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Assessment of genotoxicity of herbal medicinal products: A co-ordinated approach

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ABSTRACT

The submission of data on genotoxicity is a precondition for marketing authorisation respectively registration of herbal medicinal products (HMPs) with well established or traditional use in some countries. In European regulatory guidelines prepared by the Committee on Herbal Medicinal Products (HMPC) of the European drug regulatory agency EMA, a test strategy is defined giving a pragmatic framework adapted to the assessment of the potential genotoxicity of HMPs. It describes a stepwise approach, including the possibility to reduce the number of extracts of a herbal drug to be tested by the use of a bracketing and matrixing approach. According to this strategy, Kooperation Phytopharmaka, a scientific society in the field of HMPs, has so far coordinated the conduction of genotoxicity tests for 30 herbal drugs within the frame of a joint project of several manufacturers of HMPs. Results are delivered to the cooperation partners for use in regulatory applications.

Regulatory situation and impact on the assessment of HMPs

During the past few years the discussions on safety of HMPs have particularly focused on the issue of genotoxicity. The "Guideline on Non-Clinical Documentation for Herbal Medicinal Products in Applications for Marketing Authorisation (Bibliographical and Mixed Applications) and in Applications for Simplified Registration" adopted in 2006 (EMEA/HMPC/32116/2005) states in general that for many herbal preparations in traditional or well-established use, an adequate safety profile is confirmed already by their long-term use. However, additional preclinical testing e.g. on genotoxicity would be required for specific herbal preparations, if published literature on this subject is not available or insufficient. This may be a pre-condition for registration/marketing authorisation. For the performance of tests, the guideline refers to the stepwise approach described in the respective ICH step 5 guidelines on genotoxicity testing (CPMP/ICH/174/95; CPMP/ICH/141/95).

More detailed guidance on the assessment of genotoxicity was provided by the "Guideline on the Assessment of Genotoxicity of Herbal Substances/Preparations" published in 2008 (EMEA/HMPC/107079/2007). It includes practical approaches on how to perform the tests and to interpret the results and describes a stepwise testing strategy, starting with the Ames test. In case of positive results, this should be followed by a mammalian cell assay and, in case of a still positive result in that assay, by *in vivo* genotoxicity tests. If the respective step yields negative results, progressing to the next test step is not required. This guideline also mentions the option to extrapolate the results obtained with a specific preparation to closely related preparations such as extracts prepared with ethanol/water mixtures of different, but similar concentrations – the so-called "bracketing and matrixing" concept. Using such an approach to the test materials means that a representative range of materials is tested rather than requiring individual manufacturers to undertake their own testing on all their specific preparations. This reduced test design assumes that the genotoxic potential of any intermediate preparation is represented by the test results of the extremes tested.

In order to propose possible approaches for reduced testing designs following this idea, a test strategy was developed in cooperation between Kooperation Phytopharmaka, a German scientific organisation in the field of HMPs and German regulatory authorities. This proposal was implemented in a further guidance document (EMEA/HMPC/67644/2009) (Fig. 1). It provides examples for a standard range of test materials, which might be considered representative for commonly used preparations of an herbal substance. The use of this approach within collaborative projects performed by applicants offers a strategy to lower the number of test materials used, and thus to lower the burden for manufacturers to perform their own investigations on each individual preparation of an herbal substance.

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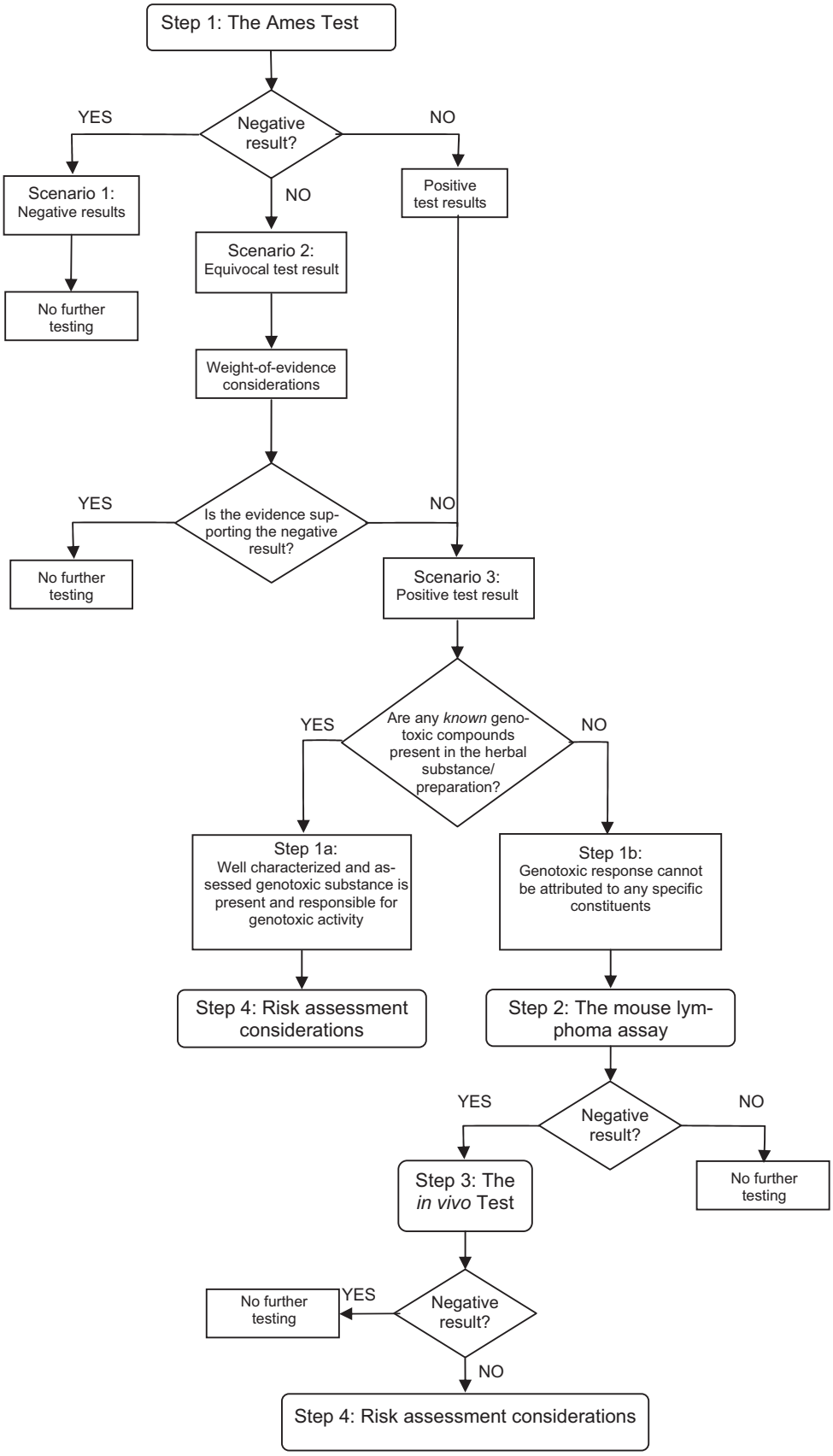

Fig. 1. Decision tree on the assessment of genotoxicity of herbal preparations (from EMEA/HMPC/67644/2009).