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Guidance for companies seeking scientific support and advice on traditional herbal medicinal products

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Guidance for companies seeking scientific support and advice on traditional herbal medicinal products

The following guidance has been established for companies who may want to seek scientific support and advice from the Committee on Herbal Medicinal Products (HMPC) on traditional herbal medicinal products. It provides an outline of the procedure to obtain scientific support and advice and clarifies the scope of such advice.

This guidance should be used in conjunction with the form 'Request form for scientific support and advice on traditional herbal medicinal products' (EMA/HMPC/119889/2005 Rev.1).

Before considering seeking advice from the HMPC, companies are reminded of the following other options to obtain guidance on herbal medicinal products:

1. **Scientific and regulatory advice can be obtained from the national competent authorities in the Member States of the European Union**

Links to the websites of these national competent authorities for medicinal products for human use are provided here:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general_content_000155.jsp&murl=menus/partners_and_networks/partners_and_networks.jsp&mid=WC0b01ac0580036d63

2. **Scientific advice can be obtained from the Scientific Advice Working Party (SAWP) established by the Committee for Medicinal Products for Human Use (CHMP). In particular, the SAWP can be contacted for advice on herbal medicinal products other than traditional herbal medicinal products. The SAWP will liaise with the HMPC where appropriate.**

Information on how to request scientific advice is provided here:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000049.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800229b9

The HMPC adopts its scientific recommendations on the medicinal uses of herbal substances and herbal preparations (laid down in Community herbal monographs) by either consensus or a majority vote. The members of the HMPC (chosen for their role and experience in the evaluation of herbal medicinal products and representing the national competent authorities) express their divergent position when they do not support the entire content of a monograph. The divergent positions are published on the Agency website, as an appendix to the HMPC opinion. **These positions may provide valuable information for companies as to the specific approaches taken by some regulatory authorities on a national level.** The names of the members who expressed the divergent positions can be obtained upon submission of a request for access to documents according to the 'EMA Policy on access to documents (related to medicinal products for human and veterinary use)' (EMA/110196/2006, 30 November 2010), which can be found here:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/document_library/document_listing/document_listing_000312.jsp&murl=menus/document_library/document_library.jsp&mid=WC0b01ac0580022517

Note: It should be noted that this document has been produced for guidance only and should be read in conjunction with the relevant legislation and guidance, including:

- Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004
- Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use.
- Regulation (EC) No 1905/2005 of the European Parliament and of the Council of 14 November 2005 amending Regulation (EC) No 297/95 on fees payable to the European Medicines Agency
- Rules for the implementation of Council Regulation (EC) No 297/95 on fees payable to the European Medicines Agency and other measures (EMA/MB/757388/2010)
- HMPC rules of procedures (EMA/HMPC/139800/2004 Rev.2)
- EMA policy on the appropriate coordination between the scientific committees of the Agency (Policy 0009, EMA/124704/2005 Rev.1)

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1. What is the legal basis for scientific support and advice by the HMPC for traditional herbal medicinal products?

The legal basis and scope of Scientific Advice (SA) provided by the Agency as per the provisions of Article 57(1)(n) of Regulation (EC) No 726/2004 ["*advising undertakings on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products*"] can be found in the 'European Medicines Agency Guidance for companies request Scientific Advice and Protocol Assistance' (EMA/H/4260/2001 Rev.6).

The HMPC shall be responsible for providing scientific support and advice on traditional herbal medicinal products as defined in Article 1(29) of Directive 2001/83/EC as amended.

It is the responsibility of the HMPC to provide scientific support and advice to industry by answering questions based on documentation provided by the company. It is not the role of the HMPC to substitute the industry's responsibility in developing their products and the advice is given in the light of the current scientific knowledge.

Scientific support and advice is prospective in nature. It allows input on developments, which can be amended after HMPC advice. Scientific support and advice focus on development strategies rather than pre-evaluation of data, to support a simplified traditional use registration process in a Member State. It is limited to scientific issues, thus regulatory aspects should be the matter of a separate request. Companies seeking scientific support and advice must note that any advice given is not legally binding on national competent authorities with regard to any future registration application in a Member State.

If companies are established outside the European Economic Area (EEA), it is advisable for them to nominate a contact point within the EEA to facilitate communication between the Agency and such companies. This contact point may be the same as the applicant, or not.

2. What falls under the scope for scientific support and advice on traditional herbal medicinal products?

Scientific support and advice can be request on:

- Single areas e.g. questions concerning quality or safety or long-standing use and experience
- Multiple areas i.e. a combination of single area requests

Quality aspects including issues concerning:

Collection/harvesting, tests and acceptance criteria for the herbal substance(s), herbal preparation(s) and herbal medicinal product, combination, manufacturing, chemical, pharmaceutical and biological testing.

Deviations or interpretations of HMPC guidelines.

Safety, non-clinical aspects including issues concerning:

Evidence that the product is not harmful in the specified conditions of use, non-clinical tests necessary for assessing the safety (literature data replacing non-clinical tests and their interpretation, choice of non-clinical tests to be carried out, evaluation of unexpected findings, etc).

Deviations or interpretations of HMPC guidelines.

Long-standing use and experience including issues concerning:

Adequacy of evidence of long-standing use and experience, plausibility of pharmacological effects or efficacy, appropriateness of indications (use of traditional herbal medicinal product without the supervision of a medical practitioner for diagnostic purposes or for prescription or for monitoring of treatment; use of traditional herbal medicinal product after serious conditions have been excluded by a medical doctor).

The following remain outside of the scope of the scientific advice and support by the HMPC:

- Judgement as to whether data can support a well-established medicinal use application
- Classification-related questions and borderline issues
- Regulatory advice concerning marketing authorisation and traditional use registration procedures
- Scientific advice on herbal medicinal products other than traditional herbal medicinal products, including those intended for marketing authorisation according to provisions of Article 10a of Directive 2001/83/EC as amended.

3. How do I request scientific support and advice?

- The **request form** for scientific support and advice on traditional herbal medicinal products should be completed by the applicant (available on the Agency website).
- The request form should be sent by email or post to the HMPC secretariat (as stated on the form).
- The request contains information on the applicant, the product and specifies what type of documentation will be made available to the HMPC.
- The last section of the form is intended for the specific questions to be addressed by the HMPC on:
  - Quality
  - Safety
  - Long-standing use and experience.
- The HMPC secretariat in liaison with the HMPC Chair will decide, based on the received request, whether it is **eligible** for scientific support and advice by the HMPC.
- If it is not the case, the secretariat may advise the applicant on how to proceed (consult a national competent authority in a Member State, seek SA from the CHMP SAWP for examples).
- If the secretariat considers that the request falls under the scope for scientific support and advice, it will discuss the questions posed in the request together with the applicant. It is possible that the content of the request form and scope of the questions need to be revised or clarified to obtain satisfactory answers.
- When the request has been validated, the applicant submits the **briefing document** with the questions to the HMPC and, for each question, the company's position and a justification for this position. This briefing document contains in annex the list of all the documents/information in support of the request such as expert report(s), tabulated overview(s), HMPC monograph(s), published and unpublished data, pharmacopoeia monograph etc. These supporting documents shall be submitted separately (each document individually or all in one pdf document).

4. What are the fees and when should they be paid?

Scientific support and advice on traditional herbal medicinal products appear under 'Scientific services' in Annex II to the 'Rules for the implementation of Council Regulation (EC) No 297/95 on fees payable to the European Medicines Agency and other measures':

'Evaluation of traditional herbal medicinal products

The following ranges and classification shall apply for fees for evaluation of traditional herbal medicinal products:

- *EUR 19 500 for request for scientific support and advice by the HMPC on multiple areas related to traditional herbal medicinal products.*
- *EUR 12 900 for requests for scientific support and advice by the HMPC on single areas, e.g. quality or safety or long-standing use, related to traditional herbal medicinal products.'*

The fees are paid after the scientific support and advice is agreed upon by the HMPC. An invoice will be issued by the Agency on the date when the administrative validation is communicated to the applicant. The fees should be paid within 45 calendar days of the date of the start of the procedure.

5. What are the fee reductions for small and medium-sized enterprises (SME)?

Pursuant to Article 70.2 of regulation (EC) No 726/2004 of 31 March 2004, SMEs are eligible for fee reductions, fee deferrals and conditional fee exemptions in accordance with Regulation (EC) No 2049/2005 of 15 December 2005. This includes fee reductions for SA, pre- and post-authorisation inspections, scientific services and a full waiver for administrative services (with the exception of parallel distribution). It should be noted that fee reductions can only be considered once the applicant has been assigned SME status by the Agency. SME applicants wishing to request a fee reduction should address a letter of intent to the SME office of the Agency, at least 2 weeks in advance of the request for scientific support and advice.

Further information is available at:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/wrapper_page.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058002d4f0

6. How long in advance should the Agency be notified about future submission of requests for scientific support and advice?

The Agency secretariat should be formally notified of the intent to submit a request for scientific support and advice by the HMPC. A notification one month before the submission is requested. As the HMPC meets every other month, it is advisable to submit an initial request to the HMPC secretariat at least 8 weeks before the meeting when HMPC Rapporteur (Rapp) and Co-Rapporteur (Co-Rapp) will be expected to be appointed. This allows for the HMPC secretariat and Chair to form an opinion on the eligibility of the request and to revise it together with the applicant prior to circulation to the HMPC in pre-meeting mailings.

7. To whom shall I submit the notification and initial request for scientific support and advice?

The notification and the initial request for scientific support and advice should be sent by the applicant or contact point to hmpc.secretariat@ema.europa.eu.

8. What are the timelines to receive a scientific support and advice?

A timetable for the scientific support and advice procedure shall be adopted. The following schedule is a tentative timetable that shall be adapted for each procedure, according to meeting dates for all involved parties.
D = Day of the HMPC meeting when the scientific support and advice procedure is expected to start.

- **D - 12 weeks** The **notification** is received at the Agency.
- **D - 8 weeks An initial request** for scientific support and advice is submitted to the HMPC secretariat. If the request falls/appears to fall under the scope, the applicant and the secretariat may work together to revise the request if necessary.
- **D - 6 weeks** The applicant is informed of the **administrative validation** of the request (initial or revised). The applicant sends the **briefing document** and supporting documentation. The secretariat sends out the request + the briefing document + the supporting documentation to HMPC members.
- **D** During the **HMPC meeting**, the committee decides whether the request is eligible for scientific support and advice and subsequently appoints a Rapp and a Co-Rapp. The procedure starts.
- **D + 21 days** The reports by the Rapp and Co-Rapp are sent to HMPC members for comments. Coordination with the Q DG and/or MLWP if recommended by the Rapp and Co-Rapp and agreed by the HMPC Chair to be sought.
  Coordination may also be established with other scientific groups at the Agency, e.g. the CHMP Safety Working Party, according to the 'EMA policy on the appropriate coordination between the scientific committees of the Agency'.
- **D + 40 days** Deadline for comments by HMPC members.
- **D + 50 days** The Rapp and Co-Rapp prepare a joint report taking into account the comments received and input from Q DG and/or MLWP and other consulted group(s).
- **D + 60 days** The **joint report** is discussed during the **HMPC meeting**. It is decided whether the advice can be adopted without further consultations with the applicant. If there are issues that need to be discussed, this can be arranged by written procedure (minor issues) and/or at a hearing with the applicant (list of questions).

In case of questions raised by the HMPC to the applicant:

- **D + to be established** The HMPC discusses the preliminary conclusions by the Rapp and Co-Rapp drawn in a joint report on the applicant's responses to the issues raised by the HMPC.
- **D + to be established** The Rapp and Co-Rapp's final joint report and draft advice letter are submitted to the HMPC secretariat and are adopted by the HMPC at a meeting or by written procedure.

9. What is the role of the Rapporteur and Co-Rapporteur?

The Rapp and Co-Rapp are HMPC members that have been appointed on the basis of their expertise and in absence of conflicts of interest. As appropriate, the HMPC may appoint only a Rapp.

The Rapp and Co-Rapp ensure that any experts assisting them have declared their interests before being involved in the scientific support and advice procedure. Conflicts of interest declared by experts will be handled in accordance with the 'European Medicines Agency Policy on the handling of conflicts of interests of scientific committee members and experts' (EMA/513078/2010). All experts are bound by a confidentiality agreement.

The Rapp and Co-Rapp are responsible for providing reports in response to the scientific support and advice request respecting the adopted timetable. These reports are considered as working documents only and will not be released to the applicant. They prepare the joint report that shall form the basis of the advice. If necessary, the Rapp and Co-Rapp may ask for any additional documents or explanation and the HMPC secretariat shall transmit the request to the applicant. They will compile the list of issues that require clarification before the scientific support and advice can be given. They will prepare the final joint report that will be adopted and be the foundation to the scientific support and advice letter on the single or multiple areas of the request.

10. Is the scientific support and advice provided by the HMPC binding to national competent authorities?

The scientific support and advice given by the HMPC is not legally binding to national competent authorities with regard to any future simplified traditional use registration application. However these authorities shall take into consideration any HMPC advice as a result of a request for scientific support and advice.

It is expected that the HMPC will be consistent in its opinion if the Committee is requested to issue a scientific opinion on the traditional herbal medicinal product during a referral by a Member State according to Article 16c(1)(c) or Article 16c(4) of Directive 2001/83/EC as amended as far as the questions and supporting documentation/data put forward by the referring Member State are identical to those assessed by the HMPC in the scientific support and advice, unless other available data justify a different opinion.

The advice is also expected to be taken into account during any future establishment or revision of a monograph or list entry directly concerned by the scope of the advice.

Advice will be given in good faith but circumstances could change. However, if applicants choose not to apply the advice when applying for simplified traditional use registration, they are advised to clearly justify their position in their national registration application(s).

11. Is it possible to approach national competent authorities on the same topic?

Yes, it is possible and even recommended to seek advice at a national level before requesting advice from the HMPC.