

20 July 2010

Appropriate Regulatory Framework for Ayurvedic Health Products and Traditional Chinese Medicines in the EU

Introductory comment:

This note is based on a first discussion draft of 29 June 2010, the discussions on the draft during a workshop on 30 June, and comments received after the workshop. The exchange of views and detailed input from many sources have proven to be very useful. The current note seeks to address, where possible, all comments made, either by incorporating the proposed provisions or other wording covering the issue in question, or providing a brief explanation why the text does not contain certain proposals. Due to the high number of comments, this is only partially feasible.

The discussions have also identified differences in priorities and regulatory choices between different parties. This note seeks to strike a balance between the various approaches, but because of this also unavoidably presents a less coherent proposal. It may better reflect the various needs and concerns, but may be less easy to present to policy makers and regulators than the initial version.

Key terms used in this note are:

- Traditional System of Medicine Products (TSMP) (replacing the term “specific traditional remedy”). This term is chosen because it strengthens the link with the traditional system of medicine and puts the emphasis on the latter.*
- Characterising ingredient.*
- Traditional System of Medicine Products Advisory Group (TSMP-AG) (replacing the term “Specific Traditional Remedies Advisory Group” or STRAG).*
- Written request for dispensing.*

This note discusses the need for an improved EU regulatory framework for specific types of medicines that are mainly based on traditional systems of medicine that have a long tradition outside the EU. These products typically contain herbal ingredients and other traditional components. The note in particular addresses Ayurvedic health products and Traditional Chinese Medicines (TCM) as main examples of this category of products.

Conceptually, the proposed rules can also apply to other traditional systems of medicine from outside the EU (Tibet, Vietnam, Africa, South America, etc.). It is, however, advisable to initially focus on two systems and to design basic rules that can later also be applied to other systems.

The note first provides a problem statement in the form of a brief description of the main characteristics of the products in question and the difficulties of finding an adequate regulatory framework for these products under the existing EU pharmaceutical legislation. It then presents an outline of the regulatory framework that is proposed to address specific concerns, and concrete elements of legislative changes to Directive 2001/83 to establish that framework.

The current version of this note is a draft for discussion purposes. In several instances it refers (in comments between square brackets) to specific points that need further elaboration.

A. Problem Statement

1. Specific characteristics of Ayurvedic health products and TCM

[Focus on:

- *herbal and other typical ingredients, including minerals, vitamins, materials of animal origin, ghee, etc.*
- *long local tradition for using these products*
- *embedded in a traditional system of medicine, originally practiced outside the EU, and in some cases specifically emphasizing the need for maintenance of good health*
- *relevance to ethnic communities resident in the EU, but also attracting increasing broader scientific and medical interest*
- *formulations partially based on individualised recipes for each patient*
 - *using ingredients covered by relevant pharmacopoeias*
 - *recipe based on relevant traditional text books and subsequent interpretative texts [latter OK?]*
 - *certain recipes are used rather frequently or require complex processing and can be made in advance (which improves quality and reliability); others are made by a pharmacist or herbalist.*
- *this requires for certain products patient examination by specialist in the traditional system of medicine in question, who issues a recommendation or a “written request for dispensing” (it is probably better to avoid the word “prescription” as it could be seen as an implied recognition of the specialists as physicians).]*

2. EU regulatory regime is not adequate

[Focus on various problems of applying the existing medicines rules (standard approval route, well established medicinal use and THMP).]

B. Overview of the Proposed New Regulatory Framework

The proposal is based on a dual approach:

(i) Improving the provisions of the THMPD

The Traditional Herbal Medicinal Products Directive (THMPD) amended Directive 2001/83 and put in place a special registration scheme for traditional herbal medicines. The main amendments to this regime are broadening it to cover also non-herbal active (or functional) ingredients, broadening the scope of therapeutic indications, and correcting the quality standards.

(ii) Designing a new regime for products used in a Traditional System of Medicine

The traditional system of medicine products (TSMPPDs) that are covered by the new rules will be identified in an Annex, but must have a sufficiently well established tradition outside the EU. The rationale for the new regime is a partial recognition by the EU of the reliability of these systems and the products which are used in their context.

The regime is based on positive lists of characterising ingredients, a set of references that are used to determine how the ingredients are used to prepare products, and a notification requirement for products placed on the market. Specific rules are proposed governing sales without prescription and advertising.

This “blanket approval” system is very different from the product specific MAs and registrations under the current medicines rules (and is a bit similar to the German Standardzulassungen). It does not fit in the same articles that cover the traditional herbal medicines registration scheme.

This new regime will cover all products for human use that are marketed with health or therapeutic claims and that are intended or expressly or impliedly presented for use in the context of a listed Traditional System of Medicine. It will not apply to products that:

- are marketed as medicines in accordance with Directive 2001/83 (and where relevant Regulation 726/2004);

This allows companies to voluntarily use the THMPD or well-established medicinal use route for certain products if considered more appropriate. It could also be used to shift (sometimes referred to as “upgrade”) a product from TSMP to a status under Directive 2001/83.

- are marketed as cosmetics in accordance with the Cosmetics Regulation 1223/2009;

- are marketed as medical devices in accordance with Directive 93/42;

- are marketed as food, in accordance with Regulation 178/2002 and other EU food rules.

To reflect the special status of the products, the new regime will be laid down in a separate Regulation.

This dual approach seems necessary to reconcile the diverging views and allows for extra flexibility, but it obviously also weakens the proposal as it constitutes a higher “demand” and is less clearly defined.

It would also be possible to seek an amendment of the rules on well-established medicinal use (bibliographical applications), but this would further complicate the proposal.

C. Overview of the Proposed Regulatory Framework for “Traditional System of Medicine Products”

The proposed regulatory framework is based on the following key elements:

a. Status of “Traditional System of Medicine Products”

Many of the products in question fall under the definition of a medicinal product under Article 1.2 of Directive 2001/83 because:

- they are (at least implicitly, because of the context in which they are being selected and dispensed, and the framework of established tradition based medical text books) presented as “having properties for treating or preventing disease in human beings”; and
- they may also restore, correct or modify physiological functions by exerting a pharmacological action.

Hence, the new regulatory framework must take into account that the products are normally covered by Directive 2001/83. Some products may, however, not necessarily fall under the medicines definition.

To reflect the specific nature of the products, a new general term “Traditional System of Medicine Products” (TSMP) is proposed. It will, for instance, cover TCMs and Ayurvedic health products. The regime will only apply to those categories of TSMPs that will be identified in an Annex to the Regulation and for which the Annex will provide detailed provisions.¹

b. Authorisation for placing on the market

To reflect the wide inherent variations in finished products (based on a multitude of standard mixtures and highly individually determined mixtures - both based on the tradition based medical text books), and the written tradition based use of functional ingredients, a specific system of authorisation to place on the market is proposed, based on the following elements:

- (i) *Positive list of characterising ingredients*

¹ Annex will subsequently be amended in this respect by the Commission under delegated powers, in accordance with the provisions of the Lisbon Treaty.

A positive list will be established for characterising ingredients. This list will cover the ingredients that qualify as “active substances” under Directive 2001/83, but also other ingredients that in the tradition in question are a key component of the remedy (such as certain minerals, ghee, etc).

(ii) *Standards for marketing and using characterising ingredients*

Any person placing on the market:

- mixtures of characterising ingredients, possibly with excipients, specifically intended for use as or in TSMPs (“TSMP premixes”)
- finished TSMPs

In light of the revised approach, the marketing of “characterising ingredients intended for use as or in TSMPs” is not covered any more.

must comply with the following requirements:

- that person must notify each TSMP premix or TSMP it places on the market to the competent authorities;
- the notification must include full details of the products, including all ingredients and specifications
- the characterising ingredients, mixtures or remedies must comply with the specifications and standards for use in the positive list of characterising ingredients.

Any deviation of these requirements requires a specific product authorisation, granted by the competent authorities of each Member State when the product is marketed.

Specific rules apply to officinal products and named patient products made (or for) a pharmacy or other entity recognised by the authorities of a Member State.

c. Dispensing at retail stage

TSMPs should only be dispensed by pharmacies (or other entities recognised by the Member State where they are established) on the basis of a written request for dispensing issued by a specialist in the specific area of traditional system of medicine in question, following an examination of the patient and based on the recognised textbooks and guidance in that area.

A written request for dispensing will not be required for TSMPs that only contain characterising ingredients that are listed under Class A in the Annex.

d. Traditional System of Medicine Products Advisory Group (TSMP-AG)

The coordination group of national competent authorities established under Article 27.1 of Directive 2001/83 (for purposes mainly of the decentralised and mutual recognition procedures) shall establish a Traditional System of Medicine Products Advisory Group (TSMP-AG) that will provide regulatory and scientific advice to the Commission together with the EMA. The group will include experts in the various traditional systems of medicine.

The TSMP-AG will work closely together with the experts and institutions in the countries from where the traditional system of medicine originates, and with the EMA, EFSA, and other relevant EU and national bodies. It shall specifically propose the positive hits and amendments thereto.

[*or place in EMA?*]

e. Quality controls

[*overview of proposed system – based on the outline in Attachment 1]*

f. Limited therapeutic indications

The TSMPs will not carry any specific therapeutic indications, except a reference to the health benefit as described in the traditional system of medicine. A product description and instructions for use are also possible.

g. Advertising

Advertising for TSMPs will be permitted towards specialists in the traditional system of medicine. For products that can be dispensed without written request for dispensing, advertising to the public is possible.

h. Labelling of premixes and TSMPs

[*Specify what labelling requirements should apply, on or in pack, and possibly professional product information sheet.*]

[*More points needed?*]

D. Amendments to Directive 2001/83

The following provides an outline of how specific rules can be inserted in Directive 2001/83. It does not constitute a complete set of amendments but provides a basis for preparing a more comprehensive legislative proposal.

Article 16a of Directive 2001/83 (as inserted by the THMPD) is amended as follows:

Article 16a

1. A simplified registration procedure (hereinafter ‘traditional-use registration’) is hereby established for herbal medicinal products which fulfil all of the following criteria:

(a) they have indications exclusively appropriate to traditional herbal medicinal products which, by virtue of their composition and purpose, are intended and designed for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment; this includes indications where an initial diagnosis is made by a medical practitioner (or in the case of a traditional system of

medicine from outside the Union, another specialist) but the product can subsequently be used without additional supervision;

...

2. Notwithstanding Article 1(30), the presence in the herbal medicinal product of vitamins or minerals for the safety of which there is well-documented evidence shall not prevent the product from being eligible for registration in accordance with paragraph 1, provided that the action of the vitamins or minerals is ancillary to that of the herbal active ingredients regarding the specified claimed indication(s).

2a. In addition, notwithstanding Article 1(30), the presence in the herbal medicinal product of minerals and animal derived ingredients shall not prevent the product from being eligible for registration in accordance with paragraph 1, provided that (i) the minerals and animal derived ingredients comply with the Union standards for foods or their safety is otherwise demonstrated by well-documented evidence, and (ii) the minerals and animal derived ingredients are recognised by a traditional system of medicine from outside the Union as characterising ingredients in products used within that system.

This may be need to be refined, because the word “minerals” in par. 2a may have a different meaning from the word in par. 2.

[A separate amendment is needed to reflect the concerns about quality, in particular stability testing. This requires more reflection and is probably best included in Annex 1

Any need to change the 15/30 year rule?]

Logically speaking, a link could be made to the new Regulation on TSMPs (e.g. as to the “other ingredients”), but it is better to keep the two separate as the intention is to provide alternative regulatory pathways.

E. New Regulation on TSMPs

The new Regulation will contain the key provisions outlined below. The recitals will make reference to the importance of traditional systems of medicine in countries outside the EU and the need to take into account the experience and standards developed by and applied in these systems for allowing the marketing of specific health products.

As mentioned, the form of a Regulation is chosen to better reflect the separate status of the TSMPs, including avoiding an implied statement that they necessarily are medicines. The latter will help in maintaining food status, at least for a while. Ultimately, however, the TSMPs should be considered medicines or at least ad hoc health products.

If for tactical reasons it is better to switch back to a separate title in Directive 2001/83, this can easily be done.

a. Definitions

Article 1 – Definitions

Traditional system of medicine product

Any substance or combination of substances intended for oral use, inhalation, or topical use in human beings and presented for use, or specifically used, as a health product in the context of a traditional system of medicine that is listed in the Annex to this Regulation. The Annex shall also list the categories of products that shall qualify as traditional system of medicine products.

Based on specific comments, topical and inhalation use is added.

Traditional system of medicine product premix

[to be defined - concrete mixtures of characterising ingredients, intended to be used as or in TSMPs – possibly based on the following: “A combination of two or more ingredients that is intended to be used as a traditional system of medicine product after final preparation or packaging, or that is intended to be used in the preparation of a traditional system of medicine product.”]

b. Scope of application of the Regulation

Article 2 - Scope

1. This Regulation shall apply to the traditional system of medicine products listed in the Annex and to the related traditional system of medicine product premixes.

This Regulation shall not apply to products that:

- are marketed as medicinal products in accordance with Directive 2001/83/EC on the Community code relating to medicinal products for human use or in accordance with Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency
- are marketed as cosmetic products in accordance with the Cosmetics Regulation (EC) 1223/2009 on cosmetic products
- are marketed as medical devices in accordance with Directive 93/42/EEC concerning medical devices
- are marketed as food, in accordance with Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety and other Union food rules.

2. Traditional system of medicine products listed in the Annex shall be subject to the provision of this Regulation and the provisions of Directive 2001/83 referred to in this Regulation. They shall not be subject to:

- other provisions of Directive 2001/83;
- Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency;
- Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products;

- Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004;
- [*Other?*].

Products that are not traditional system of medicine products listed in Annex I and that are medicinal products, shall be subject to Directive 2001/83.

c. Substantive provisions in the Regulation

Article 3

1. The coordination group, established under Article 27.1 of Directive 2001/83, shall set up a Traditional System of Medicine Products Advisory Group (referred to in this Title as “the Advisory Group”).

2. [*composition – make sure adequate presence of experts in the relevant traditional systems of medicine*]

3. [*secretariat in EMA? + other basic provisions*]

4. The Advisory Group shall establish a detailed dialogue with institutions and experts in the third countries from where the traditional systems of medicine listed in the Annex result. This dialogue shall aim at a better understanding of the systems and reliance, where possible, on specialised local expertise in these countries. It will also be used to take into account new information and developments in reference text books that are relevant for updating the provisions in the Annex.

The Advisory Group shall also collaborate with Union agencies, such as the Agency and the European Food Safety Authority, Union advisory bodies and the national agencies and advisory bodies in the Member States that have specific expertise that is relevant for traditional system of medicine products.

[*There should be concrete ideas how the TSMP-AG will be financed.*]

Closer links with EMA and HMPC? Use the HMPC?

Article 4

1. The Annex shall list the traditional systems of medicine that are taken into account for this Regulation, and shall list the corresponding categories of traditional system of medicine products that are regulated by this Regulation.

2. For each of these categories of traditional system of medicine products, the Annex shall establish the principles that must be followed for placing the products of that category on the market. These principles will be based on the following elements:

(a) Positive list of characterising elements

- A positive list of characterising ingredients will be established on the basis of the relevant tradition of the system of medicine in question and of relevant monographs. The list shall cover all ingredients that are not technical additives (such as preservatives, stabilisers, thickeners, emulsifiers, etc.), bulking agents, colours, flavourings, aromatic substances, coatings or similar components [*review this list*].
- The list shall contain three classes of characterising ingredients:
 - (i) Class A, covering all characterising ingredients that can be used in products that do not require a written request for dispensing; [*maybe add: safety can be ensured through the long history of use, documented through reference text books, and quality assurance;*]
 - (ii) Class B, covering all characterising ingredients not covered by Class A and Class C; [*maybe add: safety can be ensured through the long history of use, documented through reference text books, and quality assurance;*]
 - (iii) Class C, covering all characterising ingredients that can intrinsically have significant toxicological properties and may require special processing and quality assurance measures.

[*Add a recital to the introduction of the Regulation*

“Class A and B characterising ingredients can also be used in foodstuffs provided they meet the requirements of Union food law.”]

- The list shall be established, taking into account relevant safety information on the ingredients and their use. For all Class C ingredients, a monograph that addresses the detoxification procedures or other relevant precautions will be required, based on long history of use, documented through reference text books. For Class A and B ingredients, specifications based on analytical properties will normally be sufficient.
- The list shall be established following advice by the Advisory Group. The list, and any updates, shall be published in the Official Journal, and an updated version of the list shall be maintained on the Commission website.

[*Or EMA website?*]

- [*other criteria?*]
- For each listed characterising ingredient, the following details will, where relevant and needed, be added:
 - description of the ingredients and, for instance, for herbal ingredients the parts of the plants used and after what processing or in the form of what preparations;
 - purity and safety specifications;
 - specific conditions of use in combination with other ingredients in mixtures and finished traditional system of medicine products;
 - specific labelling requirements.

(b) Standards for preparing mixtures and traditional system of medicine products

The Annex shall also list the various reference text books, and other sources of information on the traditional system of medicine in question, that provide standards for preparing mixtures of characterising ingredients and finished traditional system of medicine products.

[*more?*]

- (c) Reference to what other ingredients can be used in traditional system of medicine products and in mixtures of characterising ingredients or combined with characterising ingredients.

[needed? more?]

The list of characterising ingredients will be regularly updated. Other parts of the Annex may also be revised. The Advisory Group shall provide recommendations for updates and revisions.

[Insert reference to procedure for Commission decision under delegated.

Insert transitional rule for products that become unlawful because of amendment to lists]

Article 5

1. The placing on the market at any stage of the distribution of traditional system of medicine products and of traditional system of medicine product premixes is only permitted when the product complies with Article 4 and relevant provisions of the Annex, or when the product is specifically intended (i) for export outside the EU or (ii) for technical, scientific or clinical research, and is clearly labelled as such.

If the only deviation from Article 4 and the provisions of the Annex is the use of a specific combination of listed characterising ingredients that is not covered by the reference texts listed in the Annex, the placing on the market is also permitted provided the Advisory Group has issued a positive opinion on the combination. That opinion will be taken into account in a subsequent revision of the Annex.

2. Any person placing on the market any product mentioned in paragraph 1 must notify the competent authorities of the Member State where the product is placed on the market. The notification must include the following information (and additional information listed in the Annex):

- Full name and address of the person
- Name of the product
- Full qualitative and quantitative composition of the product
- Detailed justification of compliance of the product with this Regulation, including the Annex

[Add a specific provision on quality details? For instance that data must be kept available for inspection?]

[more?].

[Ideally insert provision limiting the levels of fees that can be charged by the national authorities.]

A one time or grouped notification may be preferable, but does not seem realistic.

Further detail needed on: registers kept nationally? are registers public? duration of validity of notification indefinite? variations?]

3. Paragraph 1 shall not apply to products prepared in a pharmacy (or other entity recognised by the Member State where the entity is established) in accordance with the standards laid down in the Annex *[check]* and intended to be supplied directly to the user, who is served by

the pharmacy in question. The notification under paragraph 2 must contain a justification in case the product deviates from Article 4 or the provisions in the Annex.

This covers officinal products and envisages a notification requirement but allows for deviations from the composition rules – like officinal medicines are accepted without MA.

4. Paragraphs 1 and 2 shall not apply to a product prepared in a pharmacy (or other entity recognised by the Member State where the entity is established) in accordance with a written request for dispensing referred to in Article 6.

This allows for named patient products outside the restrictions of the Regulation and without notification.

Instead of preparing the product himself, the pharmacist or other recognised person can also request a manufacturer of traditional system of medicine products to prepare the product covered by the written request for dispensing. The manufacturer must notify the competent authorities of the Member State where he is established at least on a monthly basis of the preparations made under this provision. Further details can be laid down in the Annex.

5. In derogation of the provision of paragraph 1, the competent authorities of a Member State can authorise the placing on the market of a product that does not comply with Article 4 and the Annex. Such specific product authorisation shall only be granted on the basis of an application, which must be submitted in accordance with the rules for applications laid down in the Annex. It shall be valid for five years and can be renewed for subsequent periods of five years. When for a specific product a specific product authorisation is granted in one Member State, the competent authorities of other Member States where a specific product authorisation for the same product is applied for shall take due account of the first authorisation.

In light of the new structure, allowing for alternative regulatory routes, the monopoly on using the terms Ayurvedic and TCM is deleted.

Article 6

1. Member States will determine which healthcare professionals can be considered to be specialists in the various traditional systems of medicine identified in the Annex.

2. A traditional system of medicine products must only be dispensed by a pharmacy or other entity recognised by the Member State where the entity is established. It must only be dispensed on the basis of a written request for dispensing issued by a specialist referred to in paragraph 1.

The written request for dispensing must at least contain the following information:

- Full name, address, and where relevant identification code of the specialist;
 - The first name and family name of the person for whom the remedy is intended;
 - Adequate specification of the product;
 - Where relevant, specific instructions for use and additional labelling for the user
- [more?]

However, a written request for dispensing is not required for a traditional system of medicine product that does not contain any other characterising ingredients than those listed in Class A in the Annex. The competent authorities may also exempt specific categories of traditional system of medicine products that contain characterising ingredients in Classes A and B in the Annex.

Traditional system medicine products that can be dispensed without written request can also be sold to the public outside pharmacies. Member States can restrict these sales to certain types of outlets, in compliance with Union law, including the principle of proportionality.

3. Pharmacies and other entities entitled to dispense under this Article shall keep copies of the written requests for dispensing [*and more?*].

[*Need to restrict internet sales and mail order business?*]

Article 7

1. Traditional system of medicine products dispensed at the retail stage must carry the following information on the outer packaging or in a leaflet included with the product:

- Name of the product as traditional description of the preparation;
 - List of all ingredients in descending order, by weight; [*percentages needed?*]
 - Name and address of the manufacturer or, in case of products imported into the Union, the importer;
 - Specific instructions for use and where relevant warnings or precautions, including, at least, the specific labelling requirements imposed by the positive list of characterising ingredients;
 - Specific recommendations for storage;
 - Expiration date
- [*more?*]

In addition, the outer packaging and, when used, the leaflet shall (unless this is not required under an authorisation pursuant to Article 5.5) contain the following statement in a clearly visible presentation:

“This product is a [reference to the category of traditional system of medicine products listed in the Annex]. It should only be used on the basis of an examination by a person specialised in [reference to the corresponding traditional system of medicine listed in the Annex].

This product has not been reviewed by the competent authorities and its effects have not been scientifically proven. [*or “and there may not be scientific proof of its effects”?*]

In case of questions or presumed side effects, contact a medical doctor or pharmacist.”

[*to be carefully reviewed*]

The person dispensing the product must also indicate his or her name, and the name of the user, on the outer packaging.

2. The label, and other information disseminated on the product, can make references to health benefits in accordance with the principles of the traditional system of medicine.

The label and other information disseminated on the product cannot make direct prophylactic or therapeutic claims with regard to a disease. This will not prevent the possibility of using a traditional description of the product that implies a therapeutic or prophylactic property, provided that the description is recognised in the text books or other materials listed in the Annex. That description will only be used to identify the product.

Article 8

Advertising to the public for traditional system of medicine products covered by this Regulation and requiring a written request for dispensing under Article 6 shall be prohibited. This shall not prevent answers to specific questions for information [*company websites with product information that is accessible at the initiative of the member of the public,...*].

Advertising to healthcare professionals and specialists in the traditional system of medicine shall meet the following requirements:

[*Insert some restrictions, such as presenting the product in a balance way, in respect of the principles of the traditional system in question, etc.*]

This provision does not affect the labelling of the products.

Article 9 etc.

[*specific rules on*
- *manufacturers, importers and wholesalers*
- *quality control!*
- *pharmacovigilance*
---]"

Add transitional rules for products already on the market.

d. Annex to the Regulation - Traditional System of Medicine Products

A. Traditional Systems of Medicine and Traditional System of Medicine Products Covered

The following traditional systems of medicine are listed in implementation of Article 1:

- Ayurvedic medicine [*add basic explanation*]
- Traditional Chinese medicine [*add basic explanation*]
- [*-other?*]

This Annex applies to the following traditional system of medicine products and the related premises:

- Ayurvedic health products [*add basic explanation*]

- Traditional Chinese medicines [*add basic explanation*]
[-*other?*]

B. Categories of traditional system of medicine products

1. Ayurvedic health products

1.1. Positive list of characterising ingredients

The Commission [*or EMA?*] will, after having obtained the opinion of the Traditional System of Medicine Products Advisory Group establish a list of characterising ingredients that can be used in Ayurvedic traditional system of medicine products. The list will be regularly updated to reflect new information and technical developments.

The list and further updates and amendments will be published in the Official Journal and a consolidated list shall be maintained on the website of the Commission [*or EMA?*].

The list will for each ingredient include:

- a description of the ingredient, including in the case of a herbal ingredient the binominal scientific name of the plant (genus, species, variety and author) and chemotype (where relevant), the parts of the plant to be used, the forms in which they are to be used or the preparations (such as extractions, distillations, expressions, fractionations, purifications or fermentations) that are to be used;
- specific quality standards;
[Include specific reference to Indian compendia like Ayurvedic Pharmacopoeia of India?]
- restrictions on the use, such as maximum levels or restrictions on combinations; [*OK ?*]
- specific labelling requirements including, where relevant, warning statements for the ingredients or mixtures or finished remedies combining them.

The list will group characterising ingredients in three classes:

Class A covers characterising ingredients that can be used in products that can be made available without a written request for dispensing. Specifications based on analytical properties will normally be sufficient

Class B covers characterising ingredients that do not belong in Class A and Class C. Specifications based on analytical properties will normally be sufficient

Refer to Ayurvedic Pharmacopoeia of India Part I, ICMR, IP & Nighantoo?

Class C covers characterising ingredients that intrinsically have significant toxicological properties. The list shall contain a monograph (or other specifications) that addresses the maximum dosage, detoxification procedures or other relevant precaution.

Does this classification sufficiently take into account the various processes (extraction etc.) that the herbal and other ingredients undergo before they are used as ingredients?

Refer to Shodhan vidhi as per Ayurvedic Formulary of India?

In addition, Ayurvedic traditional system of medicine products can, based on the tradition, contain other ingredients that are generally recognised as excipients for use in medicinal products or in food supplements or other special foods.

[Insert relevant reference to Ayurvedic monographs and how they apply].

1.2. Standards for use of characterising ingredients

The characterising ingredients can be used alone or in combination in Ayurvedic health products, based on the following principles:

- The use including combination of different characterising ingredients, must be in compliance with the principles laid down in one or more of the following reference works:
[...]
- The use, including combination of different characterising ingredients must not go against specific limitations contained in the positive list of characterising ingredients.

[Is this precise enough?]

- *[More?]*

1.3. Other ingredients

Mixtures of characterising ingredients and finished traditional system of medicine products, or preparations containing one characterising ingredient, can contain other components, such as additives. The following other components are allowed:

- authorised food additives and flavourings
 - excipients generally accepted for use in medicinal products
- [- more?]*

2. Traditional Chinese medicines

2.1. Positive list of characterising ingredients

The Commission *[or EMA?]* will, after having obtained the opinion of the Traditional System of Medicine Products Advisory Group establish a list of characterising ingredients that can be used in traditional Chinese medicines. The list will be regularly updated to reflect new information and technical developments.

The list and further updates and amendments will be published in the Official Journal and a consolidated list shall be maintained on the website of the Commission *[or EMA?]*.

The list will for each ingredient include:

- a description of the ingredient, including in the case of a herbal ingredient the binominal scientific name of the plant (genus, species, variety and author) and chemotype (where relevant), the parts of the plant to be used, the forms in which they are to be used or the

preparations (such as extractions, distillations, expressions, fractionations, purifications or fermentations) that are to be used.

- specific quality standards,
- restrictions on the use, such as maximum levels or restrictions on combinations [OK ?]
- specific labelling requirements including, where relevant, warning statements for the ingredients or mixtures or finished remedies combining them.

The list will group characterising ingredients in three classes:

Class A covers characterising ingredients that can be used in products that can be made available without a written request for dispensing. Specifications based on analytical properties will normally be sufficient. [*maybe add: In the case of Chinese traditional medicines, few characterising ingredients are expected to qualify as Class A.*]

Class B covers characterising ingredients that do not belong in Class A and Class C. Specifications based on analytical properties will normally be sufficient

Class C covers characterising ingredients that intrinsically have significant toxicological properties. The list shall contain a monograph (or other specifications) that addresses the maximum dosage, detoxification procedures or other relevant precaution.

Does this classification sufficiently take into account the various processes (extraction etc.) that the herbal and other ingredients undergo before they are used as ingredients?

In addition, traditional Chinese medicines can, based on the tradition, contain other ingredients that are generally recognised as excipients for use in medicinal products or in food supplements or other special foods.

[*Insert relevant reference to Ayurvedic monographs and how they apply*].

2.2. Standards for use of characterising ingredients

The characterising ingredients can be used alone or in combination in traditional Chinese medicines, based on the following principles:

- The use including combination of different characterising ingredients, must be in compliance with the principles laid down in one or more of the following reference works:

[...]

- The use, including combination of different characterising ingredients must not go against specific limitations contained in the positive list of characterising ingredients.

- [*More?*]

1.3. Other ingredients

Mixtures of characterising ingredients and finished traditional system of medicine products, or preparations containing one characterising ingredient, can contain other components, such as additives. The following other components are allowed:

- authorised food additives and flavourings
- excipients generally accepted for use in medicinal products
- [- more?]

C. Notification procedure

[Further details on the notification procedure under Article 5. Make clear how the justification of compliance is to be demonstrated in accordance with Article 5.2, last point.]

D. Specific product authorisation procedure

[Further details on the authorisation procedure under Article 5.5]

Attachment 1

Comments:

- *This part and any other provisions concerning quality of the TSMPs require an in depth review.*
- *Some suggested a less concrete and detailed approach. That risks resulting in stricter rules*
- *Any room for reliance on certificates issued by local authorities or inspection bodies? The new Directive on Falsified Medicines may also trigger more dialogue between the EU and local inspection authorities.*
- *Review the accreditation systems for laboratories.*

Overview of critical steps in Quality and Safety control for Traditional Medicinal products.

1.GAP (Good Agricultural Practice) steps

- Requires maximal traceability back to growing- and cultivation areas.
- Authentication protocol for botanical species: Macroscopical, microscopical, organoleptic determination criteria and bibliographic data on taxonomy converge into an Identification Protocol File (IPF). Since GAP is batch-related it is the first step (visual) in batch homogeneity control.
- Records of local contamination risks.

2. GMP (Source Batch Control) steps

For Ayurvedic products, check Schedule T to the Rules.

Below also include references to Ayurvedic Pharmacopoeia of India?

- IP approved material must match the HPTLC chemical profile. Confirmation of identity.
- Chemical profile database shall contain the fingerprint of adulterants, substitutes and/or non-preferred materials, in order to be excluded from further processing.
- Chemical profile through HPTLC in second phase of batch homogeneity control. HPLC or LCMS in specific cases.
[LCMS acceptable also from a cost perspective? Needed?]
- Standard testing procedures: Loss on drying, Total ash content, Acid insoluble ash content, Loss on drying, Water- and alcohol solubility.
- Heavy Metal testing: Lead, Cadmium, Arsenic, Mercury, Total HM content.
- Microbiology tests: E-coli, Salmonella, Total bacteria count, Total of moulds and yeasts, Staphylococcus aureus.
- Mycotoxin test: Aflatoxin B1, Total Aflatoxins, Ochratoxin in specific items.

-Pesticides.

-Source batch back-up sampling and register.

3. GMP (Post batch-release) steps:

-Local GMP licences and inspection-reports. Inspection reports by third parties.

-Site Master File of production unit.

-In- process control through SOP-flowchart/ batch specific.

-HPTLC –check of end-product conformity with traditional pharmacopea references on galenic form, full-spectrum extraction and preparation methods.

-HPTLC quality- and safety control by approximate quantitative determination of relevant biomarkers HPLC/LCMS for critical items requiring maximal accuracy . Resulting data are valid for future stability-study, quality- and safety-assessment.

Verify that this is clear enough to avoid an excessive quality standard.

-End- product back-up sampling and register.

-Total size of batch and full traceability records required.

-Standardisation of procedures, methodologies, limit-values, etc..according to international standards (WHO/PIC). However, the ongoing development of innovative QS control methods like System biology cannot be ignored, since these approaches tend to generate more relevant information about traditional preparations and also incorporate the specific parameters and tenets of traditional medicinal systems.

4. GMP (Ingredient –related QS control procedures)

As an ingredient of a customized prescription, all products require a certificate of analysis (COA), provided by an accredited lab. In this COA all relevant data from critical steps 1, 2 and 3 are considered.

Additional control on end-products

[The references to lists 1 to 3 must be checked against the classes A to C used above.]

- List 1: Quantitative HPLC/LCMS for active and toxic markers. Full control on end-product and stability-study required. Limitation or absence of toxic markers (Aristolochic acid, Pyrrolizidine alkaloids, Tropane alkaloids, a.o.).

[Further restrict the need for testing on toxic markers?]

-List 2: Partial end-product control according to percentage rule for active markers. Additional microbiology-test on end-product, in case it is not available on COA. Additional

testing for heavy metal contamination and pesticides in concentrated extracts, in case not available on COA.

-List 3: Additional microbiology tests on end-product, in case not available on COA. Additional testing for heavy metal contamination and pesticides in concentrated extracts, in case not available on COA.