European Medicines Agency
Inspections

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE "GUIDELINE ON SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR HERBAL SUBSTANCES, HERBAL PREPARATIONS AND 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 (HF)
4	European Herbal Practitioners Association (EHPA)
5	Louis Womack
6	British Herbal Medicine Association (BHMA)
7	Chinese Herbal Medicine Association of Suppliers (CMAS)
8	Irish Health Trade Association (IHTA)
9	IFAH-Europe
10	International Register of Consultant Herbalists and Homoeopaths (IRCH)
11	Association of Master Herbalists (AMH)

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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 HMPC - there seem to be some inconsistencies regarding the headings of the chapters in the table of contents
- product quality and patient safety of THMP would be better achieved by certain specific guidelines appropriate for such products; - because of the multi-herb character of many THMP quality should be achieved through the identification and control of quality of the raw material rather than through extremely difficult, comprehensive quantitative testing of the end product; - stability testing of the final product should concentrate on microbial, physical and finger-print chromatographic testing and should only include the quantification of the active, or marker in cases of single-herbal products; - for products with a long tradition of safe use the quantification of actives would only be necessary as a potential indicator of efficacy which is accepted for THMP by evidence of traditional use; - the proposed quality and safety model would also be supported by a mandatory pharmacovigilance system
- many THMP are multi-herb preparations, therefore the relatively rigid standards being implemented by these Guidelines are proving technically very difficult and in many cases unworkable in practice; - quality and safety of multi herb products should be assured by the identification and control of the raw materials 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) 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; - quantification is also 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
- supports the proposed revision of the guideline; - a HMP meets certain quantitative standards and often minimal level of markers –these standards and other provisions of GMP certainly apply to HMP registered under 2004/24/EC
- blanket quality requirements are being applied on herbal products regardless of the nature of the product; - general principles of quality which were formulated for APIs are not applicable to multi-component herbal pills

- the approach to quality assurance may not be appropriate for THMP; - is concerned with: - the approach towards development pharmaceutics and the requirements for product characterisation; - ensuring requirements for the production process particularly in respect of the identification of active ingredients and/or marker substances through the production process and in the finished product; - the implication of stability studies; - it is recognised that there is a burden upon manufacturer to ensure that all THMP are produced to a uniform and consistent quality and that quality specifications and production procedures must establish safety and efficacy, but specific quality standards are required to reflect the nature (e.g. trad. herb.) of the preparations used; - insufficient cognisance has been taken of the requirements imposed on production process by working with complex preparations whose precise chemical structure is not traditionally considered necessary to precisely define; - industry does not consider that the lack of precise chemical characterisation of THMP reflects a quality deficiency; - distinction between traditional preparations and those preparations that might fall into the well-established category will primarily be based on clinical data, but this distinction should also reflect additional data on the quality of a preparation
- table of contents: the headline of chapter 3.3 is missing**,** bullet points are missing for 2.2 - the wording 'finished products' should be changed into 'Herbal medicinal products'; - the wording 'marker substances' should be changed into 'marker'
- approves the proposed revision
- proposed standards are far to rigid
- agrees with the general principle proposed that the quality of a medicinal product is independent of its traditional use, nevertheless, it should be recognised that the Guideline was developed for assuring the quality of "well-established use"-products; - the Guideline should be redrafted to to suit the new class of THMP; - many THMP are multi-herb preparations, therefore the relatively rigid standards being implemented by these Guidelines are proving, technically very difficult and in many cases unworkable in practice; - THMP was constructed on a 15/30 year rule which by definition ensures that productss cannot be licensed unless they can prove a good safety record for those years
SPECIFIC COMMENTS ON TEXT

1 INTRODUCTION – 1.1. OBJECTIVE OF THE GUIDELINE

Line no. + para no.	Comment and Rationale	Outcome
2nd paragraph	The insertion 'The quality of a medicinal product is independent of its traditional use; therefore all general principles of quality also apply to traditional herbal medicinal products for human use' negates the whole	(1) not agreed; In article 16c(1)a of Directive 2001/83/EC it is pointed out, that the

	document. It is impossible to apply the standards (which were drawn up for synthetically produced active pharmaceutical ingredients) to naturally occurring (plant) materials.	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.

1 INTRODUCTION – 1.3. SCOPE OF THE GUIDELINE		
Line no. + para no.	**Comment and Rationale**	**Outcome**
final paragraph	The Guidelines as presently stated are not considered to be appropriate as 'universal acceptance criteria'. It seems unreasonable to express an aspiration for new technological development for an established product category that offers within itself no room for product innovation.	(2) not agreed; The need for the described pattern of acceptance criteria is independent of the possibility of product innovation or the estimation of a product category to be more or less established, see (1).

2 GENERAL CONCEPTS - 2.1. CHARACTERISATION		
Line no. + para no.	**Comment and Rationale**	**Outcome**
introductive paragraph	In Traditional Medicine the dosage, formulation and applicability are already by definition defined. For the majority of traditional medicines, it is historic validation by reference to existing analytical procedures and stability data that will be used. The phrase '… may need to be taken into account …' should be replaced by '… can be taken into account…'.	(3) not agreed; Although THMP trace back to known formulations etc., acceptance criteria cannot be endorsed as given "by definition". Even for these products, "historic validation" is never sufficient. Keeping current quality standards need to be proven, see (1). The wording "may need to be taken into account" stresses that data mentioned in this context are only sufficient if information from batches used in pre-clinical/clinical studies or information described in relevant bibliographic data are missing (the former is usually the case for THMP). Historic data can only contribute to the setting of acceptance criteria in combination with other significant data proposed in this context.

2.1.2. Phytochem. Characteris.	Add to "… marker substances" the phrase in parentheses: (where appropriate)	(4) not agreed; Phytochemical characterisation by the use of marker substances is always considered to be necessary.
2.1.2. Phytochem. Characteris.	Nature of data which are required in respect of 2.1.2 will define whether the procedures are appropriate to traditional medicinal products or not. For initial product characterization and for ensuing product specification, further guidance is needed as to the circumstances under which the chemically undifferentiated, herbal substances and/or herbal preparations can be considered to be active and the circumstances under which chemical differentiation should be required. Industry practice focus on quality assurance of raw materials supported by chromatographic evidence for the traditional forms with more detailed ingredient differentiation being applied in general only to more sophisticated extracts.	(5) 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.
2.1.3. Pot. Impur./ Contamin./ Degr. Prod.	The wording under the headline should be changed into: '- Potential impurities: This includes residual solvents and other process related impurities. - Contaminants: This includes heavy metals, pesticides, fumigants etc. - Major impurities: This includes toxicological relevant impurities arising from degradation of herbal preparation (herbal substances) in exceptional cases.'	(6) not agreed; Because of inconsistencies concerning the terms used in context with impurities, e.g degradation products, major impurities, potential impurities, inorganic and organic impurities, (un)identified degradation products, identified impurities, the chapter dealing with impurities has been changed in total and brought in accordance with the Guidelines for chemically defined substances where appropriate. The following wording was accepted after discussion in the Quality Drafting Group (QDG) and the HMPC: "2.1.3.Impurities Impurities can be classified as follows: - impurities arising from starting materials (active substances, excipients) and containers; - process related impurities arising from the manufacturing process. In addition, for herbal substances, herbal preparations and/or herbal medicinal products the following groups of impurities should be addressed, if appropriate: Contaminants, which are impurities such as heavy metals, pesticides,

		mycotoxins, fumigants as well as microbial contamination, including those arising from extraneous sources, and radioactive substances, if relevant. Degradation products, which in the context of this Guideline, - due to the particular nature of herbal substances, herbal preparations and herbal medicinal products, should primarily address toxicologically relevant impurities arising from degradation of herbal substances / preparations. Residual solvents, which are impurities arising from manufacturing processes."
2.1.3. Pot. Impur./ Contamin./ Degr. Prod.	Degradation products should not be included in the general quality concept of both THMPs and HMP. Identification and measurement of degradation products should be removed for THMP (AMH). These tests cannot be justified in absence of safaty concerns.	(7) not agreed; See (6). At least toxicologically relevant degradation products need to be included.
2.1.4. Biol. Var.	The text should be changed into: 'Includes historical batch data and published information concerning biological variation for justification of specification.'	(8) agreed The following wording was accepted after discussion in the QDG and the HMPC: "Includes the use of historical batch data and published information concerning biological variation for justification of specification."
2.1.4. Biol. Var.	The meaning of this point, especially of the "historical batch data" should be clarified by the legislator.	(9) not agreed; There is no need for further clarification.

2 GENERAL CONCEPTS – 2.3. PHARMACOPOEIAL TESTS AND ACCEPTANCE CRITERIA		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	The following sentence should be added: "If the European Pharmacopoeia does not contain a monograph for a herbal substance or a herbal preparation, other pharmacopoeias, e.g.	(10) not agreed; The chapter "Pharmacopoeial tests and acceptance criteria" of the guideline refers to both general methods and monographs and to specific

	national pharmacopoeias from European countries or the USP can be used as a reference."	monographs for particular herbal substances/preparations of the EP. According Annex 1 of Directive 2001/83/EC (Introduction and general principles, (5)), all monographs including general monographs and general chapters of the EP are applicable with respect to the quality part of the dossier. For cases for which a specific monograph of the EP as well as of a pharmacopeia of a member state s is missing, according to chapter 3.2 (6), Part 1, Annex 1 of the Directive 2001/83/EC a monograph of a third country pharmacopoeia can be accepted under there defined conditions.
	Where the European Pharmacopoeia has no specific monograph on a particular herb, then national pharmacopoeia of any Member State or other reputable and established pharmacopoeia (e.g. USP, JP) as well as the Indian or Chinese pharmacopoeias for Ayurvedic or Chinese herbs may act as valid source materials. In addition, where appropriate, other well-known herbal texts such as ESCOP monographs and the British Herbal Pharmacopoeia should be accepted as valid sources.	(11) not agreed; See (10).

2. GENERAL CONCEPTS – 2.5. RELEASE VERSUS SHELF-LIFE ACCEPTANCE CRITERIA		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Regarding degradation products, reference is made to comment on 2.1.3. The identification and measurement of degradation products should be removed for THMP. These tests cannot be justified in the absence of any safety concerns.	(12) not agreed; Mentioning "degradation products" in this context allows less rigid criteria for shelf-life specifications than for release-specification, where appropriate. Concerning degradation products, see (6).
	Differences in acceptance criteria should be a general concept, also valid for herbal extracts/preparations (not only for herbal products), because testing of potential impurities or of some physical parameters does not seem necessary for stability purposes.	(13) partially agreed; The following wording was accepted after discussion in the QDG and the HMPC: "The concept of different acceptance criteria for release versus shelf-life specifications applies to herbal medicinal products, and - only in exceptional cases - if justified to herbals substances and herbal

		preparations.”
	Stability studies of herbal extracts/preparations are also useful for setting a retest period (quality control of extract x months after extraction to release the batch for use in the herbal products production). In this case, the results should comply with the release specification and not with the stability specification. The retest period, which might be shorter than the full shelf-life should be mentioned.	(14) not agreed; The chapter only refers to the setting of acceptance criteria, but not to the procedures in testing itself.
	For THMP, the need for quantification of each herbal active during shelf-life testing and finished product release should be removed except where claims are made for active or marker substances in the finished product.	(15) 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.

2. GENERAL CONCEPTS – 2.8. EVOLVING TECHNOLOGIES		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Evolving technologies should not necessarily be applied even when they “offer additional assurance of quality” if they are less accessible and existing methods are achieving acceptable quality standards.	(16) not agreed; As described in chapter 1.3., last paragraph, the Guideline reflects the state of the art at the time it has been written. If “additional assurance of quality” becomes possible by the use of new technologies, of course the use of these methods must be preferred.

3 GUIDELINES – 3.1. SPECIFICATIONS: DEFINITION AND JUSTIFICATION		
Line no. + para no.	**Comment and Rationale**	**Outcome**

3.1.2. Justific. of Specific. (herb. subst.)	Stability requirements for herbal substances exceed the existing Guidelines on stability testing; it should be sufficient that the herbal substance (herbal drug) corresponds to the respective pharmacopoeia monograph prior to further processing.	(17) not agreed; Stability of constituents should be considered when developing a specification for a herbal substance (e.g. for choosing an appropriate marker), this does not mean that stability testing is required for herbal substances.
3.1.2. Justific. of Specific. last paragraph	It should be mentioned, in which cases deviations from the existing requirements for chemical substances are possible, e.g. a range of +/- 10% of the initial value, introducing of overages, if justified.	(18) not agreed; Mentioning general reasons for exceeding the range of +/- 5% during the proposed shelf-life is not appropriate, because such a justification is product specific. The use of overages is regulated in CPMP/QWP/155/96.
3.1.2. Justific. of Specific. last paragraph	The sentence "Due to the inherent complexity … that profiles the stability characteristics" should neither result in an increase of requirements nor in an increase in the extent of stability testing.	(19) not agreed; Because of the particularities of herbal products, their inherent complexity must of course be taken into consideration when choosing appropriate stability tests. Sometimes an increase in data required for herbals in comparison to chemically defined products cannot be avoided.
3.1.2. Justific. of Specific. last paragraph	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.	(20) 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. We additionally refer to CPMP/QWP/2819 rev 1, chapter 8, 3rd paragraph, where exceptions for combination products are given.
3.1.2. Justific. of Specific. last paragraph	For Traditional Herbal medicinal products quality assurance is established through raw material identity and in process controls rather than by more sophisticated chemical analysis. Quality and safety of these products should therefore be achieved through the identification and control of the quality of the raw material rather than through an attempt at extremely difficult quantitative testing of the end product.	(21) 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

	Stability testing of the final product should concentrate on microbial, physical and finger-print chromatographic testing and the quantification of the active should only be introduced in single herb products when an active ingredient is claimed, or a marker substance is available.	necessary in the production of herbal medicinal products. In addition, see (20).

3 GUIDELINES – 3.2. UNIVERSAL TESTS/CRITERIA		
Line no. + para no.	**Comment and Rationale**	**Outcome**
3.2.1 Herb. Subst.	Agreement with the appropriate use of these guidelines for herbal substances used in THMP.	(22)
3.2.2 Herb. Prep.	Agreement with the appropriate use of these guidelines for herbal preparations used in THMP.	(23)
3.2.2. Herb. Prep. a)	The text should be changed into: "Definition: a statement of the botanical source, and the type of preparation (e.g. dry of liquid extract). The ratio of the herbal substance to the native herbal drug preparation must be stated (DER native)."	(24) partially agreed; The wording "herbal drug preparation" must be avoided because it is no official term defined in Directive 2001/83/EC. The following wording is appreciated: "Definition: a statement of the botanical source, and the type of preparation (e.g. dry of liquid extract). The ratio of the herbal substance to the genuine herbal preparation must be stated."
3.2.2. Herb. Prep. e)	The second sentence should be changed into: 'Where possible, a specific procedure should be included to determine their content in the herbal preparation'.	(25) not agreed; We hold fast to the insertion "stability indicating", because the choice of an appropriate method for the determination of the herbal substances content in the herbal preparation needs to take into consideration stability of the measured compound (it must be sufficiently stable but also reflect possible changes during shelf-life).
3.2.3. Vitamins and Minerals …	Many vitamins are not particularly stable but have widespread acceptance in food supplements and 'fortified' foods. It should only be necessary to ensure that the product contains a minimum of (say) 80% of the claimed content during shelf-life and appropriate overages may	(26) not agreed; We refer to the CPMP/QWP/2819 rev 1, chapter 1 "Introduction", second paragraph, last three sentences.

	used to achieve this. It is not appropriate to monitor any degradation products produced during the self-life for these well established and accepted active ingredients. Stability should be controlled by limiting the overage (according to the nutrient) and ensuring a minimum content of the nutrient throughout shelf-life.	The second sentence in chapter c), second paragraph was deleted in agreement with QDG and HMPC. Concerning degradation products, see (6).
3.2.3. Vitamins and Minerals … c)	The reference to 'minerals' should get deleted through the whole text, because the concept of degradation products is not applicable to minerals.	(27) not agreed; Minerals may consist of salts with organic compounds.
3.2.3. Vitamins and Minerals …	Regarding degradation products, reference is made to comment on degradation products, see 2.1.3.	(28) not agreed; see (7)
3.2.3. Vitamins and Minerals …	Vitamins are not very stable, for this reason overages as described in the USP are permitted.	(29) not agreed; see (26). The use of overages is regulated in CPMP/QWP/155/96.
3.2.3. Vitamins and Minerals …	"Degradation products" should be deleted from the list of quality specifications for vitamins and minerals for THMP, because vitamins are considered as known and well-established substances and do not pose safety problems in quantities close to the RDAs. Concerning degradation products, the same criteria should apply both for vitamins and minerals.	(30) not agreed; We refer to the last sentence of this chapter.
3.2.4. Herb. Med. Prod. c)	The second sentence should get changed into: 'Where possible a specific procedure should be included to determine their content in the herbal medicinal product.', because in products containing herbal substances and/or herbal preparations with constituents of known therapeutic activity these have to be determined not the amount of herbal substance(s) or herbal preparation(s) and the concept of stability indicating assays is not applicable.	(31) not agreed; In products containing herbal substances and/or herbal preparations with constituents of known therapeutic activity, these constituents have to be determined anyway (see first sentence in this chapter). Nevertheless, it is unusual but possible to determine the content of the herbal substance(s) and/or herbal preparation(s) in the herbal medicinal product via another, specific, stability indicating procedure referring to other constituents. Therefore the wording "Where appropriate …." in the beginning of the second sentence was chosen.

		We hold fast to the insertion "stability indicating", because the choice of an appropriate method for the determination of the content of the herbal substance(s) and/or herbal preparation(s) in the herbal medicinal product needs to take into consideration stability of the measured compound (it must be sufficiently stable but also reflect possible changes during shelf-life).
3.2.4. Herb. Med. Prod. c)	The removal of need for quantification of each herbal active in THMP is strongly proposed, except where claims are made for active or marker Substances in those finished products. 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 for Traditional Herbal Medicinal Products.	(32) 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. The following sentence was added in the second paragraph after the first sentence: "The choice of such markers should be justified."
3.2.4. Herb. Med. Prod. d)	The headline should get changed into: 'Impurities and contaminants' and the first point should get changed into: 'Contaminants arising from the herbal substance(s) and/or the herbal preparation(s) such as pesticides/fumigants residues …', because contaminants are not "impurities" as defined by other CPMP or ICH guidance documents.	(33) Concerning degradation products, see (6).
3.2.4. Herb. Med. Prod. d)	The first sentence of the third point should get changed into: 'In these exceptional cases where major impurities arising from degradation of the herbal preparation (herbal substance) are evident (e.g. Emodines from hydroxyanthacene glycosides or pyrrolizidinalkaloids), they should be monitored in the herbal medicinal product', because there are only few examples for "major impurities". In the case, that "major impurities" are included in the glossary, further	(34) partly agreed; Pyrrolizidinalkaloids must be deleted, because they are no degradation products. In accordance with (6) and after discussion in the QDG and the HMPC the wording was changed as follows: "In cases where degradation products of the herbal substance/preparation are evident (e.g. aglycones from hydroxyanthracene glycosides), they should be monitored in the herbal medicinal product. Acceptance limits should be stated for such degradation products."

	explanation in the NfG is not necessary	
3.2.4. Herb. Med. Prod. d)	The following paragraph must be (slightly changed) added to the preceding paragraph as follows or deleted: 'When it has been demonstrated conclusively by provision of a significant body of data, generated using appropriate analytical methodologies, that these herbal substance(s) and/or herbal preparation(s) do not degrade in the specific formulation and under the specific storage conditions proposed in the marketing authorisation, degradation product testing may be reduced or eliminated upon approval by the regulatory authorities.' The concept of degradation product testing is not applicable at all to herbal substances, herbal preparations and herbal medicinal products, which is indirect also implicated by the paragraph above. Stability of the herbal medicinal product is evaluated in the course of stability studies.	(35) agreed; The slightly changed paragraph is endorsed.
3.2.4. Herb. Med. Prod. d)	Degradation products should not be included in the general quality concept of both THMPs and HMP. Therefore the phrase "to monitor, to identify and to analyse impurities arising from degradation products" should be deleted. It is proposed that identification and measurement of degradation products are removed when concerning THMP.	(36) not agreed; See (35). At least toxicologically relevant degradation products need to be included.
3.2.4. Herb. Med. Prod. d)	Impurities should be controlled in the herbal substance/preparation and contaminant testing of the finished product is not necessary (except for occasional microbiological testing). Identification or quantification of degradation products should only be applied in simple, single herbal products with well documented identification and analysis of degradation products.	(37) not agreed; See (33). The updated text differentiates between contaminants arising from herbal substance(s) and impurities arising from the production process of the herbal medicinal product. Occasional microbial testing cannot be accepted without justification, because microbial impurities can also derive from the production process. The necessity for the determination of degradation products is independent from the number of constituents but dependent from the possibility of these constituents to cause relevant degradation products.

3 GUIDELINES – 3.3. SPECIFIC TESTS/CRITERIA		
Line no. + para no.	**Comment and Rationale**	**Outcome**
3.3.1. Herb. Med. Prod. 3.3.1.1. Tablets a)	The first sentence should get changed into: 'In the case of immediate release herbal medicinal products for which constituents with therapeutic activity are not known, the test for in-vitro active ingredient release can be generally omitted.'	(38) not agreed; Inserting "generally" should be avoided because exceptions are possible in cases where difficulties in ingredient release are known.
3.3.1. Herb. Med. Prod. 3.3.1.2. Oral liquids f.)	Data on extractables from the container and closure system should not be requested for materials which are described in the Ph.Eur. or the USP or which are permitted in the EU for packaging liquid foods. The need to determine extractables (during development or subsequently) should not be necessary in the case of containers manufactured from acceptable 'food contact material' or materials recommended for such in the EP or USP.	(39) not agreed; The necessity to provide data on extractables is dependent from both the container and closure system and the product properties of the individual herbal medicinal product (e.g. fluids containing essential oils).
3.3.1. Herb. Med. Prod. 3.3.1.3. … cont. excl. herb. subst. title	The title should also include 'or in two-piece hard gelatine capsule'	(40) not agreed; Herbal teas are only given as an example; of course other formulations are also included.
3.3.1. Herb. Med. Prod. 3.3.1.3. … cont. excl. herb. subst. title	The title should get changed into: 'Herbal medicinal Products containing exclusively herbal teas', because in most cases herbal teas are cut and therefore herbal preparations and not herbal substances, however in some case they might be defined as herbal substance.	(41) not agreed; Reference is made to the definitions given in Directive 2001/83/EC. Cut dried plants are considered to be herbal substances.

3.3.1. Herb. Med. Prod. 3.3.1.3. … cont. excl. herb. subst. b)	This point should get deleted, because this test normally is performed for the herbal substance if applicable.	(42) agreed
3.3.1. 3.3.1.3. e)	e) is occurring twice!	(43) agreed
3.3.1. Herb. Med. Prod. 3.3.1.3. … cont. excl. herb. subst. e)	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.	(44) 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.
3.3.1. Herb. Med. Prod. 3.3.1.3. … cont. excl. herb. subst. e)	Reproducibility for Traditional Herbal medicinal Products should be justified by a combination of quality control of the herbal substance/preparation, GMP during manufacture and a chromatographic finger-print comparison of the herbal contents.	(45) not agreed; See (44)
3.3.1. Herb. Med. Prod. 3.3.1.3. … cont. excl. herb. subst. f)	(assay): The first two sentences should get changed into: 'In the case of such herbal medicinal products containing herbal teas (?) with constituents of known therapeutic activity, validated assays for these constituents are required along with details of the analytical procedure(s). Where possible, a specific procedure should be included to determinate their content in the herbal medicinal product."	(46) not agreed; See (41). In products containing herbal substance(s) with constituents of known therapeutic activity, these constituents have to be determined anyway (see first sentence in this chapter). Nevertheless, it is unusual but possible to determine the content of the herbal substance(s) in the herbal medicinal product via another, specific, stability indicating procedure referring to other constituents.

3.3.1. Herb. Med. Prod. 3.3.1.3. … cont. excl. herb. subst. h)	It should be added, that the requirement "absence of objectionable bacteria (e.g. Staphylococcus aureus, E. coli, Salmonella, Pseudomonas)" is only applicable to preparations except herbal tea, because this would be in accordance with the EP, Chapter 5.1.4, Category 4.	(47) not agreed; Testing of objectionable bacteria is also part of the demands laid down in EP, Chapter 5.1.4, Category 4.

4 DEFINITIONS		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Degradation products should be deleted, because the definition given has been taken over from chemical substances and is not applicable for herbals.	(48) Concerning degradation products, see (6).
	Degradation product should be connected with the term 'for vitamin'	(49) See (48)
Herbal substances	'cut' must be deleted as cut plant are herbal preparations.	(50) not agreed; Reference is made to the definitions given in Directive 2001/83/EC. Cut dried plants are considered to be herbal substances.
Herbal preparations	The sentence 'They may contain excipients or not' should be added.	(51) not agreed; Reference is made to the definitions given in Directive 2001/83/EC. Concerning presence of excipients, we refer to the term "Genuine herbal preparations".
Genuine herbal preparations	The definition should be: 'refer to the herbal preparation without any excipients. Soft and liquid extracts and tinctures in their entirety are defined as genuine herbal preparations'.	(52) not agreed; The following wording was accepted after discussion in the QDG and the HMPC: "**Genuine (Native) herbal preparation:** refers to the preparation without 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. “
Genuine drug extract ratio ($DER_{genuine}$)	The following definition should get added: ‘is the ratio of the mass of the herbal substance to the mass of the resulting genuine herbal preparation (genuine extract, formally called “native extract”), even if for technological reason the genuine herbal preparation is not available’.	(53) not agreed; The following wording was accepted after discussion in the QDG and the HMPC: **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.
Active substance	The following definition should get added: ‘(syn. drug substance) is the herbal substance or the genuine herbal preparation in its entirety’.	(54) not agreed; Use of the wording “active substance” in the guideline is appreciated, but it should not occur in the glossary because there is no legally binding definition given for this term in Directive 2001/83/EC.
Markers	The definition should be: ‘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 or pharmacological activity or not’. there should be a classification of markers as follows: ‘Constituents with known therapeutic activity: are constituents or groups of constituents which are generally accepted to be solely responsible for the acknowledged and documented therapeutic activity of a herbal substance, a herbal preparation or a herbal medicinal product. 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 exclusively serve for analytical purposes.’	(55) agreed; but the definition is divided into two parts (`constituents with known therapeutic activity` and `markers`) and some changes concerning the wording were done: “**Constituents with known therapeutic activity:** are chemically defined substances or groups of substances which are generally accepted to contribute substantially to the therapeutic activity of a herbal substance, a herbal preparation or a herbal medicinal product.” “**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 substance or herbal preparation. There are two categories of markers:

		Active markers are constituents or groups of constituents which are generally accepted to contribute to the therapeutic activity. Analytical markers are constituents or groups of constituents that serve for analytical purposes.”
Standar-disation	The definition should be: ‘means adjusting the herbal preparation to a defined content of constituents with known therapeutic activity respectively either by adding excipients or by blending batches of the herbal substance and/or herbal preparations (standardised extracts)’.	(56) not agreed; The following wording was accepted after discussion in the QDG and HMPC: “means adjusting the herbal substance/preparation to a defined content of a constituent or a group of constituents with known therapeutic activity respectively either by adding excipients or by blending batches of the herbal substance and/or herbal preparation (e.g. standardised extracts)”
Extraction solvents	The following definition should get added: ‘are solvents that transfer the extractable matter from the matrix of the herbal substance to the eluate’.	(57) not agreed; The following wording was accepted after discussion in the QDG and HMPC: “are solvents which are used for the extraction process.”
Solvent	The definition should be: ‘an inorganic or an organic liquid used for the preparation of solutions or suspensions in the manufacture of a herbal preparation or the manufacture of a herbal medicinal product’.	(58) agreed
Fixed combination	The following definition should get added: ‘a herbal medicinal product which contains more than one herbal preparation or herbal substance’.	(59) not agreed; The Guideline does not refer to `Fixed combinations` in the sense of Directive 2001/83/EC.