17 January 2019
EMA/HMPC/22535/2019 **FINAL**
Inspections, Human Medicines Pharmacovigilance & Committees Division

Committee on Herbal Medicinal Products (HMPC)

Minutes for the meeting on 19-20 November 2018

Chair: Marisa Delbò Vice-Chair: Emiel van Galen

19 November 2018, 14:00 – 19:00, 2F

20 November 2018, 09:00 – 13:00, 2F

Health and safety information

In accordance with the Agency's health and safety policy, delegates are briefed on health, safety and emergency information and procedures prior to the start of the meeting.

Disclaimers

Some of the information contained in the minutes is considered commercially confidential or sensitive and therefore not disclosed.

Of note, it is a working document primarily designed for HMPC members and the work the Committee undertakes.

Note on access to documents

Some documents mentioned in the minutes cannot be released at present following a request for access to documents within the framework of Regulation (EC) No 1049/2001 as they are subject to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006).

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1. Introduction

1.1. Welcome and declarations of interest of members, alternates and experts

In accordance with the Agency's policy on handling of declarations of interests of scientific Committees' members and experts, based on the declarations of interest submitted by the Committee members, alternates and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced that no restriction in the involvement of meeting participants in upcoming discussions was identified.

Participants in this meeting were asked to declare any changes, omissions or errors to their declared interests and/or additional restrictions concerning the matters for discussion. No new or additional interests or restrictions were declared.

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure and as included in the list of participants. All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 22 or more members were present in the room).

Swap of roles membership (IE): Una Mockler (alternate) as of 09 October 2018

End of membership (BE): Wim Huygh (alternate); End of mandate: 17 October 2018

New Membership (UK): Elizabeth Griffiths (alternate); Start of mandate: 20 September 2018

New Commission Representative as of 11 October 2018

1.2. Adoption of agenda

HMPC agenda for 19-20 November 2018

Time schedule for 19-20 November 2018

Outcome:

Agenda adopted.

Time schedule endorsed.

1.3. Adoption of the minutes

HMPC minutes for 24-25 September 2018

Outcome:

Minutes adopted.

2. European Union herbal monographs and list entries

2.1. Report on MLWP activities

2.1.1. Appointment of Rapporteurs and Peer-reviewers

Report: HMPC Chair

Action: for discussion

Preparation for Rapporteur transfer - for adoption in January 2019

(Agrimoniae herba - Rapporteur)

(Boldi folium - Rapporteur)

Calendulae herba - Rapporteur

Frangulae cortex - Rapporteur

Rhamni purshianae cortex - Rapporteur

Rhei radix - Rapporteur

Thymi aetheroleum - Rapporteur

Mentha folium/aetheroleum – Rapporteur

Preparation for Peer-Reviewer transfer - for adoption in January 2019

Bursae pastoris herba – Peer Review

(Colae semen – Peer Review)

(Lupuli flos – Peer Review)

(Melissae folium – Peer Review)

Rosmarini aetheroleum – Peer Review

Rosmarini folium – Peer Review

(Sabalis serrulatae fructus – Peer Review)

(Thymi herba – Peer Review)

Violae tricoloris herba – Peer Review

Outcome:

The HMPC confirmed the Rapporteur for Thymi aetheroleum with discussion of revised documents announced for the January meeting.

Some volunteers were already identified for potential Rapporteur/PR transfer if required. Members were asked to signal further interest before distribution can be allocated and decided for adoption at the HMPC January meeting.

The Committee discussed the preparation for a possible Rapporteur/PR transfer in order to allow knowledge transfer for those assessment not yet finalised by UK before 29 March 2019. While some members already had responded to the draft work plan 2019, other

members should also signal their interest in order to be able to decide and adopt at the last plenary before March.

Members also discussed difficulties with the finalisation of the Mentha flos/aetheroleum revision. The Rapporteur was asked to present the latest versions at the HMPC January meeting as well as the controversial points on slides as basis for discussion and follow-up.

2.1.2. Report from the MLWP September 2018 meeting

Report: MLWP Chair/MLWP Vice-Chair
Action: for information
Document: Draft minutes for the MLWP meeting on 25-27 September 2018

2.2. Revised EU herbal monographs and list entries for final adoption

2.2.1. Monograph on Gentianae radix and supporting documents

Action: for adoption
Documents: MO, AR, LoR; References: 44/46

Outcome:

Final revised monograph and supporting documents adopted by consensus. The Norwegian delegate expressed a favourable position.

2.2.2. Monograph on Rusci aculeati rhizoma and supporting documents

Action: for adoption
Documents: MO, AR, LoR, OoC; References: 39/62

Outcome:

Final revised monograph and supporting documents adopted by consensus. The Norwegian delegate expressed a favourable position.

Rapporteur to provide missing references before publication.

Some corrections were introduced in the overall conclusions of the Assessment report.

2.3. Revised EU herbal monographs and list entries for public consultation

None

2.4. Reviewed EU herbal monographs and list entries for decision on revision

2.4.1. Monograph on Echinaceae angustifoliae radix and supporting documents

Action: for adoption
Documents: Review report, Presentation; References: 00/09

Outcome:

The HMPC agreed by majority not to revise the monograph, assessment report and list of references on Echinaceae angustifoliae radix.

The following members did not agree with the decision of the HMPC and were of the position that there are findings of relevance for the content of the monograph and a revision is needed: H Foth, I Chinou, J Wiesner, L Anderson, H Pinto Ferreira.

Changes in the review report were introduced. Rapporteur to provide missing references before publication of the review report as addendum to the existing assessment report.

Members discussed the views of Rapporteur and MLWP taking into account available new data, consistency with other monographs and effective use of resources. While preferable alignment with other Echinacea monographs regarding the wording of the indication and the warning section was supported, a majority did not see a current urgent need of these changes, that could be introduced at later stage when new scientific/market data are available.

2.4.2. Monograph on Millefolii flos and supporting documents (postponed)

2.4.3. Monograph on Millefolii herba and supporting documents (postponed)

2.5. EU herbal monographs, list entries and public statements for final adoption

2.5.1. Monograph on Fragariae folium and supporting documents

Action: for adoption
Documents: MO, AR, LoR, OoC; References: 106/119

Outcome:

Final monograph and supporting documents with minor changes in monograph (sections 1 and 4.4.) and assessment report adopted by majority vote (23 out of 24). The Norwegian delegate expressed a favourable position.

Divergent opinion: J Wiesner

Members discussed the minimum requirements to establish the safe use in particular for substances with few data available and limited use in only some member states.

The divergent opinion considered insufficiency of data to support a traditional use in accordance with Article 16a of Directive 2001/83/EC, as regards the evidence for continuous use with specified posologies.

2.5.2. Monograph on Malvae sylvestris flos and supporting documents

Action: for adoption
Documents: MO, AR, LoR; References: 164/115

Outcome:

Final monograph and supporting documents adopted by consensus. The Norwegian delegate expressed a favourable position.

2.5.3. Monograph on Malvae folium and supporting documents

Action: for adoption
Documents: MO, AR, LoR; References: 164/115

Outcome:

Final monograph and supporting documents adopted by consensus. The Norwegian delegate expressed a favourable position.

2.6. EU herbal monographs, list entries and public statements for adoption for release for public consultation

None

2.7. EU herbal monographs, list entries and public statements - post finalisation

2.7.1. Monograph on Cynarae folium and supporting documents

Action: for adoption
Documents: MO, AR, LoR; Email correspondence dated 5 September 2018

Outcome:

Corrections in the monograph and assessment report were adopted.

Corrections in the posology detected during editorial review post-adoption were introduced in the monograph in line with the AR.

3. Referral procedures

None

4. Guidelines and guidance documents

4.1. Non-clinical/clinical safety and efficacy and multidisciplinary

4.1.1. Public statement on the use of herbal medicinal products containing estragole

Action: for adoption
Documents: Draft revised PS, OoC; Comments from SE; SWP subgroup comments; Presentation

Outcome:

Rapporteur I to implement HMPC conclusions in the PS and adapt the overview of comments accordingly.

Rapporteur II to draft for January an addition to the revised PS (e.g. in form of a decision tree) as basis for discussion.

Rapporteurs of monographs on estragole containing substances were asked to test implementation of HMPC recommendations for discussion at the HMPC January meeting.

4.1.2. Public statement on the contamination of herbal medicinal products/traditional herbal medicinal products with pyrrolizidine alkaloids (EMA/HMPC/328782/2016)

Action: for discussion
Documents: PS; Presentation; Information received from AESGP

Outcome:

HMPC took due account of the presentation given by the Rapporteur and agreed to extend the deadline for the original 3 years transition period for another 2 years.

Rapporteur with the assistance of the secretariat to prepare in an appropriate format a statement with the justification for the extension of the transitional period for adoption at the January 2019 meeting.

The Committee shared risk considerations and agreed the necessary careful re-assessment of a generally acceptable exposure to pyrrolizidine alkaloids (PAs) via medicines taking into account new information such as EFSA publications (see 4.1.3.).

For the specific case of quality issues due to contamination with PAs that are not naturally part of the active substance, practical difficulties in implementation as experienced by industry were acknowledged. While some more data and experience has been made available, uncertainties remain such as suitability of GACP/GMP measures, appropriate testing requirements, substances affected. The work of the EDQM Working Party to develop a general method for testing PAs is still on-going with challenges regarding validation or reference substances.

In order to take full account of new developments on safety and quality aspects HMPC has agreed to uphold the transitional limit of 1 µg/day in line with the PS EMA/HMPC/328782/2016 for another 2-year-period. During that period the higher value of 1.0 µg PAs/day is considered acceptable while the underlying PS EMA/HMPC/893108/2011 will be revised (see 4.1.3.).

4.1.3. Public statement on the use of herbal medicinal products containing toxic, unsaturated pyrrolizidine alkaloids (PAs) (EMA/HMPC/893108/2011)

Action: for discussion
Documents: PS; Expert report; Statement by EFSA CONTAM panel on Risks for human health related to the presence of pyrrolizidine alkaloids in food

Outcome:

HMPC took due account of the presentation given by the Rapporteur.

In view of new information available including a 2017 EFSA CONTAM statement it was agreed to revise the PS within the next 2 years after careful consideration of models and data used for the benefit/risk assessment of medicinal products. Coordination with CHMP/SWP will be sought.

Rapporteurs were confirmed.

4.2. Quality

4.2.1. Q&A on elemental impurities - evaluation in herbal medicinal products

Report: QDG Chair, HMPC Chair
Action: for adoption
Documents: Draft Q&A; Outcome written procedure; Replies from members; Comments received

Outcome:

Draft Q&A adopted by majority for addition to HMPC quality Q&A EMA/HMPC/41500/2010 (Rev. 6).

Remaining comments on the Q&A were discussed. It was considered relevant to mention that Herbal MPs were for more formal reasons excluded from the Q3D ICH guideline, while there is no assumption of less risk. It was raised that a date for implementation would be of advantage for MRP/DCP procedures, however, it was clarified that an HMPC Q&A is not appropriate to impose deadlines for NCAs implementation of guidance for NAPs. The message is provided with publication of the Q&A. When taken into herbal quality guidelines a formal date for coming into effect is provided.

The Committee discussed further the Ph. Eur. provisions to be applied and PDE value calculations that are far more complicated for veterinary products (longer transition period) than for human products.

On a procedural note, the Chair reminded the members on the participation in written procedures according to the HMPC Rules of procedure.

4.3. Regulatory / Procedural

4.3.1. Procedure on management of proposals submitted by interested parties for EU List Entries or EU Herbal Monographs (EMA/HMPC/328575/2007 Rev.2)

Report: ORGAM DG Chair
Action: for adoption
Document: Draft revised procedure

Outcome:

Draft revised procedure with minor changes adopted for public consultation.

After introduction of some editorial changes and improvements to the newly introduced template, the draft revised procedure was endorsed. It was welcomed that the revision on one side provides simplification for interested parties. On the other hand it puts emphasis on relevant key information (instead of exhaustive literature provision) to enable HMPC to make informed decisions when prioritising substances for assessment and the HMPC work programme. Public consultation was agreed as done for the first version of the procedure because the subject is the interaction with stakeholders.

4.4. Report on HMPC Drafting Groups activities

4.4.1. Quality DG

None

4.4.2. ORGAM DG

None

5. Organisational, regulatory and methodological matters

5.1. Mandate and organisation of the HMPC

5.1.1. Strategic Review and Learning Meetings

Austria Presidency meeting – Vienna, 15-17 Oct 2018
Action: for discussion
Documents: Presentations; Minutes; Industry dialogue presentations

Outcome:

The minutes were noted. Follow-up on discussions regarding working methodology and future activities are planned for the HMPC January 2019 meeting and the next SRLM in April.

5.2. Coordination with EMA Scientific Committees or CMDh-v

5.2.1. Scientific Coordination Board Meeting

Report: HMPC Chair
Action: for information
Document: Draft Minutes 10 September 2018; Draft Agenda 22 November 2018

Outcome:

Minutes and draft agenda were noted.

5.3. Coordination with EMA Working Parties/Working Groups/Drafting Groups

None

5.4. Cooperation within the EU regulatory network

5.4.1. Coordination with the European Commission

- Clarification of classification on Saccharomyces cerevisiae CBS 5926
  Report: HMPC Chair
  Action: for discussion
  Documents: EMA letter to EC, EC response, Draft MO, draft LE, draft AR, draft LOR

Outcome:

Postponed.

5.4.2. Coordination with European Pharmacopoeia

- EDQM 13A expert group meeting held on 16-17 October 2018
  Report: M. Bald (EDQM)
  Action: for information
  Document: SoD

- EDQM 13B expert group meeting held on 18-19 September 2018
  Report: M. Bald (EDQM)
  Action: for information

- EDQM TCM expert group meeting held on 2-3 October 2018
  Report: M. Bald (EDQM)
  Action: for information
  Document: SoD

- EDQM PA working party meeting held on 20 September 2018
  Report: M. Bald (EDQM)
  Action: for information
  Document: SoD

Outcome:

HMPC noted updates on 13A, 13B, TCM and PA expert group activities and monographs adopted or in preparation at the Ph. Eur. Commission.

Particularly mentioned was the planned revision of the Menthae aetheroleum monograph related to pulegone/menthofurane (13B) the revision of Sennae monographs (13B), and some but slow progress with the pilot phase on assay alternatives (TCM, example Leonuri herba not the most suitable for semi-quantitative HPTLC) and with the method development for pyrrolizidine alkaloids (PA-WP, validation and reference substance issues).

5.5. Cooperation with International Regulators

5.5.1. 9th EU-India Joint Working Group on Pharmaceuticals, Biotechnology and Medical Devices

Action: for information
Document: Presentation - feedback from 9th EU-India Joint WG on Pharmaceuticals, Biotechnology and Medical Devices, Brussels 27-28 September

Outcome:

Proposal for a technical virtual working group with Indian regulators for a continuous cooperation (TCs) was in principle welcomed. Due to current BCP-related constraints (e.g. working party activities put on hold) implementation will be considered once the Agency will restore these type of activities.

HMPC expressed preference for a smaller group adjacent to HMPC and/or MLWP. The objective could be to inform on standard procedures, standard data requirements as well as importance of Ph. Eur. monographs on quality, which has been previously communicated to Indian representatives as well as to EDQM.

5.6. Contacts of the HMPC with external parties and interaction with the Interested Parties to the Committee

5.6.1. AESGP – hearing at MLWP September 2018

Report: MLWP Chair
Action: for adoption
Documents: Draft hearing report; Presentation on Pyrrolizidine Alkaloids

Outcome:

The Draft hearing report was adopted by consensus.

Members discussed the topics raised by industry and the useful feedback from interested parties on HMPC activities. While there is agreement on some priorities there are different views on some points. Nonetheless, the platform for exchange is beneficial to foster the mutual understanding on different positions.

5.7. Work plan

5.7.1. HMPC work plan 2018

Report: HMPC Chair
Action: for information
Document: Work plan 2018 – current status November 2018

- 1.3.1. Activity area: Implementation of a modified review/revision procedure for EU herbal monographs

Report: HMPC Chair

- 1.3.2. Activity area: Forward planning and prioritisation
- 1.3.3. Activity area: Coordination on safety assessments of herbal constituents

Action: for discussion
Documents: Presentation; Information on PAHs

- 1.3.4. Activity area: European collaboration
- 2.1.1. Activity area: Patients involvement in assessment work

Outcome:

Updates were given on projects 1.3.2, 1.3.3. and 1.3.4.
The need and opportunities for follow-up on some topics in the coming years (with limitations in 2019) was already taken into consideration.

5.7.2. HMPC work plan 2019

Report: HMPC Chair
Action: for adoption

Documents: Draft work plan 2019 including Annex 1 (monographs) and Annex 2 (guidelines); Comments received from members

Outcome:

Changes were introduced, comments discussed and some volunteers identified.

Discussion of Annexes (monographs and guidelines) postponed to the January meeting.

Final comments or confirmation of Rapporteurs for 2019 to be sent to the secretariat before finalisation and adoption at January 2019 meeting.

The specific situation due to BCP phase 3 including temporary suspension of subgroup activities (in particular MLWP) was emphasised with few essential topics remaining on the work plan on top of the challenging task to maintain committee core business.

5.8. Planning and reporting

None

5.9. Legislation and regulatory affairs

5.9.1. WEU/Bibliographic application regarding Art. 10a Dir. 2001/83/EC for HMPs – Reference to other products

Report: HMPC Chair
Action: for discussion
Documents: Comments by EUCOPE; Draft response to EUCOPE; Guideline on the assessment of clinical safety and efficacy; Regulatory Q&A

Outcome:

Draft response letter was adopted.

HMPC agreed that due to the different scope and purpose of the Q&A EMA/HMPC/345132/2010-Rev.4 (R7) and the Guideline EMA/HMPC/104613/2005–Rev. 1 there is no need to revise the Q&A.

6. Any other business

6.1. Topics for discussion

6.1.1. Workshop on Pyrrolizidine Alkaloids (PAs) – see also 4.1.2. & 4.1.3.

Action: for discussion
Documents: Agenda; Presentation

Outcome:

HMPC noted presentation and short feedback on work shop presentations and discussions.

New information was taken into account for the discussions on the HMPC public statements on pyrrolizidine alkaloids (see 4.1.2. and 4.1.3.).

6.1.2. Management of references for the review and revision of EU herbal monographs and EU list entries

Action: for discussion
Documents: Draft MLWP September 2018 minutes; Best practice guide for revision of MO and LE

Outcome:

HMPC agreed to MLWP proposal and confirmation of practice regarding reference management.

Full set of references should be provided before HMPC adoption (for new assessments, but also revisions and review outcomes) as essential part of the 'package'. Some members expressed preference for even earlier access (MMD) to support discussions. Without references other documents will not be added in the HMPC agenda and adoption postponed. It was noted that in many recent cases (mostly reviews/revisions) references have not been available. The Chair underlined that the previously agreed HMPC practice should be re-instated in 2019 given the importance of reference availability for peer-review, editorial review, HMPC members, and especially monograph review/revision (after several years with sometimes new Rapporteurs).

All references cited in the **revised** assessment report and included in the new version of the list of references should be available as full text. The Rapporteur either (1) provides the full set of references (via eudralink) or (2) provides only the new references and confirms that all previous references are available as full text (contact the secretariat at the start of review/revision). In this case, the Rapporteur highlights the new entries in the revised list of references.

Key references listed in systematic **review reports** are to be provided as full text to allow peer-review and informed decision of the Committee on the need for revision.

6.2. Documents for information

6.2.1. HMPC

Table of Decisions from HMPC meeting held on 24-25 September 2018

Overview of expertise of members HMPC and subgroups

Meeting report from HMPC meeting held on 24-25 September 2018

Overview of status of HMPC assessment work – priority list

Inventory of herbal substances for assessment work

Abbreviations in HMPC agendas/minutes

Common names of herbal substances in all languages

6.2.2. MLWP

- Overview of status of HMPC/MLWP assessment work

6.2.3. ARSP

- English template
- English summaries for publication:
  - Turmeric
  - Milkthistle
  - Senna leaf
  - Senna pods

No objections were raised regarding ARSPs before publication.

6.2.4. Other

- PCWP/HCPWP meetings:
  - PCWP - Agenda PCWP meeting 25 Sep 2018
  - PCWP/HCPWP - Agenda Joint PCWP/HCPWP meeting 25 Sep 2018
  - HCPWP - Agenda HCPWP meeting 26 Sep 2018
- EU herbal monographs, list entries and public statements post adoption
  - Allii sativi bulbus: Scientific literature compilation and open questions; post adoption delays (MO, AR, LoR, OoC)
  - Pistacia lentiscus, resinum (mastic) (MO, AR, LoR)
- HMPC meeting dates 2019

6.2.5. Feedback on national experiences with HMPC monographs and guidelines

- draft template
- summary feedback

7. List of participants

List of participants including any restrictions with respect to involvement of members/alternates/experts following evaluation of declared interests for the 19-20 November 2018 meeting.

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Marisa Delbò	Chair	Italy	No interests declared	
Reinhard Länger	Member	Austria	No interests declared	
Heidi Neef	Member	Belgium	No interests declared	
Iliana Ionkova	Member	Bulgaria	No interests declared	
Ivan Kosalec	Member	Croatia	No interests declared	
Darko Trumbetic	Alternate	Croatia	No interests declared	
Maria Stavrou	Member	Cyprus	No interests declared	
Marie Heroutova	Member	Czech Republic	No interests declared	
Eeva Sofia Leinonen	Member	Finland	No interests declared	
An Le	Member	France	No interests declared	
Jacqueline Wiesner	Member	Germany	No interests declared	
Ioanna Chinou	Member	Greece	No interests declared	
Zoi(Zoe) Karampourmpouni	Alternate	Greece	No interests declared	
Zsuzsanna Bíróné Dr Sándor	Member	Hungary	No interests declared	
Una Mockler	Alternate – via TC	Ireland	No restrictions applicable to this meeting	
Evita Skukauska	Member	Latvia	No interests declared	
Rugile Pilviniene	Member	Lithuania	No interests declared	
Emiel Van Galen	Member	Netherlands	No interests declared	
Steinar Madsen	Member	Norway	No interests declared	
Wojciech Dymowski	Member	Poland	No interests declared	
Ana Paula Martins	Member	Portugal	No interests declared	
Milan Nagy	Alternate	Slovakia	No interests declared	
Samo Kreft	Member	Slovenia	No restrictions applicable to this meeting	
Adela Núñez Velázquez	Member	Spain	No interests declared	
Karin Erika Svedlund	Member	Sweden	No interests declared	
Malin Kyllikki Hobro Soderberg	Alternate	Sweden	No interests declared	
Linda Anderson	Member	United Kingdom	No interests declared	
Elizabeth Griffiths	Alternate	United Kingdom	No interests declared	
Ewa Balkowiec Iskra	Co-opted member	Poland	No interests declared	
Gert Laekeman	Co-opted member	Belgium	No interests declared	
Heidi Foth	Co-opted member	Germany	No interests declared	

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Maria Helena Pinto Ferreira	Co-opted member	Portugal	No interests declared	
Melanie Bald	Observer – via TC	EDQM	No interests declared	
	EC Representative	European Commission		