

DIRECTIVE ON TRADITIONAL HERBAL MEDICINAL PRODUCTS –ANSWERS TO SOME FREQUENTLY ASKED QUESTIONS

July 2004

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1. OVERVIEW

Q1.1 What is the purpose of the Directive?

- A. To establish within the Community a harmonised legislative framework for authorising the marketing of traditional herbal medicinal products, involving a simplified registration procedure. The aim is to remove the differences which create obstacles to the free movement of medicinal products in the European Union, while ensuring protection for public health.

Q1.2 What are the main requirements of the Directive?

- A. The Directive requires Member States to introduce the simplified registration procedure. Traditional herbal medicines which do not fulfil the criteria for a marketing authorisation under the provision of Community law relating to medicines will receive a traditional use registration, if the applicant provides the necessary evidence of traditional use, safety and quality.

Q1.3 What is the Government's position on the Directive?

- A. Ministers take the view that a new regulatory scheme giving enhanced status and recognition to herbal medicines, requiring consistent standards and proper consumer information, could give a boost to the herbal sector as well as addressing important public health issues. Many in the herbal sector have indicated to Ministers that they take a similar view.

Q1.4 What is wrong with the current UK arrangements for regulating over the counter herbal remedies?

- A. The current arrangements for unlicensed herbal remedies under Section 12(2) of the Medicines Act 1968 have widely acknowledged weaknesses. These relate mainly to the lack of specific requirements as to safety and quality as well as the inadequacy of the requirements relating to product information. During MHRA's extensive discussions with the herbal sector, very few interest groups have argued that the present arrangements are adequate.

Q1.5 Do herbal remedies present significant public health issues?

- A. It is necessary to keep the public health risk from herbal remedies in perspective. However, herbal remedies are genuine medicines which can have a significant effect on the body. Like any medicines they have the potential for interactions and side effects. To help inform debate on the public health case for regulating herbal remedies more effectively, the MHRA placed in the libraries of the House a document: "*Safety of herbal medicinal products*". This highlights international experience that safety issues with herbal remedies typically tend to arise out of poor quality standards in parts of the sector. In the UK, some of these products reach the market taking advantage of the weakness of the Section 12 scheme. There have been safety concerns as a result. The MHRA Herbal Safety News webpages (<http://medicines.mhra.gov.uk/ourwork/licensingmeds/herbalmeds/herbalsafety.htm>) are regularly updated and hold details of the products and herbal ingredients associated with risks to public health in the UK.

2. A NATIONAL OR A EUROPEAN SCHEME?

Q2.1 What are the roles of individual Member States and Europe?

- A. The main common European features of the Directive are that:
- all Member States will be required to put in place arrangements complying with this European legislation
 - the proposed Committee for Herbal Medicinal Products will be part of the European Medicines Agency (EMA)
 - the Committee will develop Community herbal monographs and a positive list of herbal substances. (Applicants will not need to demonstrate compliance with the criteria for traditional use and safety where herbal substances met the criteria set out in the positive list).
 - the committee will also have a role in considering the evidence of traditional use in cases where a remedy had less than 15 years usage in the EU.

Q2.2 Would the Directive allow Member States to grant a registration to any traditional herbal medicines that are found only in one Member State?

- A. Yes. This, for example, could allow Member States to accommodate herbal medicines used by ethnic groups in their territory. (Equally, there is nothing in the Directive to preclude a company making an application in, say, the UK based on the evidence of traditional use in another Member State).

3. SCOPE OF THE DIRECTIVE

Q3.1 What products are covered?

- A. Traditional over-the-counter (OTC) herbal medicinal products i.e. that are suitable for use without the intervention of a medical practitioner. These can be combined with vitamins and minerals, where there is evidence of safety and where the action of the nutrient is ancillary to the herb. Homeopathic medicines and herbal medicines which satisfy the requirements for a marketing authorisation (based on demonstration of efficacy as well as safety and quality) are not covered.

Q3.2 What effect will the Directive have on Borderline products?

- A. The Directive relates only to products which are classified as medicines. The Directive does not affect current law or policy on which products are classified as medicines. Many herbal products can legally be sold in other regulatory categories, such as foods, cosmetics or general consumer products.

Q3.3 Can more potent herbal medicines receive a traditional use registration?

- A. No. Registrations will be restricted to herbal medicines that are intended and designed for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment.

Q3.4 Are there restrictions on the route of administration of the medicine?

- A. Traditional use registrations are restricted to herbal medicines that are taken orally, or are for external use or inhalation.

Q3.5 Will the Directive cover non herbal traditional medicines?

- A. Currently, any non herbal traditional medicines on the UK market require a marketing authorisation, based on demonstration of safety quality and efficacy. The Directive does not extend the simplified registration scheme to these products, and so the present position is not changed (but see Q3.7 below).

However, the Directive contains an early date, no later than three years after it enters into force, for a review of the scope of the Directive. The UK Government and the herbal sector pressed for a relatively early date for such a review during negotiations. However, it is important to note that if the registration scheme is extended to non herbal traditional medicines there may well be significant safety and/or quality issues with some of these such as traditional medicines including heavy metals or animal parts.

Q3.6 What is the comparison between the terms of the existing UK regime for unlicensed herbal remedies and the Directive in relation to the inclusion of non herbal ingredients?

- A Under Section 132 of the Medicines Act 1968, which defines a herbal remedy for the purpose of the current UK regime for unlicensed herbal remedies, the only non herbal ingredient(s) permitted in a herbal remedy are “*water or some other inert substance*”.

The Directive specifically allows vitamins and minerals to be added to the traditional herbal remedy subject to certain conditions (see Q3.7 below). Also the remedy may contain excipients. These are not restricted to herbal ingredients.

Q3.7 Will the Directive permit herbal nutrient combinations?

- A. The Directive allows herbs to be combined with vitamins and minerals, where there is evidence of safety and where the action of the nutrient is ancillary to the herb.

Where these combination products are classified as medicines, currently they are not covered by the present UK regime for unlicensed herbal remedies and therefore require a marketing authorisation. This provision therefore offers greater flexibility on the issue of herb/nutrient combinations than does current UK legislation. This approach will give industry flexibility it has been seeking and could also be of benefit to some traditional ethnic medicines where considerable use is made of nutrients.

Q3.8 Could companies modify the presentation of a product currently sold legally as a food or cosmetic and apply for registration under this Directive?

- A. There is no reason to prevent a company applying for a traditional use registration for any product that could meet the various requirements of the Directive. There are a number of herbal ingredients that have accepted usage in a range of different regulatory categories besides medicines, including food, cosmetics or general consumer products. If a product is sold legally, for example as a food, companies may choose to continue to sell it on that basis. However, it may be that in some cases

companies might welcome an opportunity to present the product as a medicine and make minor medicinal claims based on traditional use.

Q3.9 Can flower remedies be covered by the Directive?

- A. The MHRA has offered the opinion in response to a request for advice that, in principle, it might be possible for a company to make a successful application for a traditional use registration for a flower essence. The MHRA has subsequently become aware of anxieties in other parts of this sector that a successful application by one company might lead to other companies having to follow the same regulatory route. However, the MHRA's understanding is that many flower essences are not sold as medicines and the Agency sees no reason why this need change.

It is a common situation to find "borderline" products containing the same ingredients which can be regarded either as medicines or as foods or cosmetics, depending on presentation. The key point is that where MHRA makes a determination as to whether a specific product is a medicine this decision relates to the product under consideration based on both its ingredients and presentation. Such decisions are taken on a case by case basis, rather than by a classification by general classes or descriptions. For further information on the classification of products see MHRA's Guidance Note 8.

Q3.10 Are standardised extracts permitted under the Directive?

- A. Yes. Companies would need to bear in mind the stipulation of the Directive relating to equivalent strength and to demonstrate that the proposed product did not exceed the dose used traditionally.

Q3.11 Does the Directive cover medicines which are manufactured from isolated chemical constituents of plants?

- A. No. Such a medicine would not be regarded as a traditional herbal medicinal product.

Q3.12 What is the position on herbal medicines for which efficacy can be demonstrated?

- A. The Directive says that where the competent authorities judge that a medicine meets the requirements for a marketing authorisation (in this context the efficacy requirements will be particularly relevant) they should not grant a traditional use registration.

The MHRA's experience is that relatively few herbal medicines are presented with evidence that they satisfy the requirements for a full marketing authorisation. (This was one of the reasons why the Directive was needed). It may well be that there are some herbal medicines which have several accepted indications of which one might be appropriate for a marketing authorisation under the "well established use" provisions while another is suitable for traditional use registration.

4. TRADITIONAL USE

Q4.1 What time period is necessary to demonstrate traditional use?

- A. The applicant will need to demonstrate that the herbal medicine or “corresponding” (that is, comparable) product(s) have been in medicinal use in the European Union for 30 years at the time of the application. Evidence for up to 15 of the 30 years can relate to use outside the European Union. The Directive allows the Committee for Herbal Medicinal Products (HMPC) discretion in individual cases to lower the 15 years EU usage requirement where justified. In practice, a regulatory authority in a Member State would refer a product to the HMPC for consideration if it believed that the only reason preventing a traditional use registration being granted was the lack of evidence of 15 years EU usage. Both the Government and the UK herbal sector had been pressing for increased flexibility on this issue, and this element of discretion added to the Directive in the latter stages of negotiations may be helpful.

Q4.2 How does this time period affect existing products on the market?

- A. The Directive allows for a transitional period of seven years in relation to existing products on the market. During this period it will be possible to continue to accumulate evidence of traditional usage. Thus it could be that a traditional herbal remedy from a non EU tradition that first had EU usage in the early to mid 1990s could have acquired evidence of 15 years EU usage by the end of the transitional period - which will be on 30 April 2011. (See also Q&As about transitional arrangements).

Q4.3 What is the Government’s view on the traditional use requirement?

- A. The Government recognises that it is necessary to have demonstration of an adequate period of traditional use, in view of the lifting or modification of the normal requirements for medicines relating to efficacy and, in particular, safety.

Q4.4 Do comparable products used to establish traditional use need to be identical?

- A. No. But “corresponding” (that is, comparable) products must have the same active ingredients, the same or similar intended purpose, the same or similar route of administration, and equivalent strength. The number or quantity of ingredients may have been reduced during the qualifying period of traditional use. Herbal remedies made up by practitioners to meet the needs of individual patients are as much medicinal products as a typical manufactured over-the-counter herbal medicine. It should be possible to draw from evidence of traditional use relating to either type of product.

Q4.5 What kind of evidence will be necessary to demonstrate traditional use?

- A. Applicants would need to produce bibliographic or expert evidence of traditional use. There is a very wide range of possible sources which, taken together as necessary, potentially could provide the required evidence. These include: authoritative literature on herbalism; the practical evidence of numerous licensed or unlicensed manufactured products on the market in many EU Member States; the long-standing lists of herbal medicines accepted as traditional by regulatory authorities in a number of member states; and the testimony of recognised experts on herbalism. This last

source may be particularly helpful in confirming the patterns of usage of combinations of herbal ingredients. See the Agency's briefing note on sources of evidence of traditional use which may be acceptable under the Directive.

Our aim on this issue would be to minimise the regulatory impact on applicants of demonstrating traditional use, consistent with complying with legal requirements.

Applicants will not need to demonstrate traditional use where the herbal substance in question is contained in the positive list of herbal substances prepared by the HMPC.

Q4.6 Will the rules for traditional usage prevent medicines from non western herbal traditions from meeting the terms of the Directive?

A. The main non western herbal traditions present in the UK (Ayurveda and traditional Chinese medicine (TCM)) are well documented as to their traditional use. Many such medicines have also been used in the UK for a considerable period of time and would therefore be able to meet the requirement of usage for at least 15 years in the EU. The provision allowing the CHMP discretion to lower the 15 years EU usage requirement in specific cases should also benefit non western herbal traditions.

The Directive would not prevent herbalists making up remedies to meet the needs of individual patients. Thus such remedies, used under the professional supervision of herbalists, could continue to accumulate evidence towards meeting the requirements of the Directive.

Q4.7 Will many existing legal S12(2) unlicensed herbal remedies be unable to satisfy the definition of traditional use?

A. Strong fears were expressed in 2002, particularly by the health food retail sector, that a large number of currently legal section 12(2) herbal remedies would fall outside the definition of traditional use and will be made illegal as a result. The MHRA looked at the range of about 1000 products submitted in the form of samples or lists. This follows Ministers invitation, to the sector to send in examples of products that they feared would be made illegal as a result of the Directive.

From a total of over 270 different herbal ingredients brought to the Agency's attention, the MHRA's broad assessment is that in perhaps as few as two or three cases it would be problematic for a company to demonstrate the necessary period of traditional use. There are several other individual herbs where a period of 15 years EU use may perhaps not be currently met but is likely to be met well within the transitional period under the Directive.

Q4.8 What about the position of herbal/herbal combination remedies currently on the market?

A. In relation to herbal/herbal combination remedies, the MHRA takes the view that one of the main ways for companies to demonstrate traditional use would be for them to take the opinion of herbal experts, notably herbalists. Accordingly, the MHRA showed to two expert herbalists, in anonymised form, the information on about two hundred particular herbal combinations which companies particularly feared would not meet traditional use requirements.

Their initial feedback was that in many cases they were either familiar with the combinations themselves or could envisage the possibility, given the stated ingredients, that a herbalist might well be able to express a positive opinion on the

traditional use of the combination. There were others where the particular herbalists were not familiar with the combination. There were also, they noted, some combinations consisting of herbs from several different herbal traditions. They queried whether in all cases such a combination could be demonstrated to have traditional use. They also queried whether in some cases, where a particular herbal ingredient had only recently completed 15 years in the EU, it might not be feasible to demonstrate its traditional use across a large number of different combinations.

One of the herbalists commented that, from his preliminary perusal, in perhaps three-quarters of the particular herb-herb combinations submitted it might be likely that evidence of traditional use of the combination could be found. This is just one source and clearly a company seeking registration potentially could draw from a range of different sources. The relatively small number of herbal/herbal combinations sent in by the herbal sector represents only a minute fraction of the possible number of herbal/herbal combinations which will be permissible under the Directive.

It is important to stress that the MHRA can give only general pointers and indications at this stage. Regulatory decisions on products could only be taken in relation to individual applications for registration of a product. It will be open to a company to provide evidence of traditional use in relation to any particular product.

Q4.9 Do traditional medicines have to demonstrate efficacy in order to get a registration?

- A. No, the Directive specifically makes clear there is no requirement to present data on tests and trials relating to efficacy. The required evidence of the medicine's use for at least 30 years will often be indicative that there may well be at least some evidence as to the efficacy of the medicine. The labelling of the product will reflect this position with the wording: "traditional herbal medicinal product for use in specified indication(s) exclusively based upon long-standing use".

Q4.10 The Directive says that a registration may be refused "if data on traditional use is insufficient, especially if pharmacological effects or efficacy are not plausible on the basis of long-standing use and experience". What does this mean?

- A. The MHRA expects that evidence that a herbal remedy had an accepted use within a herbal tradition over a significant period would generally represent reasonable evidence that a degree of efficacy in relation to the relevant traditional use indication was at least plausible.

Circumstances where "plausibility" might however be an issue include situations where:

- the proposed indication was in direct contradiction to the known activity of the ingredients
- the ingredient most associated with the proposed indication was omitted from the medicine.

Q4.11 The Directive refers to the active ingredient. Is it a problem that the chemical constituent(s) of many herbal remedies which may be responsible for the medicine's reported efficacy has not been established?

- A. No. In the context of the Directive the term active ingredient refers to the herbal ingredient as a whole and not the individual chemical constituents of a plant.

5. **SAFETY**

Q5.1 **What are the main safety requirements?**

A. The applicant would need to present a bibliographic review of safety data, together with an expert report. Regulatory authorities, where justified, would be able to ask for more data in order to assess the safety of the product.

An important element of safety is that the products, including their indications must be suitable for over the counter sale and use without medical supervision.

Q5.2 **In what circumstances might the MHRA ask for more safety data?**

A. Among situations where the need may well arise would be where:

- there are specific concerns remaining as to safety of the product
- the ingredient(s) or medicine is relatively unfamiliar to science
- the medicine has been used predominantly in settings where systems of reporting of adverse incidents are not well developed.

6. **THE POSITIVE LIST AND COMMITTEE FOR HERBAL MEDICINAL PRODUCTS**

Q6.1 **What is the role of the positive list?**

A. The positive list will be established at Community level by the HMPC. The principle underlying the proposal is to remove the need for many companies each to have to produce similar evidence of traditional use and safety where this has already been clearly accepted. There will be an agreed list of herbal substances accompanied by the therapeutic indication, specified strength, route of administration and any relevant safety information. An applicant seeking to register a product containing a substance on the list in the form and for the indications as specified on the list could then refer to this list rather than have to demonstrate traditional use and safety. The applicant would still need to demonstrate quality.

Q6.2 **How will the positive list be decided?**

A. The positive list of herbal substances will be adopted by the European Commission on the basis of the scientific advice of the HMPC that would be established by the Directive.

Q6.3 **Will the positive list specifically cover traditional herbal combinations?**

A. The list will contain herbal substances, preparations and combinations thereof. The list will contain, with regard to each herbal substance, the indication, the specified strength and the posology, the route of administration and any other information necessary for the safe use of the herbal substance as a traditional medicinal product. It is not yet clear how the list will implemented in relation to combinations.

Q6.4 **Will it be possible for an applicant to get a registration for products that are not covered by the positive list?**

- A. Yes. The absence of a substance on the positive list will not prevent a successful traditional use registration subject to safety, quality and traditional use requirements being met.

Q6.5 What is the role of the Committee for Herbal Medicinal Products?

- A. The Committee (HMPC) will be part of the European Agency for the Evaluation of Medicines and will have the following main functions:
- establishing Community herbal monographs
 - setting up and maintaining a positive list of herbal substances in relation to which applicants do not need to demonstrate safety and traditional use
 - dealing with referrals/ arbitrations in relation to mutual recognition
 - considering whether the 15 years EU usage might be relaxed in relation to specified products

Q6.6 How will the Committee be appointed?

- A. The Committee will consist of one member, and an alternate member, nominated by each Member State. The appointments will last for a period of three years, which may then be renewed. Members and alternates shall be chosen for their role and experience in the evaluation of herbal medicinal products and shall represent the competent national authorities.

The Committee may also co-opt a maximum of five additional members chosen on the basis of their specific scientific competence. These members shall be appointed for a term of three years, which may be renewed, and shall not have alternates.

Q6.7 What is the MHRA's view over how the "well established use" provision for a marketing authorisation should be applied to herbal medicines?

- A. There are differences of view among Member States. The Agency believes that it is important to maintain consistency of approach in applying the criteria for full marketing authorisations to herbal and non herbal medicines alike.

7. PRODUCT REGISTRATION

Q7.1 Who can get a traditional use registration?

- A. Applications can be made by anyone within the EU who wishes to place relevant herbal medicines on the market under the scheme.

Q7.2 Will I require a registration for every product I manufacture?

- A. Yes. Most companies will wish to register their top five or ten products from day one and then register the rest of their products over the course of the seven-year transitional period.

Q7.3 I manufacture traditional herbal medicines at a site outside the EU. Can I register my products under the THMRS?

- A Only applicants, whose main place of business is located in the EU, are eligible to apply for a registration.

Anyone, including importers you may already supply to, would be eligible to apply for a registration as long as their business resides in EU and they are placing the associated products on the market.

Q7.4 Do herbal remedies supplied to herbalists require a traditional use registration?

- A This is a complicated regulatory area. The Agency has carried a recent consultation (MLX299) relating to proposals to update regulatory arrangements where herbal remedies are made up to meet the needs of an individual patient following a one-to-one consultation. The Agency is currently considering the responses to the consultation and so it is not possible to give a detailed answer. In very broad terms, however, if a company places a manufactured herbal remedy on the market and supplies the product to herbalists then in principle such a product would need to have either a marketing authorisation or traditional use registration. If, however, the herbalist commissions a third party to make up a remedy to the herbalist's requirements, that situation is being considered in the current review to ensure that the most appropriate arrangements can be made, taking account of the possible statutory registration of the herbal medicine profession.

Q7.5 Does the person who supplies herbal ingredients to another party (who subsequently uses the ingredients to make a medicine) require a traditional use registration?

- A. No. The obligation for a registration would fall on the person making the herbal remedy rather than the person supplying the ingredients. (Bear in mind, however, that there is no obligation on a herbalist making up a remedy to have a traditional use registration for the product(s) (s) he makes up for use in one to one consultations under Section 12(1).) However, while the principle is clear it may not always be easy to interpret in some situations as to whether a particular item supplied (e.g. to a herbal practitioner) should be regarded as a medicine or an ingredient. The MHRA is considering whether further guidance would be helpful.

Q7.6 What is the position if someone with a traditional use registration for a product wishes to make that remedy for a number of different companies but using their own labels?

- A Once the product has been registered the applicant can submit a variation application to add a further distributor to the authorisation. Examples of the labelling to be used should be submitted for review at this time which may be in the livery of the second (subsequent) company.

8. MANUFACTURING REQUIREMENTS

Q8.1 I am a manufacturer. What do I need to do to comply with the forthcoming requirements of the Directive?

A You will need to meet approved standards of Good Manufacturing Practice (GMP) and obtain a manufacturer's licence (ML).

Q8.2 What is Good Manufacturing Practice?

A Good Manufacturing Practice (GMP) is the part of the quality assurance which ensures that medicinal products are consistently produced and controlled to the quality standards appropriate to their intended use, the principles and guidelines of which are specified in Directive 2003/94/EC.

To meet GMP you will have to have suitable premises, technical equipment and quality control facilities for the manufacturing activities to be undertaken.

Q8.3 How do I apply for a Manufacturer's Licence?

A You will need to complete a Manufacturer's Licence Application for and submit this to the MHRA. If you manufacture in the UK, you will also need to produce a Site Master File (SMF) and submit this to the MHRA. See Guidance notes for industry on the preparation of a Site Master File.

Q8.4 Can I contract a company to manufacture a product for me?

A Yes. You can employ a contract manufacturer to manufacture a herbal remedy on your behalf. Contract manufacture must however be carefully controlled and the duties of yourself and the manufacturer set out in a contract.

Q8.5 Who can carry out contract manufacture?

A Contract manufacture can only be carried out by a manufacturer who is the holder of a manufacturer's licence and who is named on the product registration as the manufacturer.

The contract manufacturer must have adequate premises and equipment, knowledge and experience, and competent personnel to carry out the work.

Q8.6 If I employ a contract manufacturer, what do I need to do to ensure my products are compliant with the requirements of the new scheme?

A Under these circumstances you, as the registration holder, will be responsible for assessing the competence of the contract manufacturer to successfully carry out the work required and for ensuring, by a contract, that Good Manufacturing Practice is adhered to.

You will need to provide the contract manufacturer with all the necessary information they need to manufacture the product in accordance with the details on the registration and that the finished product complies with the necessary specification and is released by a Qualified Person.

Q8.7 Are there any workshops planned for manufacturers that will help me understand what I need to do?

A There are workshops planned for 2004 that will help manufacturers understand the requirements under the Directive. Details of these will be posted on the MHRA 'Conferences' web-pages.

Q8.8 In what circumstances would MHRA need to inspect a manufacturer abroad?

- A. If the manufacturer is in a country with which no Community Mutual Recognition Agreement (MRA) is in operation then the site would normally be inspected by the MHRA. MRAs are currently operational with Japan, Australia, New Zealand and Switzerland.

Q8.9 If another EU Member State has inspected a manufacturer's premises abroad would MHRA also need to do so?

- A. If another EU Member State has inspected a manufacturer's site abroad then the MHRA would use the Exchange of Information scheme to obtain the relevant information. If the Member State had, within the past 2 years, inspected the same site for the same product (or dosage form), MHRA would consider if it were necessary to inspect. In these circumstances the MHRA would probably not do so.

9. QUALIFIED PERSONS

9.1 In what circumstances is a Qualified Person (QP) required, and why?

- A. A manufacturer of a traditional herbal medicinal product will require a Manufacturer's Licence. It is a requirement of European legislation that the holder of a Manufacturer's Licence has access to at least one QP. The QP needs to be named on the Manufacturer's Licence.

Q9.2 Does a Qualified Person have to be a full time employee of the company?

- A. No. The manufacturer may employ the QP on a contract basis. A number of licensed manufacturers have for some time now employed a QP on a contract basis. A technical agreement will be required setting out the contract QP's responsibilities.

Q9.3 What are the duties of a Qualified person (QP)?

- A Article 51 of Directive 2001/83/EC defines the duties of the QP.

Q9.4 Who is eligible to be a QP?

- A A QP must be resident within the UK. Articles 49 and 50 of Directive 2001/83/EC define the requirements for eligibility. The requirements are stringent and legally binding.

Q9.5 Are there any transitional arrangements for QPs?

- A Grand parenting arrangements will be put in place to help the sector meet the eligibility requirements for QPs.

Q9.6 Will there be enough Qualified Persons with the requisite qualifications and experience to cover the expansion in workload relating to the new scheme?

A The MHRA will introduce a transitional provision for those persons working for manufacturers and importers of THMPs on the day that the new scheme is introduced. Those persons would be able to undertake the role of a QP solely for THMPs.

Q9.7 How will the MHRA ensure that the duties of the QP are fulfilled?

A Article 52 of Directive 2001/83/EC requires Member States to ensure that the duties of QPs are fulfilled, either through administrative measures or by making such persons subject to a professional code of conduct. The MHRA will ensure that the duties of QPs are fulfilled largely by routine inspections.

10 RESPONSIBLE PERSONS (RPs)

Q10.1 What does a Responsible Person (RP) do?

A. The RP is responsible for safeguarding products against potential hazards arising from poor distribution practice.

Q10.2 What are the main responsibilities of a Responsible Person (RP)?

A. The RP is responsible for safeguarding product users against potential hazards arising from poor distribution practices. He ensures that the conditions of the wholesale dealer's licence are met and that the guidelines of Good Distribution Practice are complied with.

Q10.3 Do I have to be a pharmacist to be a Responsible Person (RP)?

A. No.

Q10.4 Do I have to be a Qualified Person (QP) to be a Responsible Person (RP)?

A. No.

Q10.5 What are the eligibility requirements for a Responsible Person (RP)?

A. Where a RP is not a pharmacist or eligible to act as a Qualified Person (QP), he should have at least one year's experience in both or either of the following areas: a) handling, storage and distribution of medicinal products; b) transactions in or selling or procuring medicinal products. In addition the RP should have at least one years managerial experience in controlling and directing the wholesale distribution of medicinal product on a scale, and of a kind, appropriate to the licence for which he is nominated.

Q10.6 What is the difference between a Responsible Person (RP) and a Qualified Person (QP)?

A. The QP is someone who is eligible to act as a QP as defined in Directive 2001/83/EC. A QP will usually undertake their role in respect of a Manufacturer's Licence or a Wholesale Dealer's (Import) Licence. The RP undertakes their role in respect of a Wholesale Dealer's Licence.

Q10.7 Can the duties of a Responsible Person (RP) and a Qualified Person (QP) be undertaken by one person?

A. Yes, provided they are eligible to undertake both roles.

Q10.8 Why are the eligibility requirements for a Responsible Person (RP) different from those of a Qualified Person (QP)?

A. The requirements are different because the RP and the QP undertake different roles and have different responsibilities.

11. QUALITY REQUIREMENTS

Q11.1 What are the main quality requirements?

A. The normal quality requirements applicable to licensed medicines will apply. The MHRA will apply the provisions of the Directive and any relevant European guidelines in a way that is appropriate to the nature of the product under consideration.

Compliance with Good Manufacturing Practice (GMP) will be required and there will also be a requirement to hold a Manufacturer's Licence or Wholesale Dealers Licence where appropriate.

Q11.2 Aren't the quality requirements more applicable to pharmaceutical drugs than to traditional herbal remedies?

A. The quality requirements are ones that are designed specifically for the regulation of herbal medicines – for example, the European guidelines on Good Manufacturing Practice for herbal medicines and the European Pharmacopoeia general monographs on products of herbal origin. These are standards which are successfully met by many companies in the UK and elsewhere in the EU. They are designed to ensure that the product contains the correct ingredients of accepted quality, free from unaccepted contamination; and that the claimed shelf life of the product can be supported. It would also be difficult to justify having different quality standards as between licensed herbal remedies and herbal remedies with a traditional use registration.

There are strong similarities between the requirements for GMP relating to herbal medicines and the voluntary codes which are already operated by the Council for Responsible Nutrition, the Health Food Manufacturers Association and the British Herbal Medicine Association.

Q11.3 Community herbal monographs, where they exist, are to be used as the basis for any application. What is the position where no such monographs exist? Can an applicant use the Chinese Pharmacopoeia for example?

A. In cases where a herbal ingredient is described neither in the European Pharmacopoeia nor in the pharmacopoeia of a Member State, the Directive specifically states that monographs of a third country can be referred to in an application. In such cases, the applicant should submit a copy of the monograph with

appropriate data to support the tests and methods applied together with a translation of the monograph, where appropriate.

Q11.4 What laboratories can I approach to test my products if I do not have the facilities to test in-house?

A A list of laboratories which provide testing services can be found in the Journal of the Royal Society of Chemistry, Chemistry today. **NB: Paul Hargreaves to check.** Laboratories must be named on the manufacturer's licences and wholesale dealer's (import) licenses and be approved by the MHRA.

12.DISTRIBUTION

Q12.1 What is wholesale distribution?

A All activities consisting of procuring, holding, supplying or exporting medicinal products, apart from supplying medicinal products to the public. Such activities are carried out with manufacturers or other depositories, importers other wholesale distributors or persons supplying to the public.

Q12.2 I'm a wholesale dealer of traditional herbal medicinal products. What do I need to do to comply with the forthcoming registration scheme?

A If you are distributing products manufactured and sourced from within the European Economic Area (EEA), you will require a wholesale dealer's licence. If some, or all of your products, are sourced from outside the EC you will need a wholesale dealer's (import) licence in order to distribute these products.

Q12.3 In what circumstances will a wholesale dealers licence be required?

A Where THMPs are sold or supplied to another person such as another wholesaler, retailer, practitioner etc.

Q12.4 When will I need a wholesale dealer's licence by?

A A wholesale dealer's licence will be required as soon as the wholesaler starts to handle products registered under the traditional use registration scheme.

Q12.5 Will I require access to a Responsible Person (RP)?

A All holders of Wholesale dealer's licences that distribute medicinal products for human use are required to have available the services of a Responsible Person (RP) who must be named on the wholesale dealer's licence.

Q12.6 Where can I get further guidance on wholesale dealing?

A Part II of the MHRA's Rules and Guidance for Pharmaceutical Manufacturers and Distributors sets out the UK's legislative requirements and provides detailed UK and European guidance on wholesale dealing.

Q12.7 Are there any workshops planned for wholesale dealers that will help me understand what I need to know?

- A A practical workshop is planned for 2004. Details will be published on our 'Conferences' page of the MHRA web-site.

13.IMPORTATION

Q13.1 What is importation?

- A The buying or bringing in of goods from a non-EEA country.

Q13.2 What are the requirements relating to the import of herbal remedies with a traditional use registration?

- A. This depends on where the products are being imported from. For products from elsewhere within the EU, an importer will require a wholesale dealer's licence – see the requirements set out above. However, in relation to products imported from third countries outside of the EU, an importer will require a wholesale dealer's (import) licence, naming at least one Qualified Person.

Q13.3 How do I apply for a Wholesale dealer's (import) licence?

- A Applications should be made using the Wholesale dealer's (import) licence application form which should be accompanied by the data specified in Guidance Note 6, Notes for applicants and holders of a wholesale dealer's licence. The form and the guidance can be found on the MHRA web-site.

Q13.4 If a traditional herbal medicine is manufactured in a third country and imported by a person in the UK who then delivers to a wholesaler, does the intermediary need a wholesale dealer's licence?

- A Yes. The act of taking delivery of a product from outside the EU requires a wholesale dealer's (import) licence. A licence would not be required by the intermediary if he arranged for a wholesaler to take delivery direct.

Q13.5 If a company outside the EU (e.g. in USA or China) wishes to manufacture traditional use remedy for import onto the UK market, what specific requirements relate to that situation?

- A. The site of manufacture and batch certification would have to be named on the THMP dossier. The manufacturer would have to comply with a standard of GMP at least equivalent to the EU. The person who imports the product into the UK will require a wholesale dealer's (import) licence.

Q13.6 As an importer, will I require access to a Qualified Person (QP)?

- A All holders of Wholesale dealer's (import) licences are required to have available the services of a Qualified Person (QP), who must be named on the wholesale dealer's (import) licence.

Q13.7 Where can I find further information on Wholesale dealer's (import) licences?

A For further information see Guidance Note 6, Notes for applicants and holders of a wholesale dealer's licence, which is available on the MHRA web-site.

Q13.8 Are there any workshops planned for importers that will help me understand what I need to do?

A A practical workshop is planned for 2004. Details will be posted on the 'Conferences' page of the MHRA web-site.

14.INSPECTIONS

Q14.1 Will I/ the site be inspected and, if so, when and how often?

A Inspections are carried out whenever a company has applied for a manufacturer's or wholesale dealer's licence and periodically during the course of a licence. The maximum interval between inspections is two years for UK manufacturers and three years for overseas manufacturers.

Q14.2 What will happen at the inspection?

A A suitable date for the inspection will be arranged. A suitable date for the inspection will be arranged. The inspector will start off with an Introductory Session and explain how the inspection will be conducted: the areas that will be visited; personnel to be seen; documents to be reviewed; appropriate timetable; the summary session/ classification of deficiencies. Once the inspection is completed, a summary session will be held during which the Inspector will give the licence holder a verbal briefing of the inspection findings. This is followed by written notification to the organisation of any deficiencies found together with additional observations the inspector may have.

Additional inspections may also be carried out. For example, to follow up deficiencies raised previously, following reports of defective products, or to follow up information received from external sources. There may also be unscheduled visits if a public health issue arises.

Q14.3 If inspectors raise concerns at the inspection will I still be able to get a licence?

A Inspectors would normally expect companies to address the areas of concern before a licence is granted. However if there is an action plan setting out how the concerns will be rectified it may be possible for inspectors to take a pragmatic view and grant a licence but follow up with a visit at a later date.

Q14.4 Will I be charged for the inspection?

A Fees are charged for routine scheduled inspections.

Q14.5 Does a business need to be in operation at time of inspection?

- A No, inspectors will look at the quality system in place and will arrange a further visit once the company is in business to check that everything is operating smoothly.

15 INFORMATION

Q15.1 What medicinal claims can be made?

- A Indications exclusively appropriate to traditional herbal medicinal products which, due to their composition and purpose, are intended and designed for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring treatment.

Q15.2 What product information is required?

- A Labelling and the user package leaflet should be in English and meet the requirements of Article 54 to 65 of Directive 2001/83/EC (as amended by Directive 2004/27/EC). Compliance with the full requirements set out in Articles 54 to 65 of 2001/83/EC is required.

Q15.3 What labelling would be included on the product?

- A. Labelling and leaflets for products with a traditional use registration will be required to include information and instructions about the safe use of the product, as with any licensed medicine. In addition, it will also need to be made clear to the consumer that the indications are based on information obtained from its long-standing use and experience. There will also need to be advice that the user should consult a doctor or a qualified health care practitioner if the symptoms persist during the use of the medicinal product or if adverse effects not mentioned in the package leaflet occur.

The Directive gives Member States the option of requiring that labelling and leaflets should state the nature of the herbal tradition. The MHRA's view is that additional information of this kind on the product might be helpful to the consumer.

Q15.4 What constitutes an advertisement?

- A An "advertisement" includes anything designed to promote the prescription, supply, sale or consumption of medicinal products. Advertising can take various forms and include posters, advertisements in newspapers and magazines, consumer leaflets, Internet websites, direct mailings, radio and television adverts, cinema commercials and point of sale materials.

Q15.5 What are the legal requirements for advertisements?

- A The same rules that relate to the advertising of authorised medicines will apply to registered herbal products. Advertising and promotion of traditional herbal medicines that fall within the registration scheme must meet the requirements of Articles 86 to 99 of Directive 2001/83/EC (as amended by Directive 2004/27/EC). In addition to these requirements, Directive 2004/24/EC requires any advertisement for a medicinal product registered under the scheme to contain the following statement:
- Traditional herbal medicinal product for use in specified indication(s) exclusively based upon long-standing use.

Medicines advertising in the UK is regulated by the Medicines (Advertising) Regulations 1994 and the Medicines (Monitoring of Advertising) Regulations 1994. These implemented Directive 2001/83/EC.

Q15.6 What can I say on the advertising to the public?

- A All advertising must comply with the authorised Summary of Product Characteristics (SPC) for the product, must encourage rational use of the product by presenting it objectively and without exaggerating its properties and must not be misleading.

Advertisements to the public must include the name of the product, the common name of the product where the product contains only one active ingredient, at least one indication for use (information necessary for correct use of the product) and an invitation to “Always read the label” or equivalent.

Further information about the legal requirements for medicines advertising can be found in MHRA Guidance Note No. 23 entitled “Advertising and Promotion of Medicines in the UK” which explains the regulations and provides clarification on this Agency’s interpretation of them. This guidance can be accessed from the MHRA website at <http://medicines.mhra.gov.uk/inforesources/publications/gn23/medic.htm>

Q15.7 Where can I find additional information on the regulation of advertising for medicines?

- A Additional information including a list of the applicable regulations and guidance issued with information on how the MHRA regulates advertising for medicines and reports of recent cases investigated can be found on the advertising section of the MHRA web-site.

16. REVIEW OF THE DIRECTIVE

Q16.1 What arrangements are there for the review of the Directive?

- A. An early date, no later than three years after the date of entry into force of the proposal, is specified for a review of the scope of the Directive. The UK Government and the herbal sector had been pressing for a relatively early date for such a review.

17. TIMETABLE AND TRANSITIONAL ARRANGEMENTS

Q17.1 What are the transitional arrangements within the Directive?

- A. See the MHRA’s guidance on provisions of the Directive on Traditional Herbal Medicinal Products which highlights planned dates for the introduction of the new scheme and the end of the transitional period.

18. CHANGES TO EXISTING REGULATORY ARRANGEMENTS

Q18.1 What will happen to the existing Section 12 herbal exemptions?

- A. The position will vary between the two herbal exemptions:

- **Section 12(2):** The Government’s intention is that, Section 12(2) of the Medicines Act 1968 would cease to be the regulatory regime under which most over-the-counter (OTC) herbal remedies would be regulated. Prior to the introduction of the new scheme, the Government will consult on our provisional view that 12(2) should be repealed.
- **Section 12(1):** The Directive does not directly affect the provisions of Section 12(1) of the Medicines Act 1968 which permits herbal remedies to be made up, without a medicines licence, to meet the needs of individual patients identified by a personal consultation. The arrangements for Section 12(1) have been under review by the Herbal Medicine Regulatory Working Group (Chaired by Professor Pittilo) which has also examined the issue of the statutory registration of the herbalist profession. The Working Group made recommendations regarding the regulation of herbal medicine practitioners and acupuncturists in its report in September 2003. Its report also included a number of recommendations for assuring the safety and quality of herbal remedies supplied under Section 12(1) of the Medicines Act. These recommendations are the subject of MLX299 “Proposals for the reform of the regulation of unlicensed herbal remedies in the United Kingdom made up to meet the needs of individual patients”. Further information on this is available on the Agency’s website (www.mhra.gov.uk)

Q18.2 What will be the effect of the Directive on existing licensed herbal medicines?

- A. In the UK, as in many Member States, there is a range of herbal medicines with an existing marketing authorisation. Often these licences have been held for many years. We have no present plans to review existing herbal marketing authorisations with a view to determining whether any of the products concerned might in future more appropriately come within the category of the traditional use registration scheme. The Directive establishes a European Committee for Herbal Medicinal Products. It may be that in due course this Committee, produces guidance on the distinction between well established use (applicable to marketing authorisations) and traditional use under the registration scheme in this Directive. In the event that the Committee produced such guidance, we would of course consider the implications carefully.

Q18.3. Some herbal medicines with a marketing authorisation have product information referring to traditional use. Will it be possible to remove such references to distinguish the products from those with a traditional use registration?

- A. Licensed herbal medicines were granted specific indications in the light of the standards of efficacy, and their interpretation, as applied at the time the product was considered. In many cases, this was more than a decade ago. It is open to a marketing authorisation holder at any time to apply for a variation where it has evidence to support such a change. The MHRA has no present plans to review existing herbal marketing authorisations, with a view to re-determining what regulatory status and indications for the product might now be justified by the evidence of efficacy currently available.

19. FEES

Q19.1 Can the MHRA give an indication of the likely fee for a traditional use registration?

- A. It is not possible at this stage to give a specific indication of registration fee levels in relation to the Directive. Further work will be required before this is possible and there are important issues where policy on implementation is under development by the MHRA. However the MHRA has sought to give the herbal sector some indicative information in the draft of the partial Regulatory Impact Assessment.

Q19.2 Will there be a single fee level for traditional use registrations?

- A. In line with normal practice, the MHRA will look to have a differentiated fee structure where feasible, reflecting the varying level of work that has to be carried out by the MHRA for different kinds of applications. For example, where a product complies with the forthcoming European positive list, there would be no need for a company to demonstrate safety or traditional use and patient information would be standard. With such a product only quality aspects would require any significant consideration. It might well also be possible to have a lower fee, reflecting lower assessment costs, where for example a product is made to a very simple process, for example a single herb tincture as compared with a standardised extract.

Q19.3 How will fee levels be determined?

- A. The MHRA is a Government Trading Fund and, as such, is fully funded for its medicines regulatory work by fees paid by industry. The MHRA is currently considering the amount of work that will be involved in assessment of applicants for registrations in order to ensure, as far as possible, that the fees charged for a particular application reflect the cost of the work undertaken. Initial ideas for a particular Regulatory Impact Assessment but there is further work to be done.

There will be a public consultation on the proposed fee levels in due course. The fees charged will be monitored and reviewed annually.

20. REGULATORY IMPACT

Q20.1. What is the likely impact of the Directive on business?

- A. The MHRA recognises that the Directive is likely to have a significant effect on many businesses and that the impact will vary considerably, depending on the specific situation of each business. The Agency prepared a partial Regulatory Impact Assessment (RIA) which has been developed following a formal public consultation (MLX 283), ongoing dialogue with herbal interest groups and changes to the Directive. The MHRA is currently seeking comments on the latest RIA which can be viewed on the MHRA website.

Q20.2 What happens next in relation to regulatory impact assessment?

- A. Further work will continue on a number of fronts on issues that have a bearing on regulatory impact. These include dossier requirements, fee structure and fee levels. The MHRA will update the RIA in the light of new information and of continuing dialogue with the sector.

Q20.3 Will the requirements for dossiers be burdensome?

- A. The various dossier requirement headings which applicants need to consider exist for good reasons. However, the MHRA is working with the Herbal Forum to streamline dossier requirements where possible. The Herbal Forum has prepared two dummy

quality dossiers which have been used during workshops in a practical exercise to contain costs.

It is already the case under existing requirements – whether for herbal medicines or any other products with a marketing authorisation - that the size and complexity of dossiers provided by companies will vary quite widely according to the nature of the product. Many products likely to be put forward for traditional use registration will fall very much at the simpler end of the spectrum and hence require less documentation.

Q20.4 What other action is planned to contain the regulatory impact of this Directive?

- A. A wide ranging programme is being taken forward in discussion with the Herbal Forum. It includes detailed discussions on a wide range of technical papers, programme of visits to manufacturers and suppliers, workshops on issues such as manufacturer's licences and wholesale dealers licenses. Further information on herbal workshops can be found on the Agency's website (www.mhra.gov.uk).

GLOSSARY

<i>THMPD</i>	Traditional Herbal Medicinal Products Directive
<i>OTC</i>	Over-the-counter
<i>HMPC</i>	Committee on Herbal Medicinal Products
<i>THMP</i>	Traditional herbal medicinal product(s)
<i>Section 12(1)</i>	Section 12(1) of the Medicines Act 1968 permits herbal remedies to be sold, supplied, manufactured or assembled without a product or manufacturer's licence, on premises occupied by the supplier provided that they are sold or supplied to meet the needs of an individual patient following a one-to-one consultation
<i>Section 12(2)</i>	Section 12(2) of the Medicines Act 1968 permits the sale, supply, manufacturer or assembly of an over-the-counter (pre-prepared) remedy without a product licence or manufacturer's licence as long as it is not accompanied by any written therapeutic claims, comprises of only plant materials and is not sold under a brand name.
<i>Guidance Note 8</i>	Guidance explaining "What is a Medicinal Product". This is available on the MHRA website.