25 January 2023
EMA/HMPC/697513/2022
Committee on Herbal Medicinal Products (HMPC)

Call for scientific data for use in HMPC assessment work on *Cannabis sativa* L., flos (Cannabis sativa flowering tops)[1]

Submission period: 15 February 2023 – 14 May 2023

The HMPC invites all interested parties such as pharmaceutical industry associations, health care professional groups, learned societies, consumers and patients' associations, governmental institutions as well as EU and EEA-EFTA Member States to submit selected specific scientific data, which may be used in the assessment of *Cannabis sativa* L., flos as part of the establishment of European Union herbal monographs and/or European Union list entries.

Please note that HMPC is seeking to receive copies of scientific contributions limited to those suitable as referred to in the Annex to this call for submission of scientific data.

Scientific contributions should be sent in electronic format by e-mail or Eudralink to hmpc.secretariat@ema.europa.eu

A list of all scientific contributions and their references should be enclosed.

The name and contact details of the interested party providing the scientific contributions is required.

Submitting parties are bound to obey existing **copyrights**. Contributors should also take duly into account the rights of third parties, as the documentation provided will be used for the development of European Union list entries and European Union herbal monographs. Such development is

[1] For all definitions reference is made to "Compilation of terms and definitions for Cannabis-derived medicinal products", available at https://www.ema.europa.eu/en/documents/other/compilation-terms-definitions-cannabis-derived-medicinal-products_en.pdf

For basic questions on the scope of this Call for data reference is made to: 'Questions & Answers regarding Cannabis-derived medicinal products and the scope of EU herbal monographs for herbal medicinal products within the EU medicines legislation', available at: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/questions-answers-regarding-cannabis-derived-medicinal-products-scope-eu-herbal-monographs-herbal_en.pdf

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

underpinned by assessment reports, which will be made public in accordance with measures taken by the Agency to ensure an appropriate level of transparency.

Unpublished proprietary data may be included. However, in this case the consent of the data owner is a necessary requirement and therefore it must be provided simultaneously with the contributions. If the party submitting the data is not the data owner, the consent of the latter is needed. If the data owner is the interested party itself, the voluntary submission of the data as a contribution to the HMPC assessment constitutes consent that the HMPC may evaluate and use the submitted data in the course of the procedure announced in the call for scientific data.

Before its publication, the owner of the data will be given the opportunity to review the assessment report to request the removal of any confidential data. Such request must be duly justified by evidencing the confidential nature of the data (e.g. that it includes confidential intellectual property). The HMPC will consider such requests on a case-by-case basis.

As regards **copyright**, it is important to clarify that the use by the HMPC of the bibliographic material is entirely for a non-commercial purpose. The HMPC is in all cases willing to confirm in writing the non-commercial use of documents sent in by interested parties.

Documents should be submitted in **English** where possible since this is the working language of the HMPC, but documents in other official languages of the European Union will be accepted. In order to facilitate the assessment, the HMPC strongly recommends the submission of an abstract in English when original references are provided.

Conditions for data submissions

Scientific contributions should be relevant to the purpose of the assessment, which exclusively will evaluate the medicinal use of the herbal substance *Cannabis sativa* L., flos (Cannabis flowering tops) and herbal preparations thereof, and **not of other *Cannabis*-derived products or substances like, for instance, isolated constituents.**

Their scope should address either:

Well-established medicinal use (WEU): Submitted data should provide evidence that the medicinal product(s) has or have a well-established medicinal use for at least 10 years in the European Union with recognised efficacy and an acceptable level of safety within the meaning of Directive 2001/83/EC.

Traditional use (TU): Submitted data should provide evidence that the medicinal product in question, or a corresponding product, has been in medicinal use throughout a period of at least 30 years preceding the date of the application, including at least 15 years within the European Union, is not administered through injection, and can be used without supervision of a healthcare professional.

Data should be submitted separately for WEU and TU, distinguishing clearly between separate indications and different preparations. For all submitted data details of herbal substance/herbal preparation, pharmaceutical form and posology in medicinal use should be given[2].

[2] Guideline on declaration of herbal substances and herbal preparations in herbal medicinal products /traditional herbal medicinal products, available at https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-declaration-herbal-substances-herbal-preparations-herbal-medicinal-products/traditional-herbal-medicinal-products-spc_en.pdf

Furthermore, the Agency encourages submission of peer-reviewed data/publications (not just the reference) as the most relevant and reliable documents. Non peer-reviewed data such as references from older standard books of phytotherapy or comparable scientific sources can be taken into consideration provided that they are of an adequate quality.

For more explanations on limitations/ conditions for data submission please read **Annex 1**.

Annex 1

to the Call for scientific data for use in HMPC assessment work on Cannabis sativa L., flos (Cannabis sativa flowering tops)

Limitations/ conditions for data submission

Due to the general high public interest in Cannabis-derived products beyond the medicinal framework, interested parties are reminded of the limited scope of this call for data.

Data submissions should follow the very specific HMPC assessment scope limited to the herbal substance or herbal preparations[3]. Particular consideration should be given to the points explained below, namely

- points 1), 2) and 4) with regard to **well-established use** and
- points 1), 3), 4), 5), 6) and 7) with regard to **traditional use**

The HMPC will solely accept, use and assess data that meet the prerequisites described below and are appropriate for the specific scope of its mandate. Interested parties should abstain from sending 'any data linked to cannabis / cannabinoids' that are not falling under the below prerequisites because a higher quantity of non-usable data may be detrimental to the assessment progress.

Essential legal requirements on data suitability for HMPC assessment

1) The requirement laid down in Article 1 of Directive 2001/83/EC on the definition of a 'herbal substance' and 'herbal preparation'.

(applicable for WEU and TU monographs)

[3] Guideline on declaration of herbal substances and herbal preparations in herbal medicinal products /traditional herbal medicinal products, available at https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-declaration-herbal-substances-herbal-preparations-herbal-medicinal-products/traditional-herbal-medicinal-products-spc_en.pdf

and

Guideline on Assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established and traditional herbal medicinal products, available at: https://www.ema.europa.eu/en/assessment-clinical-safety-efficacy-preparation-eu-herbal-monographs-well-established-traditional

Note: The HMPC cannot establish monographs on single chemical entities (e.g. isolated single plant constituents) but only on adequately described herbal substances and preparations (i.e. 'multi-compound mixtures') as active substances in Herbal Medicinal Products.

HMPC can accept and use for MO establishment	HMPC **cannot** accept and use for MO establishment
- Data obtained with herbal substances or herbal preparations as defined in Article 1 of the Directive 2001/83/EC as active substances	- Data obtained with single isolated substances (e.g. **THC or CBD**)
- Herbal substances or herbal preparations that are adequately described **with an appropriate information on its composition, so that exact strength and posology of the pertinent product are clear.** Data where the complex composition of herbal substances/preparations (Directive 2001/83/EC) as active substances, which is, apart from binomial scientific name of plant, essentially determined by various factors like cultivar (variety, chemovar, chemotype) of the plant, plant part used, the production process, the extraction solvent, the genuine drug extract ratio (DER genuine), the type/physical state of the herbal substances / preparations **is known** in order to **adequately describe the identity and quantity of the herbal substance/preparation, being the active substance of the herbal medicinal product.**	- Herbal substances or herbal preparation which are **not adequately described with an appropriate information on its composition, so that exact strength and posology of the pertinent product are not clear.** Data where the complex composition of herbal substances/preparations (Directive 2001/83/EC) as active substances, which is, apart from binomial scientific name of plant, essentially determined by various factors like cultivar (variety, chemovar, chemotype) of the plant, plant part used, the production process, the extraction solvent, the genuine drug extract ratio (DER genuine), the type/physical state of the herbal substances / preparations is **not known** in order to **adequately describe the identity and quantity of the herbal substance/preparation, being the active substance of the herbal medicinal product.**

For more information see:

- "Compilation of terms and definitions for *Cannabis*-derived medicinal products", available at https://www.ema.europa.eu/en/documents/other/compilation-terms-definitions-cannabis-derived-medicinal-products_en.pdf

- "Guideline on declaration of herbal substances and herbal preparations in herbal medicinal products / traditional herbal medicinal products", available at https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-declaration-herbal-substances-herbal-preparations-herbal-medicinal-products/traditional-herbal-medicinal-products-spc_en.pdf

- "Guideline on quality of herbal medicinal products / traditional herbal medicinal products", available at https://www.ema.europa.eu/en/documents/scientific-guideline/final-guideline-quality-herbal-medicinal-products/traditional-herbal-medicinal-products-revision-3_en.pdf

- "Reflection paper on the level of purification of extracts to be considered as herbal preparations", available at https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-level-purification-extracts-be-considered-herbal-preparations_en.pdf

2) The requirement laid down in Article 10a of Directive 2001/83/EC that the active substance has a recognised efficacy and an acceptable level of safety and that the period of well-established medicinal use has been fulfilled.

(applicable for WEU monographs)

Note: The HMPC cannot establish monographs upon scientific literature without establishing that the defined active substances of the medicinal products have been in well-established medicinal use within the EU for at least ten years, with recognised efficacy and an acceptable level of safety.

HMPC can accept and use for MO establishment	HMPC **cannot** accept and use for MO establishment
- Data obtained with herbal substances or herbal preparations (Directive 2001/83/EC) as active substances **that have been in well-established medicinal use in the EU for at least 10 years (usually existing marketing authorization for a defined medicinal product)** as described in Notice to applicants, Volume 2A - 5.4 Applications according to Article 10a of Directive 2001/83/EC.	- Data obtained with herbal substances or herbal preparations (Directive 2001/83/EC) as active substances that **have not been in well-established medicinal use in the EU for at least 10 years (usually existing marketing authorization for a defined medicinal product)**, as described in Notice to applicants, Volume 2A - 5.4 Applications according to Article 10a of Directive 2001/83/EC.

For more information see:

- "(R7) How can I relate my product to a EU herbal monograph where herbal preparations are listed and have 'well established medicinal use' indications?" in the document "Regulatory Q&A on herbal medicinal products", available at https://www.ema.europa.eu/en/documents/other/regulatory-questions-answers-herbal-medicinal-products_en.pdf

- "Guideline on the assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established and traditional herbal medicinal products", available at https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-assessment-clinical-safety-efficacy-preparation-eu-herbal-monographs-well-established_en.pdf

- Notice to Applicants, Volume 2A, Procedures for marketing authorisation, Chapter 1, Marketing authorisation, available at vol2a_chap1_en_0.pdf (europa.eu)

3) The requirement laid down in Article 16a(1)(a) of Directive 2001/83/EC that the indications are "exclusively appropriate to traditional herbal medicinal products which, by virtue of their composition and purpose, are intended and designed for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment".

(applicable for TU monographs)

Note: The HMPC cannot establish monographs solely based on scientific literature and traditional use without establishing that the defined active substances can be used without medical supervision and is suitable for self-medication.

HMPC can accept and use for MO establishment	HMPC **cannot** accept and use for MO establishment
- Data for herbal substance/preparations as active substances of products used for minor/mild indications, appropriate for use without medical supervision and is suitable for self-medication, e.g. for relief of mild symptoms of mental stress to aid sleep; for the relief of minor articular pain,	- Data for herbal substance/preparations as active substances of products used for indications, that are not appropriate for use without medical supervision, e.g. cancer, diabetes, acquired immune deficiency

headache; for the relief of symptoms associated with common cold, etc.	syndrome, neurodegenerative disorders, liver diseases, renal diseases, etc.

For more information see:

- "(R8) How can I relate my product to an EU herbal monograph where herbal preparations are listed with 'traditional medicinal use' indications?" in the document "Regulatory Q&A on herbal medicinal products", available at https://www.ema.europa.eu/en/documents/other/regulatory-questions-answers-herbal-medicinal-products_en.pdf

- "Guideline on the assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established and traditional herbal medicinal products", available at https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-assessment-clinical-safety-efficacy-preparation-eu-herbal-monographs-well-established_en.pdf

- "Public statement on the interpretation of therapeutic indications appropriate to traditional herbal medicinal products in Community herbal monographs", available at https://www.ema.europa.eu/en/documents/public-statement/public-statement-interpretation-therapeutic-indications-appropriate-traditional-herbal-medicinal_en.pdf

4) The requirement laid down in Article 16a(1)(b) of Directive 2001/83/EC that the herbal substance or herbal preparation is "exclusively for administration in accordance with a specified strength and posology" .

(applicable for TU monographs but also for WEU)

Note: The HMPC cannot establish monographs (for traditional use or WEU) of herbal substances/preparations as active substances upon scientific literature that do not adequately describe the identity and quantity of the herbal substance/preparation, being the active substance of the herbal medicinal product.

HMPC can accept and use for MO establishment	HMPC **cannot** accept and use for MO establishment
Data where the complex composition of herbal substances/preparations (Directive 2001/83/EC) as active substances **is known** in order to **adequately describe the identity and quantity of the herbal substance/preparation, being the active substance of the herbal medicinal product, so that exact strength and posology of the pertinent product are clear – see also point 1.**	Data where the complex composition of herbal substances/preparations (Directive 2001/83/EC) as active substances **is not known** in order to **adequately describe the identity and quantity of the herbal substance/preparation, being the active substance of the herbal medicinal product, so that exact strength and posology of the pertinent medicinal product are not clear – see also point 1.**

For more information see:

- "Guideline on declaration of herbal substances and herbal preparations in herbal medicinal products / traditional herbal medicinal products", available at https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-declaration-herbal-substances-herbal-preparations-herbal-medicinal-products/traditional-herbal-medicinal-products-spc_en.pdf

- "(R8) How can I relate my product to an EU herbal monograph where herbal preparations are listed with 'traditional medicinal use' indications?" in the document "Regulatory Q&A on herbal

medicinal products", available at https://www.ema.europa.eu/en/documents/other/regulatory-questions-answers-herbal-medicinal-products_en.pdf

- "(R7) How can I relate my product to a EU herbal monograph where herbal preparations are listed and have 'well established medicinal use' indications?" in the document "Regulatory Q&A on herbal medicinal products", available at https://www.ema.europa.eu/en/documents/other/regulatory-questions-answers-herbal-medicinal-products_en.pdf

5) The requirement laid down in Article 16a(1)(c) of Directive 2001/83/EC that the herbal substance/preparation is an "oral, external and/or inhalation" substance / preparation.

(applicable for TU monographs)

Note: The HMPC cannot establish monographs for active substances intended to be administered, for instance, by injection (be it intravenous, intramuscular, subcutaneous or intradermal).

HMPC can accept and use for MO establishment	HMPC **cannot** accept and use for MO establishment
- Data obtained with herbal substances or herbal preparations (Directive 2001/83/EC) as active substances that **are intended to be used by the oral, external and/or inhalation route of administration, including the delivery to the oral, nasal, rectal, vaginal mucosae or to ocular or auricular use, only if no safety concerns exist and if for external route of administration only a local action is intended.**	- Data obtained with herbal substances or herbal preparations (Directive 2001/83/EC) as active substances that **are not intended to be used by the oral, external and/or inhalation route of administration.**

For more information see:

- "Guideline on the assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established and traditional herbal medicinal products", available at https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-assessment-clinical-safety-efficacy-preparation-eu-herbal-monographs-well-established_en.pdf

- "HMPC Public statement on the interpretation of the term 'external use" for use in the field of traditional herbal medicinal products, available at https://www.ema.europa.eu/en/documents/public-statement/public-statement-interpretation-term-external-use-use-field-traditional-herbal-medicinal-products_en.pdf

6) The requirement laid down in Article 16a(1)(d) of Directive 2001/83/EC that "the period of traditional use as laid down on Article 16c(1)(c) has elapsed".

(applicable for TU monographs)

Note: The HMPC cannot establish monographs for herbal substances/preparations without a well-documented, consistent and long-standing medicinal use throughout a period of at least 30 years preceding the date of application, including at least 15 years within the EU.

HMPC can accept and use for MO establishment	HMPC **cannot** accept and use for MO establishment
- Data obtained with herbal substances or herbal preparations (Directive 2001/83/EC) as active	- Data obtained with herbal substances or herbal preparations (Directive 2001/83/EC) as active

substances that **have a well-documented, consistent and long-standing medicinal use throughout a period of at least 30 years preceding the date of application, including at least 15 years within the EU.**	substances that **do not have a well-documented, consistent and long-standing medicinal use throughout a period of at least 30 years preceding the date of application, including at least 15 years within the EU. If the documentation submitted does not contain evidence of recent usage of the product but instead refers to a period many years earlier, it is likely that such evidence would be of considerably less value in helping to demonstrate plausibility of indications and safety of the product.**

For more information see:

- "Guideline on the assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established and traditional herbal medicinal products", available at https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-assessment-clinical-safety-efficacy-preparation-eu-herbal-monographs-well-established_en.pdf

7) The requirement laid down in Article 16a(1)(e) of Directive 2001/83/EC that "the data on the traditional use of the medicinal product are sufficient; in particular the product proves not to be harmful in the specified conditions of use and the pharmacological effects or efficacy of the medicinal product are plausible on the basis of long-standing use and experience".

(applicable for TU monographs)

Note: HMPC cannot establish monographs for herbal substances/preparations without evidence on widespread, long-standing use without significant safety problems.

HMPC can accept and use for MO establishment	HMPC **cannot** accept and use for MO establishment
- Data obtained with herbal substances or herbal preparations (Directive 2001/83/EC) as active substances that **have a well-documented, consistent and long-standing medicinal use throughout a period of at least 30 years preceding the date of application, including at least 15 years within the EU.**	- Data obtained with herbal substances or herbal preparations (Directive2001/83/EC) as active substances that **do not have a well-documented, consistent and long-standing medicinal use throughout a period of at least 30 years preceding the date of application, including at least 15 years within the EU. If a traditional herbal medicinal product had long fallen into disuse, this might of itself raise questions as to whether this was due to safety concerns.**

For more information see:

- "Guideline on the assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established and traditional herbal medicinal products", available at https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-assessment-clinical-safety-efficacy-preparation-eu-herbal-monographs-well-established_en.pdf