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Committee on Herbal Medicinal Products (HMPC)

Concept paper on the revision of the guideline on the assessment of genotoxicity of herbal substances/preparations (EMEA/HMPC/107079/2007)

Adopted by Committee on Herbal Medicinal Products (HMPC) for release for consultation	21 September 2022
Start of public consultation	31 October 2022
End of consultation (deadline for comments)	31 January 2023

Comments should be provided using this template. The completed comments form should be sent to hmpc.secretariat@ema.europa.eu

Keywords	Committee on Herbal Medicinal Products; HMPC; herbal medicinal products; traditional herbal medicinal products; herbal substances; genotoxicity; genotoxic compounds

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1. Introduction

The "Guideline on the assessment of genotoxicity of herbal substances/preparations" (EMEA/HMPC/107079) was published on 01 December 2008. The procedure was specified by a guideline on the selection of test material for genotoxicity testing for traditional herbal medicinal products/herbal medicinal products (EMEA/HMPC/67644/2009).

The purpose of the guideline EMEA/HMPC/107079 was to describe a general framework and practical approaches on how to assess or to test the potential genotoxicity of herbal substances/preparations with well-established and traditional use and how to interpret the results.

The guideline has now been available for approximately 15 years and a considerable practical experience has been gathered during the use of this guideline in national and European applications.

In order to guarantee that the guideline to assess genotoxicity of herbal substances/preparations reflects the state of the art on preclinical safety of (traditional) herbal medicinal products, a revision of the guideline is proposed.

2. Problem statement

The content of the guideline is still valid, but an update of the document to current standards is required taking into account advances over the last 15 years as well as established practice and legal interpretations. Furthermore, general guidelines on genotoxicity testing such as ICH S2 (R1) have been revised/updated therefore, it appears necessary to discuss potential alignments with general test strategies.

3. Discussion (on the problem statement)

The guideline has been available for more than 10 years and a considerable practical experience has been gathered beside newly available regulatory guidance (e.g. ICH) and technical and methodological progress in the area as a whole. A general update of the document should take into account developments in the scientific field of genotoxicity assessment of impurities in pharmaceuticals.

Some points for consideration are:

- With regard to the multicomponent nature of herbal substances/preparations, some aspects should be highlighted on the strengths and weaknesses of the regulatory accepted genotoxicity tests in terms of test design and evaluation.
- With the updated "ICH guideline S2 (R1) on genotoxicity testing and data interpretation for pharmaceuticals intended for human use" (CHMP/ICH/126642/2008) the concept of genotoxicity testing was extended to an approach which includes 2 *in vivo* tests. Furthermore, the guideline on the limits of genotoxic impurities (EMA/CHMP/ICH/83812/2013) was adopted. A reflection on these should be included in the guideline.

The proposed revision of the "Guideline on the assessment of genotoxicity of herbal substances/preparations" (EMEA/HMPC/107079/2007) will be applicable to authorisation and registration applications for HMPs for human use with well-established and traditional use.

4. Recommendation

With regard to the questions raised on the application of the existing "Guideline on the assessment of genotoxicity of herbal substances/preparations" (EMEA/HMPC/107079/2007), the HMPC recommends to revise this guideline to address the matters described under section 2 and 3. The revised guideline shall apply to HMPs with well-established use for human use and to THMPs for human use.

5. Proposed timetable

It is anticipated that a draft of the revised guideline could be available 6 months after adoption of the concept paper. The draft will be released for external consultation for 3 months. The revised guideline could be finalised within 6 months after external consultation. The revised guideline will replace the current guideline on the assessment of genotoxicity of herbal substances/preparations published in 2008 (EMEA/HMPC/107079/2007).

6. Resource requirements for preparation

The Rapporteur should prepare a draft of the revised guideline and mainly involve the HMPC members and also the contributions of the Joint 3Rs Working Party (J3RsWP) and Non-clinical Working Party (NCWP). Member States are invited to provide comments via their Committee and Working Party members.

7. Impact assessment (anticipated)

The guideline is primarily intended for use by NCAs, applicants and interested parties to accelerate/simplify application procedures, but it also has an impact on the work of the HMPC.

The marketing authorisations/registrations granted and the monographs prepared according to the guideline will have an impact on public health as it will influence the approval and availability of (T)HMPs in the EU.

8. Interested parties

During the consultation period on the revised guideline, comments from parties concerned with the use of (T)HMPs will be welcome.

9. References to literature, guidelines, etc.

1. Guideline on the assessment of genotoxicity of herbal substances/preparations (EMEA/HMPC/107079/2007)

2. Guideline on selection of test materials for genotoxicity testing for traditional herbal medicinal product/herbal medicinal products (EMEA/HMPC/67644/2009)

3. International council for harmonisation of technical requirements for pharmaceuticals for human use (ICH). ICH guideline S2 (R1) on genotoxicity testing and data interpretation for pharmaceuticals intended for human use (EMA/CHMP/ICH/126642/2008)

4. International council for harmonisation of technical requirements for pharmaceuticals for human use (ICH). ICH guideline M7 (R1) on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk (EMA/CHMP/ICH/83812/2013)

5. International council for harmonisation of technical requirements for pharmaceuticals for human use (ICH). ICH guideline M3 (R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals (EMA/CPMP/ICH/286/1995)

6. International council for harmonisation of technical requirements for pharmaceuticals for human use (ICH). ICH Topic Q3 A/B (R2) Note for guidance on impurities in new drug products (CPMP/ICH/2737/99; CPMP/ICH/2738/99)