information on pharmacological active, toxic constituents or marker compound(s), if applicable, should be provided. Additionally a macroscopic and microscopic description of the raw material should be presented.
For raw materials of biological origin, information on the physical and/or anatomical and histological state (where applicable) should be provided.
For minerals or chemicals, physical form, structural formula, molecular formula and relative molecular mass, where applicable, should be provided.

Supportive Data

For example, the following data should be presented

- Name and address of the supplier and supplier commitment and/or manufacturer and manufacturer's commitment , if different from the applicant
- Data on the origin/source of the material
- Synthetic or manufacturing route
- Production: (for example)

  For raw materials of botanical origin:
  - Natural state of plant (wild or cultivated)
  - Harvesting location, time of harvesting and, if possible, stage of vegetation
  - Conditions of cultivation
  - Information on pre or post harvest treatment
  - Processing, where applicable
  - Duration and conditions of storage

  For raw materials of biological (not botanical) origin:
  - Age of the animal, culture history
  - Health status, method of breeding and feeding of animals, immunisation techniques (immune sera) with description of antigens, culture media (microbial strains)
  - Conditions of slaughter and dissection of animals, culture conditions
  - Size of organ, tissue, fluid pools
  - Method of acquisition, treatments, transport conditions and storage conditions of the organ or pool of organs or microbial cultures or immune sera
  - Provisions made for tracing the origin of the raw material(s)
  - Assessment of the risk of infectivity

  For raw materials of human origin:
  - Origin of donation- clinical data
  - Identification of raw material biological fluid description, tissue description, cells nature, origin, name, reference, volume of sample, method of collection, transport, storage conditions pool
  - Assessment of the risk of infectivity

  For a mineral or chemical substance:
  - Purification stage
  - Location of collection (geographical origin)

Reference Guidelines: "Chemistry of Active Substances", " Note for guidance on specifications on quality of Herbal Medical Products", "Note for guidance on specifications: Test Procedures and Acceptance Criteria for Herbal Drugs, Herbal Drug Preparations and Herbal Medicinal Products", "Virus validation studies: the design, Contribution and Interpretation of Studies Validating the Inactivation and Removal of Viruses", "Note for guidance on Plasma-Derived Medicinal products". Points to consider on good agricultural and collection practice for starting material of herbal origin.
Reference CPMP-ICH Guidelines: "Note for guidance on specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products" and " Note for guidance on specifications - Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products- Chemical Substances"

Council Recommendation 94/463/EC on the "Suitability of Blood and Plasma Donors and the Screening of Donated Blood in the European Community"
Commission Directives 1999/82/EC, 1999/104/EC and 2004/33/EC

3.2.S.2.4 Control of Critical Steps and Intermediates (name, manufacture)

3.2.S.2.5 Process validation and/or Evaluation (name, manufacture)

3.2.S.2.6 Manufacturing Process Development (name, manufacture)

Reference to the manufacturing method of an official Pharmacopoeia shall be made.

3.2.S.3 Characterisation (name, manufacturer)

3.2.S.3.1 Elucidation of Structure and other Characteristics (name, manufacturer)

Conformation of structure based on e.g., synthetic route, spectral analyses, biological activity, purity and phytochemical characterisation should be provided, where relevant.

3.2.S.3.2 Impurities (name, manufacturer)

Information on impurities originating from the raw material(s) or arising from the manufacturing process should be provided
For example:

- Potential impurities originating from the route of synthesis
- Potential impurities arising during the production and purification (degradation products)
- Analytical test procedures and their limits of detection
- Test for foreign matters: mineral, biological or botanical other than the homeopathic active substance defined
- Test for pesticides

3.2.S.4 Control of Drug Substance (name, manufacturer)

3.2.S.4.1 Specifications (name, manufacturer)

The specifications for raw materials, the homeopathic stock(s) and final dilutions should be provided. Information provided should comply with relevant CHMP/HMPC quality guidelines.
If the raw material is described in a Pharmacopoeia, the reference to the monograph should be stated and, where applicable, supplementary tests should be described. If the

raw material is not described in a Pharmacopoeia, the monograph should be compiled based on scientific data.

3.2.S.4.2 Analytical Procedures (name, manufacturer)

Analytical procedures used for testing the raw material (s), the homeopathic stock(s) and final dilution should be provided.
For example for raw materials of botanical origin:

- Various chromatographic techniques best suited to study the composition of the plant
- Test for loss on drying or water content
- If applicable, an assay of the main ingredients
- Test for potential falsification

3.2.S.4.3 Validation of Analytical Procedures

Analytical validation information, including experimental data for the analytical procedures used for testing the raw material(s), homeopathic stock(s) and final dilution should be provided.

3.2.S.4.4 Batch Analysis (name, manufacturer)

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3.2.S.4.5 Justification of Specifications (name, manufacturer)

Justification for the raw material(s), homeopathic stock(s*)* and final dilution specifications should be provided.

3.2.S.5 Reference Standards or Materials (name, manufacturer)

Information on the reference standards or reference materials used for testing raw material(s), homeopathic stock(s*)* and final dilution should be provided.

3.2.S.6 Container Closure System (name, manufacturer)

Descriptions of container closure system(s) used for storage of the homeopathic stock(s), final dilution, intermediate dilution/trituration and raw materials (if stored) should be provided. The combination of the container closure specifications and the stock stability data may be sufficient to demonstrate suitability of the container closure system for storage and shipping of the stock.

3.2.S.7 Stability (name, manufacturer)

3.2.S.7.1 Stability Summary and Conclusions (name, manufacturer)

Stability data of the homeopathic stock(s) and final dilution(s) should be provided. Stability data or re-testing may also be required for raw materials that are not processed immediately after testing. Stability data from the homeopathic stocks are generally transferable to dilution/triturations obtained thereof, if the expiry date of the dilutions/triturations does not exceed the expiry date of the homeopathic stock.

3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment

3.2.S.7.3 Stability Data

Stability data or re-testing may also be required for all dilutions or triturations, if the stability is not linked to the expiry date of the stock and that are not processed immediately after testing.

3.2.P DRUG PRODUCT (NAME, DOSAGE FORM)

3.2.P.1 Description and Composition of the Drug Product (name, dosage form)

3.2.P.2 Pharmaceutical Development (name, dosage form)

3.2.P.2.1 Components of the Drug Product (name, dosage form)

3.2.P.2.1.1 Drug Substance (name, dosage form)

3.2.P.2.1.2 Excipients (name, dosage form)

3.2.P.2.2 Drug Product (name, dosage form)

3.2.P.2.2.1 Formulation Development (name, dosage form)

Where applicable, the differences between clinical formulations and formulation (i.e. composition) described in 3.2.P.1 should be provided.

3.2.P.2.2.2 Overages (name, dosage form)

3.2.P.2.2.3. Physicochemical and Biological Properties (name, dosage form)

3.2.P.2.3 Manufacturing Process Development (name, dosage form)

Where applicable, differences with the manufacturing process(es) used to produce pivotal clinical batches clinical should be provided.

3.2.P.2.4 Container Closure Systems

3.2.P.2.5 Microbiological Attributes (name, dosage form)

3.2.P.2.6 Compatibility (name, dosage form)

3.2.P.3 Manufacture (name, dosage form)

3.2.P.3.1 Manufacturer(s) (name, dosage form)

3.2.P.3.2 Batch Formula (name, dosage form)

3.2.P.3.3 Description of Manufacturing Process and Process Controls (name, dosage form)

3.2.P.3.4 Controls of Critical Steps and Intermediates (name, dosage form)

3.2.P.3.5. Process Validation and/or Evaluation (name, dosage form)

3.2.P.4 Control of Excipients (name, dosage form)

3.2.P.4.1 Specifications (name, dosage form)

3.2.P.4.2 Analytical Procedures (name, dosage form)

3.2.P.4.3 Validation of Analytical Procedures (name, dosage form)

3.2.P.4.4 Justification of Specifications (name, dosage form)

3.2.P.4.5 Excipients of Human or Animal Origin (name, dosage form)

3.2.P.4.6 Novel Excipients (name, dosage form)

3.2.P.5 Control of the Drug Product (name, dosage form)

3.2.P.5.1 Specification(s) (name, dosage form)

3.2.P.5.2 Analytical Procedures (name, dosage form)

3.2.P.5.3 Validation of Analytical Procedures (name, dosage form)

3.2.P.5.4 Batch Analysis (name, dosage form)

3.2.P.5.5 Characterisation of Impurities (name, dosage form)

3.2.P.5.6 Justification of Specification(s) (name, dosage form)

3.2.P.6 Reference Standards or Materials (name, dosage form)

3.2.P.7 Container Closure System (name, dosage form)

The combination of the container closure specifications and the drug product stability data may be sufficient to demonstrate suitability of the container closure system for storage and shipping of the drug product.

3.2.P.8 Stability (name, dosage form)

Homeopathic medicinal products: if no identification or assay of the active substance is possible due to the degree of dilution, stability data of the pharmaceutical form may be considered (see annex 1 of Directive 2001/83: Directive 2003/63/EC)

3.2.P.8.1 Stability Summary and Conclusions (name, dosage form)

3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment (name, dosage form)

3.2.P.8.3 Stability Data (name, dosage form)

3.2.A APPENDICES

3.2.A.1. Facilities and Equipment (name, manufacturer)

3.2.A.2 Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)

3.2.A.3. Novel Excipients

Module 3.2.R
Regional information for EU

Module 3.3.
Literature references