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Guideline on non-clinical documentation in applications for marketing authorisation/registration of well-established and traditional herbal medicinal products

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Executive summary

This guideline is intended to give advice for preparing and assessing applications for marketing authorisation of well-established herbal medicinal products and for the registration of traditional herbal medicinal products. It should be read in conjunction with the general requirements set out by Directive 2001/83/EC[1], in particular its Annex I, and general methodological requirements published by the EMA.

Revision 1 pertains to an update of the guideline after 10 years taking into account experiences gained during the use of this guideline in national and European procedures and also during establishment of EU herbal monographs. Other related guidelines not yet available at time of the first version have been taken into consideration: Assessment of genotoxicity of herbal substances/preparations (EMEA/HMPC/107079/2007), Selection of test materials for genotoxicity testing for Traditional Herbal Medicinal Products/Herbal Medicinal Products (EMEA/HMPC/67644/2009), Limits of genotoxic impurities" (CPMP/SWP/5199/02, EMEA/CHMP/QWP/251344/2006), and ICH S2 (R1) on Genotoxicity testing and data interpretation for pharmaceuticals intended for human use (CHMP/ICH/126642/2008).

Changes have been introduced accordingly in all sections of the guideline.

1. Introduction (background)

Herbal medicinal products are widely used within and outside the European Union[2]. This wide use has generated significant amount of bibliographical information relating to non-clinical safety. However, published non-clinical tests for well-established and traditional herbal preparations are often incomplete or not in accordance with today's state of the art. The complex composition of herbal preparations presents an additional challenge. In order to obtain a better understanding of the inherent risks with such products and to facilitate a continuous safety assessment, it is necessary to state the minimum requirements for non-clinical data. Published toxicological information including scientifically accepted monographs, well-presented clinical experience (with regard to the time and extent of use in humans), epidemiological studies and data as well as post-marketing experience gained by wide spread use in humans may contribute to the avoidance of unnecessary tests in animals (Directive 2001/83/EC, Annex I, Part II (1)b).

Directive 2001/83/EC allows the use of published literature in bibliographical applications for marketing authorisation. The simplified registration of traditional herbal medicinal products will be based on the expert report, bibliographical data and, if necessary, new tests. These legal provisions in no way relax the requirements of proof of safety set out by the Annex to Directive 2001/83/EC. All aspects that are relevant for the safety of the patient or consumer must be covered by appropriate literature or appropriate reference to a review of literature, and must be addressed in the non-clinical summary of an application for marketing authorisation or the expert report in a registration procedure, and justification for the lack of data should be submitted. 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.

[1] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code related to medicinal products for human use

[2] WHO: National Policy on Traditional medicines and Regulation of Herbal Medicines, WHO Geneva May 2005

2. Scope

This guideline provides guidance on the minimum requirements for non-clinical data for well-established herbal medicinal products in bibliographical applications for marketing authorisations and on the question which non-clinical safety aspects should be addressed in the expert report for the simplified registration of traditional herbal medicinal products and which additional non-clinical safety tests might be necessary to prove safety.

The guideline may also be used in the framework of assessment for establishment of a European Union herbal monograph or an entry into the list of traditional herbal substances.

3. Legal basis

Article 10a of Directive 2001/83/EC makes it clear that the applicant shall not be required to provide the results of pharmacological and toxicological tests if he can demonstrate by detailed reference to published scientific literature presented in accordance with the provisions set out by Part II (1) of the Annex I to Directive 2001/83/EC that the active substance(s) of the medicinal product have been in well-established medicinal use within the European Union for at least ten years, with recognised efficacy and an acceptable level of safety in terms of the conditions set out in Annex I.

Chapter 2a of Directive 2001/83/EC establishes specific provisions for the simplified registration of traditional herbal medicinal products with a long-standing medicinal use of at least 30 years (including at least 15 years within the European Union). According to Article 16c an application for registration shall be accompanied by, among other items, a bibliographical review of safety data together with an expert report (for more detailed information see “Guideline on the use of the CTD format in the preparation of a registration application for traditional herbal medicinal products” (EMA/HMPC/71049/2007 Rev. 2)[3]. Additional data necessary for assessing safety in accordance with Annex I can be required by the competent authority. If an application for traditional-use registration relates to an herbal substance, preparation or a combination thereof contained in the list referred to in paragraph 1 of Art. 16f, the data specified in Article 16c(1)(b)(c) and (d) do not need to be provided. Article 16e(1)(c) and (d) shall not apply. However, the Applicant should refer to aspects related to the finished traditional herbal medicinal product, especially with regard to the excipients and their influence on safety[4].

4. Non-clinical documentation

4.1. General aspects

Any assessment must be based on a 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. 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. Data on extracts produced from the same herbal substance with closely related extraction solvents such as different ethanol/water mixtures or closely related DER may be used, if justified.

[3] Guideline on the use of the CTD format in the preparation of a registration application for traditional herbal medicinal products (EMA/HMPC/71049/2007 Rev. 2)
[4] Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches (EMA/CHMP/CVMP/JEG-3Rs/450091/2012)

The documentation should be based on a comprehensive literature search in scientific literature, including handbooks and monographs specific to phytotherapy and traditional herbal medicine, and searches in electronic databases. The search strategy and the results of the search must be documented. If assessment reports of the HMPC supporting EU herbal monographs/ List entries for the herbal substances / herbal preparations in question exist, those can be seen as starting points for a comprehensive literature search starting from the given time of the literature search mentioned in the assessment report. Non-clinical studies that do not comply with the current state of the art (e.g. GLP-conformity) should be judged for credibility. A "blind" repetition of animal experiments should be avoided.

In particular, it should be assessed whether the expected effects in animal studies would modify the benefit/risk assessment and would have an impact on the granting of a marketing authorisation or registration.

Many herbal preparations contained in well-established or traditional herbal medicinal products have an accepted safety profile, which has been based on 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. The lack or the incompleteness of some specific non-clinical studies (e.g. genotoxicity studies or local tolerance studies for the finished product) may also pose a safety concern. Such additional studies should be provided to support a marketing authorisation or registration.

Where there is, in terms set out by the Directive 2001/83/EC, sufficient and well-documented experience available in humans, testing of single dose and repeated dose toxicity, toxicokinetic studies, immunotoxicity as well as local tolerance of traditional and well-established herbal substances/preparations is not necessary. Likewise, pharmacological tests including primary and secondary pharmacology, 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 must be discussed. The non-clinical overview / expert report must address these aspects and give the rationale why the documented medical experience justifies a safe use of the herbal substance / preparation, although such tests are not available (Annex I, Part 2(1)c).

In general, the documented experience gathered during the long-standing use will be the main basis of the non-clinical assessment of traditional and well-established herbal medicinal products. For this reason, particular attention should be paid to effects that are difficult or even impossible to detect clinically. These effects include toxicity to reproduction, genotoxicity and carcinogenicity. The relevance of data on isolated constituents for the assessment of the herbal substance / preparation must be discussed. Additional non-clinical testing of well-established and traditional herbal substances/preparations would be necessary, if published literature is not available or insufficient. A co-operative approach of stakeholders and interested parties is encouraged to investigate comparable herbal preparations, e.g. extracts prepared from the same herbal substance with ethanol of different strength and with comparable DERs[5].

4.2. Genotoxicity

The genotoxic potential of herbal preparations should be assessed since pharmacovigilance and long-standing use cannot be used as evidence for absence of genotoxic effects. Genotoxicity data are available for many active substance(s), however, their quality is often inadequate for safety assessment. When an adequate assessment cannot be made, further genotoxicity testing is required.

[5] Guideline on selection of test materials for genotoxicity testing for traditional herbal medicinal products / herbal medicinal products (EMEA/HMPC/67644/09)

A repetition of studies is only required in cases in which the relevance of the results is unclear or where results provide reasons for suspicion. For such cases the following aspects may be considered:

Structure-related concerns: Known genotoxicity of single constituents (e. g. safrole), herbal substances or herbal preparations must be taken into account, when closely-related active substances are evaluated. It should be checked if genotoxicity is based on particular structural elements or attributed to a group of constituents.

Extrapolation of existing data: If there are data on genotoxicity (positive or negative) for a herbal substance or herbal preparation, they may be extrapolated to other herbal substances or herbal preparations on a case-by-case basis. Data should be provided to compare the phytochemical profile or explain the application of a concept of bracketing and matrixing. A comprehensive justification must be given that differences are not expected to modify genotoxicity.

For substances in which the available genotoxicity data are insufficient it is recommended to start with *in vitro* tests[6]. It is appropriate to assess genotoxicity initially in a bacterial reverse mutation test using a test battery of different bacterial strains and metabolic activation.

The limitations of such a test (e.g. for testing mixtures of substances or antibiotic active substances) should be taken into considerations in planning the test design and the test strategy[7]. Bacterial reverse mutation test has been shown to detect relevant genetic changes and the majority of genotoxic rodent carcinogens. Herbal preparations with negative results *in vitro* also exhibit negative results *in vivo* in the majority of cases. In cases in which positive results *in vitro* are present, these are to be clarified by way of appropriate investigations, mainly *in vivo*[8]. The complete testing strategy is comprehensively displayed in other Guidelines of the HMPC[5,6].

4.3. Carcinogenicity

Carcinogenicity studies are not needed in cases where there is no suspicion for a carcinogenic potential. However, carcinogenicity investigations do not necessarily have to be performed even if there is a suspicion of a carcinogenic effect. Some points which should be considered in deciding the need for carcinogenicity studies are:

- Is the suspicion based on results of genotoxicity studies and can it be clarified in further genotoxicity studies, mainly *in vivo*?
- Is the suspicion based on a possible epi-genetic mechanism?
- Are the extent and the quality of the available scientific data (non-clinical, clinical, epidemiological, post-marketing etc.) sufficient to refute the suspicion taking into account the intended use?
- Are the extent and the quality of the available scientific data (non-clinical, clinical, epidemiological, post-marketing etc.) sufficient to come to a positive benefit-risk assessment taken into account the expected benefit from the herbal medicinal product?

4.4. Reproductive and developmental toxicity

Reproductive toxicological investigations regarding fertility are generally not necessary unless there is cause for concern. Examples that would require a more detailed assessment include literature reports

[6] Guideline on Assessment of genotoxicity of herbal substances/preparations (EMEA/HMPC/107079/2007)
[7] OECD (1997), Test No. 471: Bacterial Reverse Mutation Test
[8] ICH S2 (R1) Genotoxicity testing and data interpretation for pharmaceuticals intended for human use (EMA/CHMP/ICH/126642/2008)

on hormone-like actions as well as other endocrine disruptions or a traditional use to influence fertility. The relevance of such data for the herbal substance / herbal preparation must be discussed taking into account e.g. phytochemical characteristics, posology, route of administration, duration of use etc.

The reproductive toxicological potential with regard to embryo-foetal and peri-post-natal development should be assessed. Reproductive toxicity data are available for many old substances, however, these data are often not reliable. A repetition of the tests is required in cases in which the significance of the results is not clear and there are reasons for suspicion. If positive signals of reproductive toxicity (non-clinical, clinical, epidemiological, post-marketing, traditional use) are identified in scientific literature, further investigations of reproductive toxicity are necessary, unless justified by the applicant.

Reproductive toxicological tests in animals are not necessary if one of the following criteria is fulfilled:

- Results from post-marketing studies or epidemiological data of adequate power or post-marketing safety studies are available.
- The assessment of the results of a systematic and comprehensive scientific literature search and post-marketing experience does not identify a positive signal of reproductive toxicity and the herbal medicinal product is not intended to be used during pregnancy and lactation.
- Results from investigations in pregnant women and neonates are present.
- The medicinal product is not intended to be used in women of childbearing potential.

The clinical overview should address women of childbearing potential and pregnancy. The assessment of the information and the labelling should follow relevant EMA guidance.

5. Non-clinical overview / expert report

All relevant sections as required by Annex I of Directive 2001/83/EC must be addressed according to the CTD format[9]. The expert is obliged to justify when non-clinical testing for the herbal preparation is not performed. If an herbal medicinal product can be expected to be used together with other medicinal products the potential of interactions has to be clarified. If the literature refers to an herbal preparation other than the preparation intended for marketing, a detailed explanation must be provided why the data can be used in spite of the existing differences.

The expert should discuss available published toxicological data on closely related herbal preparations, different parts of the plant, data on related species of the same genus or plant family, where relevant. If there are toxicological data on well-defined constituents of an herbal preparation, the expert should discuss the relevance of these data for the safety assessment of the herbal preparation.

In the “Guideline on the assessment of genotoxicity of herbal substances/preparations” (EMEA/HMPC/107079/2007)[6], there are also considerations for the risk assessment related to minor constituents of herbal substances / herbal preparations.

The presentation of the data should demonstrate that the level of safety for the product is acceptable taking into account the well-established / traditional use and the conditions set out by the summary of product characteristics (SmPC). The relevance of deviations from the current state-of-the art requirements, for the interpretation of study results should be discussed.

[9] ICH - The Common Technical Document for the registration of pharmaceuticals for human use: Safety - M4S(R2) Nonclinical overview and nonclinical summaries of Module 2 organisation of Module 4