Potential Grounds for Revocation of a Traditional Herbal Registration

By Dr Rosanna Cooper

In this article we will be exploring the potential grounds for revocation of the **Traditional Herbal Registration** (THR) for product, KGY, owned by a competitor. Your product is YUK and you would like to register YUK as a THR. The key here is that instead of obtaining a marketing authorisation ('MA') to place the herbal medicinal product on the market, a traditional use application can be obtained if the criteria laid down by Directive 2001/83/ EC)'Directive') are met.

This article commences with explaining what the requirements of a marketing authorisation are as, without such marketing authorisations, medicinal products or certain herbal medicinal products cannot be placed on the market.

Applicants for a THR must provide evidence to prove that the product (or an equivalent product) **has been in use as a traditional medicinal product (TMP) in the EU for a period of at least 30 years** (or 15 years in the EU plus 15 years outside of the EU).

The article then takes an in-depth look at the provisions of the Directive regarding THR and the potential grounds for revocation of a THR.

1. Marketing Authorisation

1.1 There is a general requirement under Article 6(1) of Directive 2001/83/ EC, that a medicinal product must have a Marketing Authorisation before it can be placed on the market of a Member State, or be distributed by way of wholesale dealing in the UK.

> "No medicinal product may be placed on the market of a Member State unless a marketing authorization has been issued by the competent authorities of that Member State in accordance with this Directive..."

1.2 For the purposes of this Directive, a 'medicinal product' relates to substances (or combination of substances) which are presented as being capable of preventing disease in human beings or having an effect on the physiological functions of human beings(Article 1 Directive 2001/83 EC).

> "Medicinal product:
> (a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or
> (b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or

modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis

1.3 According to the Medicines & Healthcare products Regulatory Agency ('MHRA') Guidelines:

> …for some herbal medicines there is sufficient evidence in the public domain for an applicant to be able to obtain a Marketing Authorisation under the provisions for products containing active substances with 'well established' use by referring to appropriate scientific literature. Where this is the case the MHRA will not grant a traditional use application but will instead ask the applicant to apply for a Marketing Authorisation. Based on the MHRA's experience it is likely that this would apply in only a minority of cases. The MHRA will not take the view that a product ought to follow the 'well established' route to a Marketing Authorisation simply because the medicine contains a particular herbal ingredient. It may well be that there are some herbal medicines that 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.
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> Likewise, it may be that the 'well established use' provisions are applicable to a range of products that use a particular herbal ingredient. However, traditional use might be applicable where that ingredient is used in combination with other active herbal ingredients, particularly for other therapeutic indications. Such combinations would need to satisfy the requirements for traditional use registration including that the efficacy is plausible - based on long use and experience. Historically, in relation to herbal medicines, there have been some differences of interpretation of the 'well established' provisions between regulatory authorities in different EU Member States.

2. What is a Traditional Herbal Registration?

2.1 THR

2.1.1 A **THR** is available for placing **traditional herbal medicinal products** on the market or for their distribution by way of wholesale dealings in the UK.

> Directive 2004/24/EC
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> "Recital (8) …Herbal medicinal products differ substantially from conventional medicinal products in so far as they are intrinsically associated with the very particular notion of herbal substances and herbal preparations. It is therefore appropriate to determine specific requirements in respect of these products with regard to the standardised marketing authorisation requirements."

Directive 2004/24/EC

> "Recital 4 - Having regard to the particular characteristics of these medicinal products, especially their long tradition, it is desirable to

provide a special, simplified registration procedure for certain traditional medicinal products**. However, this simplified procedure should be used only where no marketing authorisation can be obtained pursuant to Directive 2001/83/EC, in particular because of a lack of sufficient scientific literature demonstrating a well-established medicinal use with recognised efficacy and an acceptable level of safety. It should likewise not apply to homeopathic medicinal products eligible for marketing authorisation or for registration under Directive 2001/83/EC.**

(5) The long tradition of the medicinal product makes it possible to reduce the need for clinical trials, in so far as the efficacy of the medicinal product is plausible on the basis of long-standing use and experience. Pre-clinical tests do not seem necessary, where the medicinal product on the basis of the information on its traditional use proves not to be harmful in specified *conditions of use**. However, even a long tradition does not exclude the possibility that there may be concerns with regard to the product's safety, and therefore the competent authorities should be entitled to ask for all data necessary for assessing the safety.*** *The quality aspect of the medicinal product is independent of its traditional use so that no derogation should be made with regard to the necessary physico-chemical, biological and microbiological tests. Products should comply with quality standards in relevant European Pharmacopoeia monographs or those in the pharmacopoeia of a Member State.*

(6) The vast majority of medicinal products with a sufficiently long and coherent tradition are based on herbal substances. It therefore seems appropriate to limit the scope of the simplified registration in a first step to traditional herbal medicinal products.

(7) The simplified registration should be acceptable only where the herbal medicinal product may rely on a sufficiently long medicinal use in the Community. Medicinal use outside the Community should be taken into account only if the medicinal product has been used within the Community for a certain time. Where there is limited evidence of use within the Community, it is necessary to assess carefully the validity and relevance of use outside the Community.

(8) With the objective of further facilitating the registration of certain traditional herbal medicinal products and of further enhancing harmonisation, there should be the possibility of establishing a Community list of herbal substances that fulfil certain criteria, such as having been in medicinal use for a sufficiently long time, and hence are considered not to be harmful under normal conditions of use."

2.2 Tests to prove the safety, quality and efficacy

2.2.1 Test data is required for pre-clinical and clinical tests to prove the safety, quality and efficacy of YUK and to be able to prove that there is sufficient scientific literature to demonstrate a well established medicinal use with recognised efficacy and an acceptable level of safety for this product. Therefore, this contravenes Directive 2001/83/EC.

1.1 The Directive states that where the competent authorities judge that a medicine fulfils the criteria for a Marketing Authorisation (in this context the efficacy requirements will be particularly relevant), they should not grant a Traditional Herbal Registration (Article 16a (3) Directive 2001/83). This would be the main argument that we would seek to rely on (once we have the evidential basis to do so).

"…in cases where the competent authorities judge that a traditional herbal medicinal product fulfils the criteria for authorisation in accordance with Article 6 …the provisions of this chapter shall not apply."

2.3 A simplified registration procedure

2.3.1 Article 1 of Directive 2001/83/EC defines a 'traditional herbal medicinal product' as a *"herbal medicinal product that fulfils the conditions laid down in Article 16a(1)"*.

2.3.2 The conditions are as follows:

"1. A simplified registration procedure (hereinafter "traditional- use registration") is hereby established for herbal medicinal products which fulfil all of the following criteria:

(a) they have indications exclusively appropriate to traditional herbal medicinal products which, by virtue of 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 of treatment;

(b) they are exclusively for administration in accordance with a specified strength and
posology;

(c) they are an oral, external and/or inhalation preparation;

(d) the period of traditional use as laid down in Article 16c(1)(c) has elapsed;

(e) the data on the traditional use of the medicinal product are sufficient; in particular the

product proves not to be harmful in the specified conditions of use and the pharmacological effects or efficacy of the medicinal product are plausible on the basis of long-standing use and experience."

3. Herbal Medicinal Product and Herbal substances

3.1 **A 'herbal medicinal product' is defined in Article 16a(1) as:**

"any **medicinal product**, exclusively containing **as active ingredients one or more herbal substances** or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations."

3.2 **'Herbal substances' are defined as:**

"all mainly **whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried, form, but sometimes fresh**. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author)."

3.2.1 YUK must come within the definition of a 'Herbal Medicinal Product' in order to be granted a THR.

3.2.2 For the grant of a THR, YUK must fulfil certain conditions (see above).

3.2.3 Recital 4 of Directive 2004/24/EC, which amends Directive 2001/83/EC with regard to traditional herbal medicinal products, provides that the simplified procedure of THR is only available where **no Marketing Authorisation can be obtained for the product because of a lack of sufficient scientific literature demonstrating a well-established medicinal use with recognised efficacy and an acceptable level of safety**.

3.2.4 Therefore, the aim is to show that an MA should have been obtained for KGY and as such the THR for KGY must be revoked. The argument would be that KGY met the criteria for the grant of an MA rather than a THR as the criteria in Article 6 Directive 2001/83/EC were fulfilled (for a Marketing Authorisation).

3.2.5 Traditional herbal medicinal products are herbal medicinal products which fulfil the conditions in Article 16a(1) of Directive 2001/83/EC, which are as follows:

"1. A simplified registration procedure (hereinafter "traditional- use registration") is hereby established for herbal medicinal products which fulfil all of the following criteria:

(a) they have indications exclusively appropriate to traditional herbal medicinal products which, by virtue of 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 of treatment;

(b) they are exclusively for administration in accordance with a specified strength and
posology;

(c) they are an oral, external and/or inhalation preparation;

(d) **the period of traditional use as laid down in Article 16c(1)(c) has elapsed**;

(e) **the data on the traditional use of the medicinal product are sufficient; in particular the product proves not to be harmful in the specified conditions of use and the pharmacological effects or efficacy of the medicinal product are plausible on the basis of long-standing use and experience**."

4. Potential Grounds for Revocation

4.1 There must be supporting evidence to substantiate any assertions made. A company may challenge the THR for the product KGY on the basis that although KGY has been granted a THR, it is not a *traditional* herbal medicinal product. The assertion would be that the THR ought to be revoked on the following grounds, provided that you can prove:-

- That KGY was developed as part of a pharmaceutical process using herbal; and/or
- The company that owns KGY does not own the rights to the process (know-how) and, if that's the case, the rights belong to your company; or
- The product YUK owned by your company with identical/similar composition to the product KGY has been on sale in Europe since 1998; or
- No other companies are manufacturing identical and/or similar products; or
- The product KGY is not on sale and the THR was obtained simply to licence to third parties (which would cause substantial damage to your business and its reputation; or
- There is a question mark over the safety of the product KGY; or
- The product KGY requires a Marketing Authorisation in order to supply the product in the UK and the rest of the European Union ("EU"); or
- A Marketing Authorisation already exist for an identical (if not, similar) product YUK in the EU and worldwide; or
- The efficacy of KGY ought to be reconsidered (the reasons would have to be substantiated). Based on Article 16 (d) and (e) of

Directive 2004/24/EC (i) the data on traditional use for the product KGY is insufficient, as the pharmacological effects or efficacy is not plausible on the basis of long-standing use and experience; and (ii) the pharmaceutical quality has not been satisfactorily demonstrated

4.2 The question is whether Articles 16a (1)(d) and (e) have been satisfied for KGY to be granted an MA. Evidence must have been produced to the MHRA to show that KGY, or a corresponding product, has been in medicinal use throughout a 30 year period preceding the date of application, including at least 15 years within the Community (Article 16c (1)(c)).

"(c**) bibliographical or expert evidence to the effect that the medicinal product in question, or a corresponding product has been in medicinal use throughout a period of at least 30 years preceding the date of the application, including at least 15 years within the Community**. At the request of the Member State where the application for traditional-use registration has been submitted, the Committee for Herbal Medicinal Products shall draw up an opinion on the adequacy of the evidence of the long-standing use of the product, or of the corresponding product. The Member State shall submit relevant documentation supporting the referral;"

4.3 Article 16c (2) Directive 2001/83/EC describes a 'corresponding product' as:

"A corresponding product, as referred to in paragraph 1(c), 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**."

4.4 The argument would be that KGY is not a traditional herbal medicinal product, it's a herbal medicinal product. This assertion will have to be backed up with evidence.

4.5 A further argument is that KGY has existed as a herbal medicinal product but not as a traditional herbal medicinal product. More information would have to be presented about the development of KGY in order to show that this is not a product that has existed for centuries and does not belong to anyone.

5. Evidence

5.1 The list below is not exhaustive in terms of the evidence that would be required to support the application for revocation of KGY:-

- Sales, marketing and other promotional literature for YUK;
- Details of the development process for YUK;
- Details surrounding the efficacy and safety of KGY.
- Information by way of documents, including the results of clinical trials, pre-clinical trials and other relevant tests conducted;

- Whether there are any other products on the market with the same/similar formula to YUK?

6. Conclusion

6.1 To be able to challenge the THR for the product KGY a great deal of evidence of required. .

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