COMING EU LEGISLATION: HERBAL RECIPES FOR DISASTER

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"There are two things in life you really don't want to know. How sausages are made and how laws are made." (Otto von Bismarck)

Doomsday Approaches

Ominous clouds are looming for the noble art of traditional phytotherapy. It is highly likely that the imminent implementation of the Traditional Herbal Medicinal Products Directive (THMPD) and Novel Food regulation will decimate the therapeutic repertoire of traditional medicine disciplines in most EU member states.

In 2008 the European Community/European Medicines Agency (EMA) clearly recognized that the THMPD falls short in accommodating traditional disciplines like TCM and Ayurveda, and at the same time expressed the need to assess the suitability of a separate legal framework for those traditional medicine systems. Unfortunately, we haven't heard any more about this sound intention, and worse, as doomsday approaches, there seems to be a consensus among regulators that marketing authorisation shall be restricted to THMP registration, or else made available to the patient as a magistral prescription (or unlicensed 'special') under the 2001/83/EC exemption clause. Both options are doomed to failure: the THMPD largely ignores the tenets and characteristics of traditional herbal medicine and dispensing through the magistral/unlicensed 'special' route cannot be harmonized at the EC level for various reasons (see below)

What's wrong with the THMPD from a TCM point of view?

- Apart from prohibitive registration fees when carrying a full TCM catalogue, the directive also tends to limit the number of ingredients allowed in a combination, and does not offer a solution for tailored prescriptions, specific preparation forms and animal or mineral ingredients.

- THMPD imposes onerous analytic requirements totally disproportionate to the safety risk for most ingredients, such as stability-studies and genotoxicity-tests. Furthermore the quality-safety control focuses on mono-components as biomarkers or active principles, while the majority of botanicals can be more effectively controlled by full-spectrum control. This method, a high performance thin layer chromatography (HPTLC) turns out to be more descriptive for the totum of the plant and, while the full-spectrum is the marker, tends to yield a lot more information regarding identity, chemotype, overall quality, preparation form, concentration and finally the safety of the herb. On top of that it is more cost effective.

- THMPD enforces a medicinal status upon traditional remedies, but at the same time largely ignores the very existence and the value of traditional disciplines. Consequently, an appropriate curriculum with statutory regulation for graduates is denied to qualified practitioners. Also, since THMP end-products are available over the counter, one merely creates a new safety problem. By passing over the practitioner and specific differential diagnosis one will banish herbal remedies, which are beneficial and low risk when under supervision of qualified practitioners, to the channels of self-care and food-supplements where improper use is more likely to occur. It is painful for TCM herbalists to see their therapeutic spectrum reduced and their personal experience disregarded in this way. It is striking how experienced herbalists, often by using phased therapy, very quickly adapt their prescription behaviour to local circumstances like diets, ethnicity and environmental context. Routinely narrowing TCM to standardized remedies without elementary therapeutic supervision will make it even more difficult to co-ordinate post-marketing vigilance, develop quality standards and assess efficacy.

- The implementation of the THMPD may have another indirect but perverse effect. Because of its medicinal status in law, many herbal practitioners were looking forward to the opportunity to integrate some of the more difficult ingredients like prepared aconite and ma huang. Such ingredients should obviously be kept away from the healthfood shelves, but in the hands of a qualified herbalist safe and well-monitored use is perfectly possible. However, since THMP products are OTC it is unthinkable that such ingredients could ever be registered under the directive. On the other hand the Committee on Herbal Medicinal Products

(HMPC), which displays painstaking scrutiny in safety matters, makes more delicate herbs available as OTC, even when these are, within their own tradition, subject to differential diagnosis and supervision by a qualified therapist, both for safety and efficacy reasons.

And worse, the toxicological reports already issued by EMA/HMPC concerning groups like furano-coumarines, bioflavonoids and others, point to an extremely conservative disposition regarding toxicological issues. The methodology for toxicity evaluation is invariably characterized by linear extrapolation from one active ingredient to the totality, from 'in-vitro' to 'in vivo', from animal to human and from a quantitative to a qualitative level. Such assessments are generally model-based, not evidence-based, and often lead to unreal conclusions. In the case of furanocoumarines, for example, the conclusion would be that parsnips and celery are highly carcinogenic. However, by the unfathomable ways of scientific echolalia, this conservative disposition thoroughly affects the member states' risk management policies, leading to the present disproportionate enforcement of the precautionary principle and causing further restrictions on indispensable ingredients, regardless of their status.

Concluding one could say that the legal and practical execution of the THMP Directive is generally experienced by its target sector as an attempt to keep traditional plants out of the food statutes, rather than to create a workable framework for traditional medicine.

Harmonisation ?

Where do we go from here? In the general confusion about all kinds of statutary regulation one might forget that the EU legislator's first intention was to harmonize the different approaches in the member states, within a framework of safety and quality control. This harmonisation, however, seems further away than ever.

As an alternative to the THMPD registration practitioners can, theoretically, continue to prescribe under the EU 2001/83 exemptions for « magistral/officinal » prescriptions, so long as the ingredients are not forbidden or have not been attributed to another statute. Sadly, on the EU level, this again tends to create more problems than it solves. In continental Europe a magistral prescription (also known as a 'special'), although exempt from registration or licensing, has a « full blown » medicinal status, which raises the question : who is entitled to prescribe and dispense? Between the extremely liberal approach in the Netherlands (all ingredients under the « warenwet » and free dispensing channels for the time being) and the rigidly restrictive policies of the southern European countries (prescribing reserved to MDs and dispensing to pharmacies) stretches a patchwork of semi-regulated local interpretations of the EU directives. The bottom line is that under the system of magistral prescription, both in UK (under section 12 (1) of the UK 1968 Medicines Act) and in continental Europe, statutory regulation for practitioners is paramount. In the perspective of harmonization it is of course highly inconvenient that in the UK, where excellent curriculum and training regimes for practitioners have been developed, the vast majority of prescribers aren't medical doctors and the dispensing channels are not pharmaceutical. This tends to awake the corporatist dragons in the medico-pharmaceutical establishment on the continent to the extent that harmonization on this level will prove to be extremely tricky.

Absurdities in the categorisation of traditional ingredients

Another obstacle to harmonisation is the statutory diversity of ingredients, especially in countries like Belgium, France and Italy where ingredients are supposed to go through a notification procedure to be included in a positive list for marketing authorisation. Since a magistral prescription can perfectly well consist of botanical food supplements, approved herbs are eligible as an ingredient in the prescription. Until 2-3 years ago this notification procedure was built exclusively around safety evaluation and discrete presentation criteria, as pointed out in the EU directives on Food and Food Supplements. However, as the THMPD train approached, it became increasingly difficult to transfer traditional ingredients to a positive list, not because of the tightening safety criteria, but because of the introduction of a new argument: the alleged or plausible therapeutic and pharmacological mechanism as spelled out in the THMP directive. Even those plants with a sound safety record as food ingredients are systematically labeled as a medicine by function, thus giving rise to the absurd situation that a traditional ingredient can be accepted as a medicine, although the physiological or therapeutic action is not proven, while the same ingredient is refused as a food ingredient because of an alleged therapeutic action. This is in conflict with both the EU definition of a medicine and EU Food directives, but as always this distorted type of rationale is covered with the loin cloth of the precautionary principle.

Little help from the European Pharmacopoeia

Sadly, the monographs recently introduced in the European Pharmacopoeia prove to be little help in clearing this matter. What we've seen thus far are mere compilations lacking consistency on every

level. Vital data about dosages, preparations and synergy are partial or missing, which makes any serious assessment of safety, quality or efficacy impossible. Assessment criteria for processed materials are totally absent and interesting methods to achieve this (e.g. systems biology, HPTLC) are not taken into account. The parameters for identity, quality and safety tend to be exclusively associated with the quantitative determination of biomarkers and not with the full spectrum.

Novel Food regulation

If the THMPD may not be EU's finest hour, then what to think about the Novel Food regulation? Originally conceived as a vehicle for the regulation of Genetically Modified Organisms, this administration turned into a bigger Frankenstein than the species it was supposed to regulate. All over Europe, positive listed or unlisted substances can change into Novel Foods overnight, simply based on a civil servant's presumption that a significant consumption history before 1997 cannot be demonstrated. In Belgium notification procedures are blocked because herbs like Scutellaria baicalensis and Chrysanthemum morifolium are considered Novel Foods and the entire positive list (13 years work!) is under scrutiny. The Novel Food regulation lacks transparency, is inconsistent, and is outrageously undemocratic. It institutionalizes arbitrariness and, if it communicates with the sector at all, does so retroactively and repressively. Companies are being pestered with the burden of retroactive proof of consumption-history, consumers see the meddlesome and patronizing image of EU legislation confirmed, and traditional herbalists honestly wonder why such oppressive rules blow their way from the sheltered workshops of right-mindedness.

Confusion reigns

Member states like France, Belgium, Italy and Germany have a specific legal framework for « starting materials ». Since magistral ingredients can be considered as such, local authorities (e.g. some regions of Germany) impose onerous quality controls, such as identity checks by chemical profile, on the pharmacy premises.

In every continental EU member state different interpretations of conflicting and overlapping regulation have brought about a climate of legal uncertainty about the status of food ingredients, finished polyherbal products and magistral ingredients. This utter confusion is reflected in numerous positive and negative local lists, in which any logic is hard to discern. Between the Dutch food ingredient approach and the German magistral ingredient policy there are nothing but halfway measures, involving important restrictions to the TCM pharmacopoeia.

With respect to quality-safety control it is interesting to observe that, for products with a double status (e.g. THMP-registered and local market autorisation as a food ingredient) local authorities now already tend to enforce the onerous medicinal standards, even when this is totally disproportionate to the risk.

Impact of EU directives on the TCM sector: concluding remarks

The first conclusion is that the implementation of the various EU directives is likely to create a levelling-down in the quality of the TCM products in general. Take the example of a classical formula for a very specific differentiated pathology (e.g.' Tian Ma Gou Teng Yin'). Very useful for the practitioner, but very specific and therefore not so frequently prescribed. Registration of such a formula under the THMPD is impossible in cost-benefit terms. This means that a 'state-of-the art' preparation, meeting all the GMP processing steps and requirements of the pharmacopoeia (acqueous extraction, decoction together, full-spectrum profile) and triple-checked for contaminants by accredited labs, can no longer be sold. The same formula prepared from single ingredients in a Soho basement, with a 'little less evident' quality control, would be perfectly legal.

The second conclusion is that, under the circumstances, it will be extremely difficult, if not impossible to reach a harmonization among the member states. Looking at the actual and expected divergences in approach, mutual recognition procedures will be fragmentary and the present legal uncertainty will linger on. The result will be an avalanche of legal claims. While the THMP and NF directives themselves contain discriminatory elements, the implementation will further cause discrimination on the level of the member states and even within the TCM sector itself. Why? Look at the significant differences in registration fees, the huge dissimilarities and anomalies regarding forbidden and restricted items, the disparities in control capacity and dispensing channels. As to the precautionary principle, national legislation can still prevail. So one may ask whether it makes sense to outline a harmonizing regulation which will be selectively implemented in the different member states. And how all this concords with some general principles of justice in the EU (free movement of goods, fair competition, public nature and transparency of government, the right for legal certainty, adequate motivation on necessity and proportionality etc)

Regulation and harmonization for TCM herbals can only be achieved by creating an entirely new EU legal framework for traditional systems. A proposal for such a new framework has been drawn

up by the European Benefyt Foundation. This advocates a model of maximal therapeutic freedom coupled with maximal responsibility regarding quality-safety issues. It is built around three extensive, categorizing positive lists, referring to traditional pharmacopoieas, and further emphasizes statutory regulation for qualified practioners and dispensing channels. (*See the ANH-Benefyt position paper below*)

WORKING COLLABORATIVELY TO MAINTAIN THE SUPPLY OF PRODUCTS ASSOCIATED WITH TRADITIONAL SYSTEMS OF MEDICINE IN EUROPE FROM 2011 ONWARDS

(position paper jointly drawn up by the Alliance for Natural Health International and the European Benefyt Foundation)

***Note from RCHM Journal Editor**: the first parts of this paper, describing the current legal context for traditional medicines in Europe, are presented here in an abbreviated and slightly edited form under the heading 'Background and weaknesses of the existing regulatory framework'; the later parts, under the headings 'Ways Forward', 'Actions' and 'Concluding remarks', are reproduced in full. The authors can be reached at: Chris Dhaenens, EBF, Tel: +32 (0)9 3309055, Email: chris.dhaenens@telenet.be, or at: Robert Verkerk, ANH-Intl, Tel: +44 (0)1306 646 600, Email: rob@anhinternational.org*

The relevant rules affecting the status of traditional medicines in Europe are as follows: foods are regulated under EU General Food Law (Regulation (EC) No 178/2002); novel foods under the Novel Foods Regulation (No 258/97, as amended); food supplements under the Food Supplements Directive (2002/46/EC, as amended-- implemented in England by the Food Supplements (England) Regulations 2003); medicinal product market authorisations under the Human Medicinal Products Directive (HMPD) (2001/83/EC, as amended) and Traditional Herbal Medicinal Products under the amending directive (2004/24/EC) of the HMPD.

Background and weaknesses of the existing regulatory framework

The full implementation of the Traditional Herbal Medicinal Products Directive (THMPD) (EC Directive 2004/24/EC) as of 1st April 2011 is likely to force from the European market thousands of products associated with traditional systems of medicine that have up until now been sold mainly as food supplements. The end of the 7 year transition phase of the directive will be interpreted by many Member States as a fundamental regime change whereby many herbs included in products that have been sold safely as food supplements, often for decades, will need to be registered under the THMPD if they are to continue to be available beyond 31st March 2011.

In theory, national food supplement regimes for botanicals will remain, but a number of factors suggest that it will be increasingly difficult to use this route to continue to sell or dispense finished polyherbal botanical products that have long been associated with traditional systems of medicine, particularly non-European ones. The difficulties include:

- classification as 'novel' under the terms of the Novel Food Regulation (No. 258/97) 'risk assessment guidelines for botanicals used in food supplements have been prepared by the European Food Safety Authority (EFSA).' 'The Novel Food Regulation, although originally conceived to protect consumers from genetically modified foods (that now have their own regulatory regime) and foods modified by other technologies, poses a very great threat to many botanical constituents. Its basic premise is to require pre-market authorisation of such foods following evaluation by EFSA of extensive evidence of safety. The classification is applied to any food that has not been used significantly within the EU prior to the implementation of the Regulation, in May 1997. The Regulation has been used increasingly to instigate bans on botanicals which have not been used significantly within the EU, despite them often having a history of use outside of the EU that is known to span thousands of years. Such restrictions are not generally based on any health concerns and so may be contrary to the principles of European law.'
- classification as one or more constituents (or their dosage) within the product as medicinal (under the terms of amending Directive 2004/27/EC)
- the imposition of onerous and disproportionate quality control requirements.

The THMPD provides an additional regulatory route, specifically intended for botanicals associated with traditional systems of medicine. However, a series of eligibility and technical challenges, as well as prohibitive costs, prevent a very large number of

traditional medicines, especially from non-European traditions such as Ayurveda and traditional Chinese medicine (TCM), from being registered under the scheme. A failure to alter the regulatory regime for such products is therefore likely to lead to very substantial losses of products from the European market with consequential impact on businesses manufacturing and supplying them. Typical stakeholders involved with Ayurveda and TCM generally supply a large number of polyherbal products, each with low annual sales volumes.

Consequently, after 31st March 2011, polyherbal products associated with traditional medicinal systems that are unable to negotiate the THR scheme, whether for eligibility, technical or economic reasons, are at grave risk of being classified by Member State competent authorities as unauthorised novel foods or unlicensed medicinal products. Such products would effectively fall between the two stools of European food and medicinal law. The loss of such products would be catastrophic to the many small and medium sized enterprises involved in the sector. Such a loss would also infringe human rights, so breaching the principles set out in the Charter of Fundamental Rights which is now recognized in European law following the passage of the Lisbon Treaty.

Ways forward

In order to address the problems for the sector that are otherwise due to manifest in the second half of 2011, it is imperative to take a range of concerted actions. These actions must address both the immediate problems associated with the existing regulatory frameworks, as well as helping to facilitate the development of a more appropriate framework that allows not only the viability of traditional systems of medicine in Europe, but also allows such systems to expand and flourish. Concerted actions of this type must at the same time be realistic, taking into account existing European and national legislative models, principles of European law and scientific understanding and perceptions of traditional systems of medicine.

Scientists (including pharmacognosists and pharmacists), stakeholders, practitioners and European lawyers have been brought together by ANH-Intl and EBF to develop both short and longer-term actions to facilitate the survival, viability and expansion of the sector. A key part of this process is to ensure products are subjected to appropriate quality controls to ensure both their effectiveness and safety.

Three coordinated actions are proposed by ANH-Intl and EBF as follows:

Short-term actions

a. Improvement of the food supplements regime EU-wide
b. Judicial review of the THMPD

Longer-term action

c. Facilitation of a new regulatory framework for traditional medicinal products

Further detail on each action is given below.

Note: while a changes to the health claims regime under the Nutrition and Health Claims are much needed, the Regulation is so poorly conceived that a very broad cross-section of stakeholders across the food and natural health product sectors are working to positively shape it. Accordingly, for the time being, both ANH-Intl and EBF will not directly contest the Regulation given their existing commitments.

ACTION 1: Improvement of the food supplements regime

There is a great need for clarification of the food supplements regime, in different Member States, especially to facilitate the functioning of the single market of the EU. While the EFSA guidance for botanicals will facilitate a more harmonised approach, there are many ways in which the guidance, and associated compendium, can be interpreted. Some interpretations by Member State competent authorities are not scientifically rational (e.g. France; green tea, only aqueous extracts allowed). A more equitable approach between Member States is also required given the requirements of the Mutual Recognition Regulation (No. 768/2008), which ensures that goods sold safely in one Member State should be available in others.

ANH-Intl and EBF are developing a workplan to:

a. Facilitate the expansion of the EFSA compendium of botanicals used in food supplements as well as its appropriate, scientifically-based interpretation
b. Lobby EFSA, relevant Member State authorities and the European Parliament to modify the existing compendium where necessary
c. Consult with Member State competent authorities to ensure a more 'level playing field' in the approaches taken to the approval of botanicals in food supplements
d. Reduce the inappropriate categorisation by European authorities of botanicals of non-European origin as novel foods, or unlicensed medicinal products.

ACTION 2: Judicial review of the THMPD

The legal text of the THMPD is problematic. It is this text, and its specific reference to quality control guidelines in the over-arching Directive 2001/83/EC that is responsible for the excessively restrictive eligibility requirements of the THR scheme, as well as the onerous quality controls that result in the prohibitive costs for registration of polyherbal products associated with non-European traditions, such as Ayurveda and TCM.

These regulatory requirements were not developed following adequate appraisal of the types of business operating in the sector, information that should have been available to the European Commission (the responsibility of the Directorate-General for Enterprise and Industry until late 2009), Member States and the European Parliament at the time the directive was proposed and passing through the legislative process in the European Parliament (2001-2004). Regulatory impact assessments carried out during this time were woefully inadequate and did not represent sufficiently the sectors most directly responsible for the manufacture or supply of classical medicines, especially those relating to non-European or minor traditions. Accordingly, SMEs involved with non-European and minor traditions are most adversely affected by the existing regulatory framework, which is currently set to force closure of those businesses whose operation is engaged solely with the manufacture or supply of traditional medicinal products in Europe.

Furthermore, given that regulatory systems for traditional medicinal products are in the process of development in many other parts of the world, and given the known influence of EU regulatory models outside of Europe, the existence of an inappropriate EU framework could yield negative impacts well beyond the European region.

It is therefore of paramount importance that the EU regulatory framework for traditional medicines is re-shaped, prior to it being fully 'cemented' following the expiry of its transition phase. Such amendment can be achieved in one of two ways; either through a willingness for amendment by the European Commission, Member States and the European Parliament (potentially achievable by effective lobbying and advocacy), or through judicial review.

It is the considered opinion of the ANH-Intl and EBF experts that there is inadequate willingness for amendment of the THMPD by at least the European Commission and Member States at the present time, and especially prior to 31st March 2011. A moderate level of lobbying over the problems caused by the Directive, as well as consultations by the Chinese and Indian governments which have raised many concerns to the European Commission and Member States, have so far yielded little. Accordingly, judicial review is proposed. ANH-Intl has received an opinion from a leading, London-based firm of European lawyers (11KBW), which is guiding its legal strategy.

The judicial review must be initiated through a domestic (European Member State) court and, in order to gain standing for judicial review, it would need to follow the rejection of an application to the THR scheme. The intention would be to seek from this national court a reference to the European Court of Justice.

The principle grounds for challenge have been identified as follows:

a. *Proportionality* combined with a restriction of freedom of movement of goods argument (under Article 28 EC of the Treaty of the European Community). This argument will expose the manner in which the Directive, and associated European laws and guidelines, disproportionately impacts stakeholders associated with non-European and minor traditional systems of medicine in Europe. Amongst other things, the monographs developed by the Committee on Herbal Medicinal Products will be challenged, the unnecessarily onerous nature of the technical requirements for the scheme will be exposed in terms of the intended purpose of the Directive, and, deficiencies in the technical requirements will be revealed, demonstrating that they do not adequately guarantee the safety of products

b. *Transparency*, an argument focusing mainly on the lack of transparency as to the nature of the technical (including quality control) requirements at the time the THMPD was passing through the legislative process, prior to 31st March 2004

c. A human rights/cultural discrimination argument, which will delineate the social and cultural impacts of the planned restriction of access to products associated with traditional medicinal systems.

In parallel to the proposed EU legal process, it is expected that a formal complaint may be made to the World Trade Organization by the Chinese and Indian governments, supported possibly by other governments. This complaint will ramp up the concerns already expressed to European authorities about the impact of the THMPD on exports to the EU of herbal raw ingredients and finished products from China and India. It is proposed that experts in ANH-Intl and EBF will be able to facilitate this process. Such a complaint will apply much needed

pressure on European authorities over the period that the judicial review of the THMPD is in process.

ACTION 3: Facilitation of a new regulatory framework for traditional medicinal products

The need to facilitate a new regulatory framework was the justification for the establishment of the EBF. Work on a draft regulatory model was commenced in early 2010, and has received considerable inputs from Peter Bogaert, a leading European lawyer specialising in EU medicinal law, pharmacognosists, analytical chemists, phytotherapists, practitioners of Chinese and Indian medicine systems and a diverse range of stakeholders in the sector. The model has become known as the Benefyt model.

The purpose of the model is to act as the basis for a new regulatory framework that not only replaces the THMPD, but also expands on its present scope. The model, therefore, aims not only to cater for OTC herbal medicines, but deals with practitioner prescribed and pharmacy-dispensed traditional herbal products, as well as those that are currently sold in some Member States as food supplements. The model effectively helps forge a 'third category' of products, that could be created between the regulatory regimes for foods and medicines. It is known that this type of framework, used in some other parts of the world (e.g. Canada, Australia) is of interest to regulators within the European Commission and it is intended that the Benefyt model will provide the basis for a future legislative proposal.

Critically important to the development of the model has been the inclusion of quality control requirements that are both feasible for the vast majority of stakeholders in the sector, while at the same time ensuring a very high level of quality and safety of products. A major 'selling point' of the Benefyt model to legislators and politicians alike will be that the Benefyt model offers a higher level of safety for products than the THMPD, while at the same time considerably cheaper. Additionally, the quality control elements of the Benefyt model could also readily be applied to an amended version of the THMPD.

An extremely important element of the Benefyt model has been to utilise a category-based, or graded, approach. This allows different levels of regulatory stringency to be applied to different categories of product. The present model includes 3 grades of product. Class I includes those products which present no significant risks to human health. Class III includes those products containing constituents that may cause adverse effects in certain individuals and so need to be labelled with specific precautions to protect susceptible groups. The remaining class, Class II, includes those 'ambivalent' products, that are categorised neither in Class I nor in Class III.

Considerable advocacy and lobbying work will be required by EBF, ANH-Intl and other organisations to facilitate the acceptance of this model, and its acceptance is likely to be accelerated by the judicial review of the THMPD which will expose many of the weaknesses of the existing framework.