

Guidance on arrangements for the transfer of certain herbal products with a marketing authorisation to traditional herbal registration status

Introduction

1. This guidance outlines arrangements whereby:
 - the status of certain herbal products with a marketing authorisation, that is those holding a product licence (PL), in the UK will be reviewed to assess whether some would more appropriately come within the traditional herbal registration (THR) scheme
 - in appropriate cases companies can apply for a THR under simplified arrangements to replace the PL product.
2. For convenience the guidance refers to the transfer of some products from PL to THR status. Formally, the arrangements entail the MHRA permitting a company to make a simplified THR application for a product that will replace the existing PL. These simplified arrangements will apply where the PL product that is to be withdrawn can be regarded as a “corresponding product” in relation to the THR. Under this process withdrawal or cancellation of the existing herbal PL would then be linked to the granting of the THR.
3. These simplified arrangements do not affect the right of companies to make an application for a THR at any time under the normal arrangements.
4. The review should progressively enable the sector to move to the position in which regulated over-the-counter herbal medicines are seen to come within the appropriate regulatory category. This should bring clarity to a complex market, to the benefit of both consumers and companies.

Background

5. European Directive 2004/24/EC on traditional herbal medicinal products was brought forward specifically in recognition of the position that for many herbal medicines it was difficult for companies to meet the full requirements for a marketing authorisation, particularly in relation to efficacy. Many EU Member States had pragmatic national arrangements permitting herbal medicines to remain on the market.
6. The Directive therefore required Member States to put in place specific regulatory arrangements for those traditional herbal medicinal products, suitable for use without medical supervision, for which there was evidence of traditional use but insufficient evidence of efficacy to meet the requirements for a marketing authorisation. The legal effect of the Directive is not restricted to those medicinal products which are, or have been, unlicensed (for example, in the UK, unlicensed herbal remedies under s12(2) of the Medicines Act 1968).
7. In the UK many herbal medicines were originally given a product licence of right (PLR) when medicines licensing was introduced and were subsequently granted a full PL following the

Review of Medicines. The review of herbal medicines commenced in 1988 and was completed mid 1990.

8. The CRM (Committee on Review of Medicines) recognised that these traditional products could not be assessed in the normal way and agreed that provided the product was intended for a minor condition, suitable for self-diagnosis, then evidence documenting the use of the product would be accepted in place of results of pharmacological tests and clinical trials. Where licences were granted in such circumstances they were required to be labelled with a statement along the lines of *'a herbal remedy, traditionally used for the symptomatic relief of ...If symptoms persist, consult your doctor.'* In the case of more serious disease conditions the CRM advised that it was not appropriate to relax the requirements for proof of efficacy.
9. This approach was in effect therefore a precursor of that which was subsequently taken in Directive 2004/24/EC. The consequence of this historical position is that in the UK we have a range of herbal products with PLs which, in at least some cases, are likely to come within the scope of Directive 2004/24/EC.

Priorities

10. The MHRA has been clear from the outset that for the THR scheme our top priority on public health grounds is to bring unlicensed manufactured herbal medicines, in particular those sold under s12(2), within effective regulation. This priority has been reflected in the programme of help and advice that has been offered to companies. The priority remains unchanged. However, now that the MHRA has experience of operating the THR scheme, the time is right also to introduce a programme that should progressively ensure that herbal products already within regulation are ultimately allocated to the appropriate category, in line with European and UK legislation.
11. Our aim is to instigate a steady, measured programme for this review, which builds in flexibility over timing and has full regard to the varying position of individual companies. In particular, the MHRA recognises that some companies affected by these proposals will need to give priority to preparation of applications for THR for unlicensed s12(2) products and in other cases companies may have large number of products and may well wish to review products in several stages.

Products affected

12. Products affected will be principally those herbal medicines with a PL which have a traditional indication, including those granted as "piggy-back" applications. There will in addition be a certain number of herbal PL products which were originally given a traditional indication where, for one reason or another, the reference to traditional use has been lost in the meantime. There could also be a scattering of other herbal PLs which should be considered in the exercise.

13. The MHRA envisages that there will continue to be herbal products which fully justify their PL status, for example under “well established use” marketing authorisation provisions, including many single herb laxative products based on ingredients such as senna or ispaghula.
14. The review only covers products that could come within the scope of Directive 2004/24/EC. Therefore herbal products are excluded where, for example, the product also includes active ingredients not permitted under Directive 2004/24/EC (unless these could be considered as excipients).
15. Where a PL holder is uncertain about the status of a particular herbal product the Agency will provide advice and clarification. Queries should be sent to the following email address:
thmrsqueries@mhra.gsi.gov.uk.

Compliance with existing regulatory requirements

16. Where products with a PL enter the transfer process described in this guidance this does not remove the obligation to continue to meet existing regulatory requirements applicable to PLs. Companies should, for example, continue to meet existing legislation and guidance applicable to maintaining quality dossiers, updating product information, and complying with pharmacovigilance requirements.

What are we asking companies with herbal PLs to do and by when?

17. Between the launch of the guidance and the end of 2011 companies with herbal PLs affected by the review should submit plans to the MHRA (at thmrsqueries@mhra.gsi.gov.uk) using the proforma attached showing:
 - which herbal PLs they are considering applying to transfer to THR status and which products they wish to maintain as PLs on the basis of meeting efficacy requirements; and in the case of products for transfer;
 - whether any adjustments are proposed to the formulation of the product or its indications.
18. It is acceptable for companies to spread the workload by carrying out this exercise progressively over several stages with different groups of products. Where companies wish to do this it would be helpful if they could informally outline their provisional thinking on this to MHRA either at the time they submit their first proforma – or in advance of that. The MHRA will give feedback on these plans to companies on an individual basis and have discussion as may be necessary. The MHRA may agree companies’ plans in a staged process, particularly where a large number of products are involved.
19. Where a plan is agreed between the MHRA and the company that a product should be transferred to THR status the following application process would apply, depending on the situation:

Is a simplified THR application applicable?

	A. No changes to formulation of the product. Indications remain the same (or any adjustments to indications are such that the existing herbal PL is still regarded as a “corresponding product”)	B. Where company wishes to modify/adjust the formulation of the product (where existing herbal PL is a “corresponding product”)	C. Where company wishes to modify/adjust the formulation of the product (where existing herbal PL is not a “corresponding product”)
THR application	<ul style="list-style-type: none"> • Simplified THR application, focussed mainly on product information • Company must provide updated module 1 • Other information may need to be provided or updated depending on what MHRA holds in-house in relation to the existing PL • Quality dossier to be available for MHRA at time of THR renewal • Companies should ensure quality dossier is maintained in meantime 	<ul style="list-style-type: none"> • THR application simplified as regards traditional use and safety • Application includes updated quality dossier and product information 	<ul style="list-style-type: none"> • THR application should be made in the normal way as for any other product not covered by this review
Timetable	<ul style="list-style-type: none"> • THR application to be made within 1 year from date of agreement with MHRA 	<ul style="list-style-type: none"> • THR application to be made within 2 years from date of agreement with MHRA 	<ul style="list-style-type: none"> • THR application to be made within 2 years from date of agreement with MHRA

20. MHRA will agree arrangements with individual companies for the withdrawal or cancellation of the existing herbal PL linked to the granting of the THR. Agreement by MHRA to the continued maintenance of the PL during the interim will be dependent on companies progressing the relevant THR application in line with the plans agreed with the company.

Corresponding products

21. Whether a company's existing herbal product with a PL can be regarded as a "corresponding product" in relation to an application for a THR made by that company will be used by the MHRA to decide whether a simplified form of THR application is appropriate.
22. The term "corresponding product" will be interpreted as in Directive 2004/24/EC. "A corresponding product ...is characterised by having the same active ingredients, irrespective of the excipients used, the same or similar intended purpose, equivalent strength and posology and the same or similar route of administration as the medicinal product applied for." It is also possible to refer to the corresponding product where the number or quantity of ingredients of the medicinal product is reduced during the period of traditional use.

Making adjustments to products during transfer to THR status

23. Companies may wish to take advantage of the flexibility within Directive 2004/24/EC to make some adjustments to the product as part of the process of transfer to THR. Examples of adjustments that may be beneficial for companies include: clarifying indications in a way that is more meaningful to the consumer; simplifying the formulation of the product, and hence the associated quality controls, for example by removing non essential ingredients; changing the formulation of the product from powdered herbal substances to extracts or from capsules to tablets – or vice versa.
24. Apart from any changes in indications proposed by companies the MHRA envisages that there may be occasional instances when the Agency itself wishes to propose adjustment to indications as part of the transfer process, in order for example to reflect monographs from the Herbal Medicinal Products Committee or current advice from the Herbal Medicines Advisory Committee. The MHRA will discuss any such proposals with the company.

Fees

25. Where a company submits a THR application under this transfer process a fee for THR registration will not be charged, providing that:
- the product for which the company concerned holds an existing herbal PL can be regarded as a corresponding product in relation to the proposed THR
 - the relevant herbal PL is cancelled or withdrawn at a point agreed with the MHRA.
26. The workload arising for the Agency will be kept under review. In the event that there is a significant workload arising, particularly in relation to the number of products for which

adjustments are proposed, the Agency may need to propose a fee at a later date. Any fee would be proportionate to fees applied elsewhere under the THR scheme.

Progress of the review programme

27. The timetable outlined should allow companies options to plan their activity. Ultimately, if progress against the timetable outlined is insufficient the MHRA would have the option to ask companies concerned for evidence of efficacy for herbal products with a PL where the Agency believes this is in doubt.

Commencement

28. This guideline takes effect on 1 April 2009. (This does not preclude individual companies contacting MHRA for dialogue about their particular product range in the period before April 2009.)

Further guidelines

29. Q&A briefing is attached. Further briefing or additional guidelines may be added if this appears helpful in the light of experience.

Further enquiries

30. Any enquiries about this guidance should be sent by e mail to: thmrsqueries@mhra.gsi.gov.uk.

January 2009

TEMPLATE FOR COMPANIES TO OUTLINE PROPOSALS FOR REVIEW OF THEIR HERBAL MARKETING AUTHORISATIONS

Product Licence Number	PL Holder	Proposed action*	Comments	Provisional timetable

***Action codes:**

- A. Retain PL (supporting evidence of efficacy to be available on request)
- B. PL to be transferred to THR with no amendments to formulation
- C. PL to be transferred to THR with amendments to formulation (provide summary in comments column)

Question and Answer briefing

- Q. Where a company is unsure whether it has sufficient evidence of efficacy to justify retention of the marketing authorisation what action should be taken?**
- A.** We recommend the company raises this issue with the MHRA. This can be done via an email to thmrsqueries@mhra.gsi.gov.uk or in discussion with the Agency.
- Q. Where a company has undertaken user testing for existing herbal PLs will further user testing of the product be required where it is agreed that the product will transfer to THR status?**
- A.** We envisage that there would not normally be any requirement to repeat user testing as a result of a transfer to THR status.
- Q. How will MHRA co-ordinate the review of existing herbal PLs?**
- A.** We aim to run a co-ordinated programme based round this guidance (which will be updated if necessary in the light of experience) and the opportunities for individual companies to have dialogue with MHRA about their particular circumstances. Where a company has specific concerns about how the programme affects them we recommend they contact MHRA at thmrsqueries@mhra.gsi.gov.uk .
- Q. Will MHRA publish a starting list of herbal products that are covered/not covered by the review?**
- A.** No. Within the overall numbers of marketing authorisations there is no specific regulatory category of herbal medicine. One of the key criteria for this review is that products come within the scope of Directive 2004/24/EC (the Directive on traditional herbal medicinal products). In a number of cases this will not necessarily be clear until there has been dialogue between MHRA and the company. For example, the presence of menthol in a product would mean the product was outside the scope of the Directive if menthol was an active ingredient, but not if it was regarded as an excipient.

Where THRs are granted following the review/transfer process the MHRA will make available this information in a form that allows interested parties to see that a transfer has taken place.