EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 September 2017
EMA/HMPC/124695/2011 Rev. 2
Committee on Herbal Medicinal Products (HMPC)

# Procedure for the review and revision of European Union herbal monographs and European Union list entries

Draft

| | |
|---|---|
| Draft agreed by Organisational Matters Drafting Group (ORGAM DG) | October 2010<br>February, April, June 2011 |
| Draft agreed by Working Party on European Union Monographs and European Union List (MLWP) | May 2011 |
| Adoption by HMPC for release for consultation | 12 July 2011 |
| End of consultation (deadline for comments) | 15 November 2011 |
| Agreed by ORGAM DG | December 2011 |
| Adoption by HMPC | 24 January 2012 |
| Draft revision 1 agreed by ORGAM Drafting Group | December 2014 |
| Adoption revision 1 by HMPC | 28 January 2015 |
| Draft revision 2 dicussed by ORGAM DG | 30 June 2016<br>6 September 2016<br>6 October 2016<br>14 December 2016<br>4 April 2017<br>27 June 2017<br>5 September 2017 |
| Draft revision 2 dicussed by HMPC | 30-31 January 2017<br>29-30 May 2017<br>17-18 July 2017 |
| Draft revision 2 dicussed by MLWP | 1-2 February<br>30 May – 1 June 2017 |
| Draft revision 2 adopted by HMPC for release for public consulation | 19 September 2017 |

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
**Telephone** +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
**Send a question via our website** www.ema.europa.eu/contact

| | |
|---|---|
| Start of public consultation | 27 October 2017 |
| End of consultation (deadline for comments) | 27 January 2018 |

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


| | |
|---|---|
| **Keywords** | HMPC; European Union herbal monographs; European Union list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products; herbal medicinal products; traditional herbal medicinal products; review; revision. |

# Procedure for the review and revision of European Union herbal monographs and European Union list entries

**Table of contents**

# Executive summary

The purpose of this procedure is to enable a consistent and proportionate process in reviewing, and revising all European Union herbal monographs and European Union list entries adopted by the HMPC. The aim of this document is to describe how to identify the criteria/reasons to trigger the revision of European Union herbal monographs and European Union list entries and the associated procedure and timelines for both the review and the revision.

**Revision 1** pertained to clarify that minor changes of wording without safety implications should not trigger a revision of an European Union list entry.

**Revision 2** pertains to streamline the review and revision of European Union herbal monographs and list entries. In particular, the revision aimed for improved clarity and transparancy by covering detailed guidance on the review process, including a new review template (i.e. Annex 1). In addition, the procedure for unscheduled review, i.e. review for specific reason in the Reflection paper on the reasons and timelines for revision of final European Union herbal monographs and European Union list entries (EMA/HMPC/326440/2007), has been included in the revision.

# 1. Introduction

## *1.1. Background, scope and objectives*

The main tasks of the HMPC is to prepare a draft list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products (hereafter also referred to as ' European Union list' or ' list entry') and to establish European Union herbal monographs (hereafter also referred to as 'monographs') for traditional herbal medicinal products and for well-established herbal medicinal products (Article 16f(1)and Article 16h(3) of the Directive 2001/83/EC (1)).

If an application for traditional use registration relates to a herbal substance, preparation or a combination thereof contained in the European Union list, the data specified in Article 16c(1)(b)(c) and (d) do not need to be provided (i.e. details of authorisation or registration or refusal to grant authorisation or registration, evidence of long standing use and bibliographic review of safety data).

European Union herbal monographs for the application of both the traditional use and well-established use can serve as a basis for simplified registration or bibliographical marketing authorisation applications.

The HMPC and the European Commission pointed out in their respective reports (2, 3) that the monographs adopted by the HMPC need to be periodically updated through a procedure to be put in place for retrieving and evaluating new data. Because of constant scientific progress and evolution of regulatory frameworks, monographs should be re-evaluated in a continuous process. The periodic review and, if necessary, the subsequent revision processes are essential in order to prevent European Union herbal monographs from becoming outdated.

When a European list entry exists, revision of an EU herbal monograph can have consequences for relevant changes in the existing list entry as well. The need for revision of the list entry following the revision of an EU monograph should be carefully assessed, on a case by case basis, taking into account the nature of the changes and the presence of any safety concern.

## *1.2. Responsibilities*

In principle, the Rapporteur in charge of the review/revision of a monograph and a list entry will be the HMPC/MLWP member, who did the primary assessment. When this is not possible, the HMPC will appoint a new Rapporteur. By the same principle, a Peer-reviewer should also be appointed.

The decision on the need for revision is taken by the HMPC, based on the review and proposal by the Rapporteur, peer-reviewed and agreed upon at MLWP.

## *1.3. Main principle*

To prevent monographs and list entries from becoming outdated a three-step procedure will be followed:

**Step I) Review of new data**

The review of new data that could be relevant for the content of a monograph, is to be initiated by time elapsed since the previous published version (Periodic review) or by data submitted to HMPC at any time (Unscheduled review).

**Step II) Decision on relevance of new data and the need of revision of monograph**

The revision of a monograph is initiated upon decision by HMPC following review of new data and proposal by Rapporteur. The decision to start the revision procedure has to be justified by the relevance of the reviewed data.

**Step III) Revision or no revision**

a) Revision according to HMPC standard procedures (4, 5, 6).

b) No revision and an addendum to be added to the assessment report

The details of the procedure for the review and revision of monographs is described in the sections below and illustrated in Figure 1. The HMPC voting and publication practice of finalised documents following the review and revision process is summarised in Table 1.

**Table 1.** HMPC voting and publication practice of finalised documents following the review and revision process.

| **Relevant new data - Revision** | **No relevant new data – No revision** |
|---|---|
| *New final documents to be adopted for publication* | |
| New monograph | Addendum to the assessment report |
| New Opinion | |
| New supporting documents (assessment report and list of references) | |
| *What happens with the old documents* | |
| Existing monograph, assessment report, list of references and Opinion will be replaced by the revised monograph, assessment report, list of references and Opinion. Old documents will be labelled as 'Superseded' | Existing monograph, assessment report, list of references and Opinion remain as 'current version' on the website |

When appropriate, the revision of European Union list entries will take place in parallel to or shortly after the revision of related monographs. When a European Union list entry is revised according to

Article 16f(3) of Directive 2001/83/EC (1), the Comitology procedure will be followed at the European Commission level after transmission by the EMA.

# 3. Step I: Review of new data

The review of new data that could be relevant for the content of a monograph, is to be initiated by the time elapsed since the previous published version (Periodic review) or by new relevant data submitted to HMPC at any time (Unscheduled review).

## *3.1. Periodic review*

The need for revision will be considered every 5 years since publication date of the first version (or last revised version, if applicable) of the monograph or the publication date of the last addendum to the assessment report (in case a review has been previously performed not leading to a revision) in order to ensure that European Union herbal monographs and European Union list entries are up to date (scientific state of the art).

The HMPC decides annually on the prioritisation of substances for the periodic review when drafting the work plan for the following year. The selected monographs to undergo a periodic review are included in the MLWP work plan and tracked in the priority list (7). After adoption of the work plan a call for scientific data will be initiated.

**Timelines**

The HMPC Secretariat informs the Rapporteur of the monograph that is due for the periodic review. The HMPC Secretariat will also inform the Rapporteur about the deadline of the review (date of the HMPC plenary). At the same time HMPC Secretariat to issue a call for scientific data (with 3 months deadline), using the template 'Call for scientific data for the periodic review of the monograph on' (8) after decision by HMPC.

The Rapporteur should start the review within 3 months, and the duration of the review should preferably be finalised within 6 months. If the Rapporteur is not able to start the review, the Rapporteur should inform the HMPC Secretariat and a new Rapporteur shall be appointed by the next HMPC meeting. The timelines are illustrated in Figure 1.

**Scope**

To determine whether a revision of a monograph is required, the Rapporteur shall examine new data and other aspects (e.g. consistency) not yet available/existing during the previous assessment of the monograph in accordance with the 'Review template' (Annex 1) for the periodic review.

## *3.2. Unscheduled review*

An unscheduled review may be triggered in case new relevant data brought to the attention of the HMPC by other EMA Committees/Working parties, HMPC members, National Competent Authorities, Interested Parties etc.

**Timelines**

The HMPC Secretariat informs the Rapporteur of the concerned monograph immediately on the submitted data received. The HMPC Secretariat will also inform the Rapporteur about the deadline of the review (date of the HMPC plenary). The Rapporteur should start the review within 3 months, and

the duration of the review should preferably be finalised within 6 months. If the Rapporteur is not able to start the review, the Rapporteur should inform the HMPC Secretariat and a new Rapporteur shall be appointed by the next HMPC meeting. The timelines are illustrated in Figure 1.

**Scope**

Only the new data provided will be reviewed by the Rapporteur. The Rapporteur shall use the 'Review template' (Annex 1) for the review.

## *3.3. Rapporteur's review of new data*

If the new data are likely to lead to a relevant change of a monograph, then a revision of the monograph is recommended by the Rapporteur. If the new data are of low relevance for the content of the monograph then no revision is recommended. The findings of the review and the proposal of the Rapporteur on the revision is to be presented to the HMPC plenary – peer-reviewed and agreed at MLWP - using the 'Review template' (Annex 1) by the Rapporteur. The agreement at MLWP should not require more than 1 meeting.

In the following cases, the new data can be considered as relevant and may trigger a revision:

- **Scientific data (e.g. non-clinical and clinical safety data, clinical efficacy data)**

A revision of an existing European Union herbal monograph can be initiated by the HMPC following pharmacovigilance actions resulting from assessment at national or European level.

A revision of an existing monograph can also be triggered by new safety data (e.g. safety data provided by interested parties/Member States or new relevant safety data in literature) or pharmacovigilance data which would lead to a change in the monograph (e.g. restriction in use, contraindication, adverse event).

Newly published genotoxicity data will be assessed by the Rapporteur, e.g. to assess if a list entry can be established. When the new data support the establishment of a list entry, the monograph is to be revised and a list entry drafted.

New clinical data can trigger a revision of an existing European Union herbal monograph if the new data could be relevant for a WEU indication to allow a herbal substance/preparations that previously did not meet the requirement of recognised efficacy to be eligible for WEU.

New safety or clinical data from studies in the paediatric population or during pregnancy and lactation which would lead to a change in the monograph (e.g. age range of children) can trigger a revision of an existing European Union herbal monograph.

- **Regulatory practice**

A Member State via its HMPC member may bring to the attention of the Committee any decision taken at national level that, in its view, has an impact on a final European Union herbal monograph and European Union list entry. The HMPC will assess the need to revise other monographs that may be affected by the revision.

The time elapsed since the first version/last revision may allow new herbal substances/preparations that did not meet the requirement for at least 30 years documented medicinal use or the requirement for 15 years of use in the European Union to now be eligible for inclusion in the monograph.

It is also possible that a herbal substance/preparation which did not meet the requirement for at least 10 years well-established medicinal use is now eligible for inclusion in the monograph.

The Rapporteur shall reconsider the eligibility of herbal substances/preparations which was previously not included on those grounds and, if applicable, the monograph shall be revised.

- **Consistency**

When reviewing, the Rapporteur shall consider the harmonisation to other monographs in the same therapeutic area as regards the wording of the various sections or with previous HMPC decisions (e.g. new or revised thresholds of compounds e.g. thujone, pulegone).

The Rapporteur may identify inconsistencies with other monograph(s) that HMPC may consider appropriate to be timely amended, if the change is considered relevant. In this case the Rapporteur proposes that the concerned monograph should be revised to be consistent with other monographs and a justification should be added to the assessment report.

Insconsistencies of minor importance do not justify the revision of a monograph. If inconsistencies with other monographs are of minor importance and do not trigger a revison, it should be explained in the addendum to the assessment report.

- **Referrals**

As part of the outcome of a referral to the HMPC, the Committee can include in its opinion what its position is regarding the need to revise relevant monographs and/or list entries taking into consideration the required action agreed for the specific herbal medicinal product(s) subject of the referral.

# 4. Step II: Decision on relevance of new data and the need of revision

Based on the proposal and justification provided by the Rapporteur using the 'Review template' (Annex 1) - first peer-reveiwer and agreed upon at the MLWP - the HMPC should decide whether there is a need for revision of the monograph or not.

The considerations are presented to HMPC and discussed in order to prepare a decision for one of the following pathways:

a. Relevant new data/proposed changes:

   HMPC decides a revision of the monograph and supporting documents is needed. Information about the decision is given in the HMPC meeting report and the HMPC minutes publically available at the EMA website.

b. No relevant new data/proposed changes:

   HMPC decides that the content of the monograph is still valid. The monograph is not changed, neither the assessment report nor the list of references. Instead an addendum to the old assessment report is to be published. Information about the decision not to revise the monograph and supporting documents is given in the addendum to the assessment report, the HMPC meeting report and the HMPC minutes made public at the EMA website.

# 5. Step IIIa: Revision

## *5.1. Scope*

After the HMPC decision to start a revision, the Rapporteur shall revise the monograph, supporting documents and, if applicable, the list entry according to HMPC standard procedure (4, 5, 6). In the

revision special attention should be paid to safety issues, apart from the other items which are to be considered (see section 4).

## *5.2. Documents to be revised and adopted*

All documents should be checked against the latest templates. Beyond the EMA identity features (logo, font, etc.) and the inclusion of the herbal substance common name in all EU official languages, attention should be paid to new elements of the templates, such as new headers (e.g. monograph's section 4.6 on Fertility, pregnancy and lactation) and new sections (e.g. benefit/risk statements in the assessment report's overall conclusions).

**Monograph**

The monograph will be readopted, showing the date of the revision under section 7 of the monograph 'Date of compilation/last revision' and on the cover page.

**List entry**

When an European Union list entry is revised according to Article 16f(3) of Directive 2001/83/EC as amended, the Comitology procedure will be followed at the European Commission level after transmission by the EMA.

**HMPC Opinion**

A new HMPC opinion will be adopted. There are different scenarios:

a) Opinion of the HMPC on a monograph

b) Opinion of the HMPC on a new list entry

c) Opinion of the HMPC on changes to be introduced into a list entry

d) Opinion of the HMPC to recommend the withdrawal of a list entry

**Supporting documents**

*Assessment report*

When the assessment report is modified extensively throughout all sections, the Rapporteur should consider inserting a summary of the major modifications under a section '1.4 Major changes introduced in the <first><number as appropriate> revision'.

When one or several section(s) of a monograph are modified, the relevant parts of the assessment report shall contain the new data and an explanation/justification for the changes introduced in the monograph and, where appropriate, the list entry.

*List of references*

The list of references will be updated with the new literature taken into consideration and revised. All new references supporting the updated assessment report should be included in the updated list of references together with, if applicable, a separate section for the references which were read but do not support the assessment report.

*Overview of comments*

During the 3-month public consultation of a revised monograph and, where appropriate, a list entry, comments from interested parties shall be collected and assessed. An overview of comments received during the public consultation shall be prepared accordingly.

### *5.3. Procedure and timelines*

In case the revision was decided after an unscheduled review, the call for scientific data should be published within 1 month of the HMPC decision on revision.

Duration of revision until public consultation preferably should not exceed 12 months. The timelines are illustrated in Figure 2.

1. Discussion at MLWP and Peer-review

Once discussed and agreed by the majority of MLWP members (preferably 1-3 meetings), and the Peer-reviewer, the revised draft monograph/list entry and the revised draft supporting documents are transmitted to HMPC for adoption for public consultation.

2. Adoption by HMPC for public consultation

During the following HMPC meeting the revised draft monograph/list entry and the revised draft supporting documents are adopted for public consultation.

3. Public consultation

Thereafter, the revised draft monograph/list entry and revised draft supporting documents are published for 3 months public consultation.

4. Discussion at MLWP and Peer-review

After public consultation, the received comments will be discussed at MLWP (preferably 1-3 meetings). After peer-review the revised draft monograph/list entry and revised draft supporting documents are transmitted to HMPC for final adoption.

5. Final adoption by HMPC

The revised draft monograph/ list entry and revised draft supporting documents are adopted by the HMPC during the following HMPC meeting.

Additional steps for revision of European Union list entries: The revised draft list entry is translated in all EU official languages (HMPC). Subsequently, the revised draft European Union list entry together with the HMPC opinion on the draft revised list entry, the assessment report, list of references, justification for changes where relevant, are transmitted to the European Commission followed by the publication of the link to the European Commission page where to access the Commission Decision on the EMA website.

## 6. Step IIIb: No revision and addendum to be added to the assessment report

After HMPC decision that no revision is needed, an extract from the review template (Annex 1) will be published as an addendum to the assessment report. The monograph and supporting documents will not be changed. No new opinion will be published.

A summary and conclusion on the review of new data and a list of key references (following the format provided in the template for list of references) will be included in the addendum, which will be published within 2 months after the HMPC decision.

# 7. Definitions

European Union list entry: document whose purpose is to provide structured information, including information laid down in Article 16f(1) of Directive 2001/83/EC, relating to specific herbal substances or herbal preparations or combinations of substances and preparations from a given plant for use in traditional herbal medicinal products.

European Union herbal monograph: document whose purpose is to provide a scientific summary of all data available on the safety and efficacy of a herbal substance/preparation intended for medicinal use, as referred to in Article 16h(3) of Directive 2001/83/EC as amended.

Review: examination of new data and documents referring to a monograph to determine whether there is a need for a revision of the monograph and supporting documents. There are two possible types with different scope and triggering sources:

Periodic review: the need for revision will be considered every 5 years in order to ensure that European Union herbal monographs and European Union list entries are up to date (scientific state of the art).

Unscheduled review: the need for revision considered in case of new relevant data are brought to the attention of the HMPC by other EMA Committees/Working parties, HMPC members, National Competent Authorities, Interested Parties etc. Only the new data provided will be reviewed by the Rapporteur.

Revision: the process of revising monograph/list entry and supporting documents, involving reconsideration and modification through an assessment of older data to be complemented by new data and other aspects (e.g. consistency) not yet available/existing during the previous assessment.

Addendum to the assessment report: the extract from the review template (Annex 1) including the justification for not revising the monograph/list entry and published after the decision by HMPC.

# 8. References


1. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 relating to medicinal product for human use

2. HMPC Status report on the implementation of the provisions of chapter 2a of Directive 2001/83/EC as amended by Directive 2004/24/EC as regards traditional herbal medicinal products - October 2006, Final (EMEA/HMPC/187219/06)
http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/09/WC500096377.pdf

3. Report on the experience acquired as a result of the application of the provisions of Chapter 2a of Directive 2001/83/EC (introduced by Directive 2004/24/EC) on specific provisions applicable to traditional herbal medicinal products. http://eur-lex.europa.eu/legal-content/en/ALL/?uri=CELEX%3A52008DC0584

4. Procedure for the Preparation of EU monograph for herbal medicinal products with well-established medicinal use (EMEA/HMPC/182352/2005)

5. Procedure for the Preparation of EU monograph for traditional herbal medicinal products (EMEA/HMPC/182320/2005)

6. Procedure for the preparation of an entry to the 'Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products' (EMEA/HMPC/57137/2007)

7. Overview of status of HMPC assessment work – Priority list (EMEA/HMPC/278067/2006)
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500017724.pdf

8. Procedure for calls for scientific data for use in HMPC assessment works (EMA/HMPC/1004/2006 current)

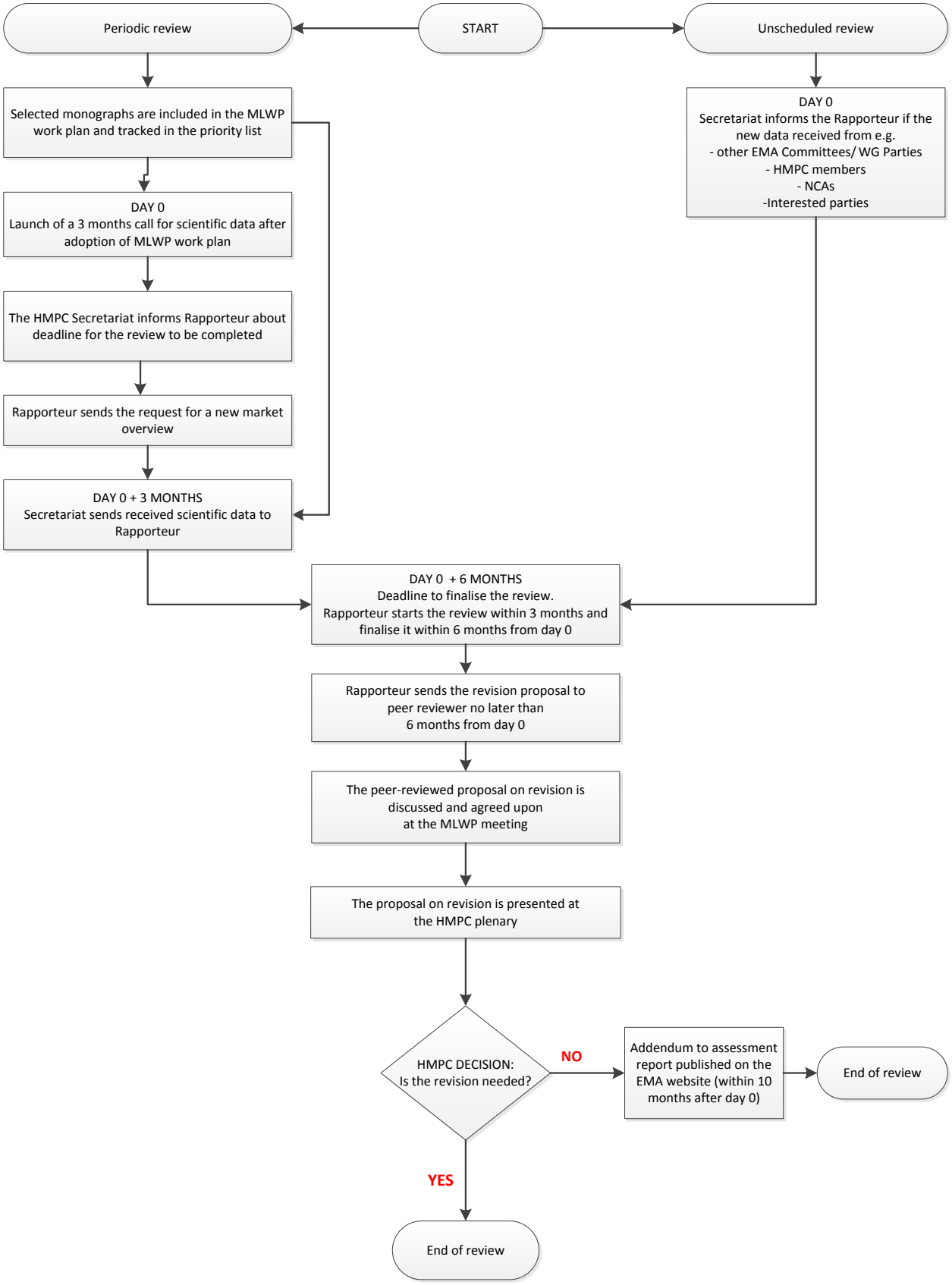
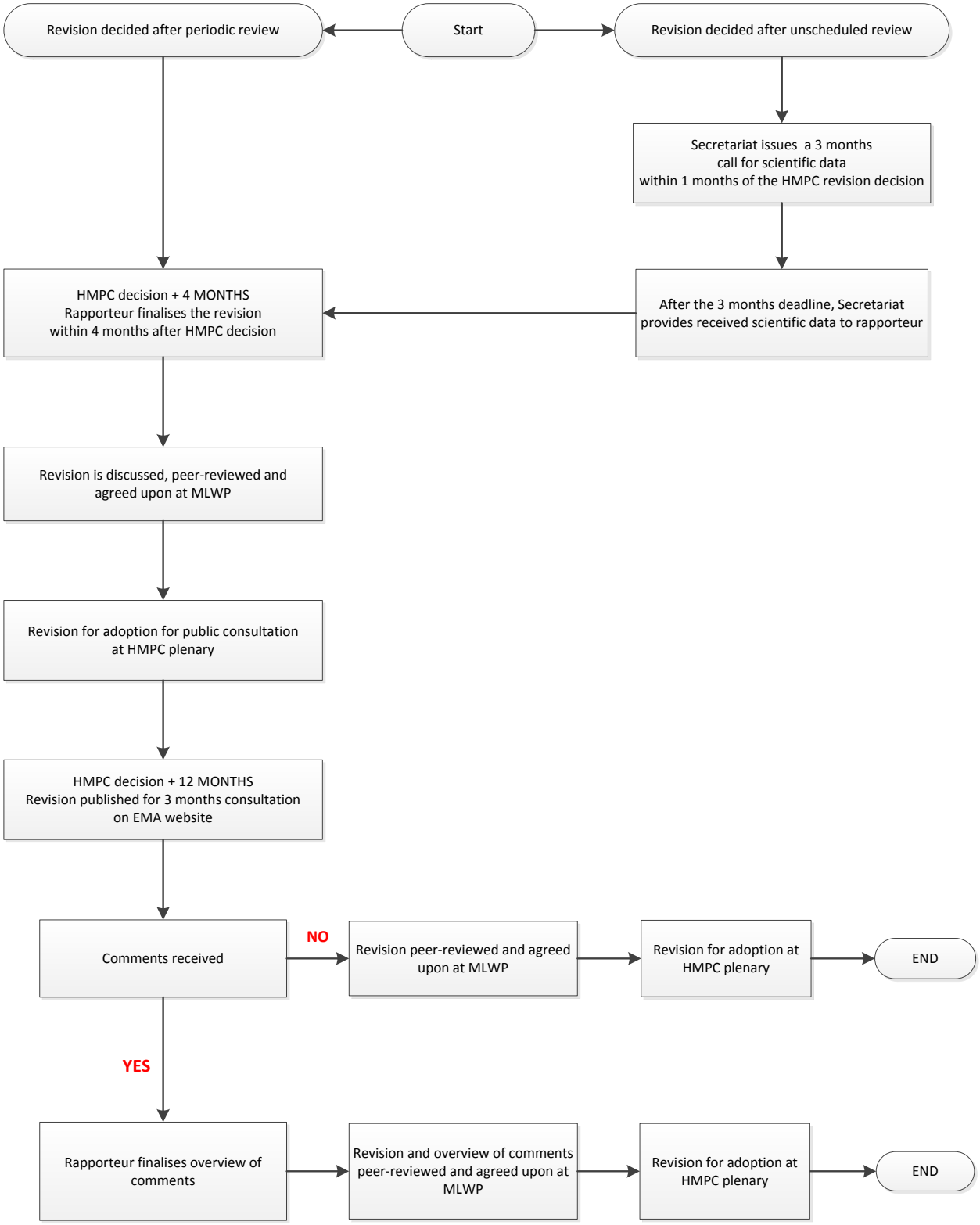



**Figure 1.** The process flow map of the procedure for the review of European Union herbal monographs.




335

336 **Figure 2.** The process flow map of the procedure for the revision of European Union herbal
337 monographs.

338

# 9. Annex 1 – Review template (EMA/HMPC/568792/2017)