

How to implement the new legislation on Herbal Medicinal Products (HMPs) in Europe

Viewpoint of the Pharmaceutical Industry

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Previous particulars for marketing authorisation applications of herbal medicinal products (HMPs)

- ◆ Results of toxicological and pharmacological tests and of clinical trials have to be provided
- ◆ Exemption:
 - HMP essentially similar to an authorised medicinal product in the member state
 - HMP essentially similar to a medicinal product in the European Union authorised for at least 6 (high tech 10) years
 - HMP constituents have a well established medicinal use basing on detailed scientific bibliography
 - The Committee E Monographs resulting from the scientific assessment of bibliographic data served in Germany as expert opinions for the proof of well established medicinal use

Why regulate Traditional Herbal Medicinal Products (THMPs) in the European market

- ◆ The need for the THMP regulation originates from the old stringent European medicines law providing no authorisation procedure for THMPs
- ◆ National markets for THMPs exist and will always exist and a ban of THMPs would create an increase of the grey food and supplement market
- ◆ The consumer should have an option to buy traditional products, he believes in
- ◆ Products preventing or reducing the risk of disease should have appropriate quality and adequate claims

Why regulate Traditional Herbal Medicinal Products (THMPs) in the European market

- ◆ The new definition of Directive 2004/27/EC for the term of “medicinal product” as

“... any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or... which may be used in or administered to human beings with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, ...”
- ◆ suggests to create regulations for THMPs to prevent that this type of products migrates into the category of food supplements

Particulars of Traditional Herbal Medicinal Products (THMPs) in the new European legislation

- ◆ The quality requirements for Herbal Medicinal Products are independent on their traditional use, there is no compromise concerning quality of THMPs but I hope that the question of overages and practicable limits and specifications will be revised
- ◆ By their definition they have a history of safe use. Bibliographic reviews of safety data and other sources of evidence, together with an expert report will be accepted as proof for safety
- ◆ Pharmacovigilance will apply as for non-traditional medicinal products
- ◆ Efficacy is defined as tradition and plausibility of use
- ◆ But ...

How to prove traditional use for a new Traditional Herbal Medicinal Product (THMP)

- ◆ The sticking point in the legislation is the definition of traditional use
- ◆ The requirement to prove a medicinal use of the THMP or a corresponding product for a period of at least 30 years including at least 15 years within the EC rises concerns
- ◆ Difficulties are expected for the supply of evidence that a HMP is traditional in view to the requirement, that the HMP used as reference for a THMP application is characterised by the **same** active ingredients, the **same** or **similar** intended purpose, **equivalent** strength and posology and the **same** or **similar** route of administration as the products were not sufficiently defined and documented

Which deviations from the reference product (THMP) are acceptable for a similar product

◆ Active ingredients

- the defined plant or plant part may have variations:
 - ❖ powdered, comminuted, granulated, concise, fresh, dried
- the production method of an extract and its technological properties may be different:
 - ❖ solvent identical or similar with the same or similar concentration or solvent with comparable polarity
 - ❖ dry, soft, fluid

◆ Dosage form:

- ❖ herbal tea for infusion, instant tea, capsule with instant tea powder, tablet with aqueous extract
- ❖ are they all comparable dosage forms

Which deviations from a reference product (THMP) are acceptable for a similar product

- ◆ Capsules with fine plant powder e. g. frequently show in vitro in artificial gastric juice a comparable release of their markers as capsules containing an aqueous extract of the same plant
- ◆ When data are submitted showing a comparable dissolution of the HMP applied for in respect of a THMP in a different dosage form the application should be considered as sufficiently similar to the traditional reference
- ◆ In this respect I refer to the workshop “dissolution testing” of yesterday and especially to the contribution of Dr. H. Sievers
- ◆ The question of comparable dosage forms is absolutely essential for applications of new THMPs

Traditional Herbal Medicinal Products versus Food Supplements, pros and cons

- ☺ The product information of a THMP provides a marketing advantage over food supplements
- ☹ But health claims of food supplements might be very close to the indications of THMPs
- ☹ The new traditional medicines regulation will not resolve the problem of the existing grey market with low cost food products of minor quality
- ☹ The process of registration with full quality documentation will have significant cost and technical implications
- ☹ The 30-years requirement may be administered too restrictive and prevent innovations and new substances in the traditional medicines market
- ? What is about the products which lost their licenses in the 90ties due to the medicines review

Traditional Herbal Medicinal Products (THMPs) versus Food Supplements

- ◆ The status of many products on the borderline between food supplements and medicinal products will cause numerous problems in view to harmonisation
- ◆ Herbal products sold as food supplement in one member state may even not get the status of a THMP in an other member state for the reason that “the product could be harmful under normal conditions of use” Article 16e, fig. 1c
- ◆ This may be justified when the product for this reason is not suited for “use without the supervision of a medical practitioner” (Article 16a, fig 1a), but this may not depend from my point of view on a “pharmacy only” distribution regulation (German interpretation)

Will Herbal Medicinal Products of “traditional use” jeopardize those of a “well established use” ?

- ◆ The British MHRA has a tendency to classify most of the herbal compounds as “traditional use” products
- ◆ Only a minority of plants is evaluated to meet the requirement of the category “well established use”
- ◆ In Germany most of the HMP licenses base on the evaluation of “well established use” in accordance with Commission E or ESCOP monographs
- ◆ In the case of an arbitration with a positive outcome for “traditional use”, all precedent positive “well established use” decisions in other member states would be at risk
- ◆ In the judgment of industry the dual system of “well established use” and “traditional use” should be maintained

„traditional use“ versus „well established use“

- ◆ According to the THMP directive a registration for “traditional use” should not be granted when a HMP fulfils the criteria for a marketing authorisation of “well established use”
- ◆ For many plants both ways (marketing authorisation and registration) are feasible depending on the data available for the definite indication, dosage form and posology
- ◆ „well established use“ provisions are applicable to a number of plants (see separate transparency). These plants have positive ESCOP monographs or positive core data of the HMPWP
- ◆ “Traditional use” may be applicable for these plants in case they are used for an other therapeutic indication or e.g. in combination with other active herbal ingredients (see separate transparency)

List of herbs basically qualified for the preparation of herbal medicinal products of well established use

- ◆ **Agni casti fructus**
- ◆ **Allii sativi bulbus**
- ◆ **Aloes**
- ◆ **Calendulae flos**
- ◆ **Capsici fructus**
- ◆ **Cardui mariae fructus**
- ◆ **Chelidonii herba**
- ◆ **Cimicifugae rhizoma**
- ◆ **Crataegi folium cum flore**
- ◆ **Cucurbitae semen**
- ◆ **Curcumae longae rhizoma**
- ◆ **Cynarae folium**
- ◆ **Echinaceae purpureae herba**
- ◆ **Eleutherococci radix**
- ◆ **Eucalypti aetheroleum**
- ◆ **Frangulae cortex**
- ◆ **Ginkgo biloba**
- ◆ **Ginseng radix**
- ◆ **Hamamelidis aqua**
- ◆ **Harpagophyti radix**
- ◆ **Hederae helicis folium**
- ◆ **Hippocastani semen**
- ◆ **Hyperici herba**
- ◆ **Lavandulae aetheroleum**
- ◆ **Lini semen**
- ◆ **Matricariae flos**
- ◆ **Melissae folium**
- ◆ **Menthae piperitae aetheroleum**
- ◆ **Passiflorae herba**
- ◆ **Pelargonii sidoidis radix**
- ◆ **Petasitis rhizoma/folium**
- ◆ **Piperitis methystici rhizoma**
- ◆ **Plantaginis ovarae semen**
- ◆ **Plantaginis ovatae testa**
- ◆ **Primulae radix**
- ◆ **Psyllii semen**
- ◆ **Rhamni purshianae cortex**
- ◆ **Rhei radix**
- ◆ **Salicis cortex**
- ◆ **Sennae folium**
- ◆ **Sennae fructus acutifoliae**
- ◆ **Sennae fructus angustifoliae**
- ◆ **Serenoae repentis fructus**
- ◆ **Symphyti radix**
- ◆ **Tanacetii parthenii herba**
- ◆ **Thymi herba**
- ◆ **Urticae folium**
- ◆ **Urticae radix**
- ◆ **Valerianae radix**
- ◆ **Visci albi herba**
- ◆ **Zingiberis rhizoma**

Exemplary list of herbs suited for a well established use and a traditional use application

Herbal drug	Indication of committee E monograph	Traditional indication according to German practice
hawthorn	Decreasing cardiac output as described in functional stage II of NYHA*	Support of the cardiovascular system. This claim bases exclusively on traditional use and long time use.
valerian	Restlessness, sleeping disorders based on nervous conditions	Improvement of the state of condition during nervous stress. This claim bases exclusively on traditional use and long time use.

* New York Heart Association

Establishment of a list of Traditional Herbal Substances

- ◆ The French l'Agence de Medicament has published a list with 96 plants and their traditional indications (Cahier de l'agence 3, 1997)
- ◆ The German Commission E published originally 191 monographs of approved herbs and 67 approved fixed combinations for "well established use". 108 herbs and 6 combinations were not approved and are partly suitable for traditional indications.
- ◆ Until 2003 ESCOP has published 80 monographs of plants suitable for products of "well established use"
- ◆ The number of monographs and their assignment to "well established use" and "traditional use" shows a high degree of conflict potential

Traditional Herbal Medicinal Products of non-European origin

- ◆ Various herbal products belonging to the traditional medicine of non-European countries are sold in the European market by various distribution channels
- ◆ Ayurvedic medicines are sold in health shops as unlicensed HMPs
- ◆ Traditional Chinese Medicines are prepared and dispensed in pharmacies according to medical prescriptions. They are not licensed and have no on-prescription status
- ◆ Both types of traditional medicine may be used without the supervision of a medical practitioner
- ◆ Since they are used for many years in Europe they should be suited for the list of herbal substances according Article 16f

Community Herbal Monographs with well-established and traditional uses

- ◆ The HMPWP has published up to now 17 monographs most of them indicating the level of evidence for efficacy and allowing a judgement, on “well established use” or “traditional use”
- ◆ The draft monographs of ESCOP and WHO were judged in this context positively in principle.
- ◆ An amendment to the “Notice to Applicants” implies that these monographs can be used as bibliographic documentation for a marketing authorisation application.
- ◆ It would be desirable to have more monographs within short.

Community Herbal Monographs with well-established and traditional uses

- ◆ The directive on traditional herbal medicinal products transfers the HMPWP into the Herbal Medicinal Products Committee (HMPC)
- ◆ The future working results of the HMPC should safeguard that well-documented HMPs in Germany having received their marketing authorisation on the basis of bibliographic data and monographs, maintain their high indication claim and are not mixed up with THMPs holding their low indication claim on the basis of tradition and long term use.

Community Herbal Monographs for combinations with well established and traditional uses

- ◆ For HMPs basing on well established use combination monographs may be considered
 - The documentation of plausibility of the combination may be derived from the individual herbal drug monographs by risk dependent assessment (see procedure of the Association of Phytotherapy)
 - In this connection the German committee E monographs and ESCOP monographs are suitable sources for information
- ◆ For HMPs basing on traditional use new combinations are not feasible
 - As THMPs must have had traditional use
 - the plausability of efficacy is based on long use and experience
 - the number or quality of ingredients of the HMP may have been reduced during the period of sale

Perspective of the new legislation from the viewpoint of Pharmaceutical Industry

- ◆ The THMP directive itself is an expression of pragmatism and it recognizes the eligibility of tradition as a justification of medicinal use
- ◆ Likewise, to achieve the EC's goal of bringing products so far unregulated under the roof of medicinal law and of carrying on safe traditional products that would not fulfil the stricter requirements of "well established use", it will have to be applied with pragmatism

Perspective of the new legislation from the viewpoint of Pharmaceutical Industry

- ◆ **Various crucial factors will determine the success of the THMPs directive**
 - comparability of product composition within the period of tradition (e.g., if the DER is not identical (or not documented) throughout the complete 30 years, this alone should not be an obstacle to the registration of such product)
 - competitiveness of THMP indications as compared to claims permitted for food supplements
 - the level and extent of documentation required for the proof of tradition (e.g., quantitative market data are not affordable for most traditional products)

Perspective of the new legislation from the viewpoint of Pharmaceutical Industry

- ◆ **The main crucial factor that will determine the success of THMPs directive**
 - the level of safety regarded as being adequate for THMPs must still be reasonable as compared to food supplements. Rejection of a THMP registration would not be reasonable where food supplements or other food products with the same or higher dosage and similar but softer claims are tolerated on the market

Perspective of the new legislation from the viewpoint of Pharmaceutical Industry

- ◆ The THMPs directive offers a great opportunity to carry on the tradition of many medicinally used plants
- ◆ If Pharmaceutical Industry and Medical Authorities will jointly take advantage of this situation they will both strengthen their positions.
- ◆ By doing so they will build a continuity of controlled use for a large number of traditional plants which may then serve as a basis for the development of even completely new medicinal products.
- ◆ They should not, however, start seeing everything through the “traditional glasses” but acknowledge “well established use” wherever feasible.



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for your kind
attention !