RESPONSE TO REFLECTION PAPER[1] BY EUROPEAN MEDICINES AGENCY (EMEA) ON STABILITY TESTING OF HERBAL MEDICINAL PRODUCTS AND TRADITIONAL HERBAL MEDICINAL PRODUCTS

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Background on ANH Consultancy Ltd

ANH Consultancy Ltd provides services to European and non-European companies in the natural products and herbal sectors, generally facilitating their compliance with appropriate regulatory systems. Our clients tend to be small businesses that are leading suppliers of high quality herbals products.

Most products sold by our clients are presently sold either as food supplements, while others are sold in the UK as herbal products exempted under the provisions of Section 12.1 or 12.2 of the Medicines Act 1968.

Together with our clients and other specialists, we have evaluated the requirements for registration under Directive 2004/24/EC (the Traditional Herbal Medicinal Products Directive [THMPD]) and it is the totality of requirements that has made it so difficult for our clients to file applications for registration. Although products may also be licenced through a conventional medicinal product marketing authorisation on the basis of well-established usage, this route would not be relevant to most of the complex products associated with either the Ayurvedic or Chinese traditions that are of prime interest to our client base. This licencing scheme would also be prohibitively expensive for our clients.

Key challenges of the THMPD

Among the range of challenges posed by THMPD are:

a) the cost of providing stability data, especially where this relates both to active substances and finished products

b) the cost of providing genotoxicity data

c) other costs associated with licencing (GMP, qualified persons, ongoing QC, etc.)

d) lock-out for specific formulations by the '15-year rule' which appears to be justified more for reasons of protectionism than for reasons of quality or safety

[1] EMEA reflection paper: www.emea.europa.eu/pdfs/human/hmpc/362609en%20.pdf

e) limited to selected/minor ailments only, while many traditional medicinal products have long histories of use on other disorders and more serious medical conditions

f) natural variation between batches, linked to seasonal, genetic (e.g. subspecies or cultivar) and environmental factors (e.g. soil type, rainfall, temperature)

g) exclusion of products containing more than 'ancillary' amounts of vitamins or minerals

These challenges are the primary reasons why so few applications have been submitted to the traditional herbal medicinal product registration scheme (THMRS). When one considers that, during the period of the scheme's development as a legislative proposal, it was promoted to governments, the European Parliament and stakeholders as one appropriate to all traditional medicinal cultures including those from India and China, it is a travesty that so few of the non-European products are presently capable of entering the THMRS. The reasons are generally technical (criteria or methodologies inappropriate), financial (too costly) or both. The result is a scheme that is substantially disproportionate.

Technical challenges relating to stability tests

The EMEA's *Guidance Note on the Quality of Herbal Medicinal Product*[2] calls for tests to demonstrate that the known constituents of any herbal medicines in the product are present in the finished product. This Guidance Note states that if an herbal medical product contains a combination of several herbs, "the determination may be carried jointly for several active substances."

The Note advises that such identification tests have to be carried out "by different appropriate chromatographic methods." The problem here is that demonstrating exactly what is present in the finished product by chromatographic means is easier said than done. These quality control measures are relatively easy to carry out for an orthodox drug which contains a single chemical entity but difficult to demonstrate when evaluating a complex herbal mixture of several herbs, each one containing a multiplicity of chemical signatures. The bulk of the UK products that are planning to seek registration under the THMPD are not single ingredient products. Instead, they are likely to be complex herb mixtures, often with 3 to 5 herbal ingredients and in the case of Ayurvedic and Chinese herbal medicines, there may be 10 or even 20 individual herbal ingredients. The proposed quality standards will be difficult, if not impossible in many cases, to apply to these complex herbals.

In practice, when using the relatively inexpensive TLC, the chromatographic fingerprint of one herb often obscures that of other herbs with which it is combined in a product so that no determination of the individual marker compounds of all the herbs can be

[2] European Medicines Agency (EMEA). Note for Guidance on the Quality of Herbal Medicinal Products. London, UK: EMEA. July 26, 2001;CPMP/QWP/2819/00; EMEA/CVMP/814/00.

made. It appears that the only way that these data might be provided for combinations of several herbs is by the use of HPLC. But even with such equipment the task of identifying markers of several herbs blended together in one formulation might well prove impossible. The cost of a basic HPLC machine is about €60,000, but the true cost of these procedures has to include the development of techniques to demonstrate the chemical markers of each herb in combination. This is likely to be expensive in terms of time and personnel involved and beyond the financial resources of the many very small, small and medium companies in the European herbal sector.

The point here is that for herbal product complexes containing more than two or three herbs, the technical difficulties of meeting the EMEA *Guidance Note* requirements is likely to be a frequent experience. It is not really reasonable or practical to consider that the majority of these multi-herb formulations can somehow negotiate the difficulties of the QC guidelines by labelling some of their herbs as excipients. Thus, these exceptions are likely to be the rule, thereby proving the guidelines more or less unworkable for small or medium herb companies with limited resources.

The *Guidance Note,* together with that on stability testing,[3] also states that by using the required "appropriate fingerprint chromatograms," herbal companies prove that herbal constituents within their products are stable. A typical test procedure is likely to occur at three-month and then six-month intervals over a minimum of three years. Again this testing is likely to require expensive HPLC machinery, and multiple tests may be required to identify all the active constituents in a complex herbal formula. For a product with other actives, such as vitamins, this would again require a further identification and assay for each one. Stability cabinets used to conduct these tests are not inexpensive.

To purchase cabinets capable of holding 20-30 products samples for up to three years is likely to cost from €10,000-15,000. However the maintenance and running is expensive. The UK Herbal Forum has recently calculated that the cost of a single herb stability study per packaging format would be in the region of £11,000 (€12,333) per item while a four-herb combination tablet per packaging format would be in the region of £31,000 (€34,760). These are large sums of money that will be difficult for many herb companies to find.

A well-known German Laboratory recently gave a written cost estimate to an American applicant, for quality assurance and stability testing sufficient to qualify an herbal tea with two active ingredients for THMPD licensing at approximately a minimum of €100,000 per product.

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[3] European Medicines Agency (EMEA). Note for Guidance on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products. London, UK: EMEA Committee for Proprietary Medicinal Products (CPMP). December 17, 2003;CPMP/QWP/122/02. Available at: http://www.emea.eu.int/pdfs/human/qwp/012202en.pdf.

Development of more proportionate, technically feasible and effective methodologies

It is apparent that the prime purpose of the THMPD is to ensure quality, safety and efficacy of the registered herbal medicinal products. Clearly, the issue of efficacy is dealt with indirectly through the verification of traditional use (although there is no scientific rationale for the exclusion of products with less than 15 years usage in the EU). The issues of both quality and safety are catered for through the imposition of pharmaceutical criteria, most of which are taken directly or adapted from conventional medicinal products, under Directive 2001/83/EC. The key questions that then need to be asked are:

a) Are the stability data as determined according to the methods proposed in the *Guidance Note on the Quality of Herbal Medicinal Products* including the requirements for stability data, necessary to achieve quality and safety?

b) Are stability data necessary for pre-market authorisation, or could responsibility for stability (shelf-life) be placed on manufacturer as per existing requirements of food law (under EC Regulation 178/2002) in relation to foods and food supplements? [Note: In many ways herbal products, particularly complex combination products, have more in common with foods than they do with conventional pharmaceuticals which are generally based on very well characterised, synthetically produced chemicals within an inert matrix]

c) Are the existing methods applicable and relevant to the full array of traditional herbal products, or are they less applicable to particular product types, notably poly-herbal products with large numbers of herbal components or particular formulation types e.g. certain water-based/low alcohol products such as Ayurvedic tonics?

d) Are there ways of simplifying the existing required procedures?

e) Could alternative methods be both suitable and more feasible?

While the reflection paper asserts that "adequate quality standards have been established", we believe this is not the case. Following are some additional concepts that could readily lend themselves to quality determinations that could be considerably more proportionate in effect largely owing to their technical feasibility and the reduced cost of the methods.

a) Development of selective chromatographic techniques that dramatically reduce the requirement for production of stability data as a requirement of pre-market authorisation. Such a system is tried and tested in Australia and is overseen by the Australian medicines regulator, the Therapeutic Goods Administration (TGA).[4] Such systems may involve developing systems appropriate to specific products which are justified by the manufacturer. Citing

[4] See section *Questions and answers on stability testing of listed medicines* on Therapeutic Goods Administration (Australia) website: http://www.tga.gov.au/cm/stabilityqa.htm

directly from the TGA's website: "It may not be possible to check the stability of all active ingredients in a multi-ingredient complementary medicine. In such cases, studies which force the sample to degrade, for example, with heat, to allow identification of changes taking place that may then be used as stability indicators for the product. With adequate experience of product formulations and their stability, it may be possible to group ingredients and to selectively monitor for a smaller number of ingredients". The key elements of the successfully operated TGA system are:

- It is the responsibility of the manufacturer to develop a stability testing protocol specific to each licenced product that allows the stated shelf life to be met and justified. The manufacturer must have available a scientific justification of the methods used;
- Since the TGA recognises the technical difficulties that may be associated with stability testing of complex polyherbal and multi-ingredient medicines, the shelf life of a licenced product may be determined by reference to stability studies performed on a similar (corresponding) product. However, should a manufacturer use this option, it must hold evidence to justify the applicability of the data from the corresponding product.
- If complete stability data are not available the manufacturer may make a judgement on an interim or abbreviated shelf life. Such a judgment must be supported by evidence and may be used until the results of stability testing are available.

b) Chemometric methods for analysis of the chromatographic fingerprint, using Fisher components (e.g. Cheng et al, *J Chem Inf Comput Sci.* 2003; 43(3): 1068-76).

c) Surface Plasmon Resonance (SPR); as used by Lu et al, *Biochim Biophys Acta*. 2001; 1512(2): 308-16).

d) Biological assays. Rather than evaluating active constituents or surrogate biomarkers, assays which evaluate biological activity could be suitable. Examples are given below:

- antioxidant activity; tests evaluating activity of reactive oxygen species, using for example peroxynitrite, hydroxyl radicals or superoxide dismutase
- assays of activity against inflammatory cytokines (e.g. TNF) and adhesion molecules (e.g. integrins, immunoglobulins)
- microbial activity; activity against yeasts, bacteria, fungi or protozoa
- activity against other organisms; e.g. brine shrimp assay (e.g. Wanyoike et al, *Ethnopharmacol.* 2004; 90(1): 129-33).

Conclusion

It is clear that the existing criteria, requirements and guidelines as set out in the *Guidance Notes* are providing a major obstacle to the submission of applications to the THMRS. This obstacle is discriminating against herbal products from non-European traditions, especially those from the Indian and Chinese traditions, but also those from southern African, South East Asian and South American traditions. The existing guidelines are clearly much more suited to single or very limited combinations of herbs, such as those that are more common to European traditions.

Therefore, it could be regarded that the existing system is acting in a protectionist manner and is imposing an international barrier to trade as well as infringing the European Convention for the Protection of Human Rights and Fundamental Freedoms[5] by preventing ethnic groups within Europe from accessing products from their indigenous non-European traditions.

The effects of the existing system will dramatically increase after the expiry of the transition phase of the THMPD on 31 March 2011 so the EMEA and the Directorate-General of Enterprise and Industry of the European Commission (DG Enterprise), together with stakeholders, must rapidly develop an alternative, proportionate and effective system that is applicable to all herbal products from traditional medicinal cultures, including those that comprise complex polyherbal and multi-ingredient formulae.

While there are a diversity of novel and older methods (some of which have been used for decades successfully within the national pharmacopoeia of, for example, India and China), establishing and validating these methods is likely to take some time.

In the meantime the system used successfully by the TGA in Australia remains one of the most proportionate systems for complex herbal and multi-ingredient products. Such procedures could readily be integrated into HACCP (Hazard Analysis and Critical Control Points) systems that should be made mandatory to ensure the quality and safety of herbal products is assured.

We are presently working both with Indian and Chinese herbal manufacturers that operate very good HACCP systems (and are also ISO 9001:2000 certified). These companies have been attempting to meet the EMEA guidelines for complex polyherbal products and are in the process of demonstrating the lack of feasibility of the proposed EMEA methods. We have agreed to pass on the results of this work to DG Enterprise, and of course would also be happy to relay it to EMEA on request.

[5] European Convention for the Protection of Human Rights and Fundamental Freedoms: http://www.eurofound.europa.eu/areas/industrialrelations/dictionary/definitions/europeanconventionfortheprotectionofhumanrightsandfundamentalfreedoms.htm