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Review Article

Marketing Authorization of Homeopathic Medicinal Product in Europe: An Overview

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ABSTRACT

The Council of the European Communities stated in the preamble to a directive that homeopathy was officially recognized in certain member states. In any case it was prescribed and used in all member states. In order to harmonize the market of homeopathic products, the council, in Directive 92/73/EEC directed the member states to implement certain changes in their national legislation. Directive 92/73/EEC was replaced by Directive 2001/83/EC on the Community code relating to medicinal products for human use. Member states are required to ensure that homeopathic products (for oral or external use) can be registered by skipping the proof of therapeutic efficacy, provided that there is a sufficient degree of dilution to guarantee the safety of the product; in particular, the product may not contain either more than 1/10,000th of the mother tincture or more than 1/100th of the smallest dose used in medicine, with regard to active principles whose presence in a medicinal product results in the obligation to submit a doctor's prescription.

Key-words: Medicines Evaluation Board (MEB); Homeopathic Drug Master File (HDMF); OTC (Over the Counter drug.

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Introduction

Regulations vary in Europe depending on the country. Some countries like Austria and Germany, no specific regulations exist, while in France and Denmark mandate licenses to diagnose any illness or dispense of any product whose purpose is to treat any illness [1]. Some homeopathic treatment is covered by the national insurance of several European countries, some parts of the United Kingdom, including France, Denmark, and Luxembourg. In other countries, such as Belgium, homeopathy is not covered. In Austria, special requirement like public insurance requires scientific proof of effectiveness in order to reimburse medical treatments, but exceptions are made for homeopathy[1]. In 2004, Germany which formerly offered homeopathy under its public health insurance scheme withdrew this exclusivity, with a few exceptions. The Swiss Government, at June 2005, withdrew insurance coverage for homeopathy and four other complement treatments, stating that they did not meet efficacy and cost-effectiveness criteria. However, following the result of a referendum in 2009 the five therapies were reinstated for a further 6-year trial period from 2012[2].

Homeopathic medicine as a distinct system of medicine is recognised by law in Belgium (1999), Bulgaria (2005), Germany (1998), Hungary (1997), Latvia (1997), Portugal (2003), Romania (1981), Slovenia (2007) and the United Kingdom (1950). The laws in Bulgaria, Hungary, Romania, Latvia and Slovenia explicitly allow the practice of homeopathic medicine to medical doctors only. In Portugal and Belgium the law does not exclude non-medical practitioners, but has not yet been enforced. In Slovenia, although the law permits medical doctors to practise homeopathic medicine, the medical association withdraws or cancel doctors' licenses if they actually practise it[3].

1. ***Provisions Applicable To Homeopathic Medicinal Products***

   A Member State may refrain from establishing a concise, special, simplified registration procedure for the homeopathic medicinal products referred to in Article 14. A Member State must inform the Commission accordingly. The concerned Member State shall allow the use in its territory of homeopathic medicinal products registered by other Member States in accordance with Articles 14 and 15.

According to Article 14 of DIRECTIVE 2001/83/EC only homeopathic medicinal products which satisfy all of the following conditions may be subject to a special and simplified registration procedure:

- they are administered orally or externally,
- no specific therapeutic indication appears on the labeling of the medicinal product or in any information relating thereto,
- there is a sufficient degree of dilution to guarantee the safety of the medicinal product; in particular, the medicinal product should not contain either more than 1/ 10 000th of the mother tincture or more than 1/100th of the smallest dose used in allopathy with regard to active substances whose presence in an allopathic medicinal product results in the obligation to submit a doctor's prescription.

At the time of registration, Member States shall determine the classification for the dispensing of the medicinal product

An application for special, simplified registration may cover a series of medicinal products derived from the same homeopathic stock or stocks. The following documents shall be included with the application in order to demonstrate, the pharmaceutical quality and the batch-to-batch homogeneity of the products concerned[4]:

a) scientific name or other name given in a pharmacopoeia of the homeopathic stock/stocks, together with a statement of the various routes of administration, degree of dilution and pharmaceutical forms to be registered, dossier describing how the homeopathic stock/stocks is/are obtained and controlled, as well justifying its/their homeopathic nature, on the basis of an adequate bibliography,
b) Manufacturing and control file for each pharmaceutical form and a description of the method of dilution and potentization,
c) Manufacturing authorization for the medicinal product concerned,
d) Copies of any registrations or authorizations obtained for the same medicinal product in other Member States, one or more specimens or mock-ups of the outer packaging and the immediate packaging of the medicinal products to be registered,
e) Data regarding the stability of the medicinal product[4].

Since the implementation of Directive 2001/83/EC, all member states of the EU have the opportunity to allow homeopathic medicinal products to enter markets. The procedures that can be followed are the:

a) marketing authorization of a homeopathic
b) for article 14 homeopathic products the decentralized procedure and the mutual recognition procedure

2. *CTD for homeopathic medicinal products*

Since 1 May 2005, all new applications in the European Union must follow the structure of the Common Technical Document (CTD and also for homeopathic medicinal products. Further guidelines for the use of the various CTD modules for homeopathic medicinal products are developed on a European level.

3. *Dossier Requirements*

Directive 2003/63/EC of the Commission of 25 June 2003 contains the Analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products as they have to be expressed in a marketing authorization dossier. The content of all four parts of this Annex 1 apply to all medicinal products, including homeopathic products.

Part III (Particular medicinal products) lays down a number of additional specific requirements for homeopathic medicinal products and the section contains the following provisions:

Part III- HOMEOPATHIC MEDICINAL PRODUCTS

This chapter is mainly dealing with the specific provisions on the application of modules 3 and 4 to homeopathic medicinal products as defined in article 1, clause 5.

- *Module 3*

  Module 3 refers to the documents submitted in accordance with article 15 under the simplified marketing authorization procedure for the homeopathic medicinal products referred to in article 14, clause 1, and to the documents for the authorization of other homeopathic medicinal products as referred to in article 16, clause 1, with the following modifications.

a) *Terminology*

The Latin name of the homeopathic stock described in the marketing authorization dossier must be the same as the Latin title in the European Pharmacopoeia or not appear in the official pharmacopoeia of a member state. Where possible relevant traditional name or names used in each member state shall be indicated.

b) *Control of starting materials*

The particulars and documents on the starting materials, i.e. all of the materials used including raw materials and intermediates up to the final dilution to be incorporated into the finished medicinal product and the application shall be supplemented by additional data on the homeopathic stock.

The general quality requirements shall apply to all of the starting and raw materials as well as intermediate steps of the manufacturing process up to the final dilution to be incorporated into the finished product. If possible, an assay is required if toxic components are present and if the quality of the final dilution to be incorporated into the finished medicinal product cannot be controlled because of the high dilution degree. Each step of the manufacturing process from the starting materials up to the final dilution to be incorporated into the finished medicinal product must be fully described. In the case of dilutions, the dilution steps should be carried out in accordance with the homeopathic manufacturing methods laid down in the relevant monograph of the European Pharmacopoeia or, as, in official pharmacopoeia of a Member State.

c) *Control tests on the finished product*

The general quality requirements shall apply to the homeopathic finished medicinal products; any exception needs to be duly justified by the applicant. Assay and identification of all the toxicologically relevant constituents shall be carried out. If it can be justified that an identification and assay on all the toxicologically relevant constituents are not possible, e.g. during dilution in the finished medicinal product, the quality shall be demonstrated by complete validation of the manufacturing and dilution process.

d) *Stability tests*

The stability of the finished medicinal product must be demonstrated and proved. Stability data from the homeopathic stocks are generally transferable to dilutions/triturations obtained thereof. Suppose if no identification or assay of the active substance is possible due to the degree of dilution and stability data of the pharmaceutical form may be considered.

- *Module 4*

  The provisions of Module 4 shall apply to the simplified registration of the homeopathic medicinal products referred to in article 14, clause one, with the following specifications. Any missing information must be justified, e.g. justifications must be given why demonstration of an acceptable level of safety can be supported although some studies are lacking [5].

4. Assessments

The Novel Foods Unit of the Medicines Evaluation Board (MEB) decides, on evaluating the marketing authorization application prepared by the applicant, whether a homeopathic product is safe and complies with current quality standards for the manufacture of a medicinal product.

Some of the requirements are specific to the homeopathic nature of the medicinal product (such as the dilution factor), but assessment of quality is based to a considerable extent on the same standards as for non-homeopathic medicinal products. The quality of both the raw material and the mother tincture are determined. The consumer is thereby guaranteed a safe homeopathic product of consistent quality. The consumer can also assume that the package leaflet contains accurate, balanced information. This also applies when different homeopathic stocks are used, which is common in homeopathic medicine. These principles are upheld by homeopathic prescribers, the manufacturers' association and the homeopathic consumer organization [6].

5. Side Effects

On the basis of that specified in Directive 2001/83/EC, a homeopathic medicinal product authorized on the basis of the simplified registration procedure in Article 14 is guaranteed harmless. Side effects are thus not expected, but the homeopathic approach suggests that an initial deterioration might develop.

Other homeopathic medicinal products, including OTC products, must also be guaranteed harmless. The MEB operates on the principle that there should be a positive balance between efficacy and safety. As the efficacy of homeopathic OTC products is supported on the basis of homeopathic literature, products with possible side effects are simply not accepted. A warning about possible hypersensitivity to an excipient is only included in exceptional cases [6].

6. Package Leaflets, Summary of Product Characteristics (SmPC) and Labelling

The regulations related to the labelling and package leaflets of pharmaceutical products are set out in Directive 2001/83/EC of the European Commission and in the Medicines Act [7].

- *SPC*

A Summary of Product Characteristics (SPC) has to be drawn up for all Article16 products. SPC is a summary of the product information and a precursor to the package leaflet, while the difference is that the SPC is written in technical language while in the package leaflet the terminology is adapted to make it easier to understand for patient. As homeopathic products are assessed differently from conventional products, the structure and level of the SPC is also slightly different. Section 5, which normally contains information on pharmacological properties, can changed to Properties. This section can contain a description of the specific homeopathic properties of the product couched in very general terms.

Sections 2, 3, 4.2 (relevant parts), and 6.1 to 6.6 are treated in the same way as for conventional medicinal products.

- *Current package leaflets*

The patient package leaflet is derived from the Summary of Product Characteristics (SPC). This package leaflet is intended for the patient or the consumer, so medical terms are translated in a patient-friendly manner in this document. The package leaflet is evaluated and approved by the MEB.

A new version of the QRD template, in which the package leaflet was amended, was published at the initiative of the MEB on 4 January 2010. The revision of the QRD-template was brought about because of research done at Utrecht University, which formed part of a larger study dealing with the creation of more patient-friendly and clearer package leaflets.

The new template for the package leaflet will first be used for new applications and for full revisions (for renewals, for example). Marketing authorisation holders will only be asked to amend the texts for full revisions [7].

The following documents are of importance when drafting of a good package leaflet

a. Package leaflet of pharmaceutical products MEB 5-4.2 (November 2012) provides an explanation of the conditions of the Medicines Act in terms of the package leaflet.
b. To help improve the readability of the package leaflet, the MEB has drawn up a patient-friendly term list (only in Dutch) with patient-friendly translations of medical terms used in package leaflets.
c. The Schrijfadviezen voor de geneesmiddelenbijsluiter (only in Dutch) is a supplement to the European Guideline on the Readability of the Labelling and Package Leaflet for Medicinal Products for Human Use.
d. The Dutch QRD templates can be found on the European Medicines Agency website
e. Declaration concerning the technical aspects of readability must be enclosed when a mock-up for the package leaflet is submitted [7].

- *Labelling*

The MEB evaluates the labelling text submitted by the company. There are fixed items that have to be printed on the label, such as the name of the medicinal product, the active ingredient, including its strength, and expiry date.

The European legislation makes it mandatory to state the name of new medicinal products on labelling in braille as well.

The following documents are important when drafting a good label text and a mock-up [7]

a. Labelling of pharmaceutical products MEB-6-3.5 (November 2012)

b. Guideline on the Readability of the Labelling and Package Leaflet for Medicinal Products for Human Use
c. More information about braille on the label, including the braille statement.

7. Homeopathic Drug Master File (HDMF)

Statutory requirements and guidelines

In analogy with the European Drug Master File procedure for active substances, use can also be made of a comparable procedure for homeopathic medicinal products, provided that certain conditions are met. However, the HDMF procedure may only be used if reference is made to a previously authorised dossier.

The following parts of the dossier must be included in the marketing authorization application submitted by the future marketing authorization holder:

a. Name and address of the manufacturer of the homeopathic stock
b. Definition of the raw material used
c. Method used to prepare the homeopathic stock, with reference to the official pharmacopoeia
d. Specifications of the raw material and the analytical methods used
e. Specifications of the homeopathic stock and the analytical methods used
f. Origin and purification or processing (if applicable) of the raw material (indicate how the material is purified/processed/stored)
g. Details of validation of the assay methods (methods described in an official pharmacopoeia do not require validation)
h. Potential impurities arising from the source, purification and degradation (routine testing for potential impurities must always be carried out, unless it can be justified that this is unnecessary)
i. Results of analysis of both the raw material and the homeopathic stock
j. Stability data for both the raw material and the homeopathic stock
k. A statement that no change will be made to the manufacturing procedure or the specifications without informing the applicant, who will then submit an application to vary the marketing authorization

All product-specific information must obviously also be included in the dossier (particularly that relating to the finished product: information on the manufacturing process, specifications, analytical results and stability) [7].

8. Legislation

Legislation on homeopathic medicines is now harmonized across the EU 9. The authorization of homeopathic medicinal products is based on Directive 2001/83/EC of the European Parliament and of the Council of 31 March 2004, and the Dutch Medicines Act (Geneesmiddelenwet). The quality and safety of authorized homeopathic medicinal products must comply with European regulations for medicinal products and with the standards of the

European Pharmacopoeia. Homeopathy is the most popular form of complementary therapy in France. Its use rose from 16% of the population in 1982 to 29% in 1987 and 36% in 1992.

A distinction is made between two groups of homeopathic medicinal products:

a. When a homeopathic medicinal product is intended for oral or external use, no specific therapeutic indication is stated, and there is a sufficient degree of dilution to guarantee the safety of the product (more diluted than a 1:10,000 dilution of the mother tincture), marketing authorization must be applied for on the basis of article 42, clause three, of the Medicines Act. This "simplified procedure" is based on the European Directive and is applicable in all 27 member states of the European Union. Only the pharmaceutical quality and the safety of the product are assessed. These homeopathic medicinal products are used by homeopathic practitioners on the basis of the homeopathic Similiar principle and are therefore not used for a particular indication.
b. All other homeopathic medicinal products that do not comply with the criteria for the above-mentioned "simplified procedure" fall under article 42, clause four, of the Medicines Act. These include homeopathic tinctures and dilutions below the 1:10,000 limit, homeopathic products that are not intended for oral or external use and those that are marketed for a particular indication as over-the-counter products[10].

9. Public Assessment Reports on Homeopathy

The MEB publishes national assessment reports containing a brief discussion of data from the marketing authorization dossier. The reports indicate the data which served as a basis for granting marketing authorization or which caused the product information to be changed at a later stage. This information can promote good pharmacotherapy on the part of doctors, pharmacists and other healthcare professionals and students.

The content of a marketing authorization dossier is regarded as confidential. To this end, the MEB has established a covenant with the pharmaceutical companies in the Netherlands on the issue of public reports. It contains general agreements on publication and the role of companies in the production of the report.

The MEB produces national public assessment reports on products authorized in the Netherlands that contain a new active ingredient and are assessed for the first time in Europe by the Netherlands. Following this national marketing authorization, a mutual recognition procedure can be started in other European Union countries.

European public assessment reports are also drawn up by other European Union countries. This happens when a product is first assessed in another European Union country and is granted marketing authorization in the Netherlands under a mutual recognition procedure. These public assessment reports are published on the HMA website, under Product Index.

The MEB's national public assessment reports contain a brief discussion of data from the marketing authorization dossier. The reports indicate the data which served as a basis for

granting marketing authorization or which caused the product information to be changed at a later stage. This information may contribute to good pharmacotherapy by doctors, pharmacists or others involved with medicinal products for professional or study reasons[11].

Conclusion

The extent to which European countries have established a statutory regulation of homeopathy and how such regulation is performed varies widely. Some countries have government-administered regulations or laws about the practice of CAM in general, some regulate specific CAM therapies such as homeopathy, while still others have no regulation at all. Homeopathy as a distinct therapeutic system is recognised by law in several countries. In some countries where the government delegates the tasks of authorisation, registration and supervision of health professionals to the national medical associations, statutory regulation has been introduced by the national medical associations. In some other countries the national medical associations have recognised homeopathy as a distinct medical method and have called on the government to provide the necessary legislation.

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