

European Herbal and Traditional Medicine Practitioners Association (EHTPA) Response to:

INTERIM REPORT OF THE REVIEW OF UNLICENSED MEDICINES - CONSULTATION QUESTIONS (MHRA)

Question 1:

Do you support the objectives of the reform outlined in the document? (para 5.1)

Response:

We do support the objectives of the reform outlined in the document? (para 5.1) with the caveats and suggestions concerning specific measures as outlined in our responses below.

Question 2:

What view do you take of the proposition that effective patient awareness and involvement in decision making over the possible prescribing of an unlicensed medicine can best be achieved through the effective implementation of good practice and professional guidance rather than through changes in medicines legislation?

Response:

We strongly take the view that effective patient awareness and involvement in decision making over the possible prescribing of an unlicensed medicine can best be achieved through the effective implementation of good practice and professional guidance rather than through changes in medicines legislation (as explained in para 5.7) and agree with the proposition in para 8.4 that initiatives to promote good practice should be pursued.

We agree (see para 5.8) that it would not be in the interests of patients to introduce of a specific legislative requirement for a prescriber to state that they are prescribing an unlicensed product as it might undermine the patient's confidence in either the prescriber or the prescribed medicine.

Please highlight any examples of good practice where this may be helpful to the work of the review.

(paras 5.2 – 5,8; 8.1 – 8.4)

Response:

We draw the MHRA's attention to its publication, *Discussion paper: no 4 Reforms of s12(1) of the Medicines Act 1968: quality standards where a practitioner prepares unlicensed herbal medicines*

(<http://www.mhra.gov.uk/Howweregulate/Medicines/Herbalandhomoeopathicmedicines/Herbalmedicines/PlacingaherbalmedicineontheUKmarket/Unlicensedherbalremediesindividualpatients/index.htm>). This paper says:

"12. The MHRA considers that the detailed requirements for quality standards to be met by herbal practitioners in their preparation of unlicensed medicines would most appropriately be met by use of a comparable code, tailored as necessary to reflect the responsible practice of herbal medicine.

Such a code would be able to set out a systematic approach to quality issues and would also be able to cover in greater depth the various areas of concern, ranging from correct identification of species and use of reputable suppliers to storage conditions, hygiene, and weights and measures. A code could incorporate the best practice already advocated for use by some practitioner professional organisations.

13. The Agency considers that use of a herbal practitioner's professional code as the principle means of giving the public assurance as to quality would accord with the principles of better regulation. In particular, this approach could potentially score well as regards consistency of approach (with the regulation of the activities of other health care professionals) targeting, proportionality and accountability within the regulatory arrangements. A code would also be more flexible than legislation and more readily adaptable in the face of new information and concerns.

14. However, this approach could only be applied effectively if it is possible to identify in law which practitioners are allowed to operate under s12(1); and if these practitioners are required to be held accountable for meeting the required standards by a body that has the capability of operating this oversight. Effective arrangements for enforcement of the code would be an important consideration."

We agree with these proposals which are reliant on the statutory regulation of herbal/traditional medicine practitioners seeing them as consistent with the proposals set out in this MHRA interim review of unlicensed medicines.

Question 3:

Do you have any comments about the suggested direction of progress in the application of quality standards? (paras 5.13 – 5.16; 8.5)

Response

Para 5.14 specifically addresses the possibility of applying "a wider range of the quality controls normally associated with licensed products". It says "notably stability testing, retention samples and sterility testing, become more realistic where there is batch production of products on a significant scale."

We comment that it needs to be borne in mind that many traditional herbal medicines made up by third-party manufacture for prescription by herbal/traditional medicine practitioners contain several different herbs in combination. We note that *the Guideline on Quality of Herbal Medicinal Products/Traditional Medicinal Products (CPMP/QWP/2819/00 Rev 1) HMPC 30/3/2006* says (Section 7. Control Tests on the Herbal Medicinal Products)

"The control tests on the finished product should allow the qualitative and quantitative determination of the composition of the active substance(s). A specification should be provided and this may include the use of markers where constituents with known therapeutic activity are unknown. In the case of herbal substances or herbal preparations with constituents of known therapeutic activity, these constituents should be specified and quantitatively determined. For traditional herbal medicinal products for human use containing vitamins and/or minerals, the vitamins and/or minerals should also be specified and quantitatively determined. If a herbal medicinal product contains a combination of several herbal substances or preparations of several herbal substances, and if it is not possible to perform a quantitative determination of each active substance, the determination may be carried out jointly for several active substances."

Unfortunately, traditional herbal registration (THR) of products containing more than three or four herbs via the Traditional Herbal Medicinal Products Directive (THMPD) has in practice proved unattainable due to the difficulties of applying quality controls normally associated with the manufacture of licensed medicinal products. The latter generally contain only one or two active constituents which, unlike multi-herbal medicinal products, can easily be assayed under the quality assurance protocols.

We note that the Herbal Medicinal Products Committee (HMPC) within the European Medicines Agency (EMA) has recently acknowledged the particular quality assurance difficulties presented by multi-herb combinations (*Doc. Ref. EMA/HMPC/CHMP/CVMP/214869/2006 -23/06/2008*)

“For some combination products, identification and assay of individual herbal substances / herbal preparations in the herbal medicinal product is difficult to perform and sometimes impossible. In those situations, the specific provisions set out by the existing legislation and guidelines need to be considered further.

This guideline addresses in more detail the approaches for identification and quantitative determination of herbal substances and/or herbal preparations in combination herbal medicinal products taking into account their complex composition and the potential for interference in analysis by other herbal substances/preparations present in the herbal medicinal product. In principle, the identity and the quantity of the active substances in the herbal medicinal product should be demonstrated. Where a comprehensive analysis of each active substance is not possible even when the specific provisions foreseen in existing guidelines are used, specific emphasis may be placed on the validation and design of the manufacturing process and detailed documentation of each critical step in addition to more global tests of identity and of quantity in the herbal medicinal product. For these products batch-to-batch consistency in quality has to be reached through appropriate manufacture of the herbal medicinal product and in particular in the choice of the in process controls [IPC] and appropriate testing of the herbal medicinal product.”

We also note that the 2008 ***Communication from the Commission to the Council and the European Parliament concerning the Report on the experience acquired as a result of the application of the provisions of Chapter 2a of Directive 2001/83/EC, as amended by Directive 2004/24/EC, on specific provisions applicable to traditional herbal medicinal products (Document on the basis of Article 16i of Directive 2001/83/EC)*** acknowledges that the THMPD has not provided a suitable legal basis for the acceptance of traditional Chinese and Ayurvedic medicine and other traditional medicine systems. It states:

“Medical traditions such as those mentioned above (i.e. Chinese, Ayurvedic and other traditional medicine systems) are based on a holistic approach and the set of requirements for the simplified registration procedure under Directive 2004/24/EC is not appropriate for a global regulation of such medical practices. The regulation of such traditions would demand a different approach from that introduced by Directive 2004/24/EC. Therefore, the Commission does not envisage extending the scope of the simplified registration procedure to cover traditional medical systems as such. Nevertheless, independently of this report, the suitability of a separate legal framework for products of certain traditions should be assessed.”

Given these difficulties, it is important to take into account the special characteristics of herbal products containing several constituent plants and ensure that quality-control guidelines that are adopted for unlicensed medicines to meet the needs of individual patients do not in practice militate against the use of such traditional medicines for this purpose.

It is noteworthy that in the Communication from the Commission mentioned above, the Commission has recently adopted a pragmatic and proportionate approach to the matter of genotoxicity testing recognising that an overburdensome approach could possibly lead to loss of “guarantees of quality, safety and efficacy”..

“During the public consultation, some stakeholders referred to the experience with the application of the requirements of the simplified registration procedure. In particular, the issue of genotoxicity data needs careful consideration from a scientific and legal point of view. The requirement for genotoxicity data should be considered on a case by case basis in the framework of the simplified registration, because wrong interpretation of the legal requirements could possibly lead to the marketing of some products under another qualification that would not necessarily offer the same guarantees of quality, safety and efficacy. Such a result would be contrary to the public health and harmonisation objectives of Directive 2001/83/EC and Directive 2004/24/EC. In order to overcome this difficulty, a case-by-case decision, where specific concerns about safety exist, appears to be a proportionate and balanced approach and in line with the objectives of the Directive. (COM(2008) 584 final)

We propose that the MHRA adopts a similar pragmatic and proportionate approach when it comes to setting quality guidelines for unlicensed herbal medicinal products made by third parties for individual patients for use by herbal/traditional medicine practitioners when they are statutorily regulated. Quality control guidelines adopted should not effectively prevent the

manufacture or import of traditional herbal formulations containing several herbs or the Article 5.1 provision will have little or no practical use for statutorily regulated practitioners using herbal medicines.

Question 4:

What view do you take of the proposals that have been made about product labelling / information under reformed arrangements? (paras 5.17 – 5.20; 8.6 – 8.9)

Response:

We agree that PILs written in English should be supplied for these products. We agree that this information should include:

- what the products is
- what it contains
- how to take the product
- any known adverse effects
- any circumstances in which the product should not be taken

However, we do have concerns about the notion of including “action and use” on these herbal products many of which are prescribed to address a perceived imbalance from the point of view of a particular traditional medicine system (termed “a global therapeutic approach that embraces the individual as a whole” by the Communication from the Commission – COM (2008) 584 final- mentioned above). For example, a well known classical Chinese herbal formulation dating back to 1119 CE is 六味地黄丸 - *Liù Wèi Dì Huáng Wán* – *Six Flavour Rehmannia Pills*. This is traditionally prescribed for Kidney and Liver Yin Deficiency (based on a traditional Chinese medicine (TCM) diagnosis) that may include a wide variety of symptoms such as low back pain, night sweats, tinnitus etc. None of these symptoms can justifiably be used by itself to inform the patient as to use. Only a trained TCM practitioner is suitably skilled to discern the condition of Kidney and Liver Yin deficiency by, for example, noting *inter alia* in the patient, a red tongue lacking coating and a rapid thin pulse. For this reason any specific list of specific indications as to use on the PIL would be confusing and could lead to misuse. This same example from TCM holds true for other traditional medicine systems.

In addition, many herbal medicines are prescribed to stimulate the patient’s powers of self-healing rather than to treat an identifiable disease. What PIL information regarding “action and use” could be included in such cases?

Our advice is to omit this information which should be properly communicated by the practitioner to the patient.

Question 5:

What view do you take of the possibility that there should be a requirement to label the products as being unlicensed in the UK? (paras 5.21; 8.10)

Response:

We wholeheartedly concur with the view expressed in para 5.21 that a requirement to state that the medicine is unlicensed in the UK could erroneously convey the impression that the product met no regulatory standards. We agree that it could also worry patients unnecessarily, not least if a medicine had for example been fully licensed to European standards in another EU Member State. We concur that it would probably not be easy to capture these kinds of complexities in a mandatory written statement.

Question 6:

What view do you take of the proposals for clarifying and strengthening pharmacovigilance requirements under reformed arrangements? (paras 5.22; 8.11)

Response:

We agree that UK manufacturers and importers should be under a duty to communicate to the MHRA all suspected adverse drug reactions, and not only had those deemed to be serious.

Question 7:

Do you have ideas on ways to encourage reporting of suspected adverse drug reactions with these unlicensed products? (paras 5.23; 8.12)

Response:

The suggestions trailed in para 5.23 to achieve this aim seem eminently sensible namely reiterating to healthcare professionals that Yellow Card reports on unlicensed medicines are just as important as those for licensed products, and including details of the Yellow Card scheme on the patient information leaflet.

Question 8:

Looking at the possibilities for structural reform of the regulatory arrangements which if any of the options 1 – 7 do you consider merit no further consideration?

Which of the options 1 – 7 merit further consideration? Do you have a preferred option at this stage? (paras 6.1 – 6.10; 8.13; initial impact assessment)

Response:

We understand the reasons (outlined in paras 6. 2 – 6.3) why the MHRA is not in favour of options 1-5. In particular, we agree that clinical governance cannot be expected to bear the full weight of responsibility for ensuring that prescribers only use Article 5.1 in accordance with the legislative scheme (as explained in para 6.4). We also concur with the MHRA's expressed opinion (para 6.4) that it is unrealistic to tailor MHRA input according to the extent and effectiveness of clinical governance across primary, secondary, tertiary care, NHS and the private sector.

For this reason, we are in favour of option 6 as described in para 6.5.

We note that one suggestion in option 6 is "Items on list (i) could be subject to specific restrictions – e.g. a requirement to notify MHRA of each supply of the product in cases where there is a need for close monitoring." We suggest that this proposal is further discussed so that it is clear what circumstances constitute "a need for further monitoring".

Question 9:

**Do you have any specific comments about the feasibility of option 7?
(paras 6.9; 8.13)**

Response:

As stated we are in favour of option 6. We do not see specific advantages accruing from the adoption of option 7 (para 6.5) as it appears to increase the amount of paperwork and expense involved without any significant benefit to the patients for whom the medicines are designed. In option 7 the notification would state the quantity proposed to be manufactured or imported. Whilst there would be no restriction on the quantity of a product able to be notified in a single notification, it is not always possible to estimate what the requirement for a particular product may be so that there would be a further and unnecessary cost involved in a new application to manufacture or import more than the originally notified quantity as a further notification would be required during the validity period granted by the licence to manufacture Article 5.1 products. The increased administration costs are to be avoided. These are alluded to in the *Impact Assessment of the Review of Unlicensed Medicines* (para 26) "Costs to economic operators of complying with a notification system in situations where this is not currently required, or if requirements are more onerous; costs could include both set up and ongoing costs."

Lastly, as the impact assessment makes clear, there is a significant risk in implementing the more complex option 7. It says "Nearly all the positives have a possible down side if arrangements were not to work effectively and smoothly."

We submit that on these grounds alone, option 7 should be ruled out.

We note that in:

Discussion paper: no 6 Reforms of s12(1) of the Medicines Act 1968: the regulation of unlicensed herbal medicines commissioned by a registered practitioner from a third party to meet the needs of individual patients (circulated by the MHRA to a range of stakeholders in January 2007), the MHRA proposed :

"Stocks of unlicensed herbal medicines may be prepared in advance, e.g. experience can be used to anticipate demand. Levels held should be consistent with the purpose of the scheme.

- Wholesalers may hold a stock of specials in anticipation of orders.*
- In the scheme that applies in conventional medicine there is a limit on the stocks to be held by the practitioner. This helps to ensure that such medicines are genuinely being used for special needs.*
- Such limits may be inappropriate for herbal medicine, where the significant use of practitioner commissioned medicines is likely to be integral to the activity of some registered herbal practitioners (e.g. in TCM and Ayurveda)."*

The ***Discussion Paper*** also proposed:

"There should be a positive list of permitted herbal ingredients/classes of ingredients for which it was not necessary for the licence holder (see section C below) to notify MHRA in advance of an intention to supply.

- There should be a negative list of ingredients/classes of ingredients that are explicitly excluded from this scheme.*
- In any other cases there should be a requirement for the relevant licence holder to notify the MHRA in advance of the supply of the unlicensed herbal medicine and the MHRA would have a period (eg of X days) within which it would have the opportunity to object to the supply.*
- The profession would have the opportunity to propose items for inclusion in the lists. The MHRA would seek the advice of the Herbal Medicines Advisory Committee on the positive list and negative lists."*

These proposals, with which we concur, appear similar in scope to option 6 rather than option 7.

Question 10:

Do you wish to suggest any additional options for structural reform or any adjustments that would improve any of the existing options?

Response:

We note the reasons why a formal appeal mechanism may be “cumbersome” (para 6.7) but where herbal medicines are concerned we would wish that the MHRA would take advice from the independent Herbal Medicines Advisory Committee (HMAC) rather than from the Commission on Human Medicines (CHM). As mentioned in our answer to Question 9 above, it was HMAC rather than the CHM that was proposed by the MHRA to be the advisory body when it came to question arising about particular herbs allowed in products manufactured or imported under Article 5.1. We would wish this to be confirmed as the advisory body where herbal medicines are concerned. It is to be hoped that the MHRA, following statutory regulation of our sector, will also take advice from any committee set up within the Regulator of the profession to give advice on the scope and safety of herbal products.

Question 11:

Do you wish to draw attention to any likely knock on effects or unintended consequences of possible reforms?

Response:

We would wish to draw the attention of the Government, Department of Health and MHRA to the urgent and compelling need to ensure statutory regulation for practitioners of acupuncture, herbal medicine, traditional Chinese medicine and other traditional medicine systems practised in the UK (currently undergoing consultation after a series of regrettable delays). Until now, a large number of herbal medicines manufactured by third parties have been available for prescription for individual patients by practitioners in this sector under s.12(2) of the Medicines Act of 1968. However, s.12(2) is to be effectively repealed once the THMPD becomes fully implemented in April 2011 after which these herbal products manufactured will no longer be available as the majority are not suitable for the THR scheme. This will significantly and adversely restrict the scope of herbal remedies currently available to the public who wish to consult herbal/traditional medicine practitioners. In addition, the loss of these herbal medicines is likely to have serious financial consequences for SMEs both at practitioner and herbal supplier levels. In particular, herbal suppliers are already coping with significant increases in costs as they gear up for the implementation of the THMPD. The loss of a significant proportion of their turnover due to the fact that practitioners are unable to use the derogation under Article 5.1, is likely to have serious negative regulatory impact on these SMEs. We urge the Government to fulfil its earlier promises to move to statutory regulation of this sector as soon as possible.

Question 12:

Do you have any other comments as to how the objectives of reforms could be met?

Response:

None

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Any questions regarding this response should be referred to the Chairman EHTPA by email ehpa@globalnet.co.uk