European Medicines Agency
Inspections

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE "GUIDELINE ON QUALITY OF HERBAL MEDICINAL PRODUCTS/TRADITIONAL HERBAL MEDICINAL PRODUCTS

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Organisation
1	German Pharmaceutical Manufactures Research Association (FAH) – Working party on Herbal Medicinal Products
2	Association Européenne des Spécialités Pharmaceutiques Grand Public (AESGP)
3	THE HERBAL FORUM
4	European Herbal Practitioners Association (EHPA)
5	British Pharmacopoeia Commission
6	International Register of Consultant Herbalists and Homoeopaths (IRCH)
7	IFAH

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Table 2:Discussion of comments

GENERAL COMMENTS - OVERVIEW
- the specific character of herbal substances/preparations and herbal medicinal products has not been adequately taken into consideration; - it should be mentioned, that the Guideline has been elaborated and discussed in the Committee on Herbal Medicinal Products; - because of the many overlaps between this Guideline and the Guideline on specification it is suggested to merge them (at a future revision for example) into a single document; - it would be useful to adapt the structure of this guideline as well as the headings to the structure of the Common Technical Document (CTD); - as a general rule, it is suggested, to replace the term 'finished product' by 'herbal medicinal product'
- it is believed, that many traditional Herbal Medicinal Products will not be able to meet the Guideline requirements; - stability testing of the final product should focus on microbial, physical and finger-print chromatographic testing and only the quantification of active (when claimed), or marker (where available) for single-herbal products or those containing few herbal actives; - THMP have a long tradition of safe use and the quantification of actives would only be necessary as a potential indicator for efficacy which again is accepted for THMP by evidence of traditional use; - pharmacovigilance should support this proposed quality and safety model
- quality guidelines for THMP should be specifically designed to recognise the characteristics and meet the needs of THMP, this should not be taken to be exactly the same as those of herbal medicinal products; - because of the fact, that many THMP are multi-herb preparations, it is submitted, that the relatively rigid standards being implemented by these Guidelines are proving, technically very difficult and in many cases unworkable in practice; - quality control measures which are formulated in the Guideline (e.g. if a herbal medicinal product contains a combination of several herbs, the determination may be carried jointly for several active substances with appropriate chromatographic methods) are relatively easy to carry out for an orthodox drug which contains a single chemical entity or for a single herbal compound for which guidelines were originally designed but often impossible to demonstrate when evaluating a complex herbal mixture of several herbs each one containing a multiplicity of chemical signatures, so the proposed Guidelines must be adapted so that they can apply to complex herbal mixtures; - quality and safety of multi herb products should be assured by the identification and control of the raw materials of these products rather than by the quantitative testing of the end product; - stability testing of the final product should focus on microbial, physical and finger-print chromatographic testing and only require the quantification of claimed active(s) or marker(s) for solely for single-herbal products where appropriate; - the quantification of actives is not necessary for establishing a safety profile because THMP must have demonstrated a good safety profile over many years and it is not necessary for the establishment of efficacy, since the basis of efficacy for the THMP is traditional use; - pharmacovigilance should support this proposed quality and safety model
-one company considers the proposed Guideline on quality standard as far too rigid, and in many cases, cannot be put into practise
-another company approves the proposed revision

1 INTRODUCTION		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	The statement "the quality of a herbal medicinal product is independent of its traditional use" is endorsed. It is pointed out, that both product quality and patient safety of traditional herbal medicines would be better achieved by the application of the principles of GMP and the rigorous and detailed definition of the herbal starting materials.	(1) not agreed In article 16c(1)a of Directive 2001/83/EC it is pointed out, that the application of a THMP shall be accompanied by the results of the pharmaceutical tests referred to in the second intent of article 8(3)(i). There are results of pharmaceutical (physico-chemical, biological or microbiological) tests in accordance with Annex 1 demanded. GMP and detailed information of the herbal starting material are always necessary in the production of herbal medicinal products.

2 SCOPE		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	The twin principles of GMP and the rigorous and detailed definition of the herbal starting material as the key to achieve quality and safety of Traditional Herbal Medicinal Products is fully supported.	(2) not agreed In article 16c (1)a of Directive 2001/83/EC it is pointed out, that the application of a THMP shall be accompanied by the results of the pharmaceutical tests referred to in the second intent of article 8(3)(i). There are results of pharmaceutical (physico-chemical, biological or microbiological) tests in accordance with Annex 1 demanded. GMP and detailed information of the herbal starting material are always necessary in the production of herbal medicinal products.

3 QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCE(S) OF A HERBAL MEDICINAL PRODUCT		
Line no. + para no.	**Comment and Rationale**	**Outcome**
first four sentences	The paragraph should get deleted	(3) not agreed The definition of the used terms should be given in the beginning. The following wording was accepted after discussion in the Quality Drafting Group (QDG) and the HMPC: 'All herbal substances/herbal preparations are essentially defined by their production process and their specifications. Standardised herbal substances or standardised extracts are adjusted to a given content of constituents with known therapeutic activity within an acceptable tolerance; standardisation is achieved by adjustment of the herbal substances/preparations with excipients or by blending batches of herbal substances and/or herbal preparations. Quantified herbal substances/preparations are adjusted to a defined range of constituents (active markers); adjustment is exclusively achieved by blending batches of herbal substances and/or herbal preparations. Other herbal preparations are active substances for which neither constituents with known therapeutic activity nor active markers are known. Other herbal preparations are not adjusted to a defined content of analytical marker. The same applies to other herbal substances. In cases where excipients for the manufacture of active substances are used (e.g for technological reasons or for adjustment of standardised herbal substances/preparations), the name and the quantity of these excipients have to be stated.'
page 3/9 – 1st paragraph – 2nd sentence	It is stated that standardised extracts are herbal preparations that have a given content of constituents with known therapeutic activity. Since it is a prerequisite that the therapeutic activity of the constituents of a standardised extract is known the following is requested: 2.(i) standardised extracts:	(4) agreed; see also (7)

	'If the constituents with known therapeutic activity are known' is to delete	
2nd paragraph	The information on the drug extract ratio is essential for a correct declaration of a herbal drug preparation produced by extraction. Thus, for transparency reasons, it is not useful to give the equivalent quantity of the herbal drug within the declaration. Therefore the respective paragraphs under 3.2(i), (iia) and (iib) dealing with "the equivalent quantity x-y" should be deleted but just leave the drug extract ratio in the text. The same applies to the example.	(5) not agreed It is widespread within the EC to give the equivalent quantity instead of the DER. Therefore it is necessary to give both ways of declaration.
	There is agreement with the existing content as well as the new paragraph 2(iib) on 'other extracts' in relation to Traditional Herbal Medicinal Products.	(6)
2nd paragraph – "2. In the case …"	After the first sentence the text should be reworded as follows: 'Furthermore the following applies or has to be indicated: All herbal preparations are essentially defined by their production process and their specifications. There are three types of extracts described in the European Pharmacopoeia. (i) Standardised extracts: If the constituents with known therapeutic activity are known standardised extracts are adjusted to a given content of constituents with known therapeutic activity within an acceptable tolerance; standardisation is achieved by adjustment of the extract with excipients or by blending batches of herbal substances and/or extracts. The ratio (a-b):1(*) of the herbal substance to the genuine herbal preparation shall be stated and the quantity of the genuine herbal preparation may be given as a range corresponding to a defined quantity of these constituents (see example). or (iia) Quantified extracts are extracts with constituents generally accepted to be relevant for efficacy and safety (active markers). Quantified extracts are adjusted to a defined range of constituents; adjustment is exclusively achieved by blending batches of herbal substances and /or extracts. The ranges should reflect those of the clinical batches. The ratio (a-b):1(*) of the herbal substance to the genuine herbal preparation shall be stated. Furthermore the content of	(7) partly agreed in combination with (3) and (5) 'In the case of a herbal preparation produced by steps which exceed comminution, the nature and concentration of the solvent and the physical state of the extract have to be given. Furthermore the following has to be indicated: (i) Standardised extracts: the equivalent quantity of the herbal substance x-y (*), or the ratio (a-b):1(*) of the herbal substance to the genuine herbal preparation shall be stated and the quantity of the genuine herbal preparation may be given as a range corresponding to a defined quantity of these constituents (see example). (iia) Quantified extracts: the equivalent quantity of the herbal substance x–y(*), or the ratio (a–b):1(*) of the herbal substance to the genuine herbal preparation shall be stated and the quantity of the genuine herbal preparation has to be given as a distinct content. Furthermore content of the quantified substance(s) shall be specified in a range. (iib) Other extracts: The equivalent quantity of the herbal substance x-y(*), or the ratio (a-b):1(*) of the herbal substance to the genuine herbal preparation shall be stated and the quantity of the genuine herbal preparation has to be given as a distinct content. *) 'a' and 'b' or 'x' and 'y' have to be justified by the applicant

	the quantified substance(s) shall be specified in a range. or (iib) Other extracts are extracts where neither constituents with known therapeutic activity nor constituents contributing to efficacy and safety are known. Other extracts are not adjusted to a defined content of analytical marker. The ratio (a-b):1(*) of the herbal substance to the genuine herbal preparation shall be stated. (*) 'a' and 'b' have to be justified by the applicant The composition of any solvent or solvent mixture and the physical state of the extract must be indicated.' *Comments:* *In (i) "excipients" might be replaced by "inert materials".* *In order to increase transparency and comparability of marketed herbal medicinal products, only one type of labelling should be approved. Labelling of the genuine amount of herbal preparation in mg is preferred instead of per cent values. The labelling of the corresponding amount of herbal substance is discouraged.* *The terms Solvent and Solvent Mixture are interpreted as Extraction Solvent and Extraction Solvent Mixture by means of the proposed amended Glossary.*	The composition of any extraction solvent or extraction solvent mixture and the physical state of the extract must be indicated.' not agreed. The term 'inert materials' is not defined. see (5) agreed
2nd paragraph – "2. In the case …"	The examples should be given as follows: 'Example 1: Standardised Extracts The following characteristics should be stated: 1. Name and physical state of the extract 2. Quantity of the genuine extract (usually as range) (mg) 3. Defined quantity of the constituent(s) with known therapeutic activity (mg) 4. Herbal substance to extract ratio as a range (DER genuine) 5. Extraction solvent(s) [%(V/V) or % (m/m)] 6. Name of excipient(s) used for the adjustment Details from the extract manufacturer e.g. in the extract specification:	(8) not agreed In respect for the readability of the Guideline, such comprehensive formulation of the examples should be avoided. There is a specific Guidance on Declaration in preparation, so that such broad information should be given there.

	Dry extract from horse chestnut seed Constituents(s) with known therapeutic activity: 19% triterpene glycosides, calculated as anhydrous β-aescin Quantity of the genuine extract: 70-95% genuine extract DERgenuine: 5-8:1 Extraction solvent: Methanol 80% (V/V) Excipients for adjustment: 30 - 5% Excipients Labelling of the herbal medicinal product containing e.g. 200 mg extract (including excipients): 1 capsule (200mg) contains: Active substance: 140 -190 mg of dry extract from horse chestnut seed (5-8:1) corresponding to 38mg triterpene glycoside, calculated as anhydrous β-aescin Extraction solvent: Methanol 80% (V/V) Example 2: Quantified Extracts The following characteristics should be stated: 1. Name and physical state of the extract 2. Defined quantity of the genuine extract (mg) 3. Herbal substance to extract ratio as a range (DERgenuine) 4. Extraction solvent(s) [%(V/V) or % (m/m)] 5. Content of the quantified constituents(s) as a range (mg) 6. Name of excipients if used Details from the extract manufacturer e.g. in the extract specification: Dry extract from ginkgo leaf Defined quantity of the genuine extract: 100% genuine extract DERgenuine: 35-67 : 1 Extraction solvent: acetone 60% (m/m) The extract is quantified to: 22.0 to 27.0% of flavonoids expressed as flavone glycosides 2.8 to 3.4% of ginkgolides A,B and C 2.6 to 3.2% of bilobalide	

	not more than 5 ppm ginkgolic acids Excipients: No excipients Declaration of the herbal medicinal product: 1 capsule contains: Active substance: 60mg of dry extract from ginkgo leaf (35-67:1) corresponding to: 13.2 to 16.2 mg of flavonoids expressed as flavone glycosides 1.68 to 2.04 mg of ginkgolides A,B and C 1.56 to 1.92 mg of bilobalide not more than 0.3 µg ginkgolic acids Extraction solvent: acetone 60% (m/m) Example 3a: Other Extracts such as dry extract The following characteristics should be stated: 1. Name and physical state of the extract 2. Defined quantity of the genuine extract (mg) 3. Herbal substance to extract ratio as a range (DERgenuine) 4. Extraction solvent(s) [%(V/V) or % (m/m)] 5. Name of excipients used Details from the extract manufacturer e.g. in the extract specification: Dry extract from valerian root Defined quantity of the genuine extract: 80% genuine extract DERgenuine: 3 - 6 : 1 Extraction solvent: Ethanol 70% (V/V) Excipients : 20% Excipients Declaration of the herbal medicinal product 1 capsule (200 mg) contains: Active substance: 160mg of dry extract from valerian root (3 - 6 : 1) Extraction solvent: Ethanol 70% (V/V) Example 3B: Other Extracts such as liquid extract The following characteristics have to be stated: 1. Name and physical state of the extract	

	2. Quantity of the genuine extract (including extraction solvent) [g] 3. Herbal substance to final extract ratio (DERgenuine) as a constant amount (without range) 4. Extraction solvent(s) [%(V/V) or %(m/m)] Details from the extract manufacturer e.g. in the extract specification: Liquid extract from Chamomile flowers (Ph.Eur. 5.1) Quantity of the genuine extract: 100% genuine extract DERgenuine: 1:1 Excipients: 0% Extraction solvent: 2,5 parts of ammonia solution 10% (m/m) 47,5 parts of water (defined potable water) 50 parts of ethanol 96% (V/V) Declaration of the Herbal Medicinal Product 100 g (≅ … ml) of oral solution contain: active substance: 100 g of liquid extract from matricaria (1:1) extraction solvent: ammonia solution 10% (m/m) / water / ethanol 96% (V/V) (2,5/47,5/50) Example 3c: Other extracts such as tinctures The following characteristics should be stated: 1. Name and physical state of the extract 2. Quantity of the genuine extract (including extraction solvent) (g) 3. Herbal substance to extraction solvents ratio or Herbal substance to final extract ratio (DERgenuine) 4. Extraction solvent(s) %(V/V) or % (m/m) 5. Name of excipients used Details from the extract manufacturer e.g. in the extract specification: Tincture from valerian root (German Pharmacopoeia 2003) Quantity of the genuine extract : 100% genuine extract	

	Herbal substance to extraction solvent ratio: 1 : 5 or Herbal substance to final extract (tincture) ratio: 1: 4-4.5 Excipients: No excipients Extraction solvent: Ethanol 70% (V/V) Declaration of the herbal medicinal product 5g (…ml) of oral solution contain: Active substance: 5g of tincture from valerian root (1 : 5) Extraction solvent: Ethanol 70% (V/V) or 5g (…ml)of oral solution contain: Active substance : 5g of tincture from valerian root (1 : 4 - 4,5) Extraction solvent: Ethanol 70% (V/V) *Comments:* *For tinctures: Fixed values without a range indicate the ratio of herbal substanceto extraction solvent. If a range is given for the DERgenuine of a tincture, the DER reflects the ratio of herbal substance to genuine extract.*	
2nd paragraph – "2. In the case …"	After the examples a table should be given, which shows the different types of extracts and gives information to: Adjustment of the content Marker characteristic for type of extract Characteristic of the marker Release specification (Marker and Genuine extract) Shelf life specification	(9) not agreed, see (8)
example – page 5/9	iia) Ginkgo biloba L. folium The correct chemical term for a flavone glycoside is a flavonoid. A flavonoid lacks C2-C3 double bond. Therefore the following is requested: Correct 'flavanoids' to 'flavonoids'	(10) agreed

4 DESCRIPTION OF THE METHOD OF PREPARATION		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	There is agreement with the content including the new reference to vitamins/minerals.	(11)
1st and 2nd sentence	The wording 'finished product' should be substituted by 'herbal medicinal product'.	(12) agreed

5 CONTROL OF STARTING MATERIALS – 1 CONTROL OF HERBAL SUBSTANCES AND OF HERBAL PREPARATIONS		
Line no. + para no.	**Comment and Rationale**	**Outcome**
1st bullet point – Control of herbal substances – 3rd paragraph, 1st sentence	There is a principally agreement with the inclusion of heavy metals, pesticides, fumigants, mycotoxins and microbial contamination in the general concept for the quality of herbal substances/preparations. It should be deemed sufficient to perform such tests in case of suspect and not on a routine basis, e.g. when pesticides have not been used during cultivation, testing for potential residues should not be required, or in case a reduction of microbial load can be demonstrated during extraction, the Ph. Eur. limits (category 4a) might be exceeded by the raw material. Proposal: to rewording the sentence as follows: 'Unless otherwise justified, herbal substances must be tested for microbial quality …'	(13) not agreed The testing of pesticides is necessary, even when pesticides have not been used during cultivation, because there might be an entry from other fields. Therefore the routine basis should be standard and individually exceptions can be done. This should be justified in the special applications. This is valid for the test of microbial contamination, too.
1st bullet point – Control of herbal substances – 3rd paragraph,	It is stated that analytical procedures not given in a Pharmacopoeia should be validated. A number of officially accepted methods and standards, e.g. WHO-/Codex Alimentarius or the German DFG § 35 methods, are not taken into consideration. The following wording is suggested: 'Analytical methods not given in a Pharmacopoeia or in an official	(14) partly agreed, The following wording was accepted after discussion in the QDG and the HMPC: 'Analytical procedures not given in a Pharmacopoeia should be validated in accordance with the ICH guideline 'Validation of analytical procedures: methodology' (CPMP/ICH/281/95) or the corresponding

last sentence	collection of analytical methods providing suitable statistical data on quality of the methods should be validated.'	VICH guideline (CVMP/VICH/591/98), unless otherwise justified.'
Control of herbal substances – page 6/9 - 1st paragraph, last sentence	It is requested either that 'scientific name' be changed to 'botanical scientific name (i.e. genus, species, subspecies, variety and author) …' or a definition of scientific name be given in the Glossary.	(15) agreed, for a uniform wording within the official documents the following wording which is based on Annex 1 of the Directive 2001/83/EC was accepted: 'The binomial scientific name of the plant (genus, species, variety and author), chemotype (where applicable) and name of its parts have to be stated.'
Control of herbal substances – page 6/9 – 2nd paragraph, 2nd sentence	It is requested that 'This should include the botanical name and authority and the common name, if used, for labelling purposes' is changed to: 'This should include the botanical scientific name, authority, plant part and the common name, if used, for labelling purposes.'	(16) agreed, see (15)
Control of herbal substances – page 6/9 – 2nd paragraph, 4th sentence	'The comprehensive specification should be established on the basis of recent scientific data.' 'Recent scientific data' implies use of sophisticated and expensive methodologies such as LC-MS and ^{13}C-NMR which may not be readily available to manufacturers. Is this implication intended?	(17) The term 'recent scientific data' implies that a specification has to be chosen which are widely accepted and which reflect the particularities of the specific item. This can also include the mentioned methodologies, depending on the herbal substance/preparation which needs to be specified.
Control of herbal substances – page 6/9 – after the 2nd paragraph	Inclusion of the following sentence after the 2nd paragraph is suggested: 'Where herbal substances may have been processed to de-nature or reduce the concentration of toxic components, assays of these components (and test procedures) are required.'	(18) not agreed, in the chapter it is referred to a "comprehensive specification", the content of such specification also in terms of toxicological relevant degradation products, is defined in the "CPMP/QWP/2820/00 rev.1".
1st bullet point – Control of herbal substances –	The following wording is suggested: 'The content must be included as a minimum content, so as to ensure reproducibility of the quality of the herbal medicinal product. In the case of herbal substances with one or more specified active markers,	(19) not agreed For standardised herbal substances a range of constituents with known therapeutic activity are necessary. For herbal substances where constituents of known therapeutic activity

2nd paragraph, 6th sentence	assays of their content (with test procedure) are required. In the case of herbal substances where constituents of known therapeutic activity are not known, assays of marker substances (with the test procedures) could be required, for example if a comminuted or powdered herbal substance is mixed in the herbal preparation or the herbal medicinal product. The choice of the analytical marker should be justified.' *Comments:* *Range of constituents: In the past never a range has to be specified; only a minimum content which is sufficient to ensure reproducibility of the quality and consistent with the EP monographs.* *It's our understanding that an assay of analytical marker is only needed for batch specific control which is with herbal substances not performed if the drug substance is further processed e.g. extracted. However in some cases batch specific control might be necessary.*	are not known a specification in the same way as the monographs of the European Pharmacopoeia are required (s. same paragraph 1st sentence). Therefore a content of marker substances has to defined and a assay has to be provided. Even in the "CPMP/QWP/2819/00 " (the former version) the content had to be included as a range for standardised herbal substances.
2nd bullet point – Control of herbal preparations – 3rd paragraph, last but one sentence	It is proposed to delete the mention of 'upper limit' for analytical marker substances because markers have to be present in a concentration which permits analytical determination; an additional upper limit is not realistic in practise.	(20) not agreed The upper limit results from the validation and can be given.
2nd bullet point – Control of herbal preparations – 3rd paragraph, 6th sentence	The following wording is suggested: 'In the case of constituents with known therapeutic activity the content must be indicated within an appropriate tolerance with both upper and lower limits stated. In the case of active markers used for quantified extracts the content of this (these) marker(s) has(have) to be given as a defined range, reflecting the range of clinical batches initially derived from the natural variation of the herbal substance and the production process. In the case of an analytical marker of an extract for which neither constituents of known therapeutic activity, nor active markers are known, the specified minimum and maximum content is related to the validated range as a base for analytical suitability within the frame	(21) partly agreed, The following wording was accepted after discussion in the QDG and the HMPC: 'For standardised herbal preparation, the content of constituents with known therapeutic activity must be indicated with the lowest possible tolerance (with both upper and lower limits). In the case of active markers used for quantified extracts the content of the markers has to be given as a defined range. In the case of an analytical marker of an extract for which neither constituents of known therapeutic activity, nor active markers are known, the specified minimum and maximum content is related to the validated analytical range as a base for analytical suitability

	of batch related control. The test methods should be described in detail.' *Comment:* *The tolerance or range must be related to the intended use and the manufacturing process (batch data), this does not need to be "the narrowest possible tolerance".*	within the frame of batch related control. The test methods should be described in detail.' For safety and quality reasons it should be the narrowest possible tolerance.
control of vitamins and minerals	There is generally agreement with the content of this section relating to starting materials including the new paragraph 2 on 'Control of vitamins & minerals'.	(22)
control of excipients	In relation to the "Control of excipients" used in Traditional Herbal Medicinal Products, excipients which are included in other Pharmacopoeia (US, Chinese, Indian) as well as additives approved in Europe for food use by Directive 95/2 (as amended) should be allowed. Such excipients would not be categorised as 'novel ingredients'.	(23) not agreed According to Annex 1 of the Directive 2001/83/EC chapter 3.2.2.4. "Control of excipients" there are exact demands for novel excipients when used the first time in a medicinal product.

6 CONTROL TESTS CARRIED OUT AT AN INTERMEDIATE STAGE OF THE MANUFACTURING PROCESS OF THE FINISHED PRODUCT

Line no. + para no.	Comment and Rationale	Outcome
	There is agreement with this section.	(24)
Headline	The wording 'finished product' should be substituted by 'herbal medicinal product'.	(25) agreed

7 CONTROL TESTS ON THE FINISHED PRODUCT

Line no. + para no.	Comment and Rationale	Outcome
Headline	The wording 'finished product' should be substituted by 'herbal medicinal product'.	(26) agreed
1st paragraph	There are a number of references in the 'Note for Guidance on specifications and control tests on the finished product (Eudralex	(27) not agreed

	3AQ11A) which should not be necessary applied to the control of finished Traditional Herbal Medicinal Products. These include: The requirement that each active ingredient should be measured and controlled to +/- 5% in the finished product is inappropriate and unachievable for herbal actives in Traditional herbal Medicinal Products except when the active is standardised. The requirement to identify and assay excipients in Traditional Herbal Medicinal Products is unnecessary when controlled by application of GMP. Pharmaceutical tests such as dissolution are unnecessary for Traditional Herbal Medicinal Products but other physical parameters such as weight variation, hardness and disintegration should be controlled.	According to Annex 1 of the Directive 2001/83/EC chapter 3.2.2.5. "Control of the finished medicinal product" the maximum acceptable deviation in the active substance content of the finished product shall not exceed +/- 5% at the time of manufacture, unless justified. see (23). The identification and the determination of the content of excipients usually are not necessary, except for colouring agents and antioxidants/preservatives. According to the "Note for Guidance on specifications" the test for in-vitro active ingredient release can be omitted in the case of immediate release herbal medicinal products and without constituents with known therapeutic activity.
2nd paragraph	The wording "a specification should be provides and this may include the use of markers …." does not provide details on the number of markers required. The use of one marker is sufficient to characterise a herbal preparation. The rephrasing of the sentence is suggested as follows: 'A specification should be provided and this may include the use of a marker substance which is able to characterise the respective herbal preparation.'	(28) not agreed, (see 29)
2nd paragraph – 1st and 2nd sentence	Instead of the first two sentences the following wording is suggested: 'The control tests on the herbal medicinal product must be such as to allow the qualitative and quantitative determination of the active substance(s) and a specification has to be given. In each case a batch related control of the content of the extract via a marker has to be carried out: By determination of the content of the chosen marker in the herbal preparation and in the herbal medicinal product the actual amount of the herbal preparation in the herbal medicinal product may be calculated allowing to verify the batch formula for the batch release. In the case of a herbal medicinal product containing a standardised extract generally constituents with known therapeutic activity are used	(29) partly agreed The following wording was accepted after discussion in the QDG and the HMPC: 'The control tests on the finished product should allow the qualitative and quantitative determination of the composition of the active substance(s). A specification should be provided and this may include the use of markers where constituents with known therapeutic activity are unknown.'

	as marker for batch specific control. In the case of a herbal medicinal product containing a quantified extract generally active markers are used as marker for batch specific control. The range(s) of the active marker(s) in the herbal preparation must be part of the release specification. Since "quantified extracts" may not be standardised to the defined range of the active marker by adding inert excipients and additionally the batch formula shall state a defined amount of the genuine extract, the range for the content of the active marker will typically be much larger than ± 10%. In the case of a herbal medicinal product containing an other extract analytical markers are used as marker for batch specific control."	The proposed sentence "Since "quantified extracts" may …much larger than +/- 10%." is not acceptable, because ranges for the content of the active marker exceeding +/- 5% are not supported, see (27).
2nd and 3rd paragraph	The control tests on the finished Traditional Herbal Medicinal Products should be modified to remove the need for quantification of each herbal active except when claimed in the final product and in shelf-life testing. Degradation products are equally often unknown and are similarly not indicating as causing and adverse effects in use. Identification and quantification of some of these chemical substances would not necessarily achieve any greater quality or safety of the product. The identification and measurement of all vitamins and minerals should be removed from these Guidelines for Traditional Herbal Medicinal Products. The assay of a proportion of measurable 'indicator' vitamins/minerals should be included otherwise the levels at release should depend on application of GMP and the results of earlier stability trials.	(30) not agreed According to article 8 of the Directive 2001/83/EC the qualitative and quantitative particulars of all the constituents of the medicinal product must be included in an application for a marketing authorisation. Because a traditional-use registration shall be refused if the qualitative and/or quantitative composition is not as declared, the quantification of each herbal active needs to be done. For herbal substances/herbal teas see CPMP/QWP/2820 rev.1. There are only a few examples for degradation products in the sense of toxicologically relevant impurities arising from degradation of herbal substances/preparations. Only these need to be monitored (see CPMP/QWP/2820 Rev.1) Identification and measurement of vitamins and minerals is even necessary in food additives. Therefore it should be done in Medicinal products, too.
page 7/9 - 3rd paragraph	It will be difficult to require quality assurance of the finished product that contains several ingredients where quantification is necessary. Assays need to have been developed and validated for each active or marker present in complex mixtures before the end of the transition period in 2011. New methods are undergoing consideration, such as PCR technology, since existing methods, such as HPLC, are not likely	(31) see (30) PCR could only be used for identification because usually there are not suitable for quantitative measurement.

	to be adequate.	
3rd paragraph – 1st sentence	The following wording is suggested: 'If a herbal medicinal product contains a combination of several herbal substances or preparations of several herbal substances, and if it is not possible (by best effort) to perform a quantitative determination of each active substance, the determination may be carried out jointly for several active substances.' *Comment:* *It's our understanding that "possible" would mean by best effort not by any effort, may be this should be explained concisely.*	(32) not agreed The wording 'by best effort' should not be given.
4th paragraph	There is agreement with this content on the microbiological quality of finished Traditional Herbal Medicinal Products.	(33)

8 STABILITY TESTS		
Line no. + para no.	**Comment and Rationale**	**Outcome**
page 8/9 – 2nd paragraph, last sentence	'The appropriateness of the tests shall be justified by the applicant.' This is applicable for herbal medicinal products in which the active ingredient can be assayed. The suitability of products relying on the assay of a marker compound within 10% of the initial assay is questioned. Marker compounds may have a different stability to the 'unidentified' active ingredient. A shelf-life limit may be more appropriate for these products.	(34) It is improper to postulate a general shelf-life limit for THMP. Individual stability data have to be presented (see Annex 1 of the Directive 2001/83/EC chapter 3.2.2.8 "stability of the finished medicinal product").
2nd paragraph – last sentence	The following wording is suggested: 'It should also be demonstrated that their proportional content remains comparable to the initial fingerprint'.	(35) agreed
2nd paragraph – last sentence	Herbal substances/preparations are very complex mixtures of substances. In most cases such substances exist in relatively low amounts and can contain isomers which are difficult to isolate. In many cases, shifting reactions might occur within groups of substances, which	(36) not agreed, see (35)

	do not influence the quality of the respective product. Variations in content of these substances appearing on fingerprint chromatograms can be explained and do not affect the quality of the final product. The wording should be changed as follows. 'The fingerprint chromatograms should demonstrate that the composition is comparable (or "similar").'	
4th paragraph	There is principally an agreement in the principle that a variation in marker content during the proposed shelf-life of +/- 10% of the initial value can be accepted if justified. There might be individual cases e.g. for traditional herbal medicinal products and/ or combinations, where a variation of +/- 10% of the initial value is not sufficient, although many attempts have been made to optimize galenic preparationa as well as analytical methods. It is suggested to add the following sentence: 'In eventual cases of wider variations, these have to be justified by the applicant based on individual data.' In addition, the option to use an overage (which has to be justified) should be taken into consideration.	(37) not agreed According to CPMP/QWP/122/02, rev. 1 the variation in content during the proposed shelf-life should not exceed +/- 5% in general. Due to the particularities of herbal medicinal products, a variation of +/- 10% is accepted, if justified. Wider variations are not supported by the legal framework. The use of overages is regulated in CPMP/QWP/155/96.
4th paragraph – last sentence	The following wording is suggested: In the case of a herbal medicinal product containing a herbal substance or herbal preparation where constituents with known therapeutic activity are unknown (quantified or other extracts), a variation in marker content during the proposed shelf-life of ± 10% of the initial assay value can be accepted in general.'	(38) not agreed Shelf-life specifications with a content variability of +/- 10% must remain an exception. See (37).
Last paragraph	There is agreement with the content of the final paragraph relating to the stability of vitamins & minerals included in Traditional Herbal medicinal Products.	(39)
Last paragraph	Vitamins are in general not very stable. Therefore overages are permitted to be included for production and stability reasons, depending on the galenic form (solid galenic forms or liquids), e.g. as mentioned in the USP for tablets and capsules for Vitamin A, D B12. Vitamins are considered known and well-established substances and do not pose	(40) not agreed We refer to the chapter 1 "Introduction", second paragraph, last three sentences.

	safety problems in quantities close to the RDAs. It is proposed to add. 'The specific character of vitamins and minerals have to be given due consideration when assessing their stability.'	
Additional paragraph	In order to take the specific character of herbal teas/herbal infusion into consideration, the inserting of an additional paragraph (before vitamins and/or minerals) is suggested: 'If a herbal medicinal product which is a herbal tea (or herbal infusion) combined with herbal substances (e.g. combination of herbal teas), the stability of the herbal medicinal tea can be determined by appropriate fingerprint chromatograms and physical and sensory tests or other appropriate tests. In this case the applicant has to justify that it is not possible to determine the stability of each active substance and that overall methods of assay are not applicable.'	(41) not agreed We refer to the 3rd paragraph, where exceptions for combination products are given.
	For Traditional Herbal Medicinal Products, stability indicating tests should only include quantification of the herbal active or marker where claimed in the finished product. Non-specific TLC or HPLC methods should be used as an alternative to indicate any changes during shelf-life determination. There should be no need to carry out extensive analytical method development only to confirm that a quantification of actives, particularly in a multi-herbal combination product, is unachievable. A chromatographic finger-print method should be allowed in such cases.	(42) not agreed, see (41)

ANNEX-GLOSSARY		
Line no. + para no.	**Comment and Rationale**	**Outcome**
page 9/9 – Herbal	It is requested that the last sentence is changed to: 'Herbal substances are precisely defined by the plant part used and the	(43) not agreed, see (15)

substances	botanical name according to the binomial system (genus, species, Subspecies, variety and author).'	
	The following definitions should be added: '**Active markers:** are constituents or groups of constituents which are generally accepted to be relevant for efficacy and safety.' '**Analytical markers:** are constituents or groups of constituents that exclusively serve for analytical purposes.' '**Extraction solvents:** are solvents which are used for the extraction process.' '**Fixed Combination:** A herbal medicinal product which contains more than one herbal preparation or herbal substance.' For the definition on standardisation a foodnote should be added: '[1]In some Member States the expression "standardisation" is used on a national level to describe all measures which are taken during manufacturing process and the quality control leading to a reproducible quality.'	(44) partly agreed, see (45) The footnote should not be given, because the terms are defined by the European Pharmacopoeia and should be used in that sense.
	The following wording is suggested for the definitions of: **Herbal substances:** are mainly whole or fragmented plants, parts of plants, algae, fungi, lichen in an unprocessed state, usually dried but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binominal system (genus, species, variety and author). *Comment:* *It's our understanding that Herbal Substances are unprocessed, which is in line with the definition provided by the EP. The process of cutting results in a Herbal Preparation. Linseed and Psyllium seed are examples for uncut Herbal Substances. This is however inconsistent with 2001/83!*	(45) partly agreed The definition given in the Directive 2001/83/EC and the EP should be used, because this is the legally binding document. The wording should be "are mainly whole, fragmented or cut plants …" The following wording was accepted after discussion in the QDG and the HMPC: "**Genuine (Native) herbal preparation:** refers to the preparation without

	Genuine (Native) herbal preparation: genuine drug extract ratio (DERgenuine): is the ratio of the mass of the herbal substance to the mass of the resulting genuine herbal preparation (genuine extract, formerly called "native extract"), even if for technological reason the genuine herbal preparation is not available. *Comment:* *Soft and liquid extracts and tinctures in their entirety are defined as genuine herbal preparations.* **Markers:** are chemically defined constituents or groups of constituents of a herbal substance which are of interest for control purposes independent of whether they have any pharmacological or therapeutic activity or not. Markers may serve to calculate the quantity of herbal substance(s) or herbal preparation(s) in the herbal medicinal product if that marker has been quantitatively determined in the herbal substance(s) or herbal preparation(s) when the starting materials were tested. (FAH)	excipients, even if for technological reasons the genuine herbal preparation is not available. However, for soft and liquid herbal preparations the genuine herbal preparation may contain variable amounts of (extraction) solvent." "**Ratio of herbal substance to genuine herbal preparation (DER genuine):** is the ratio of the quantity of the herbal substance to the quantity of the resulting genuine herbal preparation. The number (given as the actual range) written before the colon is the relative quantity of the herbal substance; the number written after the colon is the relative quantity of the genuine herbal preparation obtained." "**Markers:** are chemically defined constituents or groups of constituents of a herbal substance, a herbal preparation or a herbal medicinal product which are of interest for control purposes independent of whether they have any therapeutic activity. Markers serve to calculate the quantity of herbal substance(s) or herbal preparation(s) in the herbal medicinal product if the marker has been quantitatively determined in the herbal subtance or herbal preparations. There are two categories of markers: **Active marker:** are constituents or groups of constituents which are generally accepted to contribute to the therapeutic activity. **Analytical marker:** are constituents or groups of constituents that serve for analytical purposes."