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Patient Health Protection

# Report on 'Action plan for herbal medicines 2010-2011'

Public report

## Preamble

The set of Community herbal monographs established by the Committee on Herbal Medicinal Products (HMPC) has been continuously extended since 2004. Nearly 100 Community herbal monographs (monographs) on herbal substances and preparations thereof were finalised by the end of 2011. This represents a substantial achievement, taking into account that the total number of herbal substances with a relevant tradition of medicinal use in the European Union can be estimated probably up to 200. Although only 10 Community list entries (list entries) could be established, the relevance of the system of monographs and list entries can be demonstrated by the analysis of data on registrations of traditional herbal medicinal products in the member states. The availability of Community herbal monographs definitely improves the level of European harmonisation and can contribute to a more efficient evaluation of (traditional) herbal medicinal products at the national medicines agencies.

## Introduction

At the beginning of 2010, anticipating the end of the 7-year transition period for the member states to implement provisions of Directive 2004/24/EC (30 April 2011) and considering the outcome of an internal audit of the HMPC activities conducted in 2009, the EMA Management Board adopted an 'Action plan for herbal medicines 2010-2011', which was also endorsed by Heads of Medicines Agencies in April 2010.

Whilst a number of initiatives remained open for further progress and have now been taken up in the HMPC work programme for 2012-2015, many of the objectives have been reached and the present document reports on the status of all actions as anticipated in early 2010.

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## Objective I: To improve the output of the Committee on Herbal Medicinal Products, in particular by increasing the quality and number of Monographs and List entries

The following actions shall be addressed:

1. Action I/1: In collaboration with stakeholders, adjust the priority list of herbal substances, preparations and combinations thereof for assessment to the needs of the market operators and allocate member states resources accordingly.

   **2010**

   Interested parties were consulted on the prioritisation of future assessment works.

   **2011**

   The inventory and the priority list were updated to reflect the feedback received, in particular AESGP's suggestion to assess 3 herbal substances (Andrographidis paniculatae folium, Capsici fructus, Erysimi officinalis flos). The HMPC decided that the assessment works on Crataegus and Ginkgo would go ahead given their importance at European level. In July 2011, the HMPC appointed Rapporteurs for Adhatodae vasicae folium, Picrorhizae kurroae rhizhoma and Withaniae somniferae radix within the context of the collaboration with the Indian Authorities, which had transmitted 8 proposals for monographs in 2008. In November 2011, the HMPC agreed on the principle of running a pilot phase to establish a few monographs on Traditional Chinese Medicines to gain experience in such assessment which raises also technical, regulatory and scientific challenges that member states face at a national level with traditional use registration applications.

   The prioritisation of future assessment works based on clear criteria and the assessment of medicinal plants from non-European phytotherapy traditions are taken up in the HMPC 2012-2015 work programme.

   **Status**: Completed for 2010-2011. To be continued in 2012-2015

2. Action I/2: Implement in 2011 the orientation concerning the genotoxicity data situation discussed and to be chosen in 2010. Possible options include the use by the HMPC of unpublished data available on a national level and a labelling transparent with regard to genotoxicity information.

   The following was undertaken in **2010**:

   - In May 2010, the HMPC discussed data protection of unpublished genotoxicity study results (and other clinical or non-clinical studies) generated for old, well-established substances. The HMPC agreed to seek in July 2010 clarification from the European Commission on such data protection and on the question whether the HMPC can refer to conclusions reached by NCA after their assessment of data submitted by applicants. In October 2010, the European Commission clarified that Directive 2001/83/EC does not contain a legal basis pursuant to which a competent authority would be able to provide to the HMPC the non-clinical and clinical data included in a dossier submitted by an applicant.
   - The HMPC actively sought information on the initiative among German phytopharmaceutical industry on genotoxicity testing. A hearing with Kooperation Phytopharmaka took place in November 2010 in the MLWP. It was clarified that companies have not agreed so far to provide data from the collaborative testing to the HMPC. Kooperation Phytopharmaka agreed

to discuss with the participants of the initiative whether the data could be shared after a certain timeframe e.g. 6-10 years. The report from this hearing is published:

http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/03/WC500103468.pdf

The following was undertaken in **2011**:

- In July 2011, the HMPC reiterated its position vis-à-vis the legal binding character of list entries and the need for NCAs to have the capacity to seek from applicants appropriate data on genotoxicity and mutagenicity. The HMPC did not support other options such as a labelling transparent to the genotoxicity testing and the receipt of expert statement on safety from NCAs without disclosing individual company data.

In conclusion, the HMPC/MLWP held several discussions and explored different approaches which did not result in the selection of a suitable orientation that could be implemented in 2011 with a view to solving the 'genotoxicity data situation' raised in the 2008 Commission report (see Annex 1).

Member states have reported that within applications companies often accept the request on genotoxicity data in accordance with the guidance provided. This will at least improve the existing data on genotoxicity and may help to find an appropriate solution in future.

The matter is taken up in the HMPC 2012-2015 work programme.

**Status**: Ongoing

*3.* Action I/3: Implement the HMPC policy for the systematic assessment of the need for revision of final Community herbal monographs, aiming that they remain up to date (scientific state of the art). *Pending sufficient resources at HMPC/MLWP level.*

**2010**

On behalf of the HMPC, the DG ORGAM developed in 2010 a procedure for the systematic assessment of the need to revise a Community herbal monograph and supporting documents (EMA/HMPC/124695/2011). It proposes a set of actions with respective timelines for the 'systematic review' anticipated in the HMPC 'Reflection paper on the reasons and timelines for revision of final Community herbal monographs and Community list entries' (EMEA/HMPC/326440/2008).

**2011**

The MLWP and HMPC discussed concerns expressed about the resources implications for this activity and about the scope of the revision. On the basis of the experience in Germany where the Commission E monographs had not been kept up-to-date, the HMPC felt important to allocate some resources. The revision may also allow new preparations to be included, for which 30/15 years could not be demonstrated at the time of the finalisation. Some members suggested applying a risk-based approach in choosing which monographs should be revised. Another criteria for the selection of the monographs to be revised in priority could be the level of use of the monographs by the market operators; in that respect the data collected during the survey on TUR and MA would be informative (see Action III/1). The HMPC and MLWP agreed to run a pilot phase with a view to defining a strategy based on the experience with a few reviews/revisions and reflecting on the pros & cons of such revision (possibly a graduated approach to be defined).

The draft procedure was adopted by the HMPC in July 2011 and calls for scientific data to support the review process for 10 monographs were published (respectively 2 by Austria, 2 by Italy, 4 by Germany and 2 by Sweden).

Implementation of the pilot phase and fine-tuning of the long-term strategy are taken up in the HMPC 2012-2015 work programme.

**Status**: Completed for 2010-2011. To be continued in 2012-2015

4. Action I/4: Implement changes to the working methodology of the HMPC, its Working Party (WP) and Drafting Groups (DGs) as well as to their interaction, to improve the quality and timely delivery of monographs and list entries and related documents.

   In response to the audit in 2009, the DG ORGAM mandate and DG Quality mandate had been revised to strengthen coordination with the MLWP.

   The following changes were implemented:

   **2010**

   - HMPC/MLWP agreed to have a voluntary early peer-review of draft monographs and supporting documents when deemed necessary by the Rapporteur and Peer-reviewer, prior to the release for public consultation (start May 2010)
   - HMPC/MLWP agreed to set up small groups for the review of first draft monographs, for efficiency gains (start May 2010)
   - In May 2010, a change took place in the policy of the working party as regards the release of draft assessment reports (ARs) supporting draft monographs for public consultation. ARs are now systematically released with a disclaimer pointing to their nature as 'working documents not yet fully edited'. The MLWP/HMPC retain the discretion not to publish a draft AR, if concurring with the view of the Rapporteur and Peer-reviewer that it has not reached a sufficiently advanced stage of preparation to be released.
   - As regards cooperation with EDQM on the adjustment of respective work programmes (EMA/HMPC and Eur. Ph. Expert Groups 13A, 13B, TCM) to ensure that quality standards are in place for established Community herbal monographs, the HMPC noted in May 2010 the uptake of monographs by EDQM for which Community herbal monographs were scheduled for preparation and which had no Ph. Eur. monograph as quality standard so far (for examples Avenae herba, Hamamelidis cortex, Hamamelidis destillatum, Primulae flos, Mate folium and Vitis folium).

   **2011**

   - Until March 2011, MLWP meetings of 2.5 days' duration were immediately followed by HMPC meetings of 1.5 days' duration. Starting from May 2011, a new schedule of HMPC and MLWP meetings was implemented with Committee meetings for one day only being held before the working party meetings. Since the mandate of the Committee was first approved in 2004, volumes of documents had substantially increased. This made reporting to the HMPC immediately after a MLWP meeting difficult. The new meetings timetable aimed to make efficiency gains at HMPC, MLWP and secretariat levels and to lead to improved editorial/linguistic quality and greater consistency in documents, with an additional 2-month period of time being given to Rapporteurs and respective Peer-reviewers to finalise sets of documents before their adoption by the HMPC.

- In the first half of 2011 further improvements of particular aspects of procedures were implemented in order to better allocate the resources of members of HMPC and MLWP and the secretariat. Measures were taken to solve the backlog in the publication of monographs. The number of pre-meeting mailings was reduced and reasonable deadlines were set to allow planning and preparation and to reduce administrative workload. Coordination of communication in between the meetings was improved.
- In September 2011, the HMPC endorsed a proposal clarifying responsibilities of Rapporteurs and Peer-reviewers. The document is intended as a tool to assist Rapporteurs and Peer-reviewers for an increased quality (including editorial, linguistic and consistency) of the adopted documents, prior to their publication on European Medicines Agency website. The HMPC also decided to apply a new approach to the public consultation on draft monographs, list entries, public statements and supporting documents; as of 2012 comments from interested parties on draft documents shall be submitted together with copies of the cited references to facilitate the assessment of the comments, suggestions and corresponding justifications.
- The improvement of templates, SOP and other procedural guidance in order to produce monographs, list entries and supporting documents of high quality and consistency is taken up in the HMPC 2012-2015 work programme.
- In July 2011, the HMPC supported all initiatives proposed to continue reinforcing the cooperation with EDQM, for example in the work towards revision of the Ph. Eur. monograph on extracts.

Investigating opportunities for efficiency gains in the operations of the HMPC and its subgroups and the harmonisation of assessment practice for herbal substances of non-European origin are taken up in the HMPC 2012-2015 work programme. This will encompass a close collaboration with the Ph. Eur. groups developing pharmacopoeial standards for selected popular herbal preparations in traditional Chinese and Ayurveda medicine in parallel to the development of HMPC monographs (see also ACTION I/1).

**Status**: Completed for 2010-2011. To be continued in 2012-2015

5. Action I/5: Achieve the expected number of monographs and list entries to be established

Key Performance Indicators (KPI):

**2010**
*Community herbal monographs*
– Final: 19/20
– Released for public consultation: 20/20

*Community list entries*
– Transmitted to the European Commission: 3/5
– Released for public consultation: 2/5

**2011**
*Community herbal monographs*
– Final: 20/20
– Released for public consultation: 21/20

*Community list entries*
– Transmitted to the European Commission: 0/10*
– Released for public consultation: 0/10*

** The KPI for list entries in 2011 was made dependant on the success expected in 2010 in finding a solution concerning the genotoxicity data situation – see Action I/2 above*

Thus, for the first time in 2011, the HMPC attained fully its annual KPIs for monographs, as the committee adopted 20 final monographs (exactly meeting the KPI) and 21 draft monographs (thus exceeding the KPI by one); this achievement is also supplemented by the assessment works which were conducted and led to the release of public statements when no monograph could be established (2 final, 5 draft).

The adjustment of the annual KPIs for the establishment of monographs and list entries and the definition of new KPIs for the revision of monographs/list entries are taken up in the HMPC 2012-2015 work programme.

**Status:** Completed for 2010-2011. To be continued in 2012-2015

## Objective II: To respond to any actions arising from the end of the transition period by which Member States shall apply the provisions of Directive 2004/24/EC to traditional herbal medicinal products

The following actions shall be addressed:

1. Action II/1: Collaborate with the European Commission on guidance on complex legal issues raised by Directive 2004/24/EC such as the inclusion of some interpretative guidance on Directive 2004/24/EC in the Notice to Applicants.

   The following was undertaken in **2010**:

   In February 2010, the European Commission had been informed of the HMPC view that it would be useful, to facilitate the application of Directive 2004/24/EC, if the NTA Group discusses the inclusion in the NTA of interpretative guidance on this directive. It was also indicated that the HMPC had identified as well the need for greater clarification at European level on procedures applicable for medicinal products the active substance(s) of which have a well-established medicinal use (bibliographic applications). This need had been evidenced at European Medicines Agency when dealing simultaneously with two requests on this topic, one request from a Law Firm in one of the member states addressed to European Medicines Agency and one request from an HMPC member addressed to the HMPC. The European Commission had been provided with the Law Firm request and the response from European Medicines Agency Legal service as well as an overview of answers sent by HMPC members on approaches followed in their country. As the overview illustrated differences in national practice in the member states, it reinforced the need for Commission's guidance on the matter raised.

   The following was undertaken in **2011**:

   - In May 2011, European Medicines Agency provided comments on the proposed revision of the NTA Volume 2A Chapter 1 section 3.4 'Procedure for traditional herbal medicinal products (traditional use registration)' with a view to including two clarifications provided by the European Commission in 2010. Such clarifications were reflected on the EMA website concerning the important role of monographs to bring harmonisation to this field and to facilitate the use of the simplified registration procedure and via the publication in September

2011 of a HMPC public statement on therapeutic indications appropriate for traditional herbal medicinal products.

- In July 2011, the HMPC was informed of an event organised by some members of the European Parliament on 21 June 2011, with a Q&A session on the implementation of Directive 2004/24/EC, the problems raised by the directive and its possible revision, in the presence of officials from the European Commission and representatives from the EMA – see ACTION V/1.

**Status**: Completed

2. Action II/2: Contribute to discussions by the HMPC serving as a platform for exchange of information between the member states.

During HMPC meetings, exchange of legal, regulatory and scientific information takes place with respect to many topics on the agendas.

More specifically, HMPC members may raise specific questions and other members are invited to provide responses, often reporting on the approach taken by the NCA in their Member State on the matter raised. The member seeking information compiles the responses which are then circulated to the committee for information purposes.

In **2010**, the HMPC addressed 4 questions/requests for clarification:

- authorisation practice of products containing ingredients of non-herbal origin (animal, mineral, etc.);
- interpretation of definition of 'corresponding product';
- the inclusion of the strength of a herbal medicinal product as part of the name (SmPC, Section 1.);
- section 4.6 of SPC guideline and monographs' template as regards fertility data.

In **2011**, the HMPC addressed 3 questions/requests for clarification:

- classification of Saccharomyces boulardii dried yeast;
- proof of traditional use for combined extracts;
- classification of natural camphor.

**Status:** Completed for 2010-2011. To be continued in future

## Objective III: To report on the uptake of the traditional use registration scheme

The following actions shall be addressed:

1. Action III/1: In collaboration with the CMD-h, publish and update on a 6-monthly basis an overview of applications received, under evaluation and registrations granted per Member State (name of product, herbal substance, preparation or combination thereof used and the therapeutic indication(s) granted).

   The following was undertaken in **2010**:

   - In June 2010, the CMDh established a list of contact points for herbal medicinal products (well-established use & traditional use) in the member states and in July 2010, the HMPC commented on the questions proposed by European Medicines Agency secretariat that shall be answered on a regular basis by the contact points for herbal medicinal products.
   - In December 2010, the questionnaire was sent to all contact points.

   The following was undertaken in **2011**:

   - Publication of the first survey results on European Medicines Agency website took place on 27 May 2011 and the survey results were transmitted to the CMDh on 8 April 2011.
   - In July 2011, the HMPC noted the updated questionnaire (see ACTION III/3) and accompanying timetable for the second survey to collect data on both TUR and MA granted since the implementation of Directive 2004/24/EC. The results of the second survey (status 30 June 2011) were published in December 2011.

   This activity is taken up in the HMPC 2012-2015 work programme.

**Status**: Completed for 2010-2011. To be continued in 2012-2015

2. Action III/2: Explore the possibility to include traditional use registrations in the EU database on medicinal products.

   **2011**

   In July 2011, the HMPC was informed about a query received at European Medicines Agency in relation to the publication by the EMA of the 'Legal notice on the implementation of Article 57(2) second subparagraph of Regulation (EC) No. 726/2004' (EMA/505633/2011, dated 1 July 2011) to comply with the requirement for the electronic submission of information on medicinal products for human use authorised or registered in the Union. HMPC members were invited to liaise with their respective national competent authority ('the information on authorised medicines comes from marketing authorisation holders and is collected by regulatory authorities in member states and by the EMA').
   European Medicines Agency colleagues working on the EudraPharm database were invited to give a presentation to the HMPC. Anticipated for the 4Q2011, the presentation was unfortunately postponed and is now scheduled for the 1Q2012.

   **Status:** Ongoing

3. Action III/3: In collaboration with the CMD-h, report on the impact of published Community herbal monographs upon assessment of marketing authorisations and traditional use registrations granted by the member states.

   **2011**

   In June 2011, the questionnaire was improved with guidance introduced on the expected responses to the question related to the reference to an HMPC monograph, to allow reporting on the impact of HMPC monographs. Information is now sought with a view to identifying whether an application 'is based' on a HMPC monograph, 'makes reference' to an HMPC monograph or a relevant HMPC monograph 'is used by the national competent authority' in the assessment of the application.

   The intended report on the impact of monographs (and list entries) is taken up in the HMPC 2012-2015 work programme.

   **Status:** Ongoing

4. Action III/4: Investigate the need for revision of scientific guidance (guidelines, questions & answers, etc.) published by the HMPC for adaptation to the latest developments in the herbal sector.

   The following was undertaken in **2010**:

   - streamlining of several Questions & Answers on quality matters into one document
   - streamlining of Questions & Answers on regulatory matters (with respect to technical issues).

   The following was undertaken in **2011**:

   - A revision took place of the 'Guideline on quality of herbal medicinal products/traditional herbal medicinal products' (CPMP/QWP/2819/00 Rev 1) and 'Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products' (CPMP/QWP/2820/00 Rev 1) in order to bring them up-to-date with modified guidance mainly from the European Pharmacopoeia.
   - The above-mentioned Q&A on regulatory matters was updated in July 2011.
   - In September 2011, the MLWP discussed the possible need to revise the HMPC guideline on the assessment of genotoxicity of herbal substances/preparations.

   As part of its core-business, the HMPC adjusts the scientific content of its guidelines and other guidance documents; any revision shall be flagged in annual work programmes of the HMPC drafting groups and working party. The HMPC will abide by the rules in the 'Procedure for European Union guidelines and related documents within the pharmaceutical legislative framework'.

   **Status:** Completed for 2010-2011. To be continued in future

## Objective IV: To respond to the possible extension of the scope of the simplified registration procedure

1. Action IV/1: Contribute to the preparation of a possible extension of the scope, when requested by the European Commission.

   **2010**

In May 2010, the HMPC decided to address with the European Commission the need for clear provisions on the data source for the HMPC tasks during the future revision of Directive 2004/24/EC.

**2011**

In May and July 2011, the HMPC discussed a letter to inform the European Commission of the difficulties faced by national competent authorities in their discussions with companies for the placing or maintenance on the market of products which are not eligible to the simplified registration procedure and for which the MA procedure is not a viable option.

Further discussions took place in the 3-4Q 2011, with practical cases being discussed with a view to possibly making recommendations to the European Commission. Whilst the HMPC took note of the feedback from the European Commission representative that flexibility is supported, classification is ultimately relevant to national decisions by competent authorities; the Committee felt important to convey its scientific position to the Commission. Finalisation of written communication to DG SANCO is expected for the 1-2Q2012.

Contribution to the development of new/revised legislation is taken up in the HMPC 2012-2015 work programme.

**Status:** Completed for 2010-2011. To be continued in 2012-2015

## Objective V: To respond to any European Commission's request for enhanced co-operation between European Medicines Agency and EFSA in the area of health claims for food containing herbal ingredients and for clarification of the borderline with medical devices

1. Action V/1: Establish an ad hoc group at the level of the HMPC to prepare scientific contribution.

**2010**

The European Medicines Agency responded to the request from DG SANCO for further collaboration with EFSA via the participation in a joint meeting in June 2010 and the development of a joint EFSA/EMA explanatory document on the assessment of health claims for food products containing botanicals as performed by the EFSA (NDA panel) and therapeutic indications for herbal medicinal products as performed by the EMA (HMPC), which was transmitted to DG SANCO in July 2010.
In November 2010, the HMPC had noted the decision by the European Commission that the list of permitted claims for food supplements ('Art. 13 claims') would be established in two steps.

**2011**

In March 2011, the HMPC decided to further reflect on the borderline between therapeutic indications and health claims for herbal ingredients with a view to possibly laying down its position for publication on European Medicines Agency website and/or a publication in a scientific journal.

In June 2011, European Medicines Agency sent 2 representatives to attend a Question & Answer event at the European Parliament initiated by five members of the EP and chaired by Michèle Rivasi to address some concerns expressed by European citizens. The event aimed at clarifying some misconceptions on the provisions of Directive 2004/24/EC whose scope does not cover the regulation of medical systems nor the regulation of health care professionals practice.

As regards the borderline with medical devices, the HMPC closely monitored progress in the finalisation of guidance by the European Commission Classification Medical Devices Expert Group,

such as the ‘Medical devices: Guidance document - Borderline products, drug-delivery products and medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative’ for which the HMPC had delivered a contribution in 2009.

In the future, the HMPC will respond to any request from DG SANCO on matters relevant to cooperation with other bodies established in the EU.

**Status:** Completed for 2010-2011. To be continued in future

Note: In addition, the HMPC will contribute to ongoing DG SANCO activities in the area of risk assessment, risk management and emerging risks (with other Scientific Committees of European Medicines Agency).

The HMPC followed the outcome of annual meetings of Chairs and secretariats of EU Commission and Agencies Scientific Committees and Panels involved in risk assessment, such as the 6$^{th}$ annual meeting held in Copenhagen on 11-12 November 2010 at the European Environment Agency (EEA).

## Annex 1 to 'Action plan for herbal medicines 2010-2011'

Extract from: 'Communication from the Commission to the Council and the European Parliament concerning the Report on the experience acquired as a result of the application of the provisions of Chapter 2a of Directive 2001/83/EC, as amended by Directive 2004/24/EC, on specific provisions applicable to traditional herbal medicinal products' (COM(2008)584). The document, prepared on the basis of Article 16i of Directive 2001/83/EC, has been adopted and transmitted to the Council and the European Parliament.

The document was published on 1 October 2008.

http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/archives/2008_en.htm

**Section 2.5 Genotoxicity data issue**

"In order to ensure the successful application of the Directive, the issues relating to genotoxicity demand careful scientific and legal consideration. As stated in the HMPC report, the systematic request for genotoxicity data has made the proposal of list entries difficult since these data are generally not available. It has probably also contributed to the small number of applications received so far. Consequently, a request for genotoxicity data to assess traditional herbal medicinal products should be made on a case-by-case basis when there is a specific concern for safety, as required by the relevant provisions in the legislation. This ensures the protection of public health while allowing the registration of traditional herbal medicinal products. A more restrictive approach would create the risk that the products concerned will end up being marketed under another classification (and not as medicinal products), without the necessary quality, safety and efficacy controls applicable under pharmaceutical legislation."

**Section 4 Summary and conclusions**

"…the European Commission is prepared to consider extending the simplified registration procedure to products other than herbal substances with a long tradition of safe use.… The proposed extension would enable certain medicinal products from specific European or non-European medicine systems (such as — in alphabetical order — anthroposophic, Ayurvedic, Chinese, Kampo Korean, Mongolian, Thai, Tibetan Unani, or Vietnamese medicine) as well as traditional products with a long-standing tradition in the European Union (such as honey, royal jelly, propolis, fish oils, minerals, micro-organisms and other substances) to be eligible for the simplified registration procedure with a view to placing them on the market as traditional medicinal products."