

***THE HOMEOPATHIC NATIONAL
RULES SCHEME***

***BRIEF
GUIDANCE FOR MANUFACTURERS
AND SUPPLIERS***

September 2006

Purpose and scope of the National Rules Scheme

1. The purpose of the scheme

Homeopathic medicinal products on the UK market are currently authorised either with Product Licences of Right (PLRs), or with certificates of registration under the Simplified Registration Scheme”. Many of the products with PLRs carry indications, mainly for minor conditions suitable for self medication, whereas registered products, which are assessed only for safety and quality, are not permitted to be labelled with therapeutic indications. No new PLRs have been granted since the Medicines Act came into force in the early 1970’s.

Conventional medicinal products for human use are licensed with a “marketing authorization”. The 2001 Directive sets out the particulars and documents which must accompany an application for a marketing authorization, including a requirement that the applicant submit the results of pre-clinical tests and clinical trials. Because of the philosophy of homoeopathy and the nature of the products, it is difficult to establish efficacy for homoeopathic products by way of clinical trials.

However, article 16(2) of the 2001 Directive permits member states to introduce national rules for the pre-clinical tests and clinical trials of certain homeopathic medicinal products, in order that those products can be authorised with marketing authorizations. (Apart from special rules on safety and efficacy data, all the other rules applicable to applicants for and holders of marketing authorizations apply.) This has been achieved in the UK by the Medicines for Human Use (National Rules for Homoeopathic Products) Regulations 2006, which amend the Medicines for Human Use (Marketing Authorizations Etc.) Regulations 1994 (“the 1994 Regulations”).

As the rules do not require rigorous clinical data, indications are limited to the relief or treatment of minor symptoms or minor conditions. i.e symptoms or conditions which can ordinarily and with reasonable safety be relieved or treated without the supervision or intervention of a doctor. Indications for serious conditions are prohibited.

In this guidance, references to “the National Rules Scheme” are to the scheme introduced by the 2006 Regulations, under article 16(2) of the 2001 Directive.

You should note that this guidance represents MHRA’s view of the law and is not a definitive statement of the law – that can only be given by the courts. Whilst MHRA is happy to provide guidance to companies, it cannot give you legal advice. If you are in any doubt about your professional obligations you should always consult your professional advisors.

2. Products outside the scope of the Directive / Exemptions

Some products (see article 3 of the 2001 Directive) are outside the scope of the Directive, and do not therefore require a marketing authorization. However, domestic requirements for licences under the Medicines Act 1968 may still apply.

In addition, Schedule 1 to the 1994 Regulations contains certain exemptions from the requirement to hold a marketing authorization, including the situation where medicinal products are supplied in response to bona fide unsolicited orders, formulated in accordance with the specifications of a doctor and for use by individual patients on the doctor's direct personal responsibility, in order to fulfil the special needs of those patients.

3. Products eligible for authorization under the National Rules Scheme

The National Rules Scheme applies to any homoeopathic medicinal product which does not satisfy the requirements of the simplified scheme (see article 14(1)) of the 2001 Directive) and which is indicated for the relief or treatment of minor symptoms or minor conditions in humans.

4. Who should apply for a marketing authorization under the scheme?

If a homoeopathic medicinal product is to be marketed in the UK under the National Rules Scheme a marketing authorization must be held by the person responsible for placing it on the market, before it is placed on the market.

Applications for authorization may be made by any person who wishes to place products on the market under the scheme. However, a homeopathic marketing authorization may only be granted to an applicant established in the European Community.

Homoeopathic medicinal products which are not authorized either by registration, authorization or PLR may only be sold or supplied if there is an applicable exemption.

Companies should also be aware of the need for the following licences:

- **Manufacturers**

A company which manufactures, or which proposes to manufacture, homoeopathic medicinal products will need a *manufacturer's licence*. "Manufacture" includes all processes carried out in the course of making the product, including diluting, mixing and quality control. A manufacturer's licence is also needed for "assembly" (e.g. filling and labelling containers).

- **Wholesale dealers**

A company which acts as a wholesale dealer, or which proposes to do so, for homoeopathic medicinal products other than those it manufactures itself, will need a *wholesale dealer's licence*. For further information see **Guidance Note No. 6**. This leaflet is available from the MHRA Information Centre.

- **Importers**

A company which imports homoeopathic medicinal products from non-EC countries will need a *wholesale dealer's (import) licence*..

Further information may be obtained from the MHRA website.

How to apply for an authorization

Information on how to apply for an authorization may be found in Special Mail 5, published on the MHRA website.

The approval process

5. Assessment of the application

When your application *and* fee have been received, the assessor will check the eligibility of the application. We will inform you if the product is not eligible for authorization under the scheme.

The data accompanying your application will be assessed, and if this is satisfactory the Licensing Authority will issue a marketing authorization. If there are deficiencies in your application, the assessor will inform you and attempt to resolve these wherever possible so that the application process can be taken forward.

6. Advisory Board on the Registration of Homoeopathic Products

If advice is needed on any issue relating to safety, quality or indications, the application will generally be referred to the Advisory Board on the Registration of Homoeopathic Products (“the Board”). The Licensing Authority is required by the 1994 Regulations to consult the “appropriate committee” (which will usually be the Board in relation to marketing authorizations under the National Rules Scheme) before rejecting any application on the grounds of safety, quality or efficacy.

The Board may advise that an authorization should be granted. However, if the Board considers that an authorization should not be granted, or should be granted otherwise than in accordance with the application, the company will be informed and will be given the opportunity to make representations to the Board.

7. Persons Appointed

If, following representations to the Board by the company, the Licensing Authority decides not to grant a marketing authorization, or to grant it otherwise than in accordance with the application, the company will generally have the opportunity to appeal to a persons appointed.

8. Issue of Marketing Authorizations

Following approval, the homoeopathic marketing authorization will be sent in the post. On receipt you will be able to market the product and show the NR authorization number on the label.

9. Time scales for approval

The 2001 Directive requires the Licensing Authority to take all appropriate measures to process applications within 210 days. However, in some cases, the clock will stop running e.g. if the licensing authority requires the applicant to supplement the particulars accompanying his application.

10. Information on progress

For information on the progress of your application, contact the Regulatory Information Service (RIS) desk. by telephoning on 020 7084 3400 or by e-mail at Ris.Hom@mhra.gsi.gov.uk

Please do not make repeated checks on progress as this can hold up assessment work.

Accompanying data

11. Data required

As with applications for conventional medicinal products, information must be provided in order to demonstrate the pharmaceutical quality and batch-to-batch homogeneity of the products concerned, their safety and their efficacy.

An application for a marketing authorization for a product under the National Rules Scheme is the same as any other application for a marketing authorization – except for the rules on pre-clinical and clinical data. Therefore, the applicant must follow the rules set out in the 2001 Directive (see Articles 8, 10, 10a, 10b 10c and 11 – and see regulation 4 of the 1994 Regulations), apart from the special rules which apply in relation to pre-clinical and clinical data. Similarly the applicant must follow Annex I to the 2001 Directive, except for sections 2.4 to 2.7 and modules 4 and 5. Instead of submitting

Modules 4 and 5 as described in Annex I, the applicant must submit the data required by the new Schedule 1A to the 1994 Regulations. In other words, the application is submitted like any other marketing authorization application – except that Modules 4 and 5 will be the data required by the new legislation.

Where there references in Annex I (other than in sections 2.4 to 2.7 and modules 4 and 5) to non-clinical reports, non-clinical documentation or non-clinical data; or to clinical study reports, clinical documentation and clinical data, you should treat those references as if they were a reference to the data required by the new legislation.

You should also follow the Notice to Applicants, except insofar as it relates to pre-clinical tests and clinical trials.

You should note that the third paragraph of article 23 of the 2001 Directive (requirement to supply new information) applies equally to information which has been provided under the new scheme.

Guidance on the data which should be provided is set out below. However, you should refer to the legislation for the full requirements:

(i) Quality

The data relating to quality is provided as Module 3. Detailed rules are set out in Annex I to the 2001 Directive and the Notice to Applicants. Part III of Annex I to the 2001 Directive, section 3 (“homoeopathic medicinal products”) sets out modifications for homoeopathic products, including homoeopathic products which are the subject of an application for a marketing authorization under the National Rules Scheme.

(ii) Safety

The safety data which must be submitted by the applicant is set out in Schedule 1A to the 1994 Regulations – see Parts 1 and 2. In some cases, the applicant does not need to supply any data on safety – see below.

When an applicant is required to submit data on safety, he must follow the rules in Part 2 of the new Schedule 1A to the 1994 Regulations.

When is safety data not required?

The applicant is not required to provide any data on the safety of the product if one of the following applies:

- a. the product is intended to be administered orally and is derived from a stock which is commonly present in food;
- b. the product is derived from a stock present in a licensed medicinal product (i.e. a product which has a marketing authorization, certificate of registration, traditional

herbal registration or product licence), and that medicinal product is available by way of general sale, provided that the product which is the subject of the application has the same degree of dilution and the same route of administration as the licensed product;

- c. the product is derived from a stock diluted to at least 10^{24} and is not a material of biological origin.

However, if the applicant wants to rely on one of these exemptions, he must provide a written statement that the product meets the conditions of either (a), (b) or (c).

Where safety data is required

If the product does not fall within (a), (b) or (c) above, the applicant must provide safety data.

This should address all relevant aspects of safety, including the following: pharmacology, pharmacokinetics and toxicology (including toxicity, genotoxicity, reproductive and developmental toxicity and local tolerance).

The safety data should be “scientific data” i.e. study reports in relation to the product which is the subject of the application and/or published scientific literature. However, where the applicant has made reasonable attempts to obtain scientific data in relation to an aspect of safety and is satisfied that there is none, or considers that the available scientific data is inadequate, he may submit data other than scientific data. For example, summary of any reported adverse events together with a discussion of these events in relation to product usage..

The applicant should provide with the data:

- A table of contents;
- An evaluation of the scientific data, including an explanation as to how the data demonstrates that the product has an acceptable level of safety;
- If data other than scientific data has been provided, the applicant should confirm in writing that he meets the conditions set out above, and explain why an acceptable level of safety can be demonstrated even without the scientific data.

An expert report on the safety data should also be provided, in accordance with article 8 and 12 of the 2001 Directive (paragraph 1(3) of Schedule 1A to the 1994 Regulations).

The safety of the product will then need to be monitored for the duration of the authorization. Companies should be aware of the new pharmacovigilance requirements for electronic report of adverse reactions and submitting Periodic Safety Update Reports. Guidance may be found on the MHRA website.

(iii) Efficacy

The applicant must submit data on the efficacy of the product which is the subject of the application - see Schedule 1A to the 1994 Regulations, Parts 1 and 3.

It should be noted that results of clinical trials are not required to support applications for marketing authorizations under the National Rules Scheme. However, the applicant must provide one or more of the following:

- Study reports in relation to the product which is the subject of the application,
- Published scientific literature;
- Homoeopathic provings.

Whatever data is provided, it should be sufficient to demonstrate that UK homeopathic practitioners would accept the efficacy of the product for the indications sought.

This evidence should be presented in Module 5 of the dossier. The applicant must provide a table of contents, and an evaluation of the data, including an explanation as to how the data establishes that the product has a recommended level of efficacy in the indications sought.

12. Minor symptoms and minor conditions

As set out in the new regulation 4(1B) to the 1994 Regulations, only products which are indicated for the relief of minor symptoms and minor conditions in humans are eligible for a marketing authorization under the National Rules scheme. For these purposes, minor symptoms are those which can ordinarily and with reasonable safety be relieved or treated without the supervision or intervention of a doctor.

It is not possible to provide an exhaustive list of indications that would not be acceptable. Nevertheless, the following are **examples** of indications that **we do not consider would be permitted** under the National Rules Scheme:

- Bone diseases
- Cardiovascular diseases
- Chronic insomnia
- Diabetes and other metabolic diseases
- Diseases of the liver, biliary system and pancreas
- Endocrine diseases
- Genetic disorders
- Joint, rheumatic and collagen diseases
- Malignant diseases
- Psychiatric conditions
- Serious disorders of the eye and ear

Serious gastrointestinal diseases
Serious infectious diseases including HIV-related diseases and tuberculosis
Serious neurological and muscular diseases including epilepsy
Serious renal diseases
Serious respiratory diseases
Serious skin disorders
Sexually transmitted diseases
Treatment and Prevention of malaria

Again, it is not possible to provide an exhaustive list of conditions not requiring medical supervision. However, typical **examples** of conditions that **could be covered** include:

Indigestion, heart burn, hyperacidity, dyspepsia, halitosis (bad breath) or flatulence
Colicky pain, stomach ache or nausea, occasional or non-persistent diarrhoea or constipation
Travel sickness or related symptoms
Minor skin infections, relief of pruritus or exanthematous rashes of childhood infection and boils, athlete's foot
Common colds, coughs, conditions commonly referred to as influenza and similar upper respiratory tract infections
Minor acute inflammatory conditions of the buccal cavity and pharynx including sore throats
Muscular pain and stiffness including backache, sciatica, lumbago, fibrositis, rheumatic pain and cramp.
Hay fever, rhinitis and catarrh.
Blocked-up sinuses.
Headache including migrainous headache
Neuralgia
Difficulties falling asleep
Agitation, anxiety, irritability, nervous tension, stresses, strains, tenseness

Applicants wishing to claim indications for anything other than minor symptoms or minor conditions would need to apply for a full marketing authorization which is supported by evidence of efficacy from controlled clinical trials.

13. Legal Status

The normal procedure of assigning a legal status applies.

14. Labelling and Product literature

The usual requirements for product labelling, the Patient Information Leaflet and Summary of Product Characteristics (SPC) apply including the need for warnings and contraindications as appropriate. Companies should also be aware of the new

requirements for consultations with patient groups, or “user testing”, on patient information leaflets and for Braille labelling.

The labelling should also refer, in clear and legible form, to the homoeopathic nature of the product (article 68 of the 2001 Directive).

The authorization number will be distinguished from full marketing authorizations (MAs) and Homeopathic Registration certificates (HRs), by using the specific prefix, NR (National Rules authorizations).

15. Presentation of data

One set of data i.e. one application should cover a series of dilutions relating to one pharmaceutical form. For example, one set of data is required for Arnica tablets at dilutions of 6x, 6c, 30c and a second set of data for Arnica drops at 6x, 6c, 30c.

16. Format of presentation

Data should be presented in the CTD format.

Other Requirements

Under the 1994 Regulations, all applicants for, and holders of, a marketing authorization must comply with the provisions of Community legislation, including those in the 2001 Directive. The 2001 Directive covers matters such as labelling, advertising and pharmacovigilance, and further guidance is available on the MHRA website. Persons applying for, or holding, a marketing authorization under the new scheme will similarly need to comply with all the relevant Community provisions. In addition, sometimes, the 2001 Directive sets out specific requirements applicable to homoeopathic medicinal products, and you must also comply with those requirements unless they are stated to apply only to “products referred to in Article 14(1)” (these are the simplified scheme products).

Failure to comply with the requirements in the 2001 Directive may be an offence under the 1994 Regulations – see regulation 7 and Schedule 3.