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Committee on Herbal Medicinal Products (HMPC)

Reflection paper on the use of information in European Union herbal monographs and assessment reports for borderline issues

Draft

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1. Introduction

The simplified registration procedure for traditional herbal medicinal products ('traditional use registration') was introduced in 2004 through Directive 2004/24/EC of the European Parliament and the Council, which amended Directive 2001/83/EC and introduced the possibility of national registrations of herbal medicinal products based on traditional use only. By introducing the traditional use registration, the Directive has allowed these products to be marketed under harmonised conditions in the EU. Importantly, the traditional use registration ensures the protection of public health in the EU by making such products subject to the necessary guarantees of quality, safety and a plausible efficacy on the basis of long-standing use. The introduction of the traditional use registration has also increased the quality of the information provided to the healthcare professionals and to the patients. Overall, the major public health advantages of this regulatory provision are that the quality and safety of the products that do receive a traditional use registration have been assessed by National Competent Authorities and that they will be subject to pharmacovigilance requirements.

From a safety perspective the pre-approval assessment of medicinal products, in particular the quality of the product and the fact that most herbal preparations in medicinal products have been in clinical use for many years (for traditional herbal medicinal products, the requirements are >30 years), means that most adverse reactions are acknowledged and assessed before approval. There are also several requirements regarding the labelling, in particular, the therapeutic indication must include a statement that it is based on traditional use only. The labelling should also include duration of use, when to contact a healthcare professional as well as safety information such as contraindications and warnings to decrease possible risk during the use of the medicinal product.

The Directive 2004/24/EC also established the Committee on Herbal Medicinal Products (HMPC) for the purpose of facilitating the harmonisation of the European market of herbal medicinal products. To support EU Member States, one of the main tasks of HMPC is to establish EU standards for national procedures for herbal medicinal products. HMPC issues scientific opinions on herbal substances and preparations, along with information on recommended uses and safe conditions. This information is provided in EU herbal monographs or EU list entries. The work by the HMPC supports the harmonisation of the European market and gives Applicants and National Competent Authorities a clear reference point when preparing or assessing an application for marketing authorisation/registration of herbal medicinal products in Member States. An important part of the procedure for establishment of EU herbal monographs, is close communication between interested parties (IPs) in the stages of starting a monograph project followed by public consultation on a draft version.

Today, the HMPC has established more than 170 EU herbal monographs and a large number of additional guidance documents in the areas of quality, safety and efficacy and justification of traditional use of herbal medicinal products. Despite considerably different starting points in EU Member States regarding medicinal and regulatory approaches, the process for licensing and information on herbal substances and preparations has been highly harmonised across the EU, as a result of the work by the HMPC. It has been demonstrated that once the EU herbal monographs have become available, they are used in the vast majority of traditional use registrations and well-established use marketing authorisations by applicants and National Competent Authorities and ultimately they had a facilitating role in the marketing authorisation/registration procedures[1].

Active substances in herbal medicinal products are also found in other product categories such as food supplements, cosmetics or medical devices. The possibility of different categories of active substances/preparations of herbal origin can lead to different commercial choices such as where, e.g.,

[1] Uptake of the traditional use registration scheme and implementation of the provisions of Directive 2004/24/EC in EU Member States (europa.eu)

time/resources for product development/application for a marketing authorisation/registration and permitted indication (medicinal or health claim) are taken into account. However, there are products with herbal substances/preparations available on the EU market with considerable differences in classification. Some similar or even identical products can appear under different status in different Member States, which could be confusing for patients/consumers and healthcare professionals.

It should be emphasised that the HMPC is responsible for compiling and assessing scientific data on herbal substances, preparations and combinations, to support the harmonisation of the European market for herbal medicinal products. Importantly, it is the remit of National Competent Authorities in Member States to decide on the classification of medicinal products in their national territory. This process is different in individual Member States. However, in order to support Member States and Applicants in borderline issues, for products to be marketed under harmonised conditions in the EU and to ensure the protection of public health, EU herbal monographs and supporting assessment reports could serve as guidance when drawing the line between herbal medicinal products (including traditional herbal medicinal products), medical devices, food supplements, and cosmetics. In fact, the EU herbal monographs are recognised as an important reference in the MDCG 2022 -5[2] – (April 2022).

Although a product containing an herbal substance/preparation included in a EU herbal monograph is not automatically a medicinal product and EU herbal monographs carry legal value in the marketing authorisation/registration process only, compliance with the EU herbal monograph regarding product composition/preparation, dosage and therapeutic indication is a good indicator that a product may fall into the medicinal product definition.

2. Discussion

2.1 Considerations on medicinal products – medicinal claims and principal mode of action

In accordance with Article 1 of Directive 2001/83/EC, the definition of a medicinal product is:

> *(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or*
>
> *(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.*

Regarding the first part of the definition, medicinal products are presented as having properties for treating or preventing disease. Food supplements and cosmetics are not allowed to present such claims. It should be noted that there are several herbal substance and preparations that could also be used as food (including food supplements) or cosmetics without medicinal claims.

Regarding the second part of the above definition of a medicinal product, herbal substances/preparations are usually multicomponent mixtures, and the principal mode of action could be difficult to define when the pharmacodynamic properties are unknown. However, it is the HMPC position that the lack of data/lack of adequate data on pharmacological, immunological or metabolic action in an EU herbal monograph or HMPC assessment report, does not rule out the fact that in reality the principal intended action most probably is achieved by pharmacological, immunological or metabolic means.

[2] Guidance on borderline between medical devices and medicinal products under Regulation (EU) 2017/745 on medical devices' (April 2022).

2.2 Considerations on food and food supplements

Products marketed as food (including food supplements) in the EU must comply with general food law, i.e., Regulation (EC) No 178/2002. In addition, Article 8 of Regulation (EC) No 1925/2006, provides a procedure to prohibit the use of certain substances in food/food supplements, or to restrict their use or to subject the substance to European Union scrutiny. If a harmful effect or a possibility of harmful effects on health has been identified, the substance and/or the ingredient containing the substance shall:

- be placed in Annex III, Part A, and its addition to foods or its use in the manufacture of foods shall be prohibited; or
- be placed in Annex III, Part B, and its addition to foods or its use in the manufacture of foods shall only be allowed under the conditions specified therein; or
- be placed in Annex III, Part C.

Companies marketing products as food/food supplement i.e., food business operators, should also comply with Regulation (EC) 2015/2283 on novel food if the food has not been consumed to a significant degree by humans in the EU before 15 May 1997. Food business operators can place a novel food on the European Union market only after the Commission has processed an application for the authorisation of a novel food and adopted an implementing act authorising the placing on the market of a novel food.

Regulation (EC) 1924/2006 on nutrition and health claims made on food and its amendments were adopted to ensure consumers have access to truthful and scientifically correct information on the nutritional properties of foods and/or their health effects. Commission Regulation (EU) No 432/2012 of 16 May 2012 established a list of permitted health claims made on foods, other than those referring to the reduction of disease risk and to children's development and health.

Back in 2012, and in relation to the 'Discussion paper on health claims on botanicals used in foods' published by the European Commission (EC), the Heads of Medicines Agencies (HMA) stated[3] that this discussion paper highlights that products containing herbal substances can be considered as either medicinal products or foods (food supplements) and that there are different approaches among EU Member States on how herbal substances can be marketed, as well as on the legal framework that should apply to these products. The existence of different requirements in these two areas of EU law can lead to important differences in the level of information that is provided to consumers on products that are apparently similar.

Currently, there are products on the EU market with claims related to health effects and whose presentation (packaging, claims, ingredients, pharmaceutical form) are sometimes very similar to that of medicinal products.

Nevertheless, in May 2020, the EC completed the Evaluation of the Regulation on nutrition and health claims. The EC concluded that the objectives of the Regulation (EC) 1924/2006 on nutrition and health claims made on food have not been fully attained, highlighting e.g. poor functioning of the internal market and safety aspects. Furthermore, the notion of the concept of 'traditional use' in the efficacy assessment of health claims on plants used in foods together with the effects of the co-existence, on the EU market, of traditional herbal medicinal products on the same plant substances were discussed. In conclusion, the EC highlighted the need to further study the potential EU harmonisation in the field of plants and their preparations, including safety aspects.

[3] HMA raise concerns about discussion on progress on health claims on botanicals used in foods (HMA publication 21 December 2012)

2.3 Considerations on cosmetics

Herbal substances/preparations can also be used as ingredients for cosmetics, which are defined by Regulation (EC) No 1223/2009 of the European Parliament and of the Council. According to Article 2(1)(a) of Regulation (EC) No 1223/2009, cosmetic means any substance or mixture intended to be placed in contact with the external parts of the human body (epidermis, hair system, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavities with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance, protecting them, keeping them in good condition or correcting body odours. As a consequence, no medicinal indications/claims are allowed on their label or advertisement.

The safety and claims of cosmetics are further described in the following articles of the same regulation:

- Article 3 (safety): A cosmetic product made available on the market shall be safe for human health when used under normal or reasonably foreseeable conditions of use;
- Article 10 (safety assessment): Ensure that the cosmetic product has undergone a safety assessment;
- Article 11(2)(d) (proof of effect claimed): where justified by the nature or the effect of the cosmetic product, proof of the effect claimed for the cosmetic product;
- Article 14 (restrictions for substances listed in the Annexes): prohibited substances (Annex II) and restricted substances (Annex III);
- Article 20 (product claims): In the labelling, making available on the market and advertising of cosmetic products, text, names, trademarks, pictures and figurative or other signs shall not be used to imply that these products have characteristics or functions which they do not have.

2.4 Considerations on medical devices

According to Article 2 of Regulation (EU) 2017/745, 'medical device' means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

- diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease;

- diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability;

- investigation, replacement or modification of the anatomy or of a physiological or pathological process or state;

- providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations;

and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.

As an example, in the Commission implementing decision EU 2017/1445, the group of products whose principal intended action, depending on proanthocyanidins present in cranberry extract, is to prevent or treat cystitis, does not fall within the definition of medical devices. The conclusion in the decision was that a mechanical mode of action is highly unlikely, and a pharmacological mode of action is most probable.

Borderline issues between herbal medicinal products and medical devices are discussed in the 'Guidance on borderline between medical devices and medicinal products under Regulation (EU) 2017/745 on medical devices'[3]. This document has been endorsed by the Medical Device Coordination Group (MDCG) established by Article 103 of Regulation (EU) 2017/745. The MDCG is composed of representatives of all Member States and it is chaired by a representative of the European Commission. In this document, it is stated that since herbal medicinal products constitute multicomponent mixtures, if the pharmacodynamics are unknown the principal mode of action could be difficult to define. In the same document, there is also a reference to EU herbal monographs i.e., it is stated that *"To facilitate the harmonisation of the process of authorisation and registration for (traditional) herbal medicinal products in the European Union, there are EU monographs (established by the EMA Committee on Herbal Medicinal Products - HMPC) for certain herbal substances and preparations. To help in the qualification of some products, these monographs should be taken into account."*

2.5 Considerations on the use of information in EU herbal monographs and assessment reports for borderline issues

Although a product containing an herbal substance is not automatically considered a (traditional) herbal medicinal product, when an herbal substance/preparation is included in and complies with an EU herbal monograph regarding its composition/formulation, dosage and indication, it is an indicator that the substance in question could qualify as a (traditional) herbal medicinal product.

The EU herbal monographs established by HMPC are published together with other documents, including an annexed assessment report containing a review of all available data relevant for the medicinal use of the herbal substance/preparation. For example, the data can be on the pharmacological effects and medicinal claims of an herbal substance/preparation. Thus, the assessment report provides essential information on borderline issues related to pharmacological effects (vs. medical devices) and medicinal claims (vs. food supplements and cosmetics). Thus, the EU herbal monograph and annexed assessment report could serve as one valuable element supporting the National competent authorities in their case-by-case decision on classification of individual products.

To easily navigate the content of the annexed assessment reports, the following chapters may provide important information:

Chapter	Information provided	HMPC comment
1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof	Overview of main compounds	A statement that no constituent with known therapeutic activity or active marker can be recognised by the HMPC does not rule out that the principal intended action of the herbal substance/preparation may be achieved by pharmacological, immunological or metabolic means.
2. Data on medicinal use	Overview of therapeutic indications and posologies obtained from marketed medicinal products in the EU/EEA and historical data from literature on medicinal use.	Although a product containing an herbal substance is not automatically considered a (traditional) herbal medicinal product, when an herbal substance/preparation is included in and complies with an EU herbal monograph regarding to its composition/formulation, dosage and indication, it is an indicator that the substance in question could qualify as a (traditional) herbal medicinal product.[4]
3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof 3.4 Overall conclusion on non-clinical data	Non-clinical (in vitro and/or in vivo) pharmacological data that support the indication(s) in the monograph and results from studies which are not connected to the indication(s) agreed in the monograph.	Lack of data/lack of adequate data on pharmacological, immunological or metabolic action in an EU herbal monograph or HMPC assessment report, does not rule out the fact that the principal intended action may be achieved by pharmacological, immunological or metabolic means.
4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents	Clinical pharmacological data that support the indication(s) in the monograph.	Lack of data/lack of adequate data on pharmacological, immunological or metabolic action in an EU herbal monograph or HMPC assessment report, does not rule out the fact that the principal intended action may be achieved by pharmacological, immunological or metabolic means.
4.4. Overall conclusions on clinical pharmacology and efficacy	Summary of available clinical data in support of well-established use therapeutic indication. If no study supports a well-established use therapeutic indication, HMPC will develop a traditional use monograph for a suitable indication and posology.	Lack of data/lack of adequate data on pharmacological, immunological or metabolic action in an EU herbal monograph or HMPC assessment report, does not rule out the fact that the principal intended action may be achieved by pharmacological, immunological or metabolic means. However, the pharmacological effects or efficacy of preparations in traditional use monographs are plausible on the basis of long-standing use and experience.

[4] See also Regulatory Q&A on herbal medicinal products (in R7 and R8)

5.6 Overall conclusion on clinical safety	Summary of available clinical safety data recommended for inclusion in the product information of herbal medicinal products e.g. warnings, contraindications and undesirable effects.	In general, the safety conclusions would be applicable to an herbal preparation irrespectively if the product is placed on the market as a medicinal product, food supplement, medical device or cosmetic.

3. Conclusion

Currently there is no EU common guidance to Applicants and National Competent Authorities on the prerequisites for classification of herbal substances/preparation to be considered as medicinal products. Importantly, it is the remit of National Competent Authorities in Member States to decide on the classification of medicinal products in their national territory.

The HMPC plays a key role in harmonising and facilitating the approval process of herbal medicinal products (including traditional herbal medicinal products) among the Member States, whereby the EU herbal monograph developed by the Committee plays a fundamental part. It has been observed that the EU herbal monographs established by HMPC are used in application procedures to support the harmonisation in the European market and give Applicants and National Competent Authorities a clear reference point when preparing or assessing an application for marketing authorisation/registration of herbal medicinal products in Member States. Notwithstanding this, it should be mentioned that additional herbal substances/preparations for which there is no EU herbal monograph established, have also been approved as medicinal products by EU Member States.

To support Applicants and National Competent Authorities in borderline issues/product classification and to ensure the protection of public health while products are marketed in harmonised EU conditions, it is the HMPC's view that the EU herbal monographs and annexed assessment reports could serve as one of many valuable and essential elements when distinguishing between medical devices, food supplements, cosmetics and herbal medicinal products (including traditional herbal medicinal products). The presence of pharmacological data and medicinal claims assessed in the annexed assessment reports which accompanies the EU herbal monographs, can be the supportive evidence for clarifying the classification of an herbal substance.