EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Questions & Answers regarding Cannabis-derived medicinal products[1] and the scope of EU herbal monographs for herbal medicinal products within the EU medicines legislation

Scope of these Q&A

These Q&A aim at clarifying regulatory requirements to obtain a marketing authorisation for medicinal products in the EU (Q1) and at explaining the work of Committee on Herbal Medicinal Products (HMPC) regarding EU herbal monographs (Q2, Q3), as stakeholders involved in the manufacturing of Cannabis-derived substances may not have extensive experience with the EU pharmaceutical regulatory system.

More detailed information can be found on various places at the EMA website:

https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation

https://www.ema.europa.eu/en/human-regulatory/herbal-medicinal-products

https://www.ema.europa.eu/en/human-regulatory/herbal-products/european-union-monographs-list-entries

These Q&A focus on the EU framework for medicinal products and is without prejudice to additional national requirements that may apply to Cannabis-derived products[2].

Question 1a

Does the European Union have a specific framework for Cannabis-derived medicinal products?

[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

[2] e.g. based on the UN Single Convention on Narcotic Drugs of 1961

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Answer 1a

No, products containing Cannabis-derived substances that meet the definition of a medicinal product (as stated in Article 1(2) of Directive 2001/83/EC), must comply with the requirements of the EU pharmaceutical law, in particular those laid down in Directive 2001/83/EC and Regulation (EC) 726/2004 (for centrally authorised products), and must obtain a marketing authorisation from a Competent Authority before they can be placed on the EU market, like any other medicinal product[3]. However, there may be additional national requirements that may apply to Cannabis-derived products[4].

Question 1b

How can medicinal products including those containing Cannabis-derived active substances be authorised in the EU?

Answer 1b

In the EU, a medicinal product for human use may be authorised either by the European Commission through the centralised procedure[5], or by national competent authorities through a mutual recognition, decentralised or national procedure. When applying for marketing authorisation, companies must provide documentation showing that the product is of suitable quality, safety and efficacy.

The documentation for marketing authorisation has to be prepared in accordance with Annex 1 of Directive 2001/83/EC, taking into account the relevant scientific guidelines (EudraLex Volume 3) and the legal basis chosen by the Applicant.

A full dossier for marketing authorisation application must include the results of pre-clinical studies and clinical trials and/or literature to demonstrate the safety and efficacy of the new medicinal product.

It is also possible to demonstrate the efficacy and safety of a well-established substance (i.e. well-established medicinal use for more than 10 years in the EU) through published scientific literature as part of a well-established use marketing authorisation application (Article 10a of Directive 2001/83/EC).

The competent authority will grant a marketing authorisation if, after thorough assessment of the documentation provided, it finds out that all the conditions set in the legislation are complied with, the quality, safety and efficacy are appropriately demonstrated, and the benefit-risk ratio of the concerned medicinal product is considered positive in the applied therapeutic indication.

[3] For more detailed information see the information from the European Commission*, Legal framework governing medicinal products for human use in the EU*, available at: https://health.ec.europa.eu/medicinal-products/legal-framework-governing-medicinal-products-human-use-eu_en
and the *Notice to Applicants, volume 2a, chapter 1*, available at: https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-2_en

[4] e.g. based on the UN Single Convention on Narcotic Drugs of 1961.

[5] See also the information about the Scope of the centralised procedure, available at: https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines#scope-of-the-centralised-procedure-section

Question 1c

Are there specific provisions for herbal medicinal products?

Answer 1c

Yes, there are, however, not for all herbal medicinal products. An exception is only made for herbal medicinal products with a long tradition of safe use in the EU that do fulfil specific requirements: 'Traditional herbal medicinal products' (THMPs).

Traditional use registration for THMPs:

Herbal medicinal products that have been used for more than 30 years (including at least 15 years in the EU), and that are intended to be used without the supervision of a medical practitioner and that are not administered by injection, can be authorised in accordance with the requirements laid down in the Traditional Herbal Medicinal Products Directive (Directive 2004/24/EC), that amends Directive 2001/83/EC (Article 16a).

THMPs must justify a long history of use and experience in the European Union to demonstrate a plausible efficacy and an acceptable level of safety instead of conducting new clinical testing.[6]

THMPs are authorised through the simplified traditional use registration procedure by the national competent authorities and are not subject to medical prescription. It should be noted that some national requirements may prevent some Cannabis-derived products to be approved as medicinal products not subject to medical prescription, and therefore cannot be registered through the Traditional use registration. Advice on Traditional use registration should be sought at the national competent authorities: https://www.hma.eu/human-medicines/national-contacts.html

Herbal medicinal products that do not fulfil the requirements of well-established medicinal use as defined in Art 10a or of traditional use as defined in Article 16a(1) of Directive 2001/83/EC must comply with the general provisions as for any other marketing authorisation application. For example, any new[7] active substance of herbal or synthetic origin (including Cannabis-derived substances or synthetic cannabinoids) that fall under the definition of medicinal product must be authorised in accordance with the requirements of Article 8(3) of Directive 2001/83/EC.

Question 2a

What is an EU herbal monograph?

Answer 2a

[6] For details about the national procedures see also the information available at https://www.ema.europa.eu/en/human-regulatory/herbal-medicinal-products

[7] New active substance is defined in Annex I of the Notice to Applicants, volume 2a, chapter 1, available at https://health.ec.europa.eu/system/files/2019-07/vol2a_chap1_en_0.pdf

An European Union (EU) herbal monograph (formerly known as Community herbal monograph) contains the scientific opinion of the Committee on Herbal Medicinal Products (HMPC) on safety and efficacy data about a herbal substance and its preparations intended for medicinal use. The HMPC evaluates all available information, including non-clinical and clinical data, and also documented long-standing use and experience in the EU[8]. EU herbal monographs should not be confused with monographs of the European Pharmacopoeia that cover the quality requirements for a wide range of substances, including herbal substances and preparations[9].

Reference to established EU herbal monographs can be made in marketing authorisation applications (e.g. for well-established use) and in traditional-use registration applications[10] that are usually national procedures[11].

Question 2b

Can the HMPC establish EU herbal monographs for all plant-derived medicinal products?

Answer 2b

No. The legislation allows the establishment of EU herbal monographs only for herbal medicinal products fulfilling the criteria for either well-established use authorisation (Article 10a Directive 2001/83/EC) or traditional use registration (Article 16a of Directive 2001/83/EC).

For other plant derived-medicinal products such as those with a single compound as active substance, new active substance(s) or those falling under the mandatory scope for the Centralised Procedure[12] because of therapeutic indications, an EU herbal monograph is not possible.

Question 2c

How will data be evaluated for the establishment of an EU herbal monograph on Cannabis flos or other Cannabis-derived herbal substances and herbal preparations?

Answer 2c

The HMPC is the European Medicines Agency's (EMA) committee responsible for compiling and assessing scientific data on safety and efficacy of herbal substances, preparations and

[8] For a more detailed information about the EU herbal monographs see https://www.ema.europa.eu/en/human-regulatory/herbal-products/european-union-monographs-list-entries

[9] The European Pharmacopoeia (Ph. Eur.) provides a legal and scientific reference for the quality control of medicines. For more information about the characteristics of these monographs, consult the Q&A on EU framework also for Non-European Tradition, Question 18, available at https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/questions-answers-european-union-framework-traditional-herbal-medicinal-products-including-those-non_en.pdf

[10] https://www.ema.europa.eu/en/human-regulatory/herbal-medicinal-products

[11] https://www.hma.eu/human-medicines/national-contacts.html.

[12] https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines

combinations, to support the harmonisation of the European market. The HMPC prepares the Agency's opinions on herbal substances and preparations, along with information on recommended uses and conditions of safe use, as compiled in an EU herbal monograph.

The use can be evaluated based on the so-called well-established use (WEU), based on bibliographical evidence in accordance with Article 10a of Directive 2001/83/EC.

The use can be evaluated based on so-called Traditional Use, provided that the requirements of Article 16a of Directive 2001/83/EC are fulfilled.

Question 2d

How will data be evaluated for the establishment of an EU herbal monograph covering well-established use of Cannabis flos or other Cannabis-derived herbal substances and herbal preparations?

Answer 2d

Establishment of well-established medicinal use (WEU) monographs for Cannabis-derived substances or preparations will be possible if requirements of Article 10a of Directive 2001/83/EC are fulfilled. It is possible to replace the results of pre-clinical tests or clinical trials by detailed references to published scientific literature (information available in the public domain) if it can be demonstrated that the active substances of a medicinal product has been in use within the EU, for at least 10 years, with recognised efficacy and an acceptable level of safety. Attention must be paid to the factors which have to be considered in order to support a WEU of active substances, like:

- the time over which a substance has been used;

- quantitative aspects of the use of the substance;

- the degree of scientific interest in the use of the substance (as reflected in the published scientific literature); and

- the coherence of scientific assessments.

When assessing the safety and efficacy of an active substance, it is of utmost importance that the substance is well-defined. Published studies must contain description of the quality of the specific investigated Cannabis herbal substance or preparation thereof. Insufficient data on the quality of studied active substances and composition of products described in the literature does not permit a conclusive evaluation of their safety and efficacy nor their inclusion in an EU herbal monograph[13].

All the above-mentioned aspects should be assessed before a conclusion about the inclusion of specific therapeutic indications for specific herbal substances or preparations thereof in a EU herbal monograph could be reached by the HMPC.

[13] See also "(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

Question 2e

How will data be evaluated for the establishment of an EU Herbal Monograph covering Traditional use of Cannabis flos or other Cannabis-derived herbal substances and herbal preparations?

Answer 2e

In the case of a possible establishment of a traditional use (TU) monograph for Cannabis-derived substances or preparations thereof, beside the fact that its use is controlled according to the UN Single Convention on Narcotic Drugs of 1961, particular attention shall be paid to:

- the period of time that justifies the traditional use (at least 30 years of use, preceding the assessment of the data, including at least 15 years within the EU);

- the type of indications for which Cannabis is used (THMP indications exclusively apply 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, i.e. indications which are generally appropriate for self-medication)[14].

Question 3

How can scientific data be submitted for evaluation by HMPC and what is the procedure to be followed?

Answer 3

At the beginning of an assessment, the HMPC invites the public to submit scientific data on the concerned herbal substances and preparations. This is announced by the publication of a Call for Data on the EMA website. Such Calls at the beginning of an assessment procedure are published for 3 months. EMA can accept only data submitted within the specified 3 months' period.

Public participation is an important way for members of the HMPC to obtain a suitable set of relevant bibliographic references and scientific data for a given assessment. Details on how to submit and standards for submitted material can be found in the 'Procedure for calls for scientific data for use in HMPC assessment works' [15].

[14] See also "(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

[15] https://www.ema.europa.eu/en/human-regulatory/herbal-products/procedures-monograph-list-entry-establishment