

Guide to Registration of Homeopathic Medicinal Products

AUT-G0037-34
16 JULY 12 November 2014

This guide does not purport to be an interpretation of law and/or regulations and is for guidance purposes only.



CONTENTS

<u>1</u>	SCOPE	3	Field Code Changed
<u>2</u>	PURPOSE AND SCOPE OF THE REGISTRATION SCHEME	3	Field Code Changed
<u>3</u>	HOW TO APPLY FOR REGISTRATION	5	Field Code Changed
<u>4</u>	THE APPROVAL PROCESS	6	Field Code Changed
<u>5</u>	ACCOMPANYING DATA	7	Field Code Changed
<u>6</u>	MANUFACTURE AND WHOLESALE	9	Field Code Changed
<u>7</u>	SALE AND SUPPLY	11	Field Code Changed
<u>8</u>	VARIATION, RENEWAL AND SUSPENSION OF CERTIFICATES	11	Field Code Changed
<u>9</u>	LABELLING	13	Field Code Changed
<u>10</u>	ADVERTISING	14	Field Code Changed
<u>APPENDIX A</u>	CONTACT POINTS WITHIN THE HPRA	15	Field Code Changed
<u>APPENDIX B</u>	LEGISLATION	16	Field Code Changed
<u>APPENDIX C</u>	QUALITY AND CONTROL OF HOMEOPATHIC STOCKS	17	Field Code Changed
<u>APPENDIX D</u>	MANUFACTURE AND CONTROL OF DOSAGE FORMS	21	Field Code Changed
<u>APPENDIX E</u>	GENERAL LABELLING REQUIREMENTS	24	Field Code Changed
<u>APPENDIX F</u>	LABELLING OF REGISTERED HOMEOPATHIC PRODUCTS	25	Field Code Changed
<u>APPENDIX G</u>	LABELLING OF SMALL CONTAINERS	26	Field Code Changed

1 SCOPE

This guidance is intended for those companies wishing to obtain registration for the marketing of homeopathic medicinal products for human use in Ireland. It covers the criteria for registration as set out in the EC Directives (92/73/EC and 2001/83/EC, as amended) and includes information taken from other EC Directives as appropriate. It provides advice on the administrative aspects of the registration scheme and gives guidance on how the application should be made.

This guidance does not attempt to answer every question a company may have, and the HPRA is available to provide advice on individual queries and products. A list of contact points is provided in Appendix A.

2 PURPOSE AND SCOPE OF THE REGISTRATION SCHEME

2.1 The purpose of the scheme

The homeopathic medicines registration scheme is a simplified regulatory procedure, which enables companies to market certain homeopathic medicinal products in Ireland. The basis for the scheme is set out in the EU Directive 2001/83/EC, which superseded EU Directive 92/73/EEC. The latter was incorporated into Irish law in 1994, Medical Preparations (Licensing, Advertisement and Sale) (Amendment) Regulations, 1994, which widened the scope of existing legislation in a move towards harmonisation of the manufacture, control and supply of homeopathic products within the EU. Appendix B lists the relevant legislation.

The supply of medicinal products in Ireland is regulated by the provisions of the Medicinal Products (Control of Placing on the Market) Regulations 2007, S.I. No. 540 of 2007 and associated EU legislation. It is unlawful for any medicinal product to be placed on the market in Ireland except in accordance with a product authorisation or registration granted by the HPRA. Under the provisions of these Regulations, a product authorisation may only be granted where satisfactory evidence of safety, quality and efficacy has been established. In the case of homeopathic medicinal products, however, a product registration may be granted where satisfactory evidence of safety and quality has been established.

2.2 Products outside the scope of the registration scheme

The following are outside the scope of Directive 2001/83/EC, as amended, and are therefore not covered by this registration scheme:

- Products for use in the treatment of animals
- Products prepared in accordance with a magistral or officinal formula (i.e. those prepared in a pharmacy in accordance with a prescription for an individual patient)

- Products supplied in response to unsolicited orders, formulated in accordance with the specifications of a doctor or a dentist and for use by individual patients under the doctor or dentists direct personal responsibility

2.3 Products eligible for registration

The homeopathic registration scheme applies to homeopathic medicinal products for human use which are intended to be placed on the market and which fulfil the criteria specified in EU Directive 2001/83/EC, as amended. To be eligible for registration, a homeopathic medicinal product must satisfy all of the following criteria:

- It must be prepared from homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the European Pharmacopoeia or, in the absence of such a description, by any pharmacopoeia used officially in an EU member state,
- It must be for oral or topical use (this includes most methods of administration but excludes injections, inhalations and implants), e.g. Arnica 6c tablets, Calendula Skin cream,
- There must be no specific therapeutic indication included in the labelling or in any information relating to the product (i.e. promotional material),
- The product must bear the scientific name of the stock or stocks from which it is prepared; if the product is composed of two or more stocks, the scientific names of the stocks may be supplemented by an invented name,
- It must be sufficiently dilute to guarantee safety,
- It must contain no more than one part per 10,000 of the mother tincture or not more than 1/100th of the smallest dose where the active principle is a prescription only medicine contained in Schedule 1 of the Medicinal Products (Prescription and Control of Supply) Regulations, 2003, S.I. No.540 of 2003.

2.4 Who should apply for registration?

If a homeopathic medicinal product is to be marketed in Ireland under the registration scheme, a registration certificate must be held by the person responsible for placing it on the market. Applications for registration under the scheme may be made by any person, who wishes to place a product on the market. Companies should also be aware of the need for the following authorisations:

Manufacturers

A company which manufactures or which proposes to manufacture homeopathic medicinal products must hold a manufacturer's authorisation. 'Manufacture' includes all processes carried out in the course of making the product, including diluting, mixing and quality control. A manufacturer's authorisation is also needed for 'assembly' (e.g. filling and labelling containers), and for 3rd. country imports.

Importers

A company which imports homeopathic medicinal products from countries outside the EEA needs a manufacturer's authorisation as described above.

Wholesalers

A company which acts as a wholesaler or which proposes to do so, for the supply of homeopathic medicinal products for the purpose of resale (other than those it manufactures itself), needs a wholesaler's authorisation in accordance with the requirements of the wholesale distribution regulations (S.I. No. 538 of 2007).

3 HOW TO APPLY FOR REGISTRATION

3.1 Application form

Applications should be made on the appropriate HPRA application form accompanied by the data specified in this guide. A separate application form should be completed for each series of dilutions and for each pharmaceutical form for which you seek registration. For combination products, please complete a separate form for each formulation.

The application form, together with detailed guidance on its completion, is available on the 'Publications and Forms' section of www.hpra.ie.

3.2 Registration numbers

Before submitting the application(s) a company number is needed.

This number is combined with the product number and the prefix HOR (homeopathic registration) to produce a registration number for each product, e.g. HOR 001/001/01, (where the first 001 is the number allocated to the company, the second 001 is the product number and the last 01 is the form). This registration number is provisional until the application has been determined and the registration granted or rejected.

Company numbers can be obtained by contacting the Receipts and Validation section at submissions@hpra.ie.

If you already hold product authorisations, or clinical trial permissions or notifications, then you should use the company number already allocated to you.

3.3 Timing of applications

Before submitting your applications it would be helpful if you could indicate how many such applications you intend to make. Contact Homeopathic Medicines, in the Human Products Authorisation and Registration department (see Appendix A) to discuss the timing of your applications.

3.4 Where to send the application

Details on submission of electronic applications are outlined in the 'Guide to Electronic Submissions – Human Medicines' on the 'Publications and Forms' section of www.hpra.ie.

Application forms and data should be submitted in English and should use a legible typeface. All documents should be clearly identified with the applicant's name.

Applications must be accompanied by the correct fee – see the 'Guide to Fees for Human Products' on the 'Publications and Forms' section of www.hpra.ie for details of the fees and the method of fee payment. The fee should be sent on the same day as the application form and data. The application will not be considered until the fee has been paid. All fees must be paid in full and any associated bank charges are for your own account.

4 THE APPROVAL PROCESS

4.1 Assessment of the application

When your application and fee have been received, the Receipts and Validation section checks the eligibility of the application and informs you if the product is not eligible for registration under the scheme. If the application is eligible, it is allocated to an assessor for assessment. When assessment begins, an automatic notification e-mail is sent to you to inform you that the process has started.

The data accompanying the application is assessed and if this is satisfactory the HPRA issues a registration certificate. If there are deficiencies in the application, the assessor informs you and resolves these, wherever possible, so that a registration certificate can be granted.

4.2 Issue of registration certificates

Following approval, the registration certificate is sent to you by post. On receipt, you are able to market the registered homeopathic product citing the HOR registration number on the label.

4.3 Timescales for approval

In accordance with EU Directive 2001/83/EC, the HPRA is required to take all appropriate measures to process applications within 210 days of submission of a valid application.

5 ACCOMPANYING DATA

5.1 Data required

Under Article 15 of EU Directive 2001/83/EC, as amended, the following information must be provided in order to demonstrate the pharmaceutical quality and batch-to-batch homogeneity of the products concerned:

Product Details

- Scientific name (or other name used in a pharmacopoeia) of the homeopathic stock(s)
- Pharmaceutical form
- Route of administration
- Degree of dilution to be registered

Production and Control of Homeopathic Stocks

- A dossier describing how the homeopathic stock(s) are obtained and controlled and
- Bibliographic justification of the homeopathic use of the stock(s)

Production and Control of the Dosage Form

- A manufacturing and control file for each pharmaceutical form
- A description of the method of dilution and potentiation

Manufacturing Authorisation covering the Medicinal Product concerned

Registration by other EC Member States

- Copies of any registrations or authorisations obtained for the same medicinal product in other Member States

Labelling

- One or more specimens or mock-ups of the sales presentation of the medicinal products to be registered

Stability of the Dosage Form

- Data concerning the stability of the medicinal product

More detailed advice is provided in Appendix C *Quality and Control of Homeopathic Stocks* and Appendix D *Manufacture and Control of Dosage Forms for Homeopathic Products* on the data required for homeopathic registration.

5.2 Presentation of data

A series of dilutions relating to one pharmaceutical form may be covered by one set of data. For example, one set of data is acceptable for Arnica tablets at dilutions of 6x, 6c, 30c and a second set of data for Arnica drops at 6x, 6c, and 30c. A single registration certificate is then issued for each set. A subsequent potency of one of these products submitted at a later date attracts an additional fee and is covered by a separate certificate.

5.3 Format of presentation

Data should be submitted in two separate volumes.

Volume 1 should include:

- Application form
- Manufacturing authorisation(s)
- QP Declaration (Declaration of GMP Compliance covering all sites involved in the manufacture of the active substance)
- Braille Declaration
- Any registrations or authorisation issued by other EC member states
- Labelling mock-ups

Volume 2 should include:

- Production and control of homeopathic stocks
- Production and control of the dosage form
- Stability of the dosage form

There is no requirement for an expert report.

5.4 Homeopathic stocks

The homeopathic stock should be named with reference to an appropriate pharmacopoeial monograph. Information should be provided on the source material (e.g. name of supplier, batch data), details concerning the preparation of the homeopathic stock, and batch data. In some cases additional information may be requested before the application is approved.

If no monograph is available for the material or the homeopathic stock, a suitable in-house specification should be developed, set out in a manner similar to that of a pharmacopoeial monograph. Adequate justification should be given for this specification. Homeopathic stocks should be prepared by a homeopathic manufacturing method described in an appropriate pharmacopoeia.

Reference should be made to the European Pharmacopoeia (Ph.Eur), French or German Homeopathic Pharmacopoeias, or to the Homeopathic Pharmacopoeia of the United States.

The homeopathic use of the stocks used to prepare the medicinal product should be justified by reference to a recognised homeopathic Materia Medica.

5.5 Dosage form

Where the diluted homeopathic stock is to be added to a base (e.g. cream, ointment or pillule) details of the manufacture of that formulation must be provided.

If the information applies to a number of products produced by one company it can be provided as a formulation master file.

5.6 Stability

Stability testing (in accordance with ICH/CHMP guidelines) of the dosage form is necessary to ensure that the finished product specifications are met throughout the claimed shelf life under the designated storage condition.

Evidence is required to show that the dosage form remains stable over the claimed shelf life at a specified temperature.

6 MANUFACTURE AND WHOLESALE

6.1 Manufacturers' authorisation

Article 40 of EU Directive 2001/83/EC, as amended, requires all manufacturers of medicinal products, including importers of products from outside the EEA, to hold an appropriate authorisation. In Ireland the authorisation is in the form of a manufacturer's authorisation, issued by the HPRA or the competent authority of another Member State. To obtain an authorisation, an applicant must complete an application for a manufacturer's authorisation (Please see the 'Publications and Forms' section of www.hpra.ie).

The HPRA only issues an authorisation when it is sure the information contained in the application is accurate. It is conditional on the holder being in a position to meet approved standards of Good Manufacturing Practice (*The Rules governing Medicinal Products in the European Union, Volume 4. Medicinal Products for Human and Veterinary use: Good Manufacturing Practices*).

6.2 Compliance with Good Manufacturing Practice

Detailed guidelines on the principles of good manufacturing practice (GMP) are published by the European Commission in the 'Guide to Good Manufacturing Practice for Medicinal Products'. Holders of manufacturers' authorisations are required to manufacture medicinal products in accordance with the principles and guidelines of Good Manufacturing Practice.

6.3 Import authorisation

EU Directive 2001/83/EC, as amended, requires all importers of medicinal products from outside the EEA countries to hold an authorisation. In Ireland the authorisation is in the form of a manufacturer's authorisation. Applicants should have available the services of a Qualified Person (Article 48 of Directive 2001/83/EC, as amended).

6.4 Qualified persons

Articles 48 and 49 of Directive 2001/83/EC, as amended, require the holder of a manufacturer's authorisation to appoint a Qualified Person (QP) who is to be named on the licence. The QP's duties are specific and are intended to ensure that every batch of medicinal products has been manufactured and/or assembled and checked in accordance with legal requirements. A QP has a personal responsibility for ensuring that the required tests and controls are carried out and must sign or certify, for each batch, that the appropriate tests have been carried out and that it complies with the relevant requirements.

Article 49 of EU Directive 2001/83/EC, as amended, and Schedule 5 of S.I. No. 539 of 2007, Medicinal Products (Control of Manufacture) Regulations 2007, prescribe the qualifications for appointment as a QP. Candidates for appointment as QPs must meet specific educational and vocational requirements.

6.5 Inspection

Article 111 of Directive 2001/83/EC, as amended requires the Competent Authority to ensure, by inspection at appropriate intervals, that authorisation holders are complying with the legal requirements. Inspectors are empowered to inspect all authorised sites, to take samples and to examine all relevant documents. Following an inspection, the authorisation holder receives a copy of the inspector's report.

7 SALE AND SUPPLY

7.1 Route of sale and supply

The system by which medicines are classified as prescription only (POM), over the counter in pharmacies or general sale applies equally to registered homeopathic products. Article 14 of Directive 2001/83/EC, as amended, requires the classification of a homeopathic product to be determined at the time of registration, on a product-by-product basis. Essentially the same rules are followed for registered homeopathic products as apply to all medicinal products.

7.2 Classification of registered products

Since registered homeopathic products are sufficiently dilute to guarantee safety and are for oral or topical use, classification for general sale through non-pharmacy outlets is usually appropriate. However, the Medicinal Products (Prescription and Control of Supply) Regulations 2003, as amended by Medicinal Products (Prescription and Control of Supply) Regulations 2005 and Medicinal Products (Control of Placing on the Market) Regulations 2007, apply to homeopathic medicinal products.

8 VARIATION, RENEWAL AND SUSPENSION OF CERTIFICATES

8.1 Application for variations

Changes to a certificate of registration or the data supplied with the application must be submitted to the HPRA for approval before implementation. An application form for variations is available on the 'Publications and Forms' section of www.hpra.ie.

8.2 Duration of certificates

Certificates are normally valid for 5 years from the date of issue. One renewal is required; following this certificates are valid indefinitely. If certificates are not renewed they will automatically lapse after 5 years.

8.3 Renewal of certificates

Certificate holders should apply for renewal at least six months before the expiry date. If a certificate lapses a new application is required, and the product can not be marketed until a new certificate has been issued.

~~Further details and the application~~To apply for a renewal of a registration certificate for a homeopathic medicinal product form please use the 'Application for a registration certificate for a homeopathic medicinal product form' available on the 'Publications and Forms' section of www.hpra.ie.

8.4 Refusal

The HPRA may refuse an application for a product registration where:

- The applicant fails to submit information, documents, samples or other materials in accordance with the Directive 2001/83/EC, as amended.
- The HPRA is satisfied, following examination of such information, documents, samples or other materials that:
 - o the information contained in or furnished in connection with the application is found to be incorrect, or
 - o the product is harmful under normal conditions of use, or
 - o the qualitative or quantitative composition of the product to which the application relates is not as declared by the applicant, or
 - o the labelling or package leaflet does not comply with the provisions of Directive 2001/83/EC, as amended.

8.5 Suspension and revocation

A certificate of registration may be suspended or revoked if, for example, the product proves to be harmful in the normal conditions of use, where its composition is not as declared or where any material or information provided in connection with the application is found to be incorrect.

8.6 Withdrawal from the market

The HPRA may require a product to be withdrawn from the market if, for example, it proves harmful in the normal conditions of use, if its composition is not as declared or if details of controls have not been provided as requested.

A certificate holder may also voluntarily withdraw a certificate of registration. For details of the requirements, please see 'Guide to Withdrawal of Authorisations or Certificates for Human Medicines' on the 'Publications and Forms' section of www.hpra.ie.

8.7 Marketing status

The Medicinal Products (Control of Placing on the Market) Regulations, 2007, require the certificate holder to notify the HPRA of the date that the product was actually marketed and to notify the HPRA no less than two months in advance of a cessation in marketing, either temporary or permanent, unless there are exceptional circumstances. For details of the requirements, please see 'Guide to Notification of Marketing Status of Human Medicines' on the 'Publications and Forms' section of www.hpra.ie.

9 LABELLING

9.1 Labelling of registered products

The labelling of all containers and packages must include clear mention of the words 'homeopathic medicinal product'. In addition, specific information is required on the labelling, as set out in Article 68 and 69 of EU Directive 2001/83/EC, as amended. The labelling of registered homeopathic products cannot include any other information.

It should be noted that Article 56a of Directive 2001/83/EC as amended, requires certain information on the packaging to be in Braille for the blind and partially sighted. Please see information on these requirements in the 'Guide to Labels and Leaflets of Human Medicines' on the 'Publications and Forms' section of www.hpra.ie.

General guidance on labelling is given in Appendix E, and guidance on the labelling requirements for registered homeopathic products in Appendix F and small containers specifically in Appendix G.

9.2 Small containers

All the required particulars must appear on either the container or the package; there is no stipulation as to where specific items must appear, as long as all the specified information is present. Where the container itself is not more than 10 ml reduced labelling, as specified in Appendix G, may be applied.

9.3 Leaflets

The supply of a leaflet with the product is optional. However, if a leaflet is supplied, it must contain all the particulars required for the correct use of the product in accordance with labelling, and no other information.

9.4 Changes to approved labelling

All changes to labelling which relate to particulars on the registration certificate must be submitted for approval before supplying the product. Changes to labelling caused by related changes to the registration certificate should be submitted with the variation application.

10 ADVERTISING

10.1 What constitutes advertising?

The term advertisement includes virtually any communication which brings the availability of a medicinal product to the attention of the public or of practitioners. It covers newspapers, journals, internet, e-mail, direct mail advertising, letter, posters, photographs, films and radio and TV broadcasts as laid down in EU Directive 2001/83/EC, as amended, and the Medicinal Products (Control of Advertising) Regulations 2007.

10.2 Advertising of registered products

Registered homeopathic products are subject to the provisions of EU Directive 2001/83/EC, as amended, on the advertising of medicinal products for human use, with the exception of Article 87(1). However, only the information specified in Article 69(1) may be used in the advertising of such medicinal products. Additionally, the Medicinal Products (Control of Advertising) Regulations 2007 apply to registered homeopathic medicinal products.

10.3 Acceptable advertising

Only the information specified in labelling requirements may be used in the advertising of registered homeopathic products. No mention of a specific indication may be made. Leaflets available at the point of sale are subject to the same restrictions. Reference books and periodicals available at the point-of-sale may describe the use of homeopathic substances but must not promote any particular registered product.

10.4 Unacceptable advertising

The rules on advertising are set out in EU Directive 2001/83/EC, as amended. It is important to note that the following are not acceptable:

- Advertising, for registered homeopathic products, which makes any reference to the role of the HPRA or its committees
- Recommendations by scientists, health professionals or others who, because of their celebrity status, could encourage the consumption of registered homeopathic products
- Advertising which suggests that health may be enhanced by taking the product

10.5 Monitoring

The Compliance department of the HPRA monitors advertising and may take appropriate action to maintain standards. Other bodies, including the Department of Health and Children, the Office of the Director of Consumer Affairs and the Advertising Standards Authority are also involved in monitoring.

APPENDIX A CONTACT POINTS WITHIN THE HPRA

Postal address: Health Products Regulatory Authority,
Kevin O'Malley House,
Earlsfort Centre,
Earlsfort Terrace,
Dublin 2.

Contact details: Tel: 00 353 1 6764971
Fax: 00 353 1 6767836
Website: www.hpra.ie

The following sections can all be contacted through the main HPRA number, see above:

Homeopathic Medicines
Receipts and Validation
Finance and Corporate Affairs
Compliance

APPENDIX B LEGISLATION

EU

Directive 2001/83/EC, as amended, on the Community code relating to medicinal products for human use – available on the European Commission website

Irish

Medicinal Products (Control of Placing on the Market) Regulations, 2007, S.I. No. 540 of 2007

Medicinal Products (Control of Advertising) Regulations 2007, S.I. No. 541 of 2007

Medicinal Products (Control of Wholesale Distribution) Regulations 2007, S. I. No. 538 of 2007

Medicinal Products (Control of Manufacture) Regulations 2007, S.I. No. 539 of 2007

Medicinal Products (Prescription and Control of Supply), Regulations 2003
S.I. No. 540 of 2003, as amended by Medicinal Products (Prescription and Control of Supply)
(Amendment) Regulations 2005, S.I. No. 510 of 2005

Note: This is not a comprehensive list of all the relevant regulations, further details available on the Office of the Attorney General website.

APPENDIX C QUALITY AND CONTROL OF HOMEOPATHIC STOCKS

AC1 INTRODUCTION

Applications to register homeopathic medicinal products should be accompanied by supporting data on the production and control of the homeopathic stock. The special nature of homeopathic medicinal products is such that tests on the finished products are of limited value with regard to quality control. The quality and control of stocks is therefore of considerable importance in assuring the consistent quality of the finished product. This guidance note interprets Article 15 of the EU Directive 2001/83/EC, as amended, which requires that the pharmaceutical quality and batch-to-batch homogeneity of the products concerned should be demonstrated.

AC2 PREPARATION OF STOCKS

Homeopathic stocks must be prepared in accordance with a manufacturing method set out in a homeopathic pharmacopoeia. Where the manufacturing process departs from that of the pharmacopoeia, other justification should be provided. The European Pharmacopoeia, the German Homeopathic Pharmacopoeia, the Homeopathic Pharmacopoeia of the United States and homeopathic monographs cited in the French Pharmacopoeia may be used. Applicants should refer to the appropriate section of the homeopathic pharmacopoeia.

Raw materials and vehicles used should be of an appropriate pharmacopoeial quality unless adequately justified (see section below on raw materials).

The quantity of raw material and vehicles used for each batch should be specified. If batch sizes vary, then a representative batch size should be stated.

The nature of containers used for the maceration process should be described, together with the times and conditions used.

AC3 CONTROL OF STARTING MATERIALS

AC3.1 Raw Materials

AC3.1.1 Specifications

Raw materials used should comply with the section on raw materials set out in individual monographs of a homeopathic pharmacopoeia.

In some instances it may be necessary to include controls additional to those specified in the individual monograph, for example;

Plant material

- Microscopic examination
- Limit tests for pesticides and micro-organisms
- Description of the part of the plant used

Zoological material and minerals of natural origin

- Bioburden controls or absence of pathogens with particular reference to transmissible agents

Where no monograph exists, applicants are required to draw up a suitable monograph for the raw material, taking into account the following characteristics as appropriate to the nature of the raw material (which may be botanical, zoological or chemical in origin).

- Description, identity, name and appearance
- Assay
- Melting point, solubility
- Microbiological contamination
- Impurities (including sulphated ash, foreign material)
- Loss on drying

In some cases, for example certain minerals or organic substances, it may be necessary to refer to the European Pharmacopoeia.

Established guidelines should be taken into account, for example the Committee for Human Medicinal Products (CHMP) guidelines on biological and botanical raw materials and the Homeopathic Medicinal Products Working Group (HMPWG) of the Heads of Agencies documents on *Points to consider on Safety of Homeopathic Medicinal Products from Biological Origin* and *Points to consider on Non-clinical Safety of Homeopathic Medicinal Products of Botanical, Mineral and Chemical Origin*. Additional information should be provided as appropriate.

AC3.1.2 Supporting data

Applicants should provide data to demonstrate compliance with the proposed monograph (batch data or certificates of analysis for three batches). Where additional controls are necessary, evidence should be provided to show that these controls are met.

Where it is necessary for an applicant to establish a monograph, the controls and limits applied should be justified and analytical methods validated.

Supporting data for plant material should include details of the source of the material, cultivation and time of harvesting. Details of any drying procedure used and any treatment to reduce levels of microbial contamination should be stated. It is preferable for plant material to be grown organically. (See Guideline on Good Agricultural and Cultivation Practices (GACP))

Supporting data for zoological material should include information on the collection, treatment and storage of the source material.

AC3.2 Vehicles

Vehicles used for the preparation of homeopathic stocks should be of an appropriate pharmacopoeial quality unless justified.

AC4 CONTROL OF STOCKS

Applicants should provide satisfactory evidence in the form of batch data or certificates of analysis to demonstrate that the stock meets the agreed specification.

Where a stock is not the subject of an approved monograph, the specifications used to control the stock should be adequately justified and analytical methods validated.

Where additional controls are used for monographed stocks, evidence should be provided to show that these are adhered to.

AC5 STABILITY OF STOCKS

Evidence of stability should be provided unless stocks are freshly prepared for immediate use.

The stability of homeopathic stocks should be established with due reference to the specification used to control the stock at the time of preparation.

Stability should be monitored over a storage period in controlled conditions (e.g. temperature and humidity – ICH/CHMP stability guidelines) and an appropriate shelf-life established, on the basis of the results. This work may be carried out on an on-going basis, and applicants may wish to extend the shelf-life in the light of available information.

Manufacturers of stocks should provide clear advice concerning storage conditions, for example, below 25°C, protected from light. Diluted stocks should be assigned the same shelf-life (expiry date) as the original stock.

AC6 JUSTIFICATION OF THE HOMEOPATHIC USE OF THE STOCK

Reference should be made to a suitable Materia Medica such as Clarke or Boericke. Reference can also be made to the List of Stocks whose Homeopathic Use is Justified as published by the HMPWG on the HMA website. Where a stock has not been included in a Materia Medica or on the above list, appropriate literature references should be provided.

APPENDIX D MANUFACTURE AND CONTROL OF DOSAGE FORMS

AD1 INTRODUCTION

Applications to register homeopathic medicinal products should be accompanied by supporting data on the production and control of the dosage form as laid down in the EU Directive on Human Medicines (2001/83/EC) as amended; the provisions of the quality standards applied to homeopathic medicines are similar to those applied to all other medicinal products for human use. The special nature of homeopathic products is such that where manufacturing processes for dosage forms are standardised, the supporting data can be held in a master file on the formulation to which the applicant may cross-refer. Due to the extremely low levels of stocks present in the dosage form, it is particularly important to ensure that adequate planning and in-process control is applied to the manufacturing process in order to ensure batch homogeneity. These guidelines outline the general requirements for the accompanying data, taking account of the variety of homeopathic dosage forms, which are subject to registration.

AD2 FORMULATION MASTER FILES

Applicants may choose to present data on 'inert' or 'un-medicated' dosage forms in the form of a formulation master file to which they may cross-refer following its approval.

The Formulation Master File should contain the following information:

- Formulation details
- Development pharmaceuticals
- Container to be used for marketing
- Method of manufacture, in-process controls, including application of the diluted stock
- Specification of inert or un-medicated dosage form
- Batch data of inert or un-medicated dosage form
- Stability of inert or un-medicated dosage form

AD3 FORMULATION

Complete Composition

Full details of the formulations should be provided for each product, including the theoretical composition of excipients in the final formulation.

Development Pharmaceutics

Details should be provided of any development work, which is relevant to the formulation such as preservative efficacy data for topical creams, oral liquids and eye drops. The role of the excipients should be described.

Container

A description of the container and closure should be provided, including specifications.

AD4 MANUFACTURE

Applicants should refer to the method set out in a named homeopathic pharmacopoeia and should provide supplementary information as set out below. Applicants are expected to comply with GMP requirements (*The Rules governing Medicinal Products in the European Union, Volume 4. Medicinal Products for Human and Veterinary use: Good Manufacturing Practices*).

Batch size and manufacturing formula

Details of a typical batch size should be provided. The quantity of stock to be added to the dosage form, and the degree of dilution of the stock prior to it being added should be declared.

Manufacturing process

The key elements of the manufacturing process and any standard operating procedures used should be summarised. Any sterilisation procedures should be described.

In-process controls

Where in-process controls are used, these should be stated, for example during the dilution process.

Process validation

Information on process validation should be made available, particularly with regard to more sophisticated dosage forms. For sterile products (eye drops) an accepted pharmacopoeial method should be used.

Specifications

Specifications of excipients to be used in the un-medicated dosage form should be declared. Container specifications should be listed.

AD5 FINISHED PRODUCT SPECIFICATION

The finished product specification should control the organoleptic and physical characteristics of the product. An identity test should be included for the stock at low dilutions. The finished product specification should take account of any special characteristics of the dosage form. For example, creams might include a control for preservatives and eye drops should be sterile.

Analytical Controls

All methods used should accord with a pharmacopoeia (e.g. Ph.Eur.). Where a pharmacopoeial method is not available or appropriate, a suitable, validated alternative should be used.

Batch Data

Batch data should be made available for at least three batches, which should preferably be at production scale.

AD6 DILUTION AND POTENTISATION

Details of the homeopathic method used for dilution and potentisation should be provided, together with the method used to incorporate the diluted stock into the un-medicated dosage form. Validation data should be provided to demonstrate that the process consistently yields a uniform product. The quality and quantity of diluent should be described, and the details of any in-process controls provided.

AD7 STABILITY STUDIES

Stability studies should be carried out in the container for marketing and should be conducted at a controlled temperature or range of temperatures (ICH Guidelines). The extent of testing to be carried out requires careful consideration and depends upon the nature of the product. Examples of what might be required include preservative efficacy data for creams, or maintenance of alcohol content for oral liquids.

The stability of tablets or granules medicated using high dilution of stock can be established and the results extrapolated to other tablets provided an identical container and manufacturing process are used. The same principle applies to liquid products of similar composition.

For more complex dosage forms such as creams or multi-dose eye drops, stability should be evaluated for individual products.

APPENDIX E GENERAL LABELLING REQUIREMENTS

General labelling requirements are laid out in the EU Directive 2001/83/EC, as amended.

Legibility

Labelling should be legible, indelible and comprehensive. It should be either in the English language only or in English and one or more other languages (provided that the same particulars appear in all languages). Companies should supply an undertaking that the other language(s) provide the same particulars.

Print size or type

There is no minimum print size laid down by regulations. All labels must be easily read under normal circumstances, and companies must have regard to this when considering print size, colour and layout.

Concertina and fold-out labels/leaflets

This type of leaflet/label attached to a container is acceptable so long as the specific labelling requirements of the homeopathic registration scheme are met.

Information on inner surface of packaging

Information printed on the inner surface of packaging is not acceptable. All the labelling requirements must be shown on the outer surface of the packaging.

APPENDIX F LABELLING OF REGISTERED HOMEOPATHIC PRODUCTS

The following particulars must appear on the containers, packages and on the package leaflets of homeopathic medical preparations, and no other information should be included, as provided for by EU Directive 2001/83/EC, as amended.

- the words 'homeopathic medicinal product',
- the scientific name of the stock or stocks followed by the degree of dilution, making use of the symbols of the pharmacopoeia containing the description of the relevant homeopathic manufacturing procedure used for the manufacture of the preparation concerned; where two or more stocks are present the scientific name can be supplemented by an invented name,
- the name and address of the person responsible for placing the product on the market and, where appropriate, of the manufacturer,
- the method of administration and, where appropriate, the route of administration,
- the expiry date stating the month and year,
- the pharmaceutical form,
- the contents of the sales presentation,
- any special storage precautions,
- any special warnings necessary for the medical preparation concerned,
- the manufacturer's batch number,
- the registration number specified in the certificate of registration,
- the words 'homeopathic medical product without approved therapeutic indications',
- a warning advising the user to consult a doctor if the symptoms persist.

APPENDIX G LABELLING OF SMALL CONTAINERS

As specified in the Directive all the required particulars must appear on either the container or the package; where the container itself is not more than 10 ml reduced labelling may be applied. In this case the minimum labelling requirement for small containers of registered homeopathic medicinal products should be as follows:

- Clear mention of the words 'Homeopathic medicinal product' as part of the required statement 'Homeopathic medicinal product without approved therapeutic indications',
- The scientific name of the stock(s) followed by the degree of dilution, supplemented by an invented name where required,
- The method of administration,
- The expiry date of the product in clear terms,
- The name of the holder of the registration certificate,
- The contents of the presentation, specified by weight, volume or number of doses,
- The manufacturer's batch number, and
- That the outer packaging must in all circumstances contain all of the labelling particulars, including those already stated on the small container.