

To: entr-pharmaceuticals@ec.europa.eu
The European Commission
DG Enterprise and Industry

Date 8 August 2007

Subject: MHRA response to the European Commission's consultation on the draft report on the experience acquired in operating the provisions of Directive 2004/24/EC

Dear Sir/Madam,

Introduction

1. The MHRA welcomes the opportunity to comment on the European Commission's draft report. We are pleased that the Commission has taken the opportunity to raise a number of important issues.
2. In the UK, among a number of other EU Member States, Directive 2004/24/EC will be the principal means by which herbal medicine is brought into effective regulation to the benefit of public health and informed consumer choice. It is therefore a very significant piece of legislation.
3. In the UK herbal sector there is a preponderance of SMEs. Many of these companies have not been accustomed to operating in an environment of systematic regulation. Wide – ranging acquisition and upgrading of expertise is required in parts of the UK herbal sector by 2011 if they are to be able to operate successfully and legally in a regulated market. It is also important to bear in mind that a number of products that may fall within the scope of the Directive are close to the borderline with other regulatory categories, including food supplements. The issue of regulatory impact needs to be carefully managed if adverse incentives for companies are to be avoided.
4. In view of the extent of challenge faced by UK SMEs if they are successfully to adapt to the new regulatory requirements by the end of the transitional period in 2011, the MHRA has adopted an energetic approach to implementation. Our aim has been to manage and minimise regulatory impact while not compromising public health. In this way we believe that we can best promote fair competition and informed consumer choice. We issued initial website guidance for companies within 3 months of the Directive being agreed. The Directive was transposed into UK legislation on time, in October 2005. We have held extensive and continuing dialogue with representatives of industry before and during the implementation period. We have presented at conferences and workshops. We have held around 100 meetings with individual companies to discuss their early plans for registering products.

5. The MHRA notes that on a number of issues the report suggests that it is too early in the operation of the scheme to reach conclusions or make changes. We believe, however, that while this may be the case on some issues, the extent of experience already acquired in the UK should be given due weight during this review period and recommend that the Commission should not hold back from pursuing changes where these will contribute to the successful and proportionate implementation of the Directive across the EU.

Interpretation of statistics for traditional herbal registration

6. As at the end of July the MHRA had received 26 applications to register products from a total of 7 applicants. 4 product registrations have so far been granted.
7. The relatively modest numbers at this point in the transition period are not a surprise given the need for companies to compile registration dossiers including undertaking preparatory work, such as collecting stability data. In some cases, as indicated above, companies are having to acquire expertise before they can effectively begin these activities.
8. We are aware from our informal dialogue with companies that other UK applications to register products are likely to be made in the coming months. We expect the number of applications received and registrations granted in the UK to rise steadily. However, it is clear to us that a number of companies are finding the challenge difficult and therefore the overall number of products that we might expect to see registered in the medium and longer term remains uncertain. The eventual number of product registrations is heavily dependant on the cumulative regulatory impact. It is essential that all practical steps are taking to avoid unnecessary regulatory impact.

The positive list: genotoxicity data

9. The report draws attention to the difficulties in producing a European positive list due to concerns over the lack of genotoxicity data. The concept of a positive list represents an important regulatory easement, of particular benefit to SMEs. Without such a list there will be an additional regulatory burden and the possibility of much duplicated work by companies.
10. The question of timing is critical. Bearing in mind the time regulatory agencies need to assess registration applications once received, the remaining transitional period is eroding fast. Companies need to be taking action now to prepare registration applications if they are to have products legally on the market in 2011. It is therefore essential that a practical way forward is found to deliver promptly the benefits intended by the concept of the positive list. The MHRA would be happy to participate

in dialogue to discuss options as to the best way forward. Resolution of this issue should be a top priority.

Extension of scope to non herbal ingredients

11. The MHRA welcomes the discussion on possible extension of the scope of simplified registration to some other categories of ingredients used in non herbal ingredients. We believe it would be desirable to extend the scope of simplified registration to medicines containing some categories of non herbal ingredients where this can be fully accommodated within the overall purpose of the scheme. It is important that the overall rationale for simplified registration is fully respected in order not to undermine evidence based medicine or to diminish incentives for companies to seek a marketing authorisation.
12. There are a number of categories that could be considered for such an extension. For example:
 - **Other nutrients**, in addition to vitamins and minerals, e.g.: amino acids
 - **Isolated plant constituents or synthetic equivalents** e.g.: menthol, camphor, thymol, cineole, lecithin, bioflavonoids
 - **Minerals**, e.g.: zinc oxide, calamine (for use in topical preparations).
 - **Substances of animal origin**, e.g. shells.

The requirement for evidence of 15 years use within the EU

13. The report notes that it can be difficult for traditional herbal medicinal products originating from outside the EU to demonstrate the necessary period of 15 years use within the Community. This issue remains of concern in the UK. We also believe that the current arrangements are adversely and unnecessarily impacting on the reputation of the EU.
14. The “outermost regions” of the EU include Guyane, Guadeloupe, Martinique, Reunion, Azores, Madeira, and the Canary Islands. It is not easy in principle to justify on public health grounds why it is possible to accept the evidence of use of a product originating from these territories, whereas evidence of traditional use from, say, Switzerland, Canada or Australia is not regarded as adequate.
15. Likewise, evidence that was previously regarded as unacceptable becomes acceptable once a country joins the EU. This further illustrates the point that the present 15 years EU use requirement is a rather limited way of dealing with the issue.

16. The existing referral procedure to HMPC provides a helpful recognition in principle that the 15 years EU use requirement could be lowered in individual cases. However, we doubt that this mechanism will be much used in practice. Our concern is that a company has fully to demonstrate to the competent authority in a Member State that all the requirements of the Directive are met and if that is the case the product is referred to the HMPC which can then draw up a monograph. We doubt that many companies would think it worthwhile to pursue an application for a product without 15 years EU use all the way through a Member State against the uncertain prospect of whether the HMPC would support the product in the subsequent referral. We therefore do not think that the absence of use of the HMPC procedure should be regarded as evidence of lack of an issue. In the UK we have had company enquiries about several products which at first sight would appear reasonable candidates for registration – for example in terms of ingredients and indications - but where it is likely that insufficient evidence of use in the EU would be an issue.
17. We would therefore advocate greater flexibility in approach that would allow a realistic possibility for products without 15 years EU usage to gain a traditional herbal registration whilst ensuring that public health protection was maintained. There are a number of options as to how this could be achieved.

Other changes affecting scope of the scheme

18. We agree that there is not a strong case at present for changing provisions relating either to the kind of indications permitted or the routes of administration allowed.

Quality requirements

19. One issue that has led to concerns in the UK is the question of quality requirements as they apply to multi ingredient herbal products. The technical requirements and costs of controlling the quality of complex products are significant, especially for SMEs. Our dialogue with industry suggests that until clarification is reached on how certain aspects of the quality guidelines apply to multi ingredient products it is unlikely that many combination products will be put forward for registration in the UK. Indeed, the MHRA has suggested to companies, particularly those with less experience of operating within a framework of detailed medicines regulation, that they would be well advised to start with simpler products to gain experience of the arrangements while the situation is clarified as regards combination products. We note that the EMEA are currently consulting on draft guidelines covering this issue. We are hopeful that this may offer a way forward but would highlight the importance that this work on new guidelines is progressed expeditiously by HMPC and EMEA. We recommend that the impact of the Directive on combination products is kept under review.

Pharmacovigilance requirements

20. We are of the opinion that the pharmacovigilance requirements could benefit from scrutiny to consider whether adjustments could lead to a reduction in regulatory impact without impairing effective public health protection. The Directive incorporates the concept of a positive list where the applicant does not have to demonstrate the safety or traditional use of the product. The logical implication of this approach is that it is recognised that there will be a number of herbal medicines where the safety profile is likely remain relatively static over a period. Clearly the regulatory burden could be eased if industry were to carry out literature searches on a collaborative basis; we think it would be helpful if some way could be found to promote actively a suitably collaborative approach, perhaps at European level.

Advertising

21. The wording prescribed in Article 16g(3) of the 2001 Directive, as introduced by the amending Directive 2004/24/EC, has the serious disadvantage in the English language that it is open to more than one interpretation.
22. The MHRA fully appreciates that the intended interpretation behind the wording specified in Article 16g(3) is to communicate the fact that the product has been cleared for usage on the basis that the traditional herbal medicine in question has been in use for at least thirty years preceding the date of the application for the registration. A consumer could, however, conceivably interpret the statement to mean that the product may be efficacious only if taken over a long period of time. If this were the case the consumer would be misled in a way that could have implications concerning safe use of the product. There is a real danger that manufacturers of registered herbal medicines making such a statement in their advertisement, which the law requires, could fall foul of the provisions contained within the Misleading and Comparative Advertising Directive because of the prescribed statement contained within Article 16g(3).
23. In order to address this problem, the MHRA suggests that the European Commission consider a proposal for a limited but important amendment to the current wording of Article 16g(3) as follows:

“In addition to the requirements of Articles 86 to 99, any advertisement for a medicinal product registered under this chapter shall contain ~~the following statement: Traditional herbal medicinal products for use in specified indication(s) exclusively based upon long-standing use~~ a statement to the effect that the product is a herbal medicinal product for use in specified indication(s) exclusively based upon long-standing use.”

24. The proposed amendment draws upon that part of the Directive that relates to labelling as a precedent - namely Article 16g(2)(a) - which in the English text, rather

than prescribing that particular words be used, allows a degree of flexibility in how the intended message is provided.

25. We are unclear as to whether the existing text poses similar problems in other Member States, and it may well be that some Member States will not yet have considered operation of the advertising provisions in detail if they are currently setting up arrangements for their national arrangements for the traditional herbal registration scheme. An advantage of our suggestion is that it should not require other Member States to change their wording if they are satisfied that the existing prescribed text is not open to misinterpretation.
26. In arriving at this proposed amendment to the Directive, the MHRA has sought the views and approval of those organizations represented on the Medicines Advertising Liaison Group (MALG), which is chaired by the Agency. This group includes statutory and self regulatory bodies responsible for administering Title VIII of Directive 2001/83/EC and also the advertising of medicines under the Misleading and Comparative Advertising Directive (Directive 84/450/EEC). These organizations support the MHRA's proposal for amendment to the Directive. The following organizations from the advertising and medicines sectors are represented on MALG: the Advertising Association, Advertising Standards Authority, the British Herbal Medicines Association, the Broadcast Advertising Clearance Centre, the Committee of Advertising Practice / Broadcast Committee of Advertising Practice, Health Food Manufacturers' Association (including its Labelling, Advertising and Promotion Advice Division), the Proprietary Association of Great Britain, the Prescription Medicines Code of Practice Authority and the Radio Advertising Clearance Centre.
27. The MHRA has also consulted with the independent expert advisory Committee, the Herbal Medicines Advisory Committee, which also agrees that there is a need to adjust the provision relating to the required form of wording for advertisements in order to avoid the risk of misleading the consumer.
28. Assuming the European Commission proceeds with this proposal, the MHRA would seek to work with the members of MALG to arrive at a standard set of words that would reflect the intent of Article 16g(3), but avoid the problematic nature of the wording, in its English formulation, that the Directive presently prescribes.

Technical issues concerning Directive 2004/24/EC

29. There are several points in the text where we believe there is a need for amendments in order to achieve the original policy intention. Our understanding is that these inaccuracies have arisen as a result of the simultaneous amendment of Directive 2001/83/EC by 2004/24/EC and 2004/27/EC, which no doubt made management of cross references an unusually complicated task. We would draw attention to the following:

- Article 16c 1 provides that the application shall be accompanied by....(a)(ii) the results of the pharmaceutical tests referred to in the second indent of Article 8(3)(i). We think that the policy intention would have been to refer to the *first* indent in Article 8(3)(i)
- Article 16c 1 (a)(iii) requires the application to be accompanied by the summary of product characteristics, without the data specified in Article 11(4). However, it is surely the case that the data intended to be excluded would be that which is specified in Article 11(5), relating to pharmacological properties
- Article 16h(3) refers to “the application of Article 10(1) (a)(ii)”. We think the reference should be to Article 10a (relating to well-established use) as there is no longer a paragraph 1 in Article 10.

Conclusion

30. We hope that the Commission will give careful consideration to these points.

With best regards

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