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GUIDELINE ON NON-CLINICAL DOCUMENTATION FOR HERBAL MEDICINAL PRODUCTS IN APPLICATIONS FOR MARKETING AUTHORISATION (BIBLIOGRAPHICAL AND MIXED APPLICATIONS) AND IN APPLICATIONS FOR SIMPLIFIED REGISTRATION

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GUIDELINE ON NON-CLINICAL DOCUMENTATION FOR HERBAL MEDICINAL PRODUCTS IN APPLICATIONS FOR MARKETING AUTHORISATION (BIBLIOGRAPHICAL AND MIXED APPLICATIONS) AND IN APPLICATIONS FOR SIMPLIFIED REGISTRATION

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This Guideline is intended to give advice for preparing and assessing applications for marketing authorisation of well-established herbal medicinal products, mixed applications 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] as amended, in particular its Annex I, and general methodological requirements published by the EMEA.

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 up to date monographs, well-presented valid 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 as amended, Annex I, Part II (1)b).

Directive 2001/83/EC as amended allows the use of published literature in bibliographical applications for marketing authorisation and, should additional new tests be necessary, in mixed 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 as amended. 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.

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. If those minimum requirements cannot be fulfilled by published literature, additional non-clinical tests may be necessary, thus resulting in a "***mixed application***". It provides guidance 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 be used in the framework of preparing a documentation of a Community herbal monograph or an entry into the list of traditional herbal substances.

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[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

3. LEGAL BASIS

Article 10a of Directive 2001/83/EC as amended by Directive 2004/24/EC of the European Parliament and the Council of 31 March 2004 as regards traditional herbal medicinal products[3], 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 as amended that the active substance(s) of the medicinal product have been in well-established medicinal use within the Community 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 as amended, 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 Community). 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. 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 a 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.

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 may be used, if the DERs are comparable.

The documentation should be based on a comprehensive literature search in scientific literature, including handbooks and monographs (ESCOP, WHO) specific to phytotherapy and traditional herbal medicine, and searches in electronic databases. The search strategy and the results of search must be documented. 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 lead to a negative decision for the granting of a marketing authorisation or registration.

For many herbal preparations contained in well-established or traditional herbal medicinal products an adequate safety profile, may be 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. 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.

Where there is, in terms set out by the Directive 2001/83/EC as amended, sufficient and well-documented experience available in humans to cover organ toxicity, single dose and repeated dose toxicity, immunotoxicity as well as local tolerance testing of traditional and well-established herbal

[3] In the following referred to as Directive 2001/83/EC as amended.

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 must be discussed, and the possibility to perform pharmacokinetic interactions investigations in *in vitro* test considered. The expert report must address these aspects and give the grounds why the documented medical experience justifies a safe use of the herbal 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 would 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 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.

4.2 Toxicity to Reproduction

Reproductive toxicological investigations regarding fertility are generally not necessary unless there is cause for concern or the product is explicitly indicated in pregnancy. Examples that would require a more detailed assessment would include literature reports on hormone-like actions or on a traditional use for regulating 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, taking into consideration exposure data. 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 EMEA guidance.

4.3 Genotoxicity

The genotoxic potential of herbal preparations should be assessed. 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.

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. Findings indicating genotoxicity for one herbal preparation or for herbal constituents from one specific chemical class may provide such reasons for suspicion. The example of safrole-like substances has demonstrated, however, that genotoxic effects may depend from specific details of the structure. 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 and a justification must be provided why these 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. In cases in which positive results *in vitro* are present, these are to be clarified by way of appropriate investigations, mainly *in vivo.* [4] It is appropriate to assess genotoxicity initially in a bacterial reverse mutation test using a test battery of different bacterial strains and metabolic activation. This test has been shown to detect relevant genetic changes and the majority of genotoxic rodent carcinogens. In some cases, a genotoxic effect of an herbal preparation might be, following additional phytochemical investigations, clearly attributed to a defined constituent with well-established safety profile, such as quercetin. If positive results cannot be clearly attributed to specific constituents with a well-established safety-profile additional *in vitro*, e.g. mouse lymphoma cell assay, and, if necessary, *in vivo* studies should be performed.

4.4 Carcinogenicity

Carcinogenicity studies are not needed in cases where there is no suspicion for a carcinogenic potential.

The proposed duration of human treatment should be considered.

Even a suspicion of a carcinogenic effect of a traditional or a well-established herbal preparation does not necessarily require a carcinogenicity study to be performed. In those cases the reasons for a possible carcinogenic effect must be clarified. The following considerations should be included in the assessment:

- 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?

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[4] CPMP Note for guidance on genotoxicity: a standard battery for genotoxicity testing of pharmaceuticals (CPMP/ICH/174/95), CPMP Note for guidance on genotoxicity: guidance on specific aspects of regulatory genotoxicity tests for pharmaceuticals (CPMP/ICH/141/95) and OECD 1995.

4.5 Toxicokinetic data

Toxicokinetic data may mainly be required in connection with tests for new products in animals. Such kinetic data are mainly required if (a) herbal constituent(s) with known therapeutic activity or a defined constituent or a defined group of constituents with a specific toxicological profile can be identified.

5. NON-CLINICAL SUMMARY / OVERVIEW / EXPERT REPORT

All relevant sections as required by Annex I of Directive 2001/83/EC as amended must be addressed. The applicant/expert is obliged to point out the necessity or not of non-clinical testing for the herbal preparation. If a herbal medicinal product can be expected to be used together with other medicinal products the potential of interactions has to be clarified. Plausible presentation of the facts contributes to the acceptance of the application for marketing authorisation and facilitates the evaluation performed by the authorities. If the literature refers to a 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. If there are toxicological data on well-defined constituents of a herbal preparation, the expert should discuss the relevance of these data for the safety assessment of the herbal preparation.

The concept of thresholds of toxicological concern (TTC)[5][6] [Structured-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet] might be useful in the assessment of risks related to minor constituents of herbal substances / herbal preparations. The criteria for decision should be adapted to the particular situation of herbal medicinal products.

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

[5] Kroes R et al. *Food and Chemical Toxicology* 42 (2004) 65-83

[6] Müller L et al. Regulatory Toxicology and Pharmacology 44 (2006) 198-211