STANDARDS FOR THE ASSESSMENT OF HERBAL MEDICINAL PRODUCTS IN EUROPE AND AROUND THE WORLD

H. Cranz
European Proprietary Medicines
Manufacturers' Association (AESGP)
7 Avenue de Tervuren
B-1040 Brussels, Belgium

Keywords: Marketing Authorisation, EEC Directives, Homeopathic Medicines, Herbal Medicinal Products, EMEA, ESCOP & WHO monographs

Abstract

In the EU regulatory and legal rules are needed by a growing demand of and trade for traditional medicines. Since January 1993 progress has been made on classification, package information, advertising and wholesale distribution while the marketing authorisation process is developing. Since September 1992 Directive 92/73/EEG gives additional provisions for Homeopathic Medicines. A Simplified Procedure is foreseen while labels and packages should mention 12 prescribed items. Safety of Herbal Medicinal Products can be proved by clinical trials or by citing published bibliographical references. The European Medicines Evaluation Agency - EMEA - became operational in January 1995; published the first SPC-Summary of Product Characteristics. In 1996 the European Parliament expressed clear support for more and better use of alternative medicines. For a harmonizing system Monographs for widely used medicinal plants are essential. Besides ESCOP the WHO is preparing 60 monographs in coming years.

1. Current situation concerning traditional medicines

On the world-wide level, the situation for traditional medicines is characterised by a certain dilemma. On the one hand, there is a growing demand for these products and maybe also a growing recognition of the value of traditional medicines. On the other hand, there are regulatory and legal uncertainties, which result in quite different regulations of traditional medicines around the world. This becomes particularly evident in the quite different classification of these products. In some countries they are mainly classified as food, in others, they are mainly classified as medicines. In those countries where traditional products are recognised as medicines, they are sometimes reimbursed by social security systems.

It has to be recognised that different efforts have been made to reach some kind of consensus with regard to the assessment of traditional medicines. However, due to the traditional use and philosophies behind these medicines, this is often difficult to achieve. As there is a world-wide trend to facilitate the free movement of all goods including medicines, the question has become increasingly relevant as to how an international transfer may also be achieved for this sector. Manufacturers of traditional medicines obviously have a particular interest in these developments, at least in Europe. Harmonisation has therefore become an important element in the regulatory debates in Europe.

Although it will hardly be possible to agree on a definition of traditional medicines, from a European perspective the major categories are:

Proc. WOCMAP-2
Ind. Processing, Standards & Regulations,
Quality Control, Supply & Marketing, Economics
Eds. V. Martino *et al.*
Acta Hort. 503, ISHS 1999

- herbal medicinal products
- homeopathic medicines
- other more specific categories such as anthroposophic medicines which are of more regional importance.

2. Developments in Europe

The process of reaching more harmonisation in Europe has been particularly pursued since the establishment of the European Economic Community in 1957. Of particular importance was the goal to achieve a common market by 31 December 1992 within the then 12 Member States of the European Union. This aim also stimulated many discussions about the harmonisation of regulatory and legal requirements of medicinal products.

The harmonisation efforts were related to all kinds of legislative requirements for pharmaceuticals. Of particular importance for non-prescription medicines in general and also for most traditional medicines was a package of four directives related to classification, package information, advertising and wholesale distribution. These directives came into force by 1 January 1993 and provided a clear differentiation between prescription and non-prescription medicines, the latter category allowed to be advertised to the public. Quite specific requirements for the labels and leaflets are in line with the need to provide comprehensive information to the users of medicines, in particular in the sector of self-medication.

Generally speaking, all these requirements have to be applied to those herbal products in the European Union, which are classified as medicines. For other categories, such as homeopathic medicines, there are different kind of rules in light of their particularities. The most important differentiation is however with regard to the marketing authorisation process which remains the most problematic area in the context of traditional medicines which, as the name suggests, are classified as medicines and therefore in principle have to follow the same rules as other medicinal products.

Although recent efforts in the European Union have concentrated on the further development of a European marketing authorisation system to cover herbal medicinal products, first a short explanation of the situation of homeopathic medicines, the only category of medicines which has been placed in a specific legal framework in the European Union.

3. Homeopathic Medicines

After quite extensive and often controversial debates, the Member States of the European Union agreed on 22 September 1992 on a Council Directive 92/73/EEC widening the scope of directive 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products and laying down additional provisions on homeopathic medicinal products. This directive defines "homeopathic medicinal product" as any medicinal product prepared from products, substances or compositions called homeopathic stocks in accordance with the homeopathic manufacturing procedure established by the *European Pharmacopoeia* or, in absence thereof, by the pharmacopoeias currently used officially in the Member States. It is explicitly stated that the homeopathic medicinal product may also contain a number of principles, so that not only monocompound products are covered.

Most of the provisions of the general pharmaceutical legislation and in particular with regard to manufacture, control, import and export have to be applied also to homeopathic

medicinal products. However, the proof of therapeutic efficacy should not be required from those homeopathic medicinal products registered in accordance with the so-called simplified procedure. This simplified registration is only possible:

- if the product is administered orally or externally (no injections),
- if there are no specific therapeutic indications on the labelling of the medicinal product or in any information related to the product,
- if there is a sufficient degree of dilution to guarantee the safety of the medicinal product, in particular the medicinal products may not contain either more than one part per 10.000 of the mother tincture or more than 1/100th of the smallest dose used in allopathy with regard to active principles whose presence in an allopathic medicinal product results in the obligation to submit a doctor's prescription.

In addition to the clear mention of the words 'homeopathic medicinal product', the label and, where appropriate, the package insert for the homeopathic medicinal products which went through a simplified procedure has to mention only (and is not allowed to mention more) following 12 subjects:

- the scientific name of the stock or stocks followed by the degree of dilution, making use of the symbols of the pharmacopoeia used,
- name and address of the person responsible for placing the product on the market and, where appropriate, of the manufacturer,
- method of administration and, if necessary, route,
- expiry date, in clear terms (month, year),
- pharmaceutical form,
- contents of the sales presentation,
- special storage conditions, if any,
- a special warning if necessary for the medicinal product,
- manufacturer's batch number,
- registration number,
- 'homeopathic medicinal product without approved therapeutic indications',
- a warning advising the user to consult a doctor if the symptoms persist during the use of the medicinal product.

Not withstanding these requirements, Member States may demand the use of certain types of label in order to show the price of the medicine and the conditions of refunds by social security bodies.

The directive also foresees the marketing authorisation of homeopathic medicinal products, which can go through a normal marketing authorisation procedure and are allowed to carry claims in the same way as any other medicinal product.

Generally speaking, this directive has clarified the role of homeopathic medicines in the European Union and is widely appreciated by the parties concerned. Specific problems such as the prohibition of the tradename for homeopathic combination products, the ban on parental forms coming out of the simplified procedure or the restrictions on dilution are currently being discussed and may lead to an initiative of the European Commission to amend this directive.

It is worth mentioning in this context that the directive which has to be implemented in the legislation of the European Union Member States also had a considerable impact on so-called Central and Eastern European countries when they were reconsidering their pharmaceutical legislation at the beginning of this decade after the general political changes.

4. Herbal Medicinal Products

When talking about traditional medicines in the context of Europe and European harmonisation, the focus has to be on herbal medicinal products. In principle, herbal medicinal products are integrated in the quite sophisticated regulatory system, which has been established in the area of marketing authorisation since the first directive in this sector in 1965. Generally speaking, the European Union directives set down two principle ways of proving a product's safety and efficacy. The first is through scientific evidence, including in particular clinical trials. The second way, which is particularly relevant for herbal medicinal products, is to cite published bibliographical references as evidence of well-established use of the product.

In addition to this, many years ago guidelines were established with regard to the proof of quality in respect of Good Manufacturing Practice of herbal medicinal products. All these efforts however have not been sufficient to guarantee a free circulation of herbal medicinal products in the European Union and therefore the last two years have seen a considerable increase in the activities to define ways how at least some herbal medicinal products may enter into all European Union Member States. Let me briefly refer to some milestones in this respect.

5. Growing recognition of herbal medicinal products in the European Union

Influenced by a resolution of the Member States of the European Union in December 1995, quite a few debates took place on the role of herbal medicinal products in the context of the development of an industrial policy for the pharmaceutical sector. The resolution of the European Parliament adopted in April 1996 was particularly outspoken on herbal medicinal products. This resolution was an important basis for concrete initiatives to establish an ad hoc working group on herbal medicinal products at the recently established European Medicines Evaluation Agency – EMEA – in London and it also influenced the decision of the European Commission to carry out a study on herbal medicinal products in order to gain more transparency in the whole sector. All these elements together demonstrate an unprecedented level of activity concerning herbal medicinal products on the European level.

The strong support from the European Parliament has been a key element in the development of the support for herbal medicinal products in the European Union. Two quotes from the above-mentioned resolution may particularly demonstrate this:

The European Parliament

"Points out to the Commission that citizens' attitudes towards health have changed and demand has consequently shifted because there is greater awareness of 'gentle' forms of healing (e.g. physiotherapy) and 'alternative' medicines (herbal and homeopathic) among doctors and patients, and even today alternative treatments provide significant employment opportunities in small and medium-sized enterprises;"

"Calls on the Commission to prepare additional proposals on how also to facilitate the European marketing of herbal and homeopathic medicines...
Requests the Commission to adjust the authorisation procedure to allow such medicines to be generally available throughout the Community and in pursuit of such, calls for the setting up of a Traditional Medicines Evaluation Agency, comprising experts in this field, to assess the worth of phytomedicines;"

6. EMEA ad hoc working group on herbal medicinal products

Although the requests were maybe somewhat extreme, for example with regard to the establishment of a specific agency, the resolution was most helpful in setting up the ad hoc working group on herbal medicinal products of the EMEA. This European agency became operational in January 1995 and is today recognised as an important element for the marketing authorisation process in Europe, particularly for innovative medicines which benefit from a so-called centralised procedure allowing access to all European Union Member States. The key objectives of the new working group of the EMEA on herbal medicinal products were the provision of guidance for applicants and competent authorities concerning the marketing authorisation for herbal medicinal products. The work of this group is therefore very much related to the so-called decentralised procedure, which should allow an easy access to all European Member States as soon as one country in the European Union has granted a Marketing Authorisation. It has been evident that, due to the considerable differences with regard to the regulatory requirements for herbal medicinal products, such transferral or mutual recognition of national marketing authorisations is not as simple as it may appear in theory.

The ad hoc group met three times in 1997 and three further meetings are scheduled for this year. Already in the first year, considerable progress has been made. This is particularly true in the area of quality, where the existing Note for Guidance on Quality has been reviewed and updated together with the existing guideline on Good Manufacturing Practice. Both guidelines have now been released for a three-month consultation and will hopefully be finalised during the course of this year. The working party also issued a draft guideline on "non-clinical testing of herbal drug preparations with long-term marketing experience". This guideline is based on a similar draft for old substances in general. This guideline points out that where there is sufficient experience in humans available, quite a few safety studies are not necessary, provided that an expert report gives the ground why the documented medical experience justifies a safe use of the herbal drug preparation. Non-clinical testing of well-established herbal drug preparations should however be directed towards the study of those effects, which are difficult or even impossible to detect clinically. These effects would include toxicity to reproduction, genotoxicity and carcinogenicity.

Of particular importance was the debate in the working party on the role of so-called monographs summarising the scientific knowledge of certain plants. Such monographs have been developed by the World Health Organization (WHO) as well as by the European Scientific Co-operative on Phytotherapy (ESCOP).

A proposal for revision of the so-called Notice to Applicants suggests that

"Scientific monographs on certain substances, (e.g. those drafted by the European Scientific Co-operative on Phytotherapy (ESCOP) and the World Health Organization (WHO) for herbal drugs) offer a valuable and updated overview on published scientific literature, which together may be used in support of the documentation on the safety and efficacy of the medicinal product in the bibliographic application.

These monographs may help to avoid duplication of work and bring about gradual harmonisation in the evaluation of medicinal products, e.g. herbal medicinal products. Therefore, the Commission and the Member States recommend that the applicants and competent authorities should make use these monographs."

Besides the general recognition of monographs, the ad hoc working group started to look at the establishment of so-called core SPCs, which means an agreement on key elements of the Summaries of Product Characteristics, the summarising document at the

end of a marketing authorisation procedure. First, a core SPC was drafted for Valerianae Radix and the development of further core SPCs is planned for this year.

The work of the ad hoc working group on herbal medicinal products is an important basis to provide more guidance to those manufacturers of herbal medicinal products who would like to bring their products into more than one European Member State by using the mutual recognition procedure. At a meeting at the end of November 1997, all interested parties appreciated the work done so far by the ad hoc working group, and strongly suggested continuing its work. Through the three meetings in 1998 it is hoped to get final adoption of the different papers drafted. Together with the establishment of further core SPCs, a free circulation, at least of well-documented plant-based preparations, should be possible in the European Union.

7. WHO and Traditional Medicines

As stated before, the European efforts benefited from the work of the WHO Traditional Medicines Programme, in particularly in respect of monographs for widely used medicinal plants. These monographs are the final point of the important work of the World Health Organization clarifying the regulatory requirements for traditional medicines and in particularly for herbal medicinal products. Without covering the different guidelines in any detail, it seems worth remembering particularly the resolution of the World Health Assembly in 1991, which requested the Director General of the World Health Organization

- to continue to recognise the high importance of this programme and to mobilise increased financial and technical support as required;
- to ensure that the contribution of scientifically proven traditional medicines is fully exploited within all of the WHO programmes where plant-derived and other natural products may lead to the discovery of new therapeutic substances;
- to seek appropriate partnerships with governmental bodies and non-governmental organisations as well as with industry in implementing this resolution.

A most important basis were the WHO guidelines for the assessment of herbal medicinal products developed in 1990/91, which laid down the principle rules in the areas of pharmaceutical assessment, safety assessment, assessment of efficacy and intended use. These guidelines were complemented by different documents, primarily from Regional Offices of the WHO such as, for example:

- Research Guidelines for Evaluating the Safety and Efficacy of Herbal Medicines - Regional Office for the Western Pacific (1993)
- Guidelines on the Conservation of Medicinal Plants (1993)
- Quality Control Methods for Medicinal Plant Materials (1994)
- Selection of Essential Medicinal Plants - Regional Office for the Eastern Mediterranean (1995).

The above-mentioned monographs for certain medicinal plants were agreed as one of the priorities at the International Conference of Drug Regulatory Authorities (ICDRA) in the Netherlands in 1994 and led to the endorsement of a first series at a subsequent meeting in November 1996 in Bahrain. The information contained in these monographs can be separated into a first part linked to quality issues and a second part relevant to efficacy and safety as it defines the medical applications, pharmacology, posology and possible contra-indications and precautions. The final publication of the first series is expected during the course of this year. The following plants will be covered:

Allii Cepae, Bulbus
Allii Sativi, Bulbus
Aloe
Aloe Vera Gel
Astragali, Radix
Bruceae, Fructus
Bupleuri, Radix
Centellae, Herba
Chamomillae, Flos
Cinnamomi, Cortex
Coptidis, Rhizoma
Curcumae Longae, Rhizoma
Echinaceae, Radix
Echinaceae Purpureae, Herba
Ephedrae, Herba
Gingko, Folium
Ginseng, Radix
Glycyrrhizae, Radix
Paeoniae, Radix
Plantaginis, Semen
Platycodi, Radix
Rauwolfiae, Radix
Rhei, Rhizoma
Sennae, Folium
Sennae, Fructus
Thymi, Herba
Valerianae, Radix
Zingiberis, Rhizoma

The strong interest in these monographs encouraged the World Health Organization to commission the development of a second series, which should be drafted during the course of this year. It is intended to cover the following plants:

01. Aesculus hippocastanum
02. Althaea officinalis
03. Angelica sinensis
04. Arctostaphylos uva ursi
05. Calendula officinalis
06. Capsicum annuum
07. Chrysanthemum parthenium
08. Cimicifuga racemosa
09. Crataegus monogyna C. laevigata
10. Eleutherococcus senticosus
11. Eucalyptus globulus
12. Hamanelis virginiana
13. Harpagophtum procumbens
14. Andrographidis paniculata
15. Hypericum perforatum
16. Melaleuca alternifolia
17. Melissa officinalis
18. Mentha piperita
19. Ocimum sanctumy
20. Oenothera biennis
21. Piper methysticum
22. Polygala senega
23. Prunus (Pygeum) africana
24. Angelica sinensis
25. Rhamnus purshiana
26. Rhamnus frangula
27. Salvia miltiorrhiza
28. Sambucus nigra
29. Serenoa repens
30. Silybum marianum
31. Syzygium aromaticum
32. Urtica dioica, U. urens

It is intended to discuss the second series at a consultation in February next year and an endorsement by the International Conference of Drug Regulatory Authorities is aimed for the time of their next meeting in April 1999 in Berlin.

8. Conclusion

As the phrase 'traditional medicines' indicates, the assessment is strongly influenced by historic developments in a national context. For those traditional medicines with a clear concept on which international agreement can be found, commerce outside the national boundaries should be possible. In Europe, a legislative framework has been established for homeopathic medicines. Herbal medicinal products fall under the scope of the definition of medicines in general and should therefore be able to benefit from an easy access to other countries, at least in the European Union.

The intensive debate on the future of herbal medicinal products over the last years has however shown that it might not be possible to gain a European or international standard

for all kinds of herbal medicines. Only products which meet the requirements on safety and efficacy by either specific bibliographic reference and/or coverage through monographs or core SPCs and/or clinical trials according to an appropriate model will be able to gain European-wide access. There is a general political agreement that other herbal medicines should not disappear from the market, but due to the strong national influence in the assessment, international commerce seem to be difficult primarily due to insufficient proof of efficacy.

What has therefore been shaping up on the European level over the last years is an approach, which differentiates between products falling in areas where agreement can be reached between Member States and those which seem to be only justified in a national context. In the European Union, it will be interesting to see if this separation is a long-term solution, or whether additional legislative initiatives may clarify the whole sector.