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COMMITTEE ON HERBAL MEDICINAL PRODUCTS

(HMPC)

DRAFT

CONCEPT PAPER ON THE DEVELOPMENT OF A GUIDELINE ON THE ASSESSMENT OF GENOTOXIC CONSTITUENTS IN HERBAL SUBSTANCES/PREPARATIONS

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1. INTRODUCTION

Guidelines for genotoxicity testing of pharmaceuticals have been established by OECD, ICH and EU. Testing of pharmaceuticals involves a battery of genotoxicity tests, in which pro- and eukaryotic systems in *in vitro* and *in vivo* contexts with and without metabolic activation are employed (1, 2). The HMPC 'Guideline on non-clinical documentation for herbal medicinal products in applications for marketing authorisation (bibliographical and mixed applications) and in applications for simplified registration' (3) was adopted by the HMPC in July 2006. In this guidance a step-wise procedure for assessing genotoxicity of herbal medicinal products was established. The basic requirement is to assess genotoxicity initially in a bacterial reverse mutation test using a test battery of different bacterial strains and metabolic activation. If positive results cannot be clearly attributed to specific constituents with a well-established safety-profile for example quercetin, additional *in vitro*, e.g. mouse lymphoma cell assay, and, if necessary, *in vivo* studies should be performed.

2. PROBLEM STATEMENT

During the preparation of the HMPC guideline on non-clinical documentation and after applying the guideline to the assessment of herbal preparations in the framework of drafting Community herbal monographs and the Community list of traditional herbal substances, preparations and combinations thereof, it became clear that specific aspects of the practical application of the existing guideline to the hazard and risk assessment of herbal medicinal products needs to be further addressed. Indeed, many questions were raised on how to interpret the current requirements in order to assess the hazards and risks of negative and positive findings in testing herbal medicinal preparations. One case in point has been the assessment of genotoxicity risks associated with furocoumarins in *Angelica archangelica* L.-containing preparations (4). Similar problems are raised in earlier guidance on herbal preparations with asarone, methyleugenol and safrole for examples that were published by the HMPC (5, 6, 7).

3. DISCUSSION (ON THE PROBLEM STATEMENT)

Herbal medicinal products (HMPs) pose a number of characteristics that clearly differentiate them from others, mainly from chemically defined medicinal products.

- HMPs are made of natural substances.
- HMPs are complex mixtures with a large number of components with sometimes highly variable amounts.
- The composition of a defined preparation may vary as a function of harvesting time, geographical origin, mode of preparation etc.
- The complete composition is very difficult to unravel, so one can argue that there are always many unknown constituents and thus there may be "hidden" dangers.

In many other respects, HMPs are similar to pharmaceuticals:

- The same basic legislation determines their legal position.
- Many HMPs have been used for long time by a sizable portion of the population.
- Clinical experience, despite its shortcomings, may point to their relative safety, at least with respect to the most apparent adverse reactions, but as with pharmaceuticals, signals of adverse effects arise occasionally.

The fact that HMPs are complex mixtures pose some technical difficulties for their reliable genotoxicity assessment. An analogous precedent in some respects are industrial and environmental mixtures and pollutants, which are notoriously difficult to test in *in vitro* and *in vivo* systems. However, experience with these complex mixtures may aid in devising approaches to test HMPs.

Because HMPs shown to be genotoxic are natural substances to which people may be exposed also via food and other sources, several pertinent questions have to be presented. What is the burden to an individual, on top of natural exposure, by using HMPs? Is there a level of exposure that can be regarded as acceptable? Are there scientifically defensible procedures for determining this acceptable exposure?

Even in the case when a HMP has been shown to be genotoxic, the interpretation of the finding may remain problematic. Because HMPs are complex mixtures of natural substances, a component assumed to be responsible for genotoxicity may be a well-known genotoxicant with an established risk characterisation. In this case, the question is whether a threshold, even in principle, can be determined for such an exposure. What is the role of further studies, which should be performed to characterise the real risk of the preparation? The HMPC guideline on non-clinical documentation mentions one example, quercetin.

Another scenario is that the preparation contains, in addition to a well-characterised genotoxicant, one or more radical scavengers, antioxidants, anticarcinogens etc. A question here is whether there are interactions between the genotoxicant and other components of the preparation, which may enhance or decrease the genotoxicity.

Currently, many testing approaches and risk assessment scenarios can be used to assess hazard and risk. At this point it suffices to point out that the CHMP has developed a 'Guideline on the limits of genotoxic impurities' (8), which may be used as a model to develop the guideline for HMPs.

Last, but not least, consumers and patients have used, currently use, and probably continue to use, herbal medicinal preparations to treat themselves. The authorities should not ban this use on the basis of extrapolated suspicions, but their remit is to develop sound risk-benefit approaches for HMPs, with which to protect consumers.

4. RECOMMENDATION

With regard to the questions raised on the application of the existing HMPC guideline on non-clinical documentation to assess genotoxicity of herbal medicinal products, the HMPC recommends the development of a more specific guideline for the practical interpretation and implementation of genotoxicity testing, hazard identification and risk assessment of HMPs.

5. PROPOSED TIMETABLE

It is anticipated that a draft guideline could be available 1 year after the adoption of the concept paper. The draft will then be released for external consultation for three months. The guideline could be finalised within 6 months after external consultation.

6. RESOURCE REQUIREMENTS FOR PREPARATION

The Rapporteur and Co-Rapporteur will prepare a draft guideline. The preparation of this guideline will involve coordination with the CHMP Safety Working Party (SWP).
Member States and interested parties[1] will be invited to provide comments.

[1] Pharmaceutical industry associations, health care professional groups, learned societies, consumers and patients' associations, etc.

7. IMPACT ASSESSMENT (ANTICIPATED)

Industry attributes great importance on the application of the existing guidance documents to herbal medicinal products. Respective proposals and comments have already reached competent authorities. Further participation of industry and stakeholders is anticipated.

8. INTERESTED PARTIES

Primarily the pharmaceutical industry and National Competent Authorities involved in assessment of herbal medicinal products.

9. REFERENCES TO LITERATURE, GUIDELINES ETC

1. CPMP Note for guidance on genotoxicity: a standard battery for genotoxicity testing of pharmaceuticals (CPMP/ICH/174/95)

2. CPMP Note for guidance on genotoxicity: guidance on specific aspects of regulatory genotoxicity tests for pharmaceuticals (CPMP/ICH/141/95) and OECD 1995

3. Guideline on non-clinical documentation for herbal medicinal products in applications for marketing authorisation (bibliographical and mixed applications) and in applications for simplified registration (EMEA/HMPC/32116/2005)

4. Draft Reflection paper on the risks associated with furocoumarins contained in preparations of *Angelica archangelica* L. (EMEA/HMPC/317913/2006)

5. Public statement on the use of herbal medicinal products containing asarone (EMEA/HMPC/139215/2005)

6. Public statement on the use of herbal medicinal products containing estragole (EMEA/HMPC/137212/2005)

7. Public statement on the use of herbal medicinal products containing methyleugenol (EMEA/HMPC/138363/2005)

8. Guideline on the limits of genotoxic impurities (CPMP/SWP/5199/02 and EMEA/CHMP/QWP/251344/2006)