EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 October 2010
EMA/HMPC/5873/2010
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on draft 'Reflection paper on stability testing of herbal medicinal products and traditional herbal medicinal products' (EMA/HMPC/3626/2009)

Table 1: Organisations that commented on the draft Reflection paper as released for public consultation

Organisations and/or individuals	
AESGP	Association Européenne des Spécialités Pharmaceutiques Grand Public
ANH	ANH Consultancy Ltd, The Atrium, Dorking, Surrey RH4 1XA, UK
BPI	German Pharmaceutical Industry Association
FAH	Members of the Expert Committee 'Herbal Medicinal Products' of the German Pharmaceutical Manufactures Research Association (FAH e.V.)
GA	Society for Medicinal Plant and Natural Product Research

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Table 2: Discussion of comments

General comments

Interested party	Comment and Rationale	Outcome
AESGP	AESGP welcomes the intent to develop the above-mentioned Reflection paper which addresses specifically herbal medicinal products. By harmonising stability testing requirements, it should facilitate mutual recognition in Europe. The existing European guidelines on stability testing, e.g. the Guideline on Stability Testing (EMEA/CHMP/122/02rev.1) was originally an ICH guideline hence its scope was limited to that of the ICH i.e. to new chemical entities (NCEs) and NCEs-containing medicines. In its implementation in the EU, it then became applied *de facto* to all categories of medicines, including herbal ones although some specific exemption existed for the latter. Despite substantial progress in the analysis of herbal medicinal products, problems still persist in individual cases of combination products and/or traditional herbal medicinal products. This problem has been discussed for several years within the European herbal industry. For example in Germany, an industry working group has compiled data in the field of long-term studies (25°C/60 % RH) in order to create higher appreciation of the problems among the experts and to propose possible approaches for the resolution of these problems [1]. The evaluations of study results, illustrated by case examples in this report, could be used as a support of the product-related argumentation of companies provided the products were comparable to those tested, e.g. for substantiating or fulfilling the term "if justified" which is used in the respective guidelines. Prior to this, this working group had evaluated available literature in this field including dissertations from academic institutes as well as data from companies [2]. This data collection intended to provide a basis for argumentation in addition to a product-related justification in cases in which "accelerated testing" at 40°C/75 % RH or "intermediate" testing at 30°C/65 % RH may be omitted because such testing does not lead to utilizable results. ***It should be emphasized that our comments should not be interpreted as challenging the basic quality requirements of herbal medicines but only intend to reflect the particular characteristics of certain herbal medicinal products in the context of stability testing***.	General comment agreed.
ANH	**Key challenges of the THMPD** Among the range of challenges posed by THMPD are:	The comment is more general and not

	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 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* 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 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	directly related to the reflection paper. ANH has overlooked that the HMPC has developed and published the "Guideline on quality of combination herbal medicinal products/traditional herbal medicinal products' (EMEA/HMPC/CHMP/CVMP/214869/2006". The Guideline includes solutions for many of the problems. Other problems e.g. GMP can only be solved by the European Commission.

	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, 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. **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). Such systems may involve developing systems appropriate to specific products which are justified by the manufacturer. Citing 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 superoxidedismutase 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 Freedoms5 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.	
BPI	Introduction For herbal medicinal products, in contrast to chemically defined medicinal products, the herbal substance/herbal preparation in its entirety is regarded as active substance. Consequently, during stability testing it should be demonstrated that the total herbal substance/herbal preparation is stable, unlike for chemically defined medicinal products where one single constituent has to be stable. Despite the number of constituents present in herbal substances/herbal preparations it is not easy to find or select analytical markers as often only few of them may be easily detected with common techniques such as HPLC-UV-detection. Often the markers in question are not very typical for the preparation either or are too unstable, especially in liquid or semi-liquid formulations. Such unstable markers may lead to out of specification (OOS) results during stability testing. As they do not indicate the stability of herbal preparations in their entirety, but serve only formally as a tool for the determination of the content of the extract, unstable markers are of poor importance. As part of a total control strategy for herbal substances, herbal preparations and herbal medicinal products, a set of test criteria including qualitative and quantitative parameters has been recognised as quality indicating. With regard to stability testing, chromatographic fingerprints in different polarity ranges as well as appropriate methods of	General comment agreed. Examples considered for Q&A document EMA/HMPC/41500/ 2010.

	assay via marker substances represent the fundamental part of this concept, laid down in the shelf-life specification. Due to the number of characteristics that differentiate herbal medicinal products from chemically defined medicinal products, specific stability guidance needs to be established which covers all the particularities that are not addressed by existing general guidelines on stability. In accordance with the classification of extracts of the European Pharmacopoeia (6.1, 04/2008:0765) into standardised, quantified and other extracts a differentiated approach for the qualitative and quantitative testing during stability should be chosen depending on: - the presence of constituents with known therapeutic activity (standardised extracts) - the presence of active markers (quantified extracts) - the lack of constituents with known therapeutic activity or active markers (other extracts) For quantitative determination the following points should be considered: 1. Standardised Extracts According to the Guideline on Quality of Herbal Medicinal Products/Traditional Herbal Medicinal Products (CPMP/QWP/2819/00 Rev 1) the variation in content of constituents of known therapeutic activity (e.g. sennosides, triterpenglycosides, calculated as ß-aescin, hyoscyamine, silymarin, capsaicinoides, etc.) during the proposed shelf-life should not exceed +/- 5% of the declared assay value, unless justified. In general constituents with known therapeutic activity should also be used during stability testing. Since, however, these constituents are generally a mixture of closely related constituents the following characteristics should be considered in comparison to chemically defined constituents: 1. Closely related constituents do generally have a wide therapeutic range. 2. For a quantitative determination the sum of the single constituents is determined. The addition of measurements of single constituents, each afflicted with some measurement error, consequently leads to a larger confidence interval for the sum. 3. Owing to the manufacturing process, the adjustment to a specified content of constituents with known therapeutic activity in the herbal preparation is subject to a relative large variation of up to +/- 5%. As a consequence, the +/- 5% variation allowed during shelf life would already be depleted. Consequently it can be deduced that the +/- 5% range allowed during shelf-life for herbal medicinal products with standardised extracts is too narrow. It should be broadened to +/- 10%. From a therapeutic point of view a broadening of the range can be regarded as safe and therefore acceptable. 2. Quantified Extracts For active markers in quantified extracts a variation in content during the proposed shelf-life of +/- 10% of the initial assay value should be accepted in general. Wider ranges should be possible, if they are justified. 3. Other Extracts In principle the choice of an appropriate analytical marker for identification and stability testing should be at the manufacturers own discretion. Depending on the given characteristics of an herbal drug the analytical marker(s)	

<table>
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<td>may differ at all steps of manufacturing, i.e. herbal substance, herbal preparation and herbal medicinal product. Accordingly, different analytical markers may be used for the herbal substance, herbal preparation and herbal medicinal product during stability testing.
For example:
Leiocarposide is a characteristic analytical marker for the identification of Solidago virgaurea L.. However, this marker is not suitable for stability testing because it is not stable in most herbal preparations including comminuted and powdered herbal drugs (comp. example 4). In this case another suitable analytical marker should be used for stability testing. For the chosen analytical marker a variation in content during the proposed shelf-life of +/- 10% of the initial assay value should be accepted in general. Wider ranges should be justified.
A wider range is also particularly important for mix-extracts obtained by extracting several herbal drugs concomitantly. In this case the choice of appropriate markers is restricted due to the required selectivity. In addition, the content of the different markers is generally very low.
In all cases the quantitative determination of markers during stability testing should be combined with appropriate fingerprint chromatograms, since the herbal preparation in its entirety is considered the active substance.

4. Herbal Medicinal Products
Basically the same recommendations apply to herbal medicinal products as described above for the corresponding extracts. The criteria are summarised in the following table:

Table 1: Recommendations for the shelf-life specification of herbal medicinal products derived from extracts

<table>
<tr><td></td><td colspan="3">Classification of extract used</td></tr>
<tr><td></td><td>standardised</td><td>quantified</td><td>other</td></tr>
<tr><td>constituents</td><td>with known therapeutic activity</td><td>active marker</td><td>analytical marker</td></tr>
<tr><td>variation in assay content</td><td>+/- 10% of the declared value</td><td>+/- 10% of the initial value; wider ranges, if justified</td><td>+/- 10% of the initial value; wider ranges, if justified</td></tr>
<tr><td>selection of marker for the quantitative determination</td><td>constituent with known therapeutic activity</td><td>active marker</td><td>marker appropriate for the specific analytical problem and/or the herbal medicinal product</td></tr>
</table>

5. Combination Herbal Medicinal Products
For combination herbal medicinal products the same range in marker content should be accepted during stability testing as for the single components of the finished product, i.e. standardised, quantified and/or other extracts (see Table 1).</td>
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<td>FAH</td>
<td>Introduction
In case of herbal medicinal products the herbal substance/herbal preparation in its entirety is regarded as active</td>
<td>General comment agreed.</td>
</tr>
</table>

	substance. Consequently, during stability testing it should be demonstrated that the total herbal substance/herbal preparation is stable, unlike for chemically defined medicinal products where one single constituent has to be stable. Despite the number of constituents present in herbal substances/herbal preparations it is not easy to find or select analytical markers as often only few of them may be easily detected with common techniques such as HPLC-UV-detection. Often the markers in question are not very typical for the preparation either or are too unstable, especially in liquid or semi-liquid formulations. Such unstable analytical markers may lead to out of specification (OOS) results during stability testing. As they do not indicate the stability of herbal preparations in their entirety, but serve only formally as a tool for the determination of the content of the extract, unstable markers are of poor importance. As part of a total control strategy for herbal substances, herbal preparations and herbal medicinal products, a set of test criteria including qualitative and quantitative parameters has been recognised as quality indicating. With regard to stability testing, chromatographic fingerprints in different polarity ranges as well as appropriate methods of assay via markers represent the fundamental part of this concept, laid down in the shelf-life specification. Due to the number of characteristics that differentiate herbal medicinal products from chemically defined medicinal products, specific stability guidance needs to be established which covers all the particularities that are not addressed by existing general guidelines on stability. In accordance with the classification of extracts of the European Pharmacopoeia (6.1, 04/ 2008:0765) into standardised, quantified and other extracts a differentiated approach for the qualitative and quantitative testing during stability should be chosen depending on: - the presence of constituents with known therapeutic activity (standardised extracts) - the presence of active markers (quantified extracts) - the lack of constituents with known therapeutic activity or active markers (other extracts) For the quantitative determination the following points should be considered: **1. Standardised Extracts** According to the Guideline on Quality of Herbal Medicinal Products/Traditional Herbal Medicinal Products (CPMP/QWP/2819/00 Rev 1) the variation in content of constituents of known therapeutic activity (e.g. sennosides, triterpenglycosides, calculated as ß-aescin, hyoscyamine, silymarin, capsaicinoides, etc.) during the proposed shelf-life should not exceed +/- 5% of the declared assay value, unless justified. In general constituents with known therapeutic activity should also be used during stability testing. Since, however, these constituents are generally a mixture of closely related constituents the following characteristics should be considered in comparison to chemically defined constituents: 1. Closely related constituents do generally have a wide therapeutic range. 2. For a quantitative determination the sum of the single constituents is determined. The addition of	Examples considered for Q&A document EMA/HMPC/41500/ 2010.

	measurements of single constituents, each afflicted with some measurement error, consequently leads to a larger confidence interval for the sum. 3. Owing to the manufacturing process, the adjustment to a specified content of constituents with known therapeutic activity in the herbal preparation is subject to a relative large variation of up to +/- 5%. As a consequence, the +/- 5% variation allowed during shelf-life would already be depleted. Consequently it can be deduced that the +/- 5% range allowed during shelf-life for herbal medicinal products with standardised extracts is too narrow. It should be broadened to +/- 10%. From a therapeutic point of view a broadening of the range can be regarded as safe and therefore as acceptable. **2. Quantified Extracts** For active markers in quantified extracts a variation in content during the proposed shelf-life of +/- 10% of the initial assay value should be accepted in general. Wider ranges should be possible, if they are justified. **3. Other Extracts** In principle the choice of an appropriate analytical marker for identification and stability testing should be at the manufacturers own discretion. Depending on the given characteristics of a herbal drug the analytical marker(s) may differ at all steps of manufacturing, i.e. herbal substance, herbal preparation and herbal medicinal product. Accordingly, different analytical markers may be used for the herbal substance, herbal preparation and herbal medicinal product during stability testing. **For example**: Leiocarposide is a characteristic analytical marker for the identification of *Solidago virgaurea* L.. However, this marker is not suitable for stability testing because it is not stable in most herbal preparations including comminuted and powdered herbal drugs (comp. example 4). In this case another suitable analytical marker should be used for stability testing. For the chosen analytical marker a variation in content during the proposed shelf-life of +/- 10% of the initial assay value should be accepted in general. Wider ranges should be justified. A wider range is also particularly important for mix-extracts obtained by extracting several herbal drugs concomitantly. In this case the choice of appropriate markers is restricted due to the required selectivity. In addition, the content of the different markers is generally very low. In all cases the quantitative determination of markers during stability testing should be combined with appropriate fingerprint chromatograms, since the herbal preparation in its entirety is considered the active substance. **4. Herbal Medicinal Products** Basically the same recommendations apply to herbal medicinal products as described above for the corresponding extracts. The criteria are summarised in the following table:	

Table 1: Recommendations for the shelf-life specification of herbal medicinal products derived from extracts

	Classification of extract used		
	standardised	quantified	other
constituents	with known therapeutic activity	active marker	analytical marker
variation in assay content	+/- 10% of the **declared** value	+/- 10% of the **initial** value; wider ranges, if justified	+/- 10% of the **initial** value; wider ranges, if justified
selection of marker for the quantitative determination	constituent with known therapeutic activity	active marker	marker appropriate for the specific analytical problem and/or the herbal medicinal product

5. Combination Herbal Medicinal Products

For combination herbal medicinal products the same range in marker content should be accepted during stability testing as for the single components of the finished product, i.e. standardised, quantified and/or other extracts (see Table 1).

GA

(Traditional) Herbal Medicinal Products contain as active pharmaceutical ingredient herbal preparations which distinguish from chemically defined active substances. As a rule they are or they contain multi-component mixtures which analysis of each single compound is an invincible analytical hurdle.

Therefore supportive conventions have been established to characterize sufficiently the quality and following the stability of herbal preparations/herbal medicinal products.
The pars-pro-toto principle is to follow one chemical substance on behalf of the entire mixture. This compound may have only analytical value or may contribute or even may be responsible for the efficacy of the product. This results in a classification scheme of different extracts: **other** vs. **quantified** vs. **standardised** extracts (ref. to Ph.Eur.

	monograph on 'extracts' more specifically in 'Guideline on Quality of Herbal Medicinal Products/Traditional Herbal Medicinal Products (CPMP/QWP/2819/00 Rev 1)'. Nonetheless the herbal preparation in its entirety is regarded as the active pharmaceutical ingredient of (T)HMPs. Even though there is a manifold number of chemical compounds in herbal preparations the choice for a marker may be more difficult since these substances • have to be specific for the herbal drug • not only traceable but quantifiable by common analytical methods • but also stable in course of the stability proof. Core characteristics of herbal preparations, herbal products to be controlled in the course of product release and proving its stability are tests on identity and assay. Identity proof is determined in most cases by chromatographic fingerprinting in different polarity sectors and assay by appropriate methods determining pars-pro-toto an specific marker substance. Since from the analytical point of view the total amount of a marker substance in a multi-component mixture is in general orders of magnitude lower compared to the amount to be determined for pure chemically defined actives **the allowed range of variation should be generally expanded to +/-10% of the initial assay value** since as a matter of fact standard deviation is higher in this analytical border area. There might be cases which require an even higher range of deviation to be accepted by the competent authority if justified by the applicant. Regarding standardised extracts where therapeutically active ingredients are known the Guideline on Quality stipulates a range of +- 5% of the declared assay value. Due to the fact that determination of the active markers is affected by other constituents of the extract the deviation of +-5% should be leaning against the initial assay value but not the declared assay value. Likewise for standardised extracts assay is complicated by interacting ingredients present concomitantly in the extract.	

Specific comments on text

Section number and heading	Interested party	Comment and Rationale	Outcome
1. Introduction (background)	AESGP	The manufacturers of herbal preparations and finished medicinal products face challenges when applying the respective EU stability guidelines. We welcome this guideline which will specifically address the characteristics of herbal medicines. We call for pragmatic guidances.	Agreed
2. Problem statement	AESGP	In line 39-40 we suggest to replace the sentence *"… many herbal preparations … are known to be unstable*" by "*most herbal preparations are stable but in some cases problems might occur*". This can be shown by examination of individual cases whose particularities are described below	Not agreed. The background for this reflection paper

		as well as in the above-mentioned publication [1]. • **<u>Case of highly unstable constituents only present in certain herbal preparations and corresponding finished products</u>**: Some native (group of) constituents are known to be highly unstable due to different mechanisms. Amongst them, following examples can be given: 1. **hydrolysis of different acylated glycosides**: • flavonoid derivatives [e.g. 4'''-*O*-acetylvitexin-2''-rhamnoside in hawthorn (*C. monogyna*)] [3, 4]; • triterpenoid derivatives (e.g. acidic malonates of the dammarane saponins in ginseng: malonylginsenosides Rb1, Rb2, Rc and Rd) [5, 6]; • phenolic glucoside derivatives (e.g. salicortin, 2'-*O*-acetylsalicortin, fragilin, populin, tremulacin, … in willow) [7, 8]; 2. **trans-esterific**ation of dicaffeoylquinic acids in artichoke [1,3-dicaffeoylquinic acid (cynarin) is formed as an artefact from 1,5-dicaffeoylquinic acid, cynarin being present only in traces in the fresh or dried herbal drug] [9, 10]; 3. **volatilisation of essential oil constituents** (the higher the volatility of a constituent, the higher its relative loss). Such labile native constituents may undergo transformation or be eliminated at the stage of manufacturing the herbal preparation and not be found in it (e.g. herbal dry extracts) and corresponding finished products. In return, other simply processed herbal preparations as cut or powdered herbal drugs and corresponding finished products (e.g. herbal teas) contain such unstable constituents. For example, in powdered ginseng capsules, the content of ginsenosides Rb1 + Rg1 may increase of ca. 30% (storage for 24 months at 25°C/60% RH and for 12 months at 30°C/65% RH) to 45% (storage for 6 months at 40°C/75% RH) due to hydrolysis of malonylginsenosides Rb1. **Attention should be paid to these herbal preparations and corresponding finished products which may contain particularly unstable constituents not transformed or eliminated during manufacturing process (e.g. cutting or powdering).**	are the problems with unstable herbal preparations / herbal medicinal products. In addition the comments suggest that these products are unstable. Examples considered for Q&A document EMA/HMPC/41500/ 2010
3. Discussion	AESGP	Although many scenarios need to be assessed on a case-by-case basis (line 60), we would appreciate to clarify as many issues as possible in general within the guidance document. In particular, we welcome the mentioned approach of a reduced set of stability tests (line 56). From our point of view this could consist of • The option of group determination (e.g. flavonoids) in case of combination products is a useful tool for the assay during stability testing. Identity of all individual active substances	Agreed Cases added in Q&A document EMA/HMPC/41500/ 2010

		should be shown by chromatographic procedures (e.g. TLC). • In a combination medicine, if one or more active substances are not detectable in the finished product through appropriate analytical means, determination of these active substances during stability testing is not required from our point of view. For the other active substances, however, determination has to be performed. • The use of other methods than those described in the European Pharmacopoeia e.g. the determination of St. John's wort oily extract by a photometric method instead of HPLC should be possible. • It should be possible to substitute the marker described in the European Pharmacopoeia by another one. In this case the stability study with the alternative marker only should be sufficient, e.g. in case of hawthorn berries, the determination of flavonoids instead of oligomeric procyanidins or in case of nettle leaf, the determination of scopoletin instead of caffeoyl malic acid. • Formation of more stable constituents, as hydrolysed acylated glycosides on storage of finished products containing cut/powdered herbal drugs or other herbal preparations, should be considered as an acceptable change and not as a stability indication criterion due to high instability of those glycoside derivatives. • Stability data of only one pilot scale batch for an application for marketing authorisation/registration and only one production batch for post-approval studies, instead of two batches in each of the above-mentioned cases should be sufficient for herbal medicinal products with known active substances. • For active substances (herbal preparations) it should be possible to make reference to stability data obtained from comparable active substances (from the same herbal drug) as far as these active substances are covered by a European Pharmacopoeia monograph. • No stability testing for active substances which meet the specification and which are immediately used for further production after release should be required. • No accelerated (40°C, 75 % RH) and intermediate testing (30°C, 65 % RH) should be needed for active substances (herbal preparations) which are not intended for storage at higher temperatures • We agree that shelf-life specifications should consist of fingerprints and marker content or	

		substance group content (in case of group determinations), respectively. One fingerprint, however, should be sufficient because a second fingerprint does usually not lead to additional information. • Additive effects of analytical variations due to the drug substance/drug product and to the reference substance justify that frequently a shelf-life criteria of +/- 10% of the initial assay value is needed. A general difference of +/- 10 % of the initial value should be accepted in case of analytical markers, in individual cases a higher difference should be possible. • For assays (marker and group determination) mentioned in the EP monograph, a minimum content for analytical markers should be accepted as stability criterion at the end of shelf-life. This might possibly also be extended to other products. Indeed a stability study using minimum values of assays along with identification (eg. TLC) provide sufficient information concerning the quality of the product allowing for the determination of a product shelf life. • Stability overages should be used as far as needed to guarantee stability. We appreciate the list of examples given in the HMPC draft and we would like to comment on these examples as follows: 1) From our point of view, no stability testing should be required for active substances which are immediately used for further production after release if stability of the finished product is proven. 2) It is not appropriate to considerer that the shelf-life specification of an herbal tea made of an essential oil containing cut herbal drug should be in line with the release specification of the corresponding herbal drug according to the Ph. Eur. monograph. Criteria established by the Ph. Eur. monographs deal only with quality of starting materials, essential oil content being in the present case a criterion of freshness of the herbal drug or of the herbal preparation. Due to the fact that simply processed herbal preparations as comminuted herbal drugs and corresponding finished products still contain essential oil, determination of essential oil content may indeed be part of the stability testing but the shelf-life specification deviation from the release specification should only be based on stability evaluation, i.e. the change observed on storage. Additionally, it is not possible to demonstrate via gas or thin layer fingerprint chromatograms that proportional content of essential oil constituents remains comparable to the initial fingerprint due to different volatility of constituents.	

		3) For the same reason as explained under 1), stability testing for the active substance is not required in case of a mixture of cut herbal substances packed in a multi-dose bag. For clarification we would like to state that tea-bags do not belong to the definition of "multi-dose bags". We agree with this proposal which permits a minimum content for analytical markers or substance groups, respectively, as a stability criterion at the end of shelf-life. 4) From our point of view, in case of a ribwort plantain liquid extract with the instable marker acteoside, a general deviation of +/- 10 % of the initial value or – in justified cases – a higher deviation should be accepted.	
3. Discussion	FAH	We would like to answer with the following comments to the questions raised in Examples 1-4 and add one additional example (Example 5): *Example 1:* *A medicinal product is manufactured by a continuous production process comprising the production of the active substance and the production of the finished product. Are stability studies necessary for both the active substance and the finished product?* In case of a continuous production process the stability testing should only be performed on the herbal medicinal product. *Example 2:* *A herbal tea consists of a mixture of cut herbal substances packaged in a multi-dose bag. Are comprehensive stability studies necessary for both the active substances and the finished product?* This question is unclear. *Example 3:* *A herbal tea consists of an essential oil containing cut herbal substance (e.g. peppermint leaves). The change in the assay from the initial value is higher than 20%, but the essential oil content at the end of the shelf-life is in line with the Ph. Eur. Monograph.* A decrease in essential oil content of 20% should be accepted as long as the determined value at the end of shelf-life is in line with the Ph. Eur. Monograph. In principle this should be accepted for all monographed herbal preparations. *Example 4:* *An analytical marker is stable in the herbal substance (Pharmacopoeia monograph) and in solid dosage forms, but unstable in some liquid dosage forms (e.g. Acteoside as analytical marker of ribwort plantain [Plantago lanceolata L.]).*	Examples considered for Q&A document EMA/HMPC/41500/ 2010

		The analytical marker for the liquid extract is not appropriate. A new marker should be chosen. *Example 5:* *A) In the case of Melissa (Melissa officinalis L.) extracts rosmarinic acid is often used as an analytical marker for the determination of the extract content in finished formulations (batch related control). Especially in liquid formulations rosmarinic acid is unstable and leads to rapid OOS values during stability.* *B) In the case of stinging nettle (Urtica dioica L.) root extracts scopoletin is often used as an analytical marker. Despite of its very low concentration in the ppm range scopoletin may easily be detected by fluorescence detection. Depending on the formulation scopoletin may cause significant OOS results.* In both cases it is not easy to find alternative analytical markers, at least characteristic ones. Thus, in such cases it should be allowed to use analytical markers belonging to non-characteristic groups like carbohydrates, amino acids, aliphatic acids, etc. Their selection should be justified by the applicant and should allow a specific determination in the presence of other constituents. As usual the corresponding analytical method should be fully validated.	
4. Conclusions	AESGP	We welcome the fact that guidance will be developed based on comments and examples submitted by interested parties (line 85). Some examples for cases where problems in stability testing occur and how these problems can be resolved by pragmatic approaches, are included in the attached publication [1]. These examples focus on finished herbal medicinal product because problems during stability testing are more likely to occur for these products (combination of herbal preparations, matrix effects, interaction with excipients etc.). The arguments presented in the paper [1] might serve as a substantiation of the term "if justified" in the respective Notes for Guidance, e.g. in case a difference of ± 10 % of the initial assay values required in long-term studies. Exemplary models for this issue might be the described dosage forms with hop strobile dry extract, valerian root dry extract, hawthorn leaf and flower dry extract, garlic oil macerate and ribwort plantain liquid extract. Furthermore, there are justified individual cases in stability testing, in which an extension of the specification range to more than ± 10 % is necessary. Examples for justifications are presented by means of the mentioned dosage forms with St. John's wort dry extract (analytical marker: hypericin) and hawthorn leaf and flower liquid extract. In addition, a stability overage can be necessary in individual cases in order to achieve a marketable shelf-life. An exemplary, product-specific justification is given here by means of a dosage form with hop strobile dry extract. In addition, it should be possible in the individual case to justify the necessity of a stability	Examples considered for Q&A document EMA/HMPC/41500/ 2010

		overage on the basis of the present data evaluation if the initial assay value remains under 90 % in a long-term study, which would not result e.g. in a practically oriented shelf-life. The evaluation of the results can also substantiate statements on the stability of markers. Finally, the choice of more functional analytical markers should also be possible. This is of particular importance in cases when the markers, which are specified in a pharmacopoeia monograph, are not suitable for stability testing. For this reason, flexibility should be given in the choice of marker. Some markers are known to be unstable hence not relevant for making a statement on the quality of the product as they cannot “follow” the global quality of the product throughout its proposed shelf-life. An example is St. John's wort dry extract, in which the stability testing with the analytical marker hypericin is pointless, whereas the analytical marker rutoside yields good results in the presented case. The example of a Melissa liquid extract might show that rosmarinic acid does not meet the definition of a suitable marker. Although it is described as analytical marker in the European Pharmacopoeia, it acid decomposes rapidly due to its physico-chemical properties. This can be demonstrated by the enclosed table, figure and chromatograms. Finally, we would like to express our wish that it should be generally accepted that active substances meeting the specifications and used for the production of finished products can be used for purpose of stability testing without a limitation of time.	