European Medicines Agency

London, 12 November 2009
Doc. Ref. EMEA/HMPC/67644/2009

COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)

FINAL

GUIDELINE ON SELECTION OF TEST MATERIALS FOR GENOTOXICITY TESTING FOR TRADITIONAL HERBAL MEDICINAL PRODUCTS/ HERBAL MEDICINAL PRODUCTS

DRAFT AGREED BY HMPC DRAFTING GROUP ON QUALITY	February 2009
ADOPTION BY HMPC FOR RELEASE FOR PUBLIC CONSULTATION	12 March 2009
CO-ORDINATION WITH SWP	May 2009
CO-ORDINATION WITH QWP	June 2009
END OF CONSULTATION (DEADLINE FOR COMMENTS)	15 September 2009
AGREED BY HMPC DRAFTING GROUP ON QUALITY	14 October 2009
ADOPTION BY HMPC	12 November 2009
DATE FOR COMING INTO EFFECT	1 July 2010

KEYWORDS	HMPC; herbal medicinal products; traditional herbal medicinal products; herbal substances; herbal preparations; extracts; genotoxicity testing

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 75 23 70 51
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

GUIDELINE ON SELECTION OF TEST MATERIALS FOR GENOTOXICITY TESTING FOR TRADITIONAL HERBAL MEDICINAL PRODUCTS/ HERBAL MEDICINAL PRODUCTS

TABLE OF CONTENTS

1. INTRODUCTION (background)

The 'Community list of herbal substances , preparations and combinations thereof for use in traditional herbal medicinal products' is established by the European Commission based on proposals from the Committee on Herbal Medicinal Products (HMPC), in accordance with Directive 2001/83/EC as amended. The list is being developed gradually through entries of structured information relating to individual herbal substances or preparations.

Inclusion in the Community list of a herbal substance/preparation represents a significant advantage to applicants seeking registrations for traditional herbal medicinal products. This is because once a herbal substance/preparation is included in the Community list an applicant will not be required to provide evidence of the safe and traditional use of a medicinal product for which he seeks a traditional use registration if he demonstrates that the proposed product and related claims in the application comply with the information contained in the list.

Once a herbal substance/preparation is included in the Community list, competent authorities will not have the opportunity to require additional data to assess the safety and the traditional use of the product. In view of this, the HMPC has concluded that, where data on genotoxicity are inadequate or absent, it will not be possible to endorse the herbal substance/herbal preparation for inclusion in the Community list.

As a result, progress with the development of Community list is being hampered by the absence of genotoxicity data. Experience to date confirms that many well known traditional herbal substances/preparations, already widely available within the Community, will be excluded from the Community list solely as a consequence of absence of genotoxicity data and thus any potential benefits of the list to applicants will be lost.

To assist applicants, the HMPC has developed a guideline, 'Guideline on the assessment of genotoxicity of herbal substances/preparations' **(**EMEA/HMPC/107079/2007) which describes a general framework and practical approaches on how to assess or to test the potential genotoxicity of herbal substances/preparations and how to interpret the results. The stepwise approach described in the guideline sets out a pragmatic approach to address both scientific aspects of genotoxicity testing and the special needs of herbal medicinal products within the current regulatory framework applicable to these products.

Strictly speaking, genotoxicity testing should be carried out by individual applicants on their specific materials and it is recognised that this represents a major task and considerable duplication of effort particularly for applicants seeking registrations for traditional herbal medicinal products. Industry has therefore been encouraged to consider undertaking collaborative research on genotoxicity and one such study is underway within some Member States.

Community herbal monographs established by the HMPC set out the well-established and/or traditional uses for a particular plant species. The individual monographs usually cover a range of herbal preparations depending on the therapeutic uses of the particular plant. For example, the monographs for Melilot herb and Passiflora herb include a range of preparations as shown in the tables below. This guidance offers a strategy to reduce the number of test materials such that a representative range of herbal preparations is tested rather than requiring individual manufacturers to undertake their own testing on specific preparations.

2. SCOPE

This guideline addresses the selection of materials for genotoxicity testing in support of applications for traditional herbal medicinal products/ herbal medicinal products.

This guideline provides possible approaches to what types of materials should be subjected to testing for genotoxicity bearing in mind that different herbal preparations may have different toxicological profiles. The guideline proposes applying reduced testing designs such as a

'bracketing/ matrixing' approach to the test materials such that a representative range of materials is tested rather than requiring individual manufacturers to undertake their own testing on specific preparations.

The main objective is to achieve consensus on a standard range of test materials which could be considered representative of the commonly used herbal substances/preparations with the intention of facilitating entry to the Community list.

The same approach could also be applied to herbal ingredients of herbal products which fall within the well-established use category of herbal medicinal products.
The results of genotoxicity testing on individual herbal substances/preparations can be used for assessment of combinations of herbal substances/preparations.

3. LEGAL BASIS

This guideline supports the development of the 'Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products' in accordance with Directive 2001/83/EC, as amended.
This guideline supports applications made under the simplified registration procedure for traditional herbal medicinal products for human use.
This guideline also supports applications for marketing authorisations according to Directive 2001/82/EC, as amended and Directive 2001/83/EC, as amended.

4. SELECTION OF MATERIALS FOR GENOTOXICITY TESTING

This guideline provides an approach to developing a standard range of test materials for genotoxicity testing which could be considered to be representative of the herbal substances/preparations intended for the Community list.
The guideline is intended to assist industry groups considering collaborative work on genotoxicity testing as is currently being encouraged by the HMPC. The same approach could be applied to herbal ingredients of herbal products which fall within the well-established use category of herbal medicinal products.

The concept of applying a reduced design approach such as 'bracketing/ matrixing'to the selection of samples for genotoxicity testing is proposed. Using the 'bracketing' concept, only samples on the extremes of certain design factors would be tested. The reduced design assumes that the genotoxic potential of any intermediate preparation is represented by the test results of the extremes tested. Where a reduced testing design is proposed, evidence (usually chromatographic data) should be provided to demonstrate that the samples to be tested represent the phytochemical profile of all materials to be covered by the genotoxicity testing.

Herbal extracts are the most commonly used herbal preparations. Using herbal extracts as an example, the proposal would be to test samples prepared using the extremes of extraction solvents. In some cases, however, it may also be appropriate to test an extract of intermediate strength. In addition, where substantially different drug extract ratios are used additional testing may be required unless the phytochemical similarity of the test materials can be demonstrated.

Melilot herb and Passiflora herb are used to illustrate the approach to be considered. In both examples, their respective Community monographs list a range of herbal extracts with recognised traditional usage. However, due to the absence of supporting genotoxicity data at the present time, neither herbal ingredient can be included in the Community list.

I. Melilot herb *(Melilotus officinalis* (L.) Lam.)

The Community monograph for Melilot herb includes a range of aqueous/ethanolic extracts and two methanolic extracts. These are listed in Table 1 in order of decreasing polarity.

Table 1 Melilot herb: Aqueous and ethanolic/methanolic extracts

Herbal preparations
Herbal substance for tea preparation (100% aqueous)
Dry extracts (3 - 5:1), water (100% aqueous)
Dry extracts (7 - 9:1), methanol 30 % V/V
Liquid extracts (1:1), ethanol 30 % V/V
Dry Extracts (5 - 7:1), ethanol 50 % V/V
Dry extracts (4 - 8:1), ethanol 25 % m/m
Dry extracts (4 - 8:1), ethanol 35 % V/V
Dry extracts (4 - 8:1), methanol 50 % V/V
Dry extracts (6 - 9:1), ethanol 90 % V/V

With regard to the aqueous and alcoholic extracts of Melilot herb, testing the extremes of the range i.e. equivalent to 10% and 100% aqueous extracts would in theory cover the range of extracts. However, with such a wide range an extract mid-range e.g. 50% water should also be tested.

II Passiflora herb *(Passiflora incarnata* L.)

The Community monograph for Passiflora herb includes a range of aqueous/ethanolic extracts (Table 2).

Table 2 Passiflora herb: Aqueous and ethanolic extracts

Herbal preparations
Herbal substance for tea preparation (100% aqueous)
Liquid extract (1:8); extraction solvent 25% ethanol
Liquid extract (1:8) ; extraction solvent 45% ethanol
Liquid extract (1:1) ; extraction solvent 25% ethanol
Liquid extract (1:1) ; extraction solvent 70% ethanol

With regard to the aqueous and ethanolic extracts of Passiflora herb, testing the extremes of the range i.e. equivalent to 30% and 100% aqueous extracts would in theory cover the range of extracts in the Community monograph. Consideration should be given to including a mid-range solvent e.g. 70% aqueous, depending on the chromatographic profiles.

Herbal substance used in herbal medicinal products

Where the entire herbal substance is incorporated directly into the herbal medicinal product, e.g. in capsules, tablets, the test material for genotoxicity testing, should, in theory, cover the entire spectrum of phytochemical constituents, including polar and non-polar constituents. Test materials for genotoxicity testing should therefore include extraction solvents which encompass the entire phytochemical profile. The choice of solvents should be justified. Consideration should be given to including an extract mid-range e.g. 50% water.

Fixed oils/essential oils/expressed juices etc

Where the herbal preparations include for example fixed oils, essential oils, expressed juices etc these should be addressed on a case by case basis. Some materials may need to be tested individually as part of the genotoxicity test programme. In the case of expressed juices, it may be possible to demonstrate that the material is covered by testing of, for example, an aqueous extract.

DEFINITIONS

Herbal medicinal products: any medicinal product, exclusively containing as active substances one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations.

Herbal preparations: are obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates.

Herbal substances: all mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried form but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author).

Traditional herbal medicinal products: medicinal products for human use that fulfil the conditions laid down in Article 16a(1) of Directive 2001/83/EC, as amended.

REFERENCES

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

Concept paper on selection of test materials for genotoxicity testing for traditional herbal medicinal products/herbal medicinal products (EMEA/HMPC/315413/2008)

