IRISH MEDICINES BOARD

TRADITIONAL HERBAL MEDICINAL PRODUCTS REGISTRATION SCHEME

INDUSTRY Q&A DOCUMENT

28 December 2011 – Version 2

This document includes questions and answers relating to the European Union's Traditional Herbal Medicinal Products Directive (2004/24/EC). This directive amended the Medicinal Products Directive 2001/83/EC and was transposed into Irish law by the Department of Health and Children with the introduction of the Medicinal Products (Control of Placing on the Market) Regulations 2007 (S.I. 540 of 2007 as amended).

The Q&A document includes three sections as follows:

- Introduction to the Traditional Herbal Medicinal Product Directive (2004/24 EC);
- Irish Medicines Board (IMB) position regarding the ending of the transition period for registration of traditional herbal medicinal products;
- The Committee for Herbal Medicinal Products.

Please note that in interpreting these questions and answers, you may wish to reference the "Definitions" section at the end of the document.

INTRODUCTION TO THE TRADITIONAL HERBAL MEDICINAL PRODUCT DIRECTIVE (2004/24 EC)

1. What is the Traditional Herbal Medicinal Products Directive?

The Traditional Herbal Medicinal Products Directive (Directive 2004/24/EC) introduces a registration process for traditional herbal medicinal products (THMPs) being placed on the EU market. It establishes a simplified registration procedure – the Traditional Herbal Medicinal Products Registration Scheme.

The simplified procedure allows the registration of THMPs without requiring safety tests and clinical trials, which the applicant is obliged to provide under the full marketing authorisation procedure. The long tradition of the THMP makes it possible to reduce the need for these tests and trials. Instead, they can be replaced by documentation which indicates that the product is not harmful in specified conditions of use and that its efficacy is plausible on the basis of long-standing use and experience. However, THMPs must meet all the necessary standard quality requirements.

In addition, competent authorities of the Member States are entitled to ask for additional data, if they deem it necessary, to assess the safety of the herbal medicinal product.

2. Why did the EU decide to adopt specific legislation on traditional herbal medicines?

The Herbal Directive (Directive 2004/24/EC) was adopted in order to further protect the health and interests of consumers across Europe.

The directive will ensure that in future, consumers in all EU member states will have assurance that the traditional herbal medicines they buy in their local health food store / pharmacy / shop:

- are produced to an appropriate quality standard,
- are safe under the proposed conditions of use,
- can be expected to act in accordance with an established tradition of use and
- are appropriately labelled.

All medicines, including herbal medicines, need a marketing authorisation to be placed on the EU market. However, traditional herbal medicines have particular characteristics, notably their long tradition of use. To take account of this, the EU introduced a simpler and less costly registration procedure for them, while providing the necessary guarantees of quality, safety and efficacy based on traditional use.

3. What national legislation implements the Traditional Herbal Medicinal Products Directive (2004/24/EC)?

The national regulations, Medicinal Products (Control of Placing on the Market) Regulations 2007 (S.I. No. 540 of 2007), implementing Directive 2004/24/EC, came into force on 23 July 2007.

4. What timeframe was set for implementation of the regulations / transition period?

The regulations state that since 23 July 2007, no medicinal product can be placed on the market without a prior marketing authorisation or certificate of traditional-use registration.

The regulations provided an exemption for THMPs from this requirement until 30 April 2011. This date marked the ending of the transition period for unlicensed traditional herbal medicinal products which were on the Irish market at the time of coming into force of the Medicinal Products (Control of Placing on the Market) Regulations 2007 (S.I. No. 540 of 2007).

5. Who is responsible for implementation of the national legislation arising from this EU Directive?

The IMB is the designated competent authority in Ireland for implementation of this legislation and, on this basis, the IMB established the Traditional Herbal Medicinal Products Registration Scheme.

Under this registration scheme an applicant can apply for a certificate of traditional-use registration for their traditional herbal medicinal product. If the application is successful the traditional herbal medicinal product will be granted a certificate of traditional use registration and allocated a corresponding (TR) number.

The IMB has published a guidance document to assist those making an application under the Traditional Herbal Medicinal Products Registration Scheme.

IMB POSITION REGARDING THE ENDING OF THE TRANSITION PERIOD FOR REGISTRATION OF TRADITIONAL HERBAL MEDICINAL PRODUCTS

6. What is the IMB's regulatory position after 30 April 2011?

30 April 2011 marked the ending of the transition period for unauthorised THMPs which were on the Irish market at the time of coming into force of the Medicinal Products (Control of Placing on the Market) Regulations 2007 (S.I. 540 of 2007).

After that date manufacturers, wholesalers and importers were obliged to distribute THMPs which had been granted a certificate of traditional use registration or THMPs for which a valid THMP application had been received by the IMB (see also questions 7 and 8). However, a rundown of remaining stocks of all other THMPs at importer and wholesaler level was permitted (see question 10 below).

7. Can a THMP continue to benefit from transitional protection after 30 April 2011 if the company has made an application before 30 April 2011?

Yes, after 30 April 2011, a THMP currently on the market may continue to be distributed by way of wholesale distribution and may be sold and supplied by retail, where a valid application for a certificate of traditional use registration has been submitted to the IMB for the product in question before the 30 April 2011.

8. What is the policy relating to products which were on the Irish market before the 23 July 2007 and for which an application for registration was received after the 30 April and before the 31 December 2011?

These products can remain on the Irish market pending the assessment of the application for registration.

9. What is the policy relating to products which were not on the Irish market before the 23 July 2007 and for which an application for registration was received after the 30 April and before the 31 December 2011?

These products cannot be placed on the Irish market until a certificate of traditional use registration has been granted by the IMB.

10. What about stock of THMPs at wholesaler and importer level which have not been granted a certificate of traditional use registration or are not the subject of a valid THMP application submission to the IMB?

A rundown of remaining stock at importer and wholesaler level was permitted for these THMPs up to the end of 2011.

After 31 December 2011, THMPs which have not been granted a certificate of traditional use or are not covered under questions 7 or 8 above should not be placed on the market.

11. Will products on the market before 30 April 2011 need to be removed from retail sale after 30 April 2011?

Stocks of THMPs that were already on the market before 30 April 2011 were allowed to remain on the market.

THMPs which have not been granted a certificate of traditional use registration or are not subject of a valid THMP application submitted to the IMB, and that were on the market at retail and wholesale level before the 30 April 2011, were allowed to be supplied after that time. It was expected that the rundown of such stock would be completed at wholesale level by the end of 2011. However, stock available at retail level could still be supplied subject to the expiry date specified on the product. Such stock cannot be replenished at retail level after 31 December 2011.

12. What is the status of THMPs supplied directly to retailers in Ireland by wholesalers / manufacturers / importers based in other Member States of the European Economic Area (EEA)?

The answers to questions 7,8, 9 10 and 11 apply also, as appropriate, to THMPs supplied directly to Irish retailers by wholesalers / manufacturers / importers based in other Member States of the EEA.

To ensure adherence to these requirements retailers should:

(i) Confirm that the supplier holds a wholesaler's / manufacturer's / importer's authorisation, as appropriate, granted by the competent authority of the Member State concerned;
(ii) Strongly encourage the supplier to contact the IMB at an early date if that supplier intends to apply for a certificate of traditional use registration for any of its products.

13. What action will the IMB be taking to ensure that the regulations are complied with?

The IMB will monitor and, where appropriate, take regulatory action against unlicensed THMPs found in breach of the requirements. The IMB will work with wholesalers and other stakeholders to assist them towards meeting the requirements of the legislation.

The IMB continues to make contact with interested parties with regard to the ending of the transition period and will provide advice to them as required.

To further assist interested parties, the IMB has published product classification guidance relating to herbal substances. This guidance is available on the relevant section of the IMB wesbsite. Reference should also be made to the Food Safety Authority of Ireland.

14. Are there post-registration obligations?

Registration holders, manufacturers, importers and wholesalers are required to notify the IMB of any defect in a product or batch which may lead to an abnormal restriction on supply of a THMP or to its recall. All notifications should be sent to recallsandqualitydefects@imb.ie.

Pharmacovigilance requirements also apply as per question 15.

15. What are the Pharmacovigilance requirements for a traditional herbal medicinal product?

In accordance with Article 16g of Directive 2004/24/EC, the pharmacovigilance requirements described in Articles 101 to 108 of Directive 2001/83 EC as amended, also apply in respect of THMPs. This means that a pharmacovigilance system should be in place for THMPs.

It is important to note that revised legislation providing for strengthened and increased harmonisation of pharmacovigilance obligations will come into force in July 2012. These revisions will introduce extensive changes to all aspects of pharmacovigilance including routine activities, such as adverse reaction reporting arrangements and requirements for periodic safety update reports (PSURs), as well as for the evaluation of new and emerging safety concerns.

For further information, please see Directive 2010/84/EU and Regulation (EU) No 1235/2010.

Submission of PSURs

At present, once a medicinal product is authorised in the EU, even if it is not marketed, the marketing authorisation holder is required to submit PSURs. PSURs are normally required to be prepared and submitted if requested by a national Competent Authority, at 6-monthly intervals for the first two years following the medicinal product's authorisation in the EU, annually for the following 2 years, and thereafter at 3-yearly intervals.

There may, however, be exceptions where the cycle may be re-started, or an exemption to the requirement for 6-monthly and annual PSURs is granted.

Where an exemption is proposed, the applicant should submit, as part of the application for a marketing authorisation, a reasoned request for the exemption which, if granted, becomes part of the conditions of authorisation. If an exemption is applied for after authorisation, such an application should follow the procedures for a type II variation. Please refer to Volume 9A of The Rules Governing Medicinal Products in the European Union for further details regarding the current requirements.

In accordance with the provisions of this legislation, (specifically, Article 107b (3) of Directive 2010/84/EU) it is intended to provide a general exemption for the requirement for PSUR submission for Traditional Herbal Medicinal Products, unless:

- The authorisation provides for the submission of PSURs as a condition.
- PSURs are requested by a Competent Authority on the basis of the grounds defined in legislation.
- The active substance is included on the List of Union Reference Dates (URDs) and the requirement for submission of a PSUR according to the harmonised frequency is indicated on the list in accordance with Competent Authority consultation.

Supplementary legislation and guidance is currently being developed to facilitate implementation of the new requirements and a public consultation related to Good Vigilance Practice activities is expected early in 2012. The IMB advises stakeholders to consult the EMA and IMB websites regularly to keep up to date on this evolving area. Specific queries in relation to the pharmacovigilance requirements for THMPs can be sent by e-mail to vigilance@imb.ie.

16. What are the legal requirements for wholesalers of THMPs?

A wholesaler of THMPs, or any other medicinal product, is required to hold a Wholesaler's Authorisation in accordance with the Medicinal Products (Control of Wholesale Distribution) Regulations 2007 (S.I. No 538 of 2007, as amended).

Application details can be obtained by contacting compliance@imb.ie or on the relevant section of the IMB website.

17. What are the legal requirements for manufacturers and importers of THMPs?

A manufacturer of THMPs, or any other medicinal product, is required to hold a Manufacturer's Authorisation in accordance with the Medicinal Products (Control of Manufacture) Regulations 2007 (S.I. No 539 of 2007, as amended).

Application details can be obtained by contacting compliance@imb.ie or on the relevant section of the IMB website.

Importation of THMPs, or any other medicinal product, from countries outside the EEA is also classified as manufacture and, accordingly, requires that a Manufacturer's Authorisation be held by the importer.

18. If a herbal product is registered as per the provisions of the Directive in another Member State, does it still have to be registered separately in Ireland?

Yes. The procedure for registration of a traditional herbal medicinal product is a national procedure. Therefore, each national application, if approved, is only valid within that Member State.

However, article 16(d)(1) and (2) of Directive 2004/24/EC specifies the provisions for mutual recognition (MR) for herbal medicinal products. To avail of the MR route, a traditional herbal medicinal product must contain a herbal substance/preparation or combination thereof that is included in the list drawn up by the Committee for Herbal Medicinal Products (HMPC) or be the subject of a community herbal monograph established by the HMPC (see related questions 23 to 25).

If considering the Mutual Recognition route for the registration of a THMP it is advisable to discuss this with the IMB in advance of any application submission.

19. After 30 April 2011, will herbal products be allowed to remain on the market as food or food supplements?

Since April 2011, all herbal products fall into one of four categories:

- Herbal products that are classified as herbal medicines will require an authorisation as per Article 8.3 or Article 10(a) of Directive 2001/83/EC or a certificate of traditional use registration in compliance with the Herbal Directive (Directive 2004/24/EC) or is the subject of a valid application for registration submitted to the IMB before 30 April 2011. A herbal product will be considered a medicinal product and not a food supplement when it is presented as having properties for treating or preventing disease in human beings or where it has a pharmacological, immunological or metabolic action.
- Herbal products that were on the Irish market before the 23 July 2007 and for which applications for traditional use registration were submitted to the IMB after the 30 April and before the 31 December 2011 – see question 8.
- Herbal products that are not the subject of a THMP registration, were not on the Irish market before the 23 July 2007 and for which applications for traditional use

registration were not submitted to the IMB on or before the 30 April 2011 – see question 9. This includes those products which are not considered a food supplement by the FSAI and, accordingly, are not eligible for placing on the market in Ireland (subject to the rundown of existing stocks - see also questions 10 and 11).

- Herbal products will be classified as food or food supplements once they do not fulfil the definition of a medicine and once they comply with the applicable food law. Herbal products marketed in the form of food supplements should comply with Directive 2002/46/EC on food supplements and Regulation (EC) No 1924/2006 on nutrition and health claims made on foods. Foods and food supplements are regulated by the Food Safety Authority of Ireland (FSAI).

20. What is the fee for a Traditional Use Registration application?

Every EU member state's competent authority will be responsible for national fees for THMP licenses. In Ireland, for 2012, these are as follows:

- National application – €4,888
- National application where there is a monograph of the Committee on Herbal Medicinal Products – €3,000 (Note: This applies only where the monograph covers the specific herbal extract)
- National application – each additional form (at same time) – €4,072
- National application – each additional strength (at same time) – €525

In addition, the IMB offers a classification advice service whereby a manufacturer can have its product assessed and the IMB will advise if there is a need to apply for a Traditional Herbal Medicinal Product registration. This cost is €250.

21. Does an annual maintenance or renewal fee apply?

An annual follow up maintenance fee will be incurred by registration holders. The maintenance fee is €113.

22. Will all alternative therapies, plants and books on plants be banned after 30 April 2011 in the EU?

No. The Herbal Directive regulates traditional herbal medicines by allowing a simplified registration procedure. It does not apply to alternative therapies and does not ban any specific substances, practitioners, books or the plants as such.

THE COMMITTEE FOR HERBAL MEDICINAL PRODUCTS

23. What is the Committee for Herbal Medicinal Products (HMPC)?

The HMPC is a European scientific committee established at the European Medicines Agency (EMA) under the Directive on Traditional Herbal Medicinal Products.

24. What is the purpose of the list of traditional herbal medicinal substances/preparations and/or combinations thereof established by the European Commission?

In accordance with Directive 2004/24/EC, a list of traditional herbal medicinal substances/preparations and/or combinations will be established by the European Commission on the basis of scientific advice provided by the HMPC.

An applicant seeking to register a product containing a substance/preparation and/or combination thereof on the list (in the form and for the indications as specified on the list) can refer to this list rather than have to demonstrate traditional use and safety. The applicant must, however, still demonstrate quality.

25. What is a Community herbal monograph?

Community herbal monographs are documents based on the format of a summary of product characteristics developed by the HMPC and can be used to support an application. Further information is available from the EMA website.

Directive (2004/24/EC) Definitions

'Traditional herbal medicinal product' means a product that fulfils all of the following criteria:

(a) It has indications exclusively appropriate to traditional herbal medicinal products which, by virtue of their composition and purpose, are designed for use without the supervision of a medical practitioner or for prescription or monitoring of treatment;
(b) It is exclusively for administration in accordance with a specified strength and posology;
(c) It is an oral, external and/or inhalation preparation;
(d) The period of traditional use laid down in Article 16c(1)(c) of Directive 2001/83/EC has elapsed (i.e. the product in question or a corresponding product has been in medicinal use throughout a period of at least 30 years preceding the date of the application, including at least 15 years within the European Community);
(e) The data on the traditional use of the medicinal product are sufficient; in particular the product proves not to be harmful in the specified conditions of use and the pharmacological effects or efficacy of the medicinal product are plausible on the basis of long-standing use and experience.

'Certificate of traditional use registration' means a certificate of traditional use registration granted by the IMB in accordance with the Medicinal Products (Control of Placing on the Market) Regulations 2007 (S.I. No. 540 of 2007, as amended) in respect of a traditional herbal medicinal product.