European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON 'GUIDELINE ON NON-CLINICAL DOCUMENTATION FOR HERBAL MEDICINAL PRODUCTS IN APPLICATIONS FOR AUTORISATION (BIBLIOGRAPHICAL AND MIXED APPLICATIONS) AND IN APPLICATIONS FOR SIMPLIFIED REGISTRATION (EMEA/HMPC/32116/2005)

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

	Organisation
1.	Association of the European Self-Medication Industry (AESGP)
2.	Kooperation Phytopharmaka
3.	The Herbal Forum

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Table 2:Discussion of comments

General comment	Comment and rationale	Outcome / Proposed change
	In our view, because of their long history of medicinal use, registered Traditional Herbal Medicinal Products have demonstrated the lack of any adverse reproductive, genotoxic and carcinogenic effects. The potential requirements for additional non-clinical data in these areas are therefore considered to be unnecessary unless there is new evidence or strong suspicion of adverse effects. Additionally, in our view the provisions of the HMPWP's proposed Note for Guidance on Non-Clinical Testing of Herbal Drug Preparations with Long-Term Marketing Experience – Guidance to Facilitate Mutual Recognition and Use of Bibliographic Data (HMPWP/11/99) should, as a general rule, be more than adequate for <u>all</u> the products covered by the scope of this draft guideline, particularly in relation to genotoxicity. Only where a specific safety concern is recognised, should there be any requirement for non-clinical investigation.	Not endorsed. Some aspects of toxicity can be clarified by carefully assessing the documentation on the long-standing or well-established use of an herbal medicinal product. The guideline states however, that some toxic effects are difficult or even impossible to recognise on the basis of long-standing or well-established use. Toxicity on reproduction or carcinogenicity may be identified e.g. through large and well-designed cohort studies, although such studies are rare and unlikely to be performed with herbal medicinal products. Genotoxicity however, can only be identified through tests, as the effect cannot be observed in humans under the conditions of practical use. For this reason, absence of literature data or other information on genotoxicity does not indicate safety. This concept was already present in the previous version of the document that was prepared by the former HMPWP.
	We believe that the principles laid down in the HMPWP proposed Note for Guidance on Non-Clinical Testing of Herbal Drug Preparations with Long-Term Marketing Experience – Guidance to Facilitate Mutual Recognition and Use of Bibliographic Data are still applicable and sufficient in particular for products having been in use for a long time. We would like this draft guidance to retain this pragmatic approach (in particular concerning genotoxicity).	The "pragmatic approach" is maintained in the present document, as the methodological approach did not change and it is stated that the experience gathered during long-standing use will be taken into account.
	We would suggest modifying the outline of the document as follows: **4. Non-Clinical Documentation** (instead of "Main guideline text") 4.1 General aspects …. **5. Non-Clinical Summary / Overview / Expert report** (instead of this point being "4.6").	Endorsed.

Line no or section and paragraph no	Comment and rationale	Outcome / Proposed change
1. INTRODUCTION (background) 2nd paragraph	… The specific character of bibliographic data on herbal preparations used over a very long period of time, sometimes over centuries, requires additional guidance for applicants and competent authorities on how to prepare and to assess such applications. Only in cases of reasonable suspicion, additional appropriate non-clinical tests can be requested. The appropriateness has to be justified.	Not endorsed. All aspects related to toxicity must be addressed and the safety of the product must be established on the basis of sufficient bibliographic data or tests. The requirements are set out in the guideline.
3. LEGAL BASIS	Article l6c1(d)of Directive 2001/83 (as amended by Directive 2004/24) allows for data (additional to that from a bibliographic review) to be requested by the competent authority where 'necessary for assessing the safety of the medicinal product'. However, where there is an HMPC 'central monograph' or 'entry to list', then according to Article l6f(2), 'the data specified in Article l6c1(d) …do not need to be provided'. We would suggest that this important point should be more clearly set out in the final Guideline.	Endorsed with respect to the 'list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products.'
3. LEGAL BASIS	For clarification purposes, we suggest adding a (third) paragraph clearly mentioning that, in application of Article 16f(2), in the case of application for traditional use registration for a herbal substance, preparation or a combination thereof contained in the list, additional safety data cannot be required. The same spirit applies to well-established herbal medicinal products, which are subject to a Community monograph. Therefore a marketing authorisation application relying on the corresponding Community monograph would not be required to provide additional safety data.	See above.

4. MAIN GUIDELINE TEXT ***4.1 General aspects*** 1st paragraph	Any assessment must be based on a ~~clear~~ definition of the herbal substances / herbal preparation. Even if a "full" quality dossier may not yet be available at the time when the non-clinical documentation is prepared, the fundamental botanical and phytochemical characteristics of the herbal substance / herbal preparations must be established. Although ~~T~~the presence of different herbal preparations and combinations of herbal preparations that may have been used must be considered, and experience available in humans should be documented for specific, single and well characterised herbal preparations, it is most useful to assess herbal preparations jointly which are prepared from the same herbal substance with solvents of comparable polarity ranges and which have a comparable DER range.	Endorsed ("clear" deleted) Not endorsed. Not fully endorsed. "Comparable polarity" is not a sufficient parameter, as other interactions between solvents and herbal constituents can be expected. However, a clarification in line with other HMPC guidance has been inserted.
4.1 General aspects 1st paragraph	We do not agree that, 'The lack of some specific non-clinical studies (E.G. genotoxicity studies) may also pose a safety concern'. Many plants, (and, indeed, well-established allopathic medicines) lack such studies. This fact in isolation, particularly where an applicant can demonstrate that the herb has been used safely for 30 years, is scarcely reason for safety concern, and certainly is not sufficient justifiable basis to require such studies to be carried out. While we agree that documented experience from long-term use should be the main basis for assessment, we would stress that findings for isolated substances should not automatically be extrapolated to herbal drugs and preparations, which may not even contain those substances after manufacture. The same point applies to the second sentence of 4.3 Genotoxicity	Not endorsed. Genotoxicity will not be identified if no studies are performed. There must be "material evidence" to substantiate safety. The statement is right, in principle. However, such constituents are considered to be markers for a potential risk that need further discussion/clarification. In some examples, e.g. quercetin in genotoxicity, identification of such a constituent may be an argument for not repeating non-clinical studies (chapter 4.3).

4.1 General aspects 1st paragraph	First sentence: We would suggest removing the adjective 'clear' as it does not always reflect the reality. In the older literature, in particular, a 'clear' definition is not always available. Second sentence: Considering the number of documentations based on the long-term use of many preparations containing the same herbal substance, we propose to take the herbal substance as a basis and to modify the sentence accordingly: *"Although the presence of different herbal preparations and combinations of herbal preparations that may have been used must be considered, and experience available in humans should be documented for specific, single and well characterised herbal preparations, it is most useful to assess jointly herbal preparations which are prepared from the same herbal substance with solvents of comparable polarity ranges and which have a comparable DER range."*	Removed. See above.
4.1 General aspects 2nd paragraph	… The search strategy and the results of search must be documented. Non-clinical ~~S~~sstudies that do not comply with the current state of the art (e.g. GLP-conformity) should be judged for credibility. …	Endorsed.
4.1 General aspects 3rd paragraph	Many plants used in herbal medicinal products or traditional herbal medicinal products are able to demonstrate a long-term use as medicine or as food without any harm. Non-clinical investigations may be needed if a safety concern is recognised or suspected. ~~The lack of some specific non-clinical studies (e.g. genotoxicity studies) may also pose a safety concern.~~ If such additional studies are needed for a marketing authorisation, an application for a "mixed dossier" has to be submitted. *Reason:* *For many medicinal plants no such genotoxic studies are available. If missing data is a safety concern a large number of studies would become mandatory.*	Not endorsed. See reasons given above. The HMPC is aware of the challenge to conduct tests but the requirement is known for years and a pragmatic approach is offered in chapter 4.3. This is why the HMPC recommends a co-operative approach of stakeholders and interested parties.

4.1 General aspects 3rd paragraph	First sentence: The safe long-term use of either well-established or traditional medicinal products tends to be by far the most common situation. We would suggest rewording the beginning of this paragraph as follows: "*Many plants contained in well-established or traditional herbal medicinal products have an adequate safety profile which has been confirmed by their long-term medicinal and/or food use. However, in cases where a safety concern is recognised or suspected, non-clinical investigations may be needed."* Second sentence: We do not agree with the fact that: "The lack of some specific non-clinical studies (e.g. genotoxicity studies) may also pose a safety concern". For many plants genotoxic studies do not exist. If missing data alone constitute a concern, then a large number of studies would be requested. Being confronted with the performance of a full program of genotoxicity studies for all types of herbal medicines and herbal preparations may be difficult to sustain, especially for SMEs. We suggest deleting this sentence.	Endorsed. Not endorsed.
4.1 General aspects 4th paragraph	Where there is, in terms set out by the Directive 2001/83/EC, sufficient and well-documented experience available in humans, single dose and repeated dose toxicity, immunotoxicity as well as local tolerance testing of traditional and well-established herbal preparations is not necessary. Likewise, pharmacological tests including safety pharmacology and pharmacokinetics are not necessary, if there are no reasons to expect a specific risk. The potential for pharmacokinetic interactions between the herbal substance/preparation and other medicinal products should be ~~clarified~~ discussed.	Endorsed.

4.1 General aspects 4th paragraph	First sentence: We fully agree with this sentence. We would have the following (minor) changes to propose: "*Where there is, in terms set out by the Directive 2001/83/EC* <u>*as amended*</u>*, sufficient and well-documented experience available in humans, single dose and repeated dose toxicity, immunotoxicity as well as local tolerance testing of traditional* <u>*and*</u> *well-established herbal preparations is not necessary*". Third sentence: We would like to see this sentence modified as follows: "*The potential for pharmacokinetic interactions between the herbal substance/preparation and other medicinal products should be* ~~*clarified*~~ <u>*discussed*</u>*"*. This modification takes into account the option of discussing existing data (e.g. in the expert report).	Endorsed.
4.1 General aspects 5th paragraph	… These effects would include toxicity to reproduction, genotoxicity and carcinogenicity. <u>In particular it is important that toxicological findings obtained with isolated substances are not necessarily valid for extracts and other preparations.</u>	Partly endorsed.
4.1 General aspects 5th paragraph	We fully agree that the documented experience gathered during long-term use will be the main basis for assessment. In this context it is very important that findings available for isolated substances cannot necessarily be extrapolated to extracts and other preparations. We therefore suggest adding at the end of this paragraph (after "carcinogenicity"): <u>*"In particular, it is important that toxicological findings obtained with isolated substances are not necessarily valid for extracts and other preparations*</u>".	Partly endorsed.
4.1 General aspects 6th paragraph	… A co-operative approach of ~~stakeholder and~~ interested parties is encouraged to investigate herbal preparations with ~~the same~~ <u>comparable</u> specification<u>s (solvents with comparable polarity ranges, comparable DER ranges).</u>	Partly endorsed.
4.1 General aspects 6th paragraph	Additional non-clinical testing' should only be required if there is a specific and justifiable safety concern.	Not endorsed. See above.

4.1 General aspects 6th paragraph	First sentence: With reference to our comments above (under the 3rd paragraph), we recommend to add the sentence "*additional non-clinical testing of well-established and traditional herbal medicinal products would be necessary, if published literature is not available or insufficient <u>and if there is reasonable suspicion for safety concerns</u>*". Second sentence: From our point of view, the investigation of herbal preparations with the same specification is very narrow. As the specification differs in many cases, a large part of preparations available on the market would still have to be tested individually and thus defeating the purpose of the exercise. For this reason, we would like to suggest establishing categories formed by comparable herbal drug preparations or even containing the same herbal drug as a basis. Thus, we recommend that this sentence be modified as follows: "*A cooperative approach of stakeholders and interested parties is encouraged to investigate herbal preparations with <u>comparable</u> specification <u>(solvents with comparable polarity ranges, comparable DER ranges)</u>*".	Not endorsed. Partly endorsed.
4.2 Toxicity to Reproduction 2nd paragraph	… Reproductive toxicity data are available for many old substances, however, these data are <u>sometimes</u> ~~often~~ not reliable.	Not endorsed.
4.2 Toxicity to Reproduction 2nd paragraph	Second sentence: We suggest replacing 'often' by 'sometimes' because most of the cases data are reliable in most cases. <u>Last sentence:</u> For clarity purposes, we would suggest that the last sentence read: *"Reproductive toxicological tests in animals are not necessary <u>if one of the following criteria is fulfilled</u>:"*.	Not endorsed. Endorsed.

4.3 Genotoxicity 1st paragraph	The genotoxic potential of herbal preparations should be discussed ~~assessed~~. Genotoxicity data are available for many active substance(s), however, these findings in general cannot be extrapolated to the herbal preparation ~~their quality is often inadequate for safety assessment~~. When an adequate assessment cannot be made and if there is a reasonable suspicion for safety concerns, further genotoxicity testing is required. *Comment:* *An example is the toxicological assessment of quercetin in contrast to quercetin-containing preparations.*	Not endorsed. The relevance of the data has to be assessed in each case. Absence of information is not an acceptable proof of safety.
4.3 Genotoxicity 1st paragraph	In line with our comments made under 4.1, 4th paragraph, and taking into account the documented experience gathered during long-term use as the main basis for assessment, we propose the following modifications: First sentence: "*the genotoxic potential of herbal preparations should be discussed*" This modification takes into account the option of discussing existing data instead of implying further studies. Second sentence: "*genotoxicity data are available for many active substances, however, these findings cannot be extrapolated to the herbal preparation in general*". An example can be the toxicological assessment of quercetin vs. the one of quercetin-containing preparations. Third sentence: "*When an adequate assessment cannot be made and if there is reasonable suspicion for safety concerns, […]".* Same rationale as under 4.1, third paragraph.	Not endorsed. See above.

4.3 Genotoxicity 2nd paragraph	A repetition of ~~the~~ studies is only required in cases in which the relevance of the results is unclear or where results provide reasons for suspicion. Findings indicating genotoxicity for one herbal preparation or for herbal constituents from one specific chemical class may provide such reasons for suspicion. The ~~One~~ example of ~~would be~~ safrole-like substances has ~~The example~~ demonstrated, however, that genotoxic effects may depend from specific details of the structure ~~of the herbal constituent~~. Results not indicating genotoxicity may be extrapolated to another herbal preparation without necessitating further testing. In this case the differences between the herbal preparations have to be demonstrated ~~clarified~~ and a justification must be provided that the herbal preparations are comparable so that a ~~why these~~ different ~~ces~~ ~~are not expected to modify~~ assessment concerning genotoxicity cannot be expected. ~~genotoxicity~~. The equivalence of the herbal preparations must be demonstrated.	Partly endorsed.
4.3 Genotoxicity 2nd paragraph	Third and fourth sentences: We welcome this statement and the pragmatism applied here.	
4.3 Genotoxicity 3rd paragraph	In case reasonable suspicion of genotoxicity of a ~~For~~ herbal preparation exists, ~~substances in which the available genotoxicity data is sufficient~~ it is recommended to start with *in vitro* tests. Herbal preparations with negative results *in vitro* also exhibit negative results *in vivo* in the majority of cases.	Not endorsed. Data are needed to conclude on or to exclude "reasonable suspicion".
4.4 Carcinogenicity 2nd paragraph	Even a suspicion of a carcinogenic effect of a traditional or~~f~~ a well-established herbal preparation does not necessarily require a carcinogenicity study to be performed.	Endorsed.