Journal of Ethnopharmacology 158 (2014) 463–466

Contents lists available at ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jep

Research Paper

Requirements on efficacy of herbal medicinal products

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ARTICLE INFO

Article history:
Received 20 March 2014
Received in revised form
21 May 2014
Accepted 9 July 2014
Available online 17 July 2014

Keywords:
Herbal medicinal products
Efficacy
Clinical trials
Well-established medicinal use
Traditional use

ABSTRACT

Based on the regulatory requirements on efficacy documentation in the European Union, the herbal medicinal products have been grouped into the following sections:

(i) Herbal medicinal products for which the efficacy is demonstrated by results of a 'full' set of clinical trials that are in conformity with the relevant guidelines of the therapeutic area in question. This regulatory pathway to obtain a marketing authorisation for a new medicinal product (new chemical entity) is open to herbal medicinal products, but the examples are in reality few.
(ii) Herbal medicinal products which have a 'well-established medicinal use with a recognised efficacy and an acceptable level of safety' in the European Union. Results of new and product specific clinical trials are not required to obtain a marketing authorisation for products that fulfil these criteria, but a substantial clinical experience must be documented and sufficient scientific data on efficacy must be publicly available.
(iii) 'Traditional' herbal medicinal products, that do not fulfil the efficacy requirements for a marketing authorisation, but for which a medicinal use of at least 30 years including 15 years in the European Union can be documented. Traditional herbal medicinal products can only be registered with therapeutic indications that are considered safe for use without the supervision of a physician.

After briefly reviewing the regulatory requirements on efficacy documentation of herbal medicinal products in the European Union, some concluding remarks on the past and future developments in the area are made.

1. Introduction

The requirements on efficacy of herbal medicinal products in the European Union are set out in the Directive (2001)/83/EC on medicinal products for human use. An important amendment to this directive was made by Directive (2004)/24/EC, which introduced the possibility of national registrations of herbal medicinal products based on traditional use only. The same directive also created a European scientific committee (the Committee on Herbal Medicinal Products; HMPC) for the purpose of harmonisation of the European market of herbal medicinal products. A significant proportion of the work on herbal medicinal products, both at the national competent authorities (NCAs) and at the HMPC, is concerned with assessment of efficacy documentation of these products based on guidelines elaborated by HMPC to Directive (2001)/83/EC as amended. The purpose of this paper is to give a brief review of the pertinent parts of this piece of legislation and to discuss some aspects pertaining to the requirements on documentation of efficacy of herbal medicinal products.

Before a herbal medicinal product is put on the market within the European Union, it must be approved by an NCA or by the European Commission. There are basically three types of applications that are used by applicants who wish to obtain a marketing authorisation or marketing registration for a herbal medicinal product:

i. 'Full' marketing authorisation application [Article 8(3)[2]].
ii. 'Well-established use' marketing authorisation application [Article 10a[1]].
iii. 'Traditional use' marketing registration [Article 16a[1]].

Common to all three application types is that the applicant must submit adequate quality, non-clinical and clinical documentation of the product. The documentation must be submitted in

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[1] Disclaimer: The author represents neither the Committee on Herbal Medicinal Products (HMPC) at the European Medicines Agency, nor the Medical Products Agency, Sweden. The views expressed here are his personal views and may not be understood or quoted as being made on behalf of these agencies.

[2] Article no. refers to Directive 2001/83/EC.

http://dx.doi.org/10.1016/j.jep.2014.07.017
0378-8741/

the so called CTD format (Common Technical Document) according to the ICH (International Conference on Harmonisation). This format is mandatory for all types of products and applications irrespective of the procedure used (national, mutual recognition, decentralised or centralised procedure). The requirements on the documentation of the pharmaceutical quality of a product are the same regardless of which type of application that is used. Aspects on quality and safety documentation are not further dealt within this paper. The efficacy documentation constitutes part of the clinical documentation. As will be outlined in the following sections, the requirements on the efficacy documentation differ between the three application types listed above.

2. Full marketing authorisation

The so-called 'full' application for a marketing authorisation makes reference to article 8(3) of Directive (2001)/83/EC. It is the normal way to apply for a marketing authorisation for a new medicinal product (new chemical entity; NCE). The application shall be accompanied by the results of pharmaceutical tests (quality documentation), non-clinical (toxicological and pharmacological) studies and clinical trials. The efficacy of the medicinal product is regularly demonstrated by results of clinical trials that are in conformity with the relevant guidelines of the therapeutic area in question. Further, a safety data base of sufficient size according to guidelines is required. For approval, the effect should outweigh any safety issues, i.e. the benefit/risk balance must be considered positive. This application type is the normal way for approval of NCEs as medicinal products and it is open also for herbal medicinal products, but it is indeed not the most common type of application for herbal medicinal products. In fact there are only very few examples of herbal products that have obtained marketing authorisations in this way in the European Union. Hence this topic is not further elaborated in this paper.

3. Well-established medicinal use

A much more common type of application for marketing authorisation of herbal medicinal products is making reference to article 10a of Directive (2001)/83/EC. This regulatory pathway is open to products that have a well-established medicinal use in the European Union. The term 'well-established medicinal use' has a particular meaning in the pharmaceutical legislation and it can be applied to 'old' medicinal products, for which there is an extensive clinical experience within the Union, i.e. not only to herbal medicinal products. The Directive allows a broad spectrum of evidence to be used in the assessment. In addition to published controlled clinical trials, the assessment may be based on non-controlled clinical studies, epidemiological studies such as cohort or observational studies etc.

In Directive (2001)/83/EC it is stated that: "The applicant shall not be required to provide the results of toxicological and pharmacological tests or the results of clinical trials if he can demonstrate that the constituent or constituents of the medicinal product have a well-established medicinal use with recognised efficacy and an acceptable level of safety, by means of a detailed scientific bibliography;"

In effect this means that for a product (substance) for which a substantial clinical experience can be documented and for which sufficient scientific data are publicly available, there is derogation from the requirements of submitting the new and product specific results of clinical trials that are required within a 'normal' marketing authorisation application for an NCE. There are no limitations as to which therapeutic indications that are acceptable for a product with a 'well-established medicinal use'. The available documentation will decide the indications. The directive states that certain factors must be taken into account when deciding if a medicinal product can be considered having a well-established medicinal use, i.e.

- The time over which a substance has been in medicinal use (not less than 10 years within the European Union).
- Quantitative aspects of the use of the substance.
- The degree of scientific interest in the use of the substance (reflected in the published scientific literature).
- The coherence of scientific assessments.

Clearly, these factors (with the exception of the specified time period) have no hard end-points and the legislators must have intended to leave a certain room for flexibility and case-by-case decisions. This may facilitate decisions in some instances, but it also aggravates the difficulty of maintaining consistent decisions over time and between different substances. The issue of setting a uniform standard for deciding when a substance can be considered having a 'well-established medicinal use' has been discussed at great length and intensity in the HMPC and to align the work of the Committee and its working party (Monograph and List Working Party; MLWP), a guideline on the assessment of clinical safety and efficacy has been elaborated (EMEA/HMPC/104613/05). Besides the obvious requirement of documenting at least 10 years of medicinal usage in the European Union, the guideline recommends that the following main elements should be included or addressed in the efficacy documentation:

- A systematic review of all relevant clinical data available for the herbal medicinal product/substance must be performed.
- A scientific assessment of the clinical data must be performed. Results of all clinical data included in the systematic review shall be taken into account. Coherent and conclusive clinical recommendations cannot be obtained if major methodological deficiencies are identified in the pivotal clinical data.
- Demonstration that the clinical data are covering a sufficient number of patients and that they are conclusive and coherent with respect to the indication and efficacy.
- In general, at least one controlled clinical study (clinical trial, post-marketing study, epidemiological study) of good quality is required to substantiate efficacy.

For some products (substances), several controlled clinical studies of good or acceptable quality may be available, and sometimes the results are contradictory. The fourth bullet point of the directive, 'coherence of scientific assessments' (c.f. above), then becomes operational. The studies with positive outcomes must be balanced against the ones with negative outcomes. Meta-analyses of the results of the different trials may be very useful for this purpose. It should be noted that the guideline's requirement of 'one controlled study of good quality' to substantiate efficacy does not mean that one such study per se is sufficient to settle that a substance has a 'well-established medicinal use'. Such a clinical study is expected to be part of the documentation, but the concept of 'well-established medicinal use' relies on the broader thinking that a wide-spread medicinal use of a product within the Community for at least 10 years may have generated a sufficient body of conclusive scientific literature to allow an assessment of its efficacy. If the total body of evidence that emerges upon assessment leads to the conclusion that the substance has a 'recognised efficacy', the substance may be concluded to have a 'well-established medicinal use' from an efficacy point of view.