EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 November 2023
EMA/HMPC/402684/2013 Rev. 1
Committee on Herbal Medicinal Products (HMPC)

Questions & Answers on the European Union framework for (traditional) herbal medicinal products, including those from a "non-European" tradition

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1. Abbreviations

CHMP	Committee for Medicinal Products for Human Use
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures - Human
CTD	Common Technical Document
DCP	Decentralised Procedure
DER	Drug Extract Ratio
EC	European Commission
EDQM	European Directorate for the Quality of Medicines & HealthCare
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
GACP	Good Agricultural and Collection Practice
GMP	Good Manufacturing Practice
HMP	Herbal Medicinal Product
HMPC	Committee on Herbal Medicinal Products
MRA	Mutual Recognition Agreement
MRP	Mutual Recognition Procedure
NCA	National Competent Authority
NtA	Notice to Applicants
Ph. Eur.	European Pharmacopoeia
SAWP	Scientific Advice Working Party
SmPC	Summary of Product Characteristics
THMP	Traditional Herbal Medicinal Product
TUR	Traditional Use Registration
WEU	Well-Established Use

2. Terminology of herbal medicinal products (Q&A 1-4)

Question 1

What are herbal substances, herbal preparations, and herbal medicinal products?

Answer 1

Definitions are found in Article 1 of Directive 2001/83/EC, as amended by Directive 2004/24/EC:

- **Herbal substances:** all mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried form but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author).
- **Herbal preparations:** preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates.
- **Herbal medicinal product:** any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations.

Question 2

What are traditional herbal medicinal products (THMPs)?

Answer 2

THMPs are herbal medicinal products (HMPs) for human use that fulfil all the conditions laid down in Article 16a(1) of Directive 2001/83/EC, as amended by Directive 2004/24/EC, which are:

- they have indications exclusively appropriate to THMPs 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;
- they are exclusively for administration in accordance with a specified strength and posology;
- they are an oral, external and/or inhalation preparation;
- the period of traditional use as laid down in Article 16c(1)(c) has elapsed (this means that the HMP 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 (EU)); and
- the data on the traditional use of the HMP 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.

Article 16a(2) adds that the presence in the HMP of vitamins or minerals for the safety of which there is well-documented evidence shall not prevent the product from being eligible for registration based on traditional use, provided that the action of the vitamins or minerals is ancillary to that of the herbal active ingredients regarding the specified claimed indication(s).

Question 3

What does the term "non-European medicine systems" stand for? *Rev. Nov. 2023*

Answer 3

In its "Report on the experience acquired as a result of the application of the provisions of Chapter 2a of Directive 2001/83/EC, as amended by Directive 2004/24/EC, on specific provisions applicable to traditional herbal medicinal products"(see COM(2008) 584), the European Commission (EC) mentions a number of non-European medicine systems in which HMPs are traditionally used: Ayurvedic medicine, traditional Chinese medicine (TCM), as well as Kampo, Korean, Mongolian, Thai, Tibetan Unani and Vietnamese traditional medicines. These medicine systems, and others such as traditional African medicine (TAM), have existed for centuries in other parts of the world and have their own specific products, some of which could qualify as THMPs in the EU.

EU legislation has established specific requirements for THMPs, under the Directive 2001/83/EC, as amended by Directive 2004/24/EC, for medicinal products for human use. This legislation, laying down the procedures for placing products on the market, is based on a product-specific approach and does not regulate the practice of traditional medicine.

Question 4

Are food supplements regulated under the European Union (EU) pharmaceutical legislation for (traditional) herbal medicinal products ((T)HMPs)? *New. Nov. 2023*

Answer 4

No, food supplements are not part of the EU pharmaceutical legislation.

In the EU, food supplements are mainly regulated by the Directive 2002/46/EC. As per Article 2 of this directive:

- **Food supplements** are defined as "foodstuffs the purpose of which is to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, marketed in dose form, namely forms such as capsules, pastilles, tablets, pills and other similar forms, sachets of powder, ampoules of liquid, drop dispensing bottles, and other similar forms of liquids and powders designated to be taken in measured small unit quantities".
- **Nutrients** are described as the following substances: vitamins and minerals.

The European Medicines Agency (EMA) is responsible only for products authorised as medicinal products, meaning that food supplements fall outside its remit.

3. Regulation of herbal medicinal products in the European Union (Q&A 5-11)

Question 5

Where to find the pharmaceutical legislation and dossier requirements for herbal medicinal products (HMPs), including traditional herbal medicinal products (THMPs), in the European Union (EU)? *Rev. Nov. 2023*

Answer 5

The EU pharmaceutical legislation is available in what is known as the EudraLex, which constitutes a series of volumes providing information on "The rules governing medicinal products in the European Union". Specific volumes relating to medicinal products for human use (Volume 1) and for veterinary use (Volume 5) are provided. The basic legislation is supported by a series of guidelines provided in Volumes 2-4 and 6-10.

For the dossier requirements, refer to EudraLex Volume 2 - Notice to Applicants (NtA) and regulatory guidelines for medicinal products for human use. Prepared by the EC, in consultation with the National Competent Authorities (NCAs) of the EU/EEA Member States and the EMA, it lists regulatory guidelines related to procedural and regulatory requirements. The NtA is not legally binding and does not necessarily represent the final views of the EC.

For a detailed explanation of the marketing authorisation procedures, refer to EudraLex Volume 2A Chapter 1. A description of the different procedures, including those for THMPs is provided. The applicant has to indicate in Administrative Module 1 of the dossier with which type of application the dossier is submitted (see also Q&A 7 for legal basis/types of application).

EudraLex Volume 2A Chapter 1 also provides information about the approaches followed by Norway, Iceland and Liechtenstein vis-à-vis decisions on approval of medicinal products taken by the EU (together with the 27 EU Member States, Norway, Iceland and Liechtenstein form the European Economic Area (EEA)).

Question 6

Who is responsible for the (registration) marketing authorisation of a (traditional) herbal medicinal product ((T)HMP) in the European Union/European Economic Area (EU/EEA)? *New Nov. 2023*

Answer 6

The NCAs of EU/EEA Member States where an application is submitted are responsible for the registration of THMPs (Article 16a(1) of Directive 2001/83/EC), as amended by Directive 2004/24/EC, and the marketing authorisation of HMPs submitted as well-established use (Article 10a of Directive 2001/83/EC) and stand-alone or mixed (Article 8(3) of Directive 2001/83/EC) applications.

The EMA through its Scientific Committees is responsible for evaluating applications for HMPs based on well-established use (Article 10a of Directive 2001/83/EC) and stand-alone or mixed (Article 8(3) of Directive 2001/83/EC) applications, if the centralised authorisation procedure applies. The marketing authorisation is granted by the EC.

Applicants should contact the NCAs of EU/EEA Member States where they are seeking registration or marketing authorisation for all application types, or eventually the EMA in case the centralised authorisation procedure applies. As stated in EudraLex Volume 2A Chapter 1, Norway, Iceland and Liechtenstein form the EEA together with the 27 Member States of the EU. These countries have, through the EEA agreement, adopted the complete Union acquis on medicinal products and are consequently parties to the Union procedures.

Applicants could also seek scientific and/or regulatory advice from the NCAs of EU/EEA Member States where they are seeking (registration) marketing authorisation of a (T)HMP (see also Q&A 30).

Question 7

Which legal basis/types of application are possible for (traditional) herbal medicinal products ((T)HMPs)? *Rev. Nov. 2023*

Answer 7

The different marketing authorisation procedures and application types are described in section 3 "Marketing Authorisation procedures" and section 5 "Application types", respectively, of EudraLex Volume 2A Chapter 1 in the NtA.

Legal basis relevant for (T)HMPs are:

Regulatory pathway	Main requirements on safety and efficacy	Where to apply
Stand-alone or mixed application (Article 8(3) of Directive 2001/83/EC)	• Safety and efficacy data from the company's own development or a combination of own studies and bibliographic data.	• NCA of a Member State for national, mutual recognition and decentralised procedures. • EMA if the centralised authorisation procedure applies.
Well-established use (WEU) marketing authorisation (Article 10a of Directive 2001/83/EC)	• Scientific literature establishing that the 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. • Involves assessment of mostly bibliographic safety and efficacy data.	• NCA of a Member State for national, mutual recognition and decentralised procedures. • EMA if the centralised authorisation procedure applies.

	• EU Herbal Monograph, if applicable to be taken into account.	
Traditional use registration (TUR) (Article 16a(1) of Directive 2001/83/EC, as amended by Directive 2004/24/EC)	• No clinical tests and trials on safety and efficacy are required as long as sufficient safety data and plausible efficacy are demonstrated. • Involves assessment of mostly bibliographic safety and efficacy data. • Must have been used for at least 30 years, including at least 15 years within the EU. • Are intended to be used without the supervision of a medical practitioner and are not administered by injection. • EU Herbal Monograph or EU List Entry, if applicable to be taken into account.	• NCA of a Member State for national, mutual recognition and decentralised procedures.

The quality requirements are the same irrespective of the regulatory pathway. Products should comply with quality standards found in relevant European Pharmacopoeia (Ph. Eur.) monographs and/or those in the pharmacopoeia of a Member State. See also Q&A 18.

Several scientific guidelines have been established by the EMA's Committee on Herbal Medicinal Products (HMPC) on quality requirements for HMPs.

Question 8

Is it possible to combine the requirements from different types of application in one application? *Rev. Nov. 2023*

Answer 8

No, this is not possible. With a submission of an application dossier, the applicant has to indicate, in the Administrative Module 1, which legal basis the dossier is submitted under. The choice of the legal basis is made by the applicant but only one can be chosen.

	Stand-alone or mixed application Art. 8(3)	Well-established use application Art. 10a	Traditional use application Art. 16(a)
Compliancy with all Quality requirements	Yes	Yes	Yes
Safety	Non-clinical safety data from the applicant's own development or a combination of own studies and bibliographic references	Bibliographic data on acceptable level of safety in EU	Bibliographic expert report; safety data
Efficacy	Clinical trials data or a combination of own studies and bibliographic references	Bibliographic data on recognised efficacy in EU	Efficacy (or pharmacological effects) must be plausible on the basis of long-standing use and experience.
Period of use considered	Not applicable	At least 10 years of proven medicinal use in EU	Evidence of medicinal use for at least 30 years of which at least 15 years in EU
Traditional use considered	Not required but possibly, as supportive data	Not required but possibly, as supportive data	Yes
Indications for this application type	No restriction	No restriction	Indications are restricted. See also Q&A 12
Evaluation of applications	EMA, or NCA	EMA, or NCA	NCA

Question 9

For which indications of herbal medicinal products (HMPs) is an evaluation under the centralised authorisation procedure mandatory or optional? *Rev. Nov. 2023*

Answer 9

Only certain medicinal products are eligible for the centralised authorisation procedure.

The centralised procedure is mandatory for human medicines containing a new active substance (which was not authorised in the EU on the date of entry into force of Regulation (EC) No 726/2004, i.e., 20 November 2005) to treat:

- human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS);
- cancer;
- diabetes;

- neurodegenerative diseases;
- auto-immune and other immune dysfunctions; or
- viral diseases.

HMPs that fall under one or more of these categories must be assessed according to the centralised authorisation procedure.

HMPs having received an orphan status in a given indication will be assessed via the centralised authorisation procedure. Guidance on orphan medicinal products can be found on EMA website.

The centralised procedure is optional for medicinal products:

- containing new active substances (which were not authorised in the EU on the date of entry into force of Regulation (EC) No 726/2004, i.e., 20 November 2005) for indications other than those stated above;
- which constitute a significant therapeutic, scientific or technical innovation; or
- whose authorisation would be in the interest of public health at EU level.

For further guidance, the EMA has published the documents "Scientific aspects and working definitions for the mandatory scope of the centralised procedure" (EMEA/CHMP/121944/2007), and "European Medicines Agency pre-authorisation procedural advice for users of the centralised procedure" (EMA/821278/2015).

Question 10

What is Good Manufacturing Practice (GMP) and how does it apply for herbal medicinal products (HMPs)? *New Nov. 2023*

Answer 10

The GMP describes the minimum standard that a medicines manufacturer must meet in their production processes. Any manufacturer of medicines intended for the EU market (whether HMPs or not) must comply with GMP.

The principles and guidelines of GMP in the EU are laid down in the Commission Directive (EU) 2017/1572, supplementing Directive 2001/83/EC. EudraLex Volume 4 provides interpretation of these principles and guidelines, supplemented by a series of annexes that modify or augment the detailed guidelines for certain types of product, or provide more specific guidance on a particular topic. EudraLex Volume 4 Annex 7 provides information regarding the manufacture of HMPs.

The EMA only has a coordinating role for GMP inspections of manufacturing sites for medicines whose marketing authorisation in the EU is submitted through the centralised authorisation procedure or as part of a referral procedure.

In the EU, NCAs are responsible for inspecting manufacturing sites located in their own territories. Manufacturing sites outside the EU are inspected by the NCA of the Member State where the EU importer is located, unless a mutual recognition agreement (MRA) is in place between the EU and the country concerned. If an MRA applies, the authorities mutually rely on each other's inspections.

A GMP certificate is issued following a GMP inspection, by the NCA responsible for carrying out the inspection, to confirm the GMP compliance status of the inspected site.

General information regarding GMP and Q&As with guidance on good manufacturing practice and good distribution practice in the EU can be found at the EMA website.

Question 11

What is Good Agricultural and Collection Practice (GACP) for herbal medicinal products (HMPs)? *New Nov. 2023*

Answer 11

The GACP represents recommendations on an appropriate quality assurance system for selection of seeds, cultivation, collection and harvesting conditions of plants. The HMPC has published the "Guideline on Good Agricultural and Collection Practice (GACP) for starting materials of herbal origin" (EMEA/HMPC/246816/2005), to ensure appropriate and consistent quality of medicinal plant/herbal substances, while the concept of GMP still applies.

EudraLex Volume 4 Annex 7 includes a table illustrating the application of good practices (including GACP) to the manufacture of HMPs

There is no accredited GACP certificate. Applicants usually have to provide/include data and details of the cultivation/collection of the herbal substance/plant material in module 3. A statement of conformity (written declaration) with the GACP guideline has also to be provided and is supported by information from their suppliers.

4. Specific provisions for traditional herbal medicinal products (Q&A 12-21)

Question 12

Which indications can be granted for traditional herbal medicinal products (THMPs)? *Rev. Nov. 2023*

Answer 12

Guidance can be found in the section 3.4 "Procedure for traditional herbal medicinal products (traditional-use registration)" of EudraLex Volume 2A Chapter 1.

Indications must be exclusively appropriate to THMPs, 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. However, to prevent treatment of more serious pathologies with THMPs, it is possible for the indications of THMPs to refer to the use after exclusion of serious conditions by a medical doctor. In any case, the THMP still needs to be intended and designed for use without the supervision of a medical practitioner for diagnostic purposes, or for prescription, or monitoring of treatment. The THMP has to be a non-prescription medicinal product. The EMA has also published a "Public statement on the interpretation of therapeutic indications appropriate to traditional herbal medicinal products in Community herbal monographs" (EMA/HMPC/473587/2011) and a "Guideline on the assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established and traditional herbal medicinal products (europa.eu)" (EMEA/HMPC/104613/2005).

The HMPC has expressed the view that therapeutic indications that involve diseases, disorders or conditions such as cancer, psychiatric diseases/disorders, infectious diseases such as hepatitis or influenza, cardio-vascular diseases such as heart failure, metabolic diseases such as diabetes, are not acceptable for THMPs. Indications relating to specific concepts of traditional medicines may be acceptable if they fulfil the criteria given for safe self-medication, i.e., indications appropriate for traditional use. See also Q&A 18.

Transposition of complex traditional indications should be avoided. Terminology derived from pharmacological actions should be avoided if the indication is based on a specific traditional concept that does not derive from a pharmacological model.

Question 13

What time period of medicinal use has to be demonstrated for a traditional herbal medicinal product (THMP)?

Answer 13

Applications for registration as a THMP should be accompanied by bibliographical or expert evidence to the effect that the HMP under consideration, or a corresponding product, has been in medicinal use throughout a time period of at least 30 years preceding the date of the application, including at least 15 years within the EU.

The HMPC has established a "Guideline on the assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established and traditional herbal medicinal products (europa.eu)" (EMEA/HMPC/104613/2005), where also the term "corresponding product" is explained.

A "corresponding product" is defined as having:

- the same active ingredient(s), irrespective of the excipient(s);
- the same or similar intended purpose;
- the equivalent strength and posology; and
- the same or similar route of administration.

As the legislation refers to the "same active ingredients", the herbal substance/herbal preparation must be the same in terms of the declaration[1] of active substances. This will include the plant/part of the plant, the type of herbal preparation and, for extracts, the primary solvent. As the drug extract ratio (DER) may be difficult to retrieve from the literature, comparison with a range of similar products on the market might be acceptable.

If no comparable product is currently marketed, reference to scientific reference handbooks, official compendia for prescriptions or official pharmacopoeias of the Member States can be considered.

Evidence of the traditional use of the single active substances included in a fixed combination product will not be sufficient to establish the traditional use of the combination product.

The evidence of traditional use may also be satisfied even if the number or the quantity of ingredients in the corresponding product has been reduced during the time period. However, it should be considered whether such a reduction or elimination may have resulted in an increased dose of the remaining constituents thus making a more extensive assessment of safety necessary. The elimination of a number of active constituents or a significant reduction in posology may make it difficult to accept the "plausibility" of an indication.

See also Q&A 14 and Q&A 15.

Question 14

What can be done if there is doubt regarding the adequacy of the evidence of the long-standing use for a traditional herbal medicinal product (THMP)?

Answer 14

When a Member State has doubts about the adequacy of the evidence of the long-standing use for a THMP, it can refer the matter to the HMPC in accordance with Article 16c(1)c of Directive 2001/83/EC, as amended by Directive 2004/24/EC.

Guidance on this referral procedure is provided in EudraLex Volume 2A Chapter 3 in the NtA.

This referral may be started at the request of the Member State where an application for TUR for a THMP has been submitted.

The HMPC is asked to provide an opinion on the adequacy of the evidence of the long-standing use of the product, or of the corresponding product. Namely, the HMPC assesses whether the data on long-standing use and experience of the THMP are sufficient to demonstrate safety and plausible efficacy and pharmacological effects.

[1] Please refer to the HMPC's "Guideline on declaration of herbal substances and herbal preparations in herbal medicinal products/traditional herbal medicinal products" (EMA/HMPC/CHMP/CVMP/287539/2005).

Question 15

What can be done when a traditional herbal medicinal product (THMP) is eligible for simplified registration but has been in medicinal use for less than 15 years in the European Union (EU)?

Answer 15

When a Member State has determined that an HMP is eligible for TUR, but the HMP has less than 15 years of medicinal use in the EU, it can refer the matter to the HMPC in accordance with Article 16c(4) of Directive 2001/83/EC, as amended by Directive 2004/24/EC.

Guidance on this referral procedure is provided in EudraLex Volume 2A Chapter 3 in the NtA.

The HMPC is asked to provide an opinion on whether the HMP is eligible for TUR, although it has been used in the EU for less than 15 years.

In addition to issuing this opinion, the HMPC evaluates the possibility of establishing an EU herbal monograph for that herbal substance(s), herbal preparation(s) and/or combinations thereof. If and when the monograph is established, it should be taken into account by the Member State when taking its final decision to register the product.

Question 16

Which active ingredient(s) can be part of a traditional herbal medicinal product (THMP)?

Answer 16

Directive 2001/83/EC, as amended by Directive 2004/24/EC, requires HMPs to contain exclusively as active ingredient(s) one or more herbal substances or herbal preparations or combinations thereof. Substances of synthetic origin, constituents of animal origin and chemical substances cannot be active ingredients for (T)HMPs. According to article 16a(3), also homeopathic medicinal products cannot be evaluated as THMPs.

The HMPC has established guidance on interpretation of the definition of herbal substance and herbal preparation, especially how it relates to some purified compounds of herbal origin. This includes a "Reflection paper on the level of purification of extracts to be considered as herbal preparations" (EMA/HMPC/186645/2008) and a "Regulatory Q&A on herbal medicinal products" (EMA/HMPC/345132/2010).

THMPs can contain vitamins and minerals if they have an ancillary action. The ancillary action should be justified in the registration dossier. They should fulfil the requirements of the current "Guideline on summary of requirements for active substances in the quality part of the dossier" (CHMP/QWP/297/97 as revised).

Question 17

What is the value of data on single active ingredients in the assessment of combination products? *Rev. Nov. 2023*

Answer 17

The framework for authorisation or registration in the EU is based on one finished medicinal product. It may be a combination of one (or more) herbal substance(s) and one (or more) herbal preparation(s); however evidence must relate to the combination as such.

To support an application for a combination product, data on the combination of active ingredients are expected. However, it may be possible to include information on the individual substances (literature or actual data), to justify the absence of certain specific data on the combination.

The HMPC published the "Guideline on the clinical assessment of fixed combinations of herbal substances/herbal preparations" (EMEA/HMPC/166326/2005).

For vitamins and minerals, see also Q&A 2 and Q&A 16.

Question 18

Does European Union (EU) pharmaceutical legislation have specific requirements for traditional herbal medicinal products (THMPs), based on "non-European medicine systems"?

Answer 18

The EU pharmaceutical legislation, which establishes the possible reference to "evidence of 30 years medicinal use" to show that efficacy is plausible, does not introduce a distinction for those products whose traditional use has essentially taken place outside the EU.

The following conditions must be fulfilled for such products to be registered:

- they must comply with the definition of "traditional herbal medicinal product" (see also Q&A 2);
- the medicinal product, or a corresponding product, has been in medicinal use throughout a time period of at least 30 years preceding the date of the application; and
- there has been at least 15 years of medicinal use in the EU (see also Q&A 13).

All requirements apply in the same manner to all THMPs.

Directive 2001/83/EC, as amended by Directive 2004/24/EC, introduced some specific requirements to the labelling of THMPs, as specified in Article 16g(2). In addition to the requirements of Articles 54 to 65 of Directive 2001/83/EC, any labelling and user package leaflet must contain a statement to the effect that the product is a THMP for use in the specified indication(s) exclusively based upon long-standing use. An optional element of the labelling relates to the nature of the tradition: the Directive 2001/83/EC, as amended by Directive 2004/24/EC, allowed a Member State to require that the product's labelling and its user package leaflet state the nature of the tradition in question, for example a reference to the relevant "non-European medicine system". This is a national decision taken by the NCA in the Member State.

Question 19

What are the requirements to demonstrate the quality of a traditional herbal medicinal product (THMP)? *Rev. Nov. 2023*

Answer 19

As indicated in the Q&A 7, quality requirements are the same irrespective of the regulatory pathway. Products should comply with quality standards found in relevant Ph. Eur. monographs or in absence thereof, those in the pharmacopoeia of a Member State.

Part III of Annex I to Directive 2001/83/EC lays down specific requirements related to the nature of identified, distinctive types of medicinal products. Section 4 of that Part III describes the specific requirements for HMPs. These requirements also apply to THMPs.

The HMPC has established a number of scientific guidelines on quality of (T)HMPs. They include a "Guideline on Good Agricultural and Collection Practice (GACP) for starting materials of herbal origin" (EMEA/HMPC/246816/2005), addressing the specific concerns of growing, collecting and primary processing of medicinal plants/herbal substances that are used for medicinal purposes. Preparation of herbal material must also follow GMP, and in particular EudraLex Volume 4 Annex 7 provides specific guidance for manufacture of HMPs. The scientific guidelines should be considered when preparing applications. Deviations from guidelines must always be justified by applicants in their applications.

See also Q&A 10, Q&A 11 and Q&A 16.

Question 20

What are the requirements to demonstrate the safety of a traditional herbal medicinal product (THMP)? *Rev. Nov. 2023*

Answer 20

Applicants must substantiate the safety of the medicinal product by the means of a bibliographic review of safety data together with an expert report, complemented by any necessary data, which the Member State's NCA may request. The duration of the documented use in humans will be an important element of the evaluation.

The HMPC has established the "Guideline on non-clinical documentation for herbal medicinal products in applications for marketing authorisation (bibliographical and mixed applications) and in applications for simplified registration" (EMEA/HMPC/32116/2005). It reports that despite the wide use of HMPs published non-clinical tests for traditional herbal preparations are often incomplete or not in accordance with today's state-of-the-art. Published toxicological information, well-presented clinical experience (with regard to the length of time and extent of use in humans), epidemiological studies and data as well as post-marketing experience gained by widespread use in humans may reduce the need for unnecessary tests in animals.

The EMA has also established general scientific guidelines on non-clinical testing.

The specific character of bibliographic data on herbal preparations used over a very long period, sometimes over centuries, may require pre-submission discussion or scientific advice between applicants and NCAs on how to prepare such applications.

Question 21

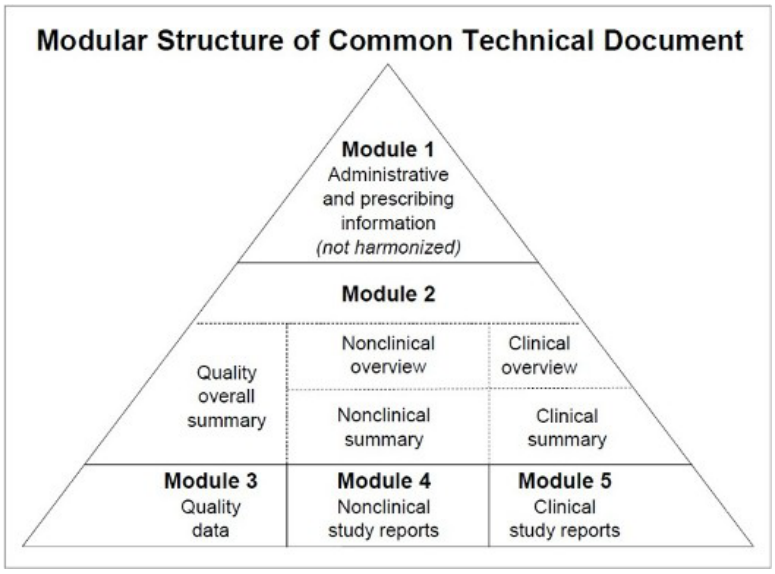
How to present an application for a (traditional) herbal medicinal product ((T)HMP)?

Answer 21

Applications have to be submitted in the format and content referred to in EudraLex Volume 2B in the NtA.

Application dossiers for medicinal products for human use should follow the structure of the common technical document (CTD), divided into five modules:

1. Administrative and prescribing information
2. Overview and summary of modules 3 to 5
3. Quality data (pharmaceutical documentation)
4. Non-clinical study reports (pharmacology/toxicology)
5. Clinical study reports – efficacy and safety (clinical trials)



For simplified registration of THMPs, the HMPC has established specific guidance, including a table of concordance in the "Guideline on the use of the CTD format in the preparation of a registration application for traditional herbal medicinal products" (EMA/HMPC/71049/2007).

Guidance on Module 2.3 and Module 3 as described in the guideline is also relevant for applications for marketing authorisations for HMPs.

5. Type and role of monographs in the European Union regulatory framework (Q&A 22-27)

Question 22

Which monographs in the European Union (EU) regulatory framework should be taken into consideration for (traditional) herbal medicinal products ((T)HMPs)? *Rev. Nov. 2023*

Answer 22

Under the EU regulatory framework, there are two distinctive types of monographs that need to be taken into consideration for (T)HMPs:

- Pharmacopoeia monographs established at European or national level; and
- EU herbal monographs established at the EMA level (formerly known as Community herbal monographs).

Pharmacopoeia monographs at European level

The Ph. Eur. is a collection of standardised specifications on the quality of medicines and their components. These specifications are laid down in either the general Ph. Eur. monographs or in specific monographs. The official standards published by the Ph. Eur. provide a legal and scientific basis for quality control during the development, production and marketing processes.

They concern the qualitative and quantitative composition and the tests to be carried out on (herbal) medicines, such as on the raw materials used in production of (herbal) medicines. All producers of (herbal) medicines and/or (herbal) substances for pharmaceutical use must therefore apply these quality standards in order to market their products in the signatory states of the Convention.

The work on the Ph. Eur. is carried out at the European Directorate for the Quality of Medicines & HealthCare (EDQM), in Strasbourg, France.

Pharmacopoeia monographs at national level

Some Member States have a national pharmacopoeia officially in use.

EU herbal monographs

A EU herbal monograph (formerly known as Community herbal monograph) contains the HMPC's scientific opinion on safety and efficacy data about a herbal substance and its preparations intended for medicinal use. They are established by the HMPC and have the objective of facilitating the (registration) marketing authorisation of (T)HMPs. Indeed, when monographs have been established, they shall be taken into account by the applicant and the Member State(s) as part of an application. Accordingly, even though the Member States are not obliged to follow the monograph, any decisions not to accept the content of the monograph as adopted by the HMPC should be duly justified considering the important role of monographs to bring harmonisation to this field.

Other herbal monographs

Worldwide, several international or national bodies have also established monographs on the medicinal uses of plants and herbal preparations and can be part of the documentation used to demonstrate the medicinal use outside the EU within the dossier to support an application for TUR.

Guidance is found in the Annex I to Directive 2001/83/EC, as amended by Directive 2004/24/EC, clarifying how to use these other monographs when they provide specifications[2] on herbal substances/preparations in the absence of a monograph in the Ph. Eur. or in the pharmacopoeia of a Member State.

See also Q&A 19.

Question 23

How does the European Pharmacopeia (Ph. Eur.) monographs relate to European Union (EU) herbal monographs?

Answer 23

EU herbal monographs describe the medicinal uses (and all related conditions for a safe use) of herbal substances/preparations. Ph. Eur. monographs provide the quality specifications for herbal substances and herbal preparations in general and individual monograph texts.

Therefore, both types of monographs are complementary. In summary:

- the specifications for quality are found in Ph. Eur. monographs (or national Pharmacopoeia monographs); and
- the HMPC conclusions on efficacy and safety are found in the EU herbal monographs.

Question 24

What information is found in European Union (EU) herbal monographs? *Rev. Nov. 2023*

Answer 24

An EU herbal monograph contains the HMPC's scientific opinion on safety and efficacy data concerning a herbal substance and its preparations intended for medicinal use. The HMPC evaluates all available information including non-clinical and clinical data but also documented long-standing use and experience in the EU and, if available, outside the EU.

EU herbal monographs are divided into two sections:

- the left column describes the conclusions on the herbal preparations that fulfil the WEU requirements (suitable for marketing authorisation); and
- the right column describes the conclusions on the herbal preparations that fulfil the traditional use requirements (suitable for simplified registration).

See also Q&A 7 and Q&A 8.

Each herbal preparation is assessed individually as information available may vary from one preparation to another. Therefore, some preparations will appear in the WEU section of the monograph and others will appear in the traditional use section. If the available data for some preparations are insufficient, they might not be included. EU herbal monographs provide all the information necessary for the use of a medicinal product containing a specific herbal substance or preparation:

[2] For definitions, please refer to the HMPC's "Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products" (EMA/HMPC/162241/2005).

- what the herbal product is used for;
- who the herbal product is intended for (e.g., adults only or children as well, in pregnant and lactating women, etc.); and
- safety information such as information regarding undesirable effects and interactions with other medicines.

EU herbal monographs are published with other documents including an assessment report containing reviews of all available data relevant for the medicinal use of the herbal substance/preparations and divergent positions of individual HMPC members if the monograph was not adopted by consensus.

When the HMPC prepares a draft EU herbal monograph, it is released for public consultation on the EMA website for a period of three months. Comments received are subsequently evaluated and discussed and the final version of the monograph is published on the EMA website.

EU herbal monographs established by HMPC are used for regulatory purposes in the framework for medicinal products and are not applicable to herbal ingredients or herbal products regulated as food supplements by Directive 2002/46/EC.

Question 25

What is the difference between European Union (EU) list entries and EU herbal monographs? *New Nov. 2023*

Answer 25

Besides the traditional-use monographs on herbal substances, the HMPC gradually develops the EU list (formerly known as Community list) through "list entries". Unlike EU herbal monographs, EU list entries are legally binding on applicants and NCAs in the Member States. Draft EU list entries are developed by the HMPC, but the final EU list entries are adopted and published by the EC.

If applicants for a TUR can demonstrate that their product and related indications comply with the information contained in the EU list entry, they will not need to provide evidence of its safe and traditional use. EU List entries are the basis for a medicinal product's summary of product characteristics (SmPC).

The existence of an EU herbal monograph on an herbal substance is not a mandatory prerequisite, although it is a helpful tool as an EU harmonised standard to achieve national registration for THMPs and could be the basis for a medicinal product's SmPC. An applicant can obtain national registration if they can demonstrate that all requirements for THMPs according to Directive 2001/83/EC, as amended by Directive 2004/24/EC, are met, even if not covered by an EU herbal monograph. This includes the proof on specified 30 years long-standing use including 15 years in the EU, for TUR. This is product-specific and should be clarified by obtaining scientific or regulatory advice from the NCA of the relevant member state.

Question 26

How to find information on which European Union (EU) herbal monographs and EU list entries are established or under development? *Rev. Nov. 2023*

Answer 26

A list of all the EU herbal monographs established by the HMPC can be found on the EMA website.

The progress of the work on EU herbal monographs is publicly accessible via two documents on the EMA website. The herbal substances that have been selected for assessment and their current assessment status can be found in the "Overview of assessment work – Priority List" (EMA/HMPC/561868/2021). The "Inventory of herbal substances for assessment" (EMA/HMPC/494079/2007) gives a full overview of all herbal substances, including those which are proposed for an EU herbal monograph by an interested party. This inventory is updated upon new valid proposals for assessment.

On the basis of the scientific opinion of the HMPC, "list entries" of herbal substances, preparations, and combinations thereof for use in certain THMPs has been established by Commission Decision 2008/911/EC. Applicants can refer to the EU list entries in relation to safety and efficacy when registering a THMP. The quality of the medicinal products still needs to be verified prior to approval. Further information is available at the EC website.

See also Q&A 25.

Question 27

How can the work on a European Union (EU) herbal monograph and EU list entry be initiated and what is its life cycle? *New Nov. 2023*

Answer 27

All necessary procedures for EU herbal monograph and EU list entry establishment are published on the EMA website.

The procedure for new proposals is described in detail in the "Procedure on management of proposals submitted by interested parties for Community list entries or Community herbal monographs" (EMA/HMPC/328575/2007). This document also presents links to guidance how to submit scientific data in support of the assessment work on EU herbal monographs.

Five years after a EU herbal monograph is established, the HMPC considers the need for revision of the monograph to prevent it from becoming outdated. The revision of a monograph is initiated upon decision by HMPC following review of new information and proposal by Rapporteur. The decision to start the revision procedure must be justified by the relevance of the reviewed data. Based on these data the HMPC either decides on a revision according to the standard procedure, or that no revision is necessary.

The HMPC has published the "Procedure for the review and revision of European Union herbal monographs and European Union list entries" (EMA/HMPC/124695/2011), which provides guidance on the steps necessary for revision of an EU herbal monograph and EU list entry.

In this document it is stated that "when an 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".

6. Advice, procedures and relevant institutions (Q&A 28-32)

Question 28

What are the main responsibilities of the Committee on Herbal Medicinal Products (HMPC)? *New Nov. 2023*

Answer 28

To support EU Member States, the HMPC focuses on two main tasks:

- establishing EU monographs covering the therapeutic uses and safe conditions of WEU and/or traditional use for herbal substances and preparations;
- drafting a EU list of herbal substances, preparations and combinations thereof for use in THMPs.

The HMPC, its working parties and other groups also:

- prepare scientific guidelines and regulatory guidance to help companies prepare marketing authorisation and registration applications for herbal medicines;
- prepare opinions on questions referred to EMA by the NCAs regarding the period and evidence of safe use for THMPs;
- cooperate with the EDQM on Ph. Eur. standards and EMA guidance on the quality of HMPs;
- coordinate with other scientific committees at the EMA on the regulation and safe use of herbal medicines;
- provide scientific and regulatory support to companies researching and developing HMPs;
- interact with interested parties;
- provide advice and training to herbal assessors of NCAs; and
- cooperate with international partners on the harmonisation of regulatory requirements.

For full details, EMA has published "HMPC rules of procedure" (EMA/HMPC/139800/2004).

Question 29

Does the Committee on Herbal Medicinal Products (HMPC) hold a specific database on (registered) authorised (traditional) herbal medicinal products ((T)HMPs)? *New Nov. 2023*

Answer 29

No. As of July 2018, the EMA publishes data from the so-called Article 57 database on all medicines authorised in the EU/EEA. Marketing authorisation holders must submit and maintain this information in accordance with EU legislation. This document is updated periodically. The primary objective of making this information public is to provide a complete list of all medicines authorised in the EU/EEA with marketing authorisation holders' dedicated contact details for pharmacovigilance enquiries.

The HMPC does not keep track of (T)HMPs authorised or registered in each Member State. Interested parties should contact the NCA of each Member State in order to obtain this information. A list of EU/EEA NCAs can be found here.

Up until 2016 the HMPC published the "Uptake of the traditional use registration scheme and implementation of the provisions of Directive 2004/24/EC in EU Member States" (EMA/HMPC/322570/2011). This survey was performed by the EMA and subsequent results were published on the EMA website as an exercise to check the implementation of Directive 2004/24/EC in

the EU Member States, as well as the assessment priorities for the HMPC in the EU. However, it does not represent an exhaustive database of (T)HMPs authorised/registered in the EU Member States.

Question 30

Where can an applicant get scientific support and advice for (traditional) herbal medicinal products ((T)HMPs)?

Answer 30

Before considering seeking advice from the HMPC, applicants are reminded of the following alternatives to obtain guidance on (T)HMPs:

- scientific and regulatory advice can be obtained from the NCAs in the Member States of the EU; or
- scientific advice can be obtained from the Scientific Advice Working Party (SAWP) established by the Committee for Medicinal Products for Human Use (CHMP). In particular, the SAWP can be contacted for advice on HMPs other than THMPs. The SAWP will liaise with the HMPC where appropriate.

Scientific support and advice specifically for THMPs can be requested from the HMPC. There is a fee for single areas, e.g., questions concerning quality or safety or long-standing use and experience, and a fee for questions on multiple areas, i.e., a combination of single issues. The fee must be paid to the EMA in accordance with the "Rules for the implementation of Council Regulation (EC) No 297/95 on fees payable to the European Medicines Agency and other measures" (EMA/MB/118263/2023).

The scientific support and advice given by the HMPC is not legally binding to NCAs with regard to any future simplified TUR application. However, these authorities should take into consideration any HMPC advice resulting from a request for scientific support and advice.

Requests for scientific support and advice have to be submitted to the secretariat of the HMPC via the email address hmpc.secretariat@ema.europa.eu. The procedure for submitting such requests is described in detail in the "Guidance for companies seeking scientific support and advice on traditional herbal medicinal products" (EMA/HMPC/127670/2011).

Question 31

Are the Mutual Recognition Procedure (MRP) and the Decentralised Procedure (DCP) possible for traditional herbal medicinal products (THMPs)? *Rev. Nov. 2023*

Answer 31

Yes, both procedures are possible. According to Article 16d of Directive 2001/83/EC, as amended by Directive 2004/24/EC, MRP and DCP applies by analogy to TUR:

- provided that a respective EU herbal monograph exists; or
- provided that the THMP submitted for registration consists of herbal substances, herbal preparations or combinations thereof contained in the EU list entries.

The MRP/DCP is also possible for registration of THMPs on a voluntary basis even if neither an EU list entry nor an EU herbal monograph exists provided that adequate and sufficient documentation for traditional use and safety is enclosed in the dossier submitted. However, it should be clarified that the use of MRP/DCP is the decision of the Member State. Discussion with Member States intended to be

included in any procedure, is recommended before submission of an application. This also applies to THMPs, based on non-European traditions.

If the registration of a THMP as described above is intended in a single Member State the respective national procedure is applicable. According to Article 16d of Directive 2001/83/EC, as amended by Directive 2004/24/EC, if the registration of a THMP as described above is intended in more than one Member State, DCP should apply. If a THMP as described above is already registered in a Member State and the applicant intends registration in further Member States, MRP applies by analogy. The applicant, however, should be aware of any divergent positions on the EU herbal monograph.

For further information the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) has established a "Q&A on traditional herbal medicinal products" (CMDh/287/2013).

Question 32

Where are decisions taken and advice given in the European Union (EU) regulatory framework? *Rev. Nov. 2023*

Answer 32

Final decision regarding	Authority
Marketing authorisation for a medicinal product falling under the scope of the centralised procedure	EC
Marketing authorisation for a HMP authorised nationally	NCA of a Member State
Registration for a THMP	NCA of a Member State
Scientific or regulatory advice for HMPs	SAWP of CHMP or NCA of a Member State
Scientific support and advice for THMPs	NCA of a Member State or HMPC
EU herbal monograph	HMPC
EU list entry (See also Q&A 27)	EC
Referral procedure on "adequacy of evidence of long-standing use" according to Article 16c(1)c	Initiated by NCA of a Member State leading to an opinion of the HMPC
Referral procedure on "period of traditional use less than 15 years in EU" according to Article 16c(4)	Initiated by NCA of a Member State leading to an opinion of the HMPC

Monographs on herbal substances (herbal drugs) / herbal preparations (herbal drugs preparations) in the Ph. Eur.	Ph. Eur. Commission