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# European regulation model for herbal medicine: the assessment of the EU monograph and the safety and efficacy evaluation in marketing authorization or registration in Member States

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## ABSTRACT

*Background:* The European Union (EU) has created a regulatory framework for herbal medicinal products (HMPs) since the enforcement of Directive 2004/24/EC. Substantial achievements have been made, with 1719 traditional use marketing registrations (TURs) and 859 well-established use marketing authorizations (WEU-MAs) for HMPs granted by the end of 2016. Apparently, the European regulation model has worked out well and in that the essential feature is the use of EU herbal monographs into those granted WEU-MAs and TURs.

*Purpose:* A systematic analysis of the European regulation model for HMPs and the EU herbal monograph's part of this model are undertaken to assist understanding of the EU legislation particularly for interested parties those from outside EU area, and afterwards, to help in decision-making in the HMPs registration in European market for pharmaceutical companies, as well as in the establishment of legislation in countries with strong traditional use of herbal remedies.

*Methods:* A search of PubMed, ScienceDirect, the European Medicines Agency website and the Heads of Medicines Agencies website was conducted (up to December 2017), and the available information on regulation of HMPs in the EU was collected.

*Results:* The evaluation of applications by National Competent Authorities (NCAs) at a national level together with the assessment of EU monographs by the Committee on Herbal Medicinal Products (HMPC) at the European level constitute the European regulation framework for HMPs. As the scientific opinion about the safety and efficacy of HMPs from HMPC, the EU herbal monographs have been given a constitutional-based meaning to the TURs and WEU-MAs of HMPs and play a supportive function in the marketing procedure in Member States.

*Conclusion:* The European framework has provided a powerful regulation model for harmonization of scientific assessment and facilitation of product marketing. For the pharmaceutical industries particularly those outside the EU, optimal use of the EU herbal monograph in their marketing procedure in Europe could be of great benefit. Furthermore, this model is well worth learning from for other countries and regions outside the EU to help the establishment of legislation in countries with strong traditional use of herbal remedies and contribute to the safe use of traditional herbal medicine.


*Keywords:* European regulation model; HMP; EU monograph; TUR; WEU-MA.

*Abbreviations:* ESCOP, European Scientific Cooperative on Phytotherapy; WHO, World Health Organization; EU: European Union; HMPs: herbal medicinal products; WEU-MAs: marketing authorizations; TURs: traditional use marketing registrations; HMPC: Committee on Herbal Medicinal Products; EMA: European Medicines Agency; NCAs, National Competent Authorities; IPs, interested parties; PS: public statement; MLWP, Monograph and List Working Party; CMDh, Co-ordination group for Mutual recognition and Decentralised procedures-human; CHMP, Committee for

Medicinal Products for Human Use; NP, national procedure; MRP, mutual recognition procedure; DCP, decentralized procedure; MHRA, Medicines and Healthcare products Regulatory Agency; GACP, good agricultural and collection practices; cGMP, current good manufacturing practice.

## 1. Introduction

Herbal medicine is the oldest form of healthcare known to mankind and remains an important element of healthcare systems in many developing and industrialized countries. With the increased popularity of herbal medicine all over the world, several monographs have been published worldwide, and regulations of herbal medicine in a legal environment have been introduced in several countries and regions as well. The overall objective was to safeguard public health by assuring quality, efficacy and safety. With respect to the monographs for herbal medicine, national compendia and pharmacopoeias defined the basic requirements for quality, while another set of monographs, e.g., monographs published by the European Scientific Cooperative on Phytotherapy (ESCOP; European scientific cooperative on phytotherapy, 2009), the Commission E (J. Brinckmann, et al, 1998) and the World Health Organization (WHO; World Health Organization, 2009), defined the safety and efficacy aspects of herbal medicine. These latter monographs were used as important sources of information (not legally binding) with respect to safety and efficacy by many countries. Regulations and laws for herbal medicine have been established in several countries and regions such as China, Japan, the United States and the European Union (EU).

The EU is one of the few cases where the term “monographs” has been created to include all the aspects of the quality, safety and efficacy, and regulation of herbal medicine. The EU monograph, formerly the Community herbal monograph, publishes scientific or historical evidence for the safety and efficacy aspects of herbal medicine and is different from the monograph of the European Pharmacopoeia, which is dedicated to quality standards. The EU monograph is established by the Committee on Herbal Medicinal Products (HMPC), which was established under the Directive 2004/24/EC as one of the scientific committees of the European Medicines Agency (EMA). As the result of scientific assessment harmonization at the European level, the EU monograph acts as a nearly legally binding set in contrast to the other monographs regarding the safety and efficacy of herbal medicines mentioned above, the ESCOP monograph, for example. The EU monograph provides a complete system for the regulation of herbal medicinal products (HMPs) in Europe together with the European Pharmacopeia which defined the basic quality requirements for the HMPs.

An essential feature of the European herbal medicinal product legislation is that the EU monograph is used as the safety and efficacy reference material and assessment standard by applicants and National Competent Authorities (NCAs) and plays a supportive function in the marketing authorization or registration procedure in

Member States (Wieland Peschel, 2014). By December 2016, 1719 (1089 mono-herbal components and 630 combinations) traditional use registrations (TURs) and 859 (704 mono-herbal components and 155 combinations) well-established use marketing authorizations (WEU-MAs) for HMPs had been granted in EU Member States (European Medicines Agency, 2017c). Among these applications, 75% and 89% of herbal substances used in the mono-herbal component products granted by the TUR and WEU-MA categories, respectively, were on the HMPC priority list. Wieland Peschel (Wieland Peschel, 2014) has also demonstrated that once the EU monographs had become available, they were used in the vast majority of TURs and WEU-MAs by applicants and NCAs and actually had a facilitating role for the marketing procedures of HMPs, according to their survey of 31 December 2012.

It is obvious that this kind of European regulation model, in which the marketing of a product is coordinated with the EU monograph, has worked out well. For this regulation model, the EU monograph has facilitated the marketing procedure and helped in offering HMPs with appropriate quality, safety and efficacy to the EU market on the basis of the basic quality requirements defined by the European Pharmacopeia. In this article, we analyzed this model and the role EU monographs have played in the European regulation of HMPs.

## 2. European regulatory framework for HMPs: a model where the marketing of a product is coordinated and facilitated by the EU monograph

The EU regulation of herbal products as medicines has demanded analytical, pharmaco-toxicological tests and clinical trials since Directive 65/65/EEC in 1965 and the amended directive 2001/83/EC (The European Parliament and the Council of the European Union, 2001). A systematic regulatory framework was established after the enforcement of the traditional herbal medicinal products directive, Directive 2004/24/EC, which registered herbal products with long-standing use in a simplified way with respect to the proof of efficacy and data on safety. With the same requirements on pharmaceutical quality, the EU regulation defines HMPs into three categories: ⅰ) new HMPs, which can be granted full marketing authorization under the same rules as for other medicinal products in that the results of non-clinical studies and clinical trials are needed; ⅱ) well-established use HMPs with a acceptable level of safety and a recognized efficacy, which can be granted marketing authorization based on published scientific data from clinical studies and documented clinical experience, and ⅲ) traditional use HMPs, which can be granted marketing registration based on their longstanding use (The European Parliament and the Council of the European Union, 2004). Products of the three categories are defined by distinct requirements for safety and efficacy documentation, where the other two categories are derogated from new HMPs, considering their history of medicinal use. The results of general toxicological (except genotoxicology is required for traditional use HMPs) and pharmacological tests or the results of clinical trials are no longer the

essential requirement for well-established use HMPs that have at least 10 years of medicinal use in the EU if evidence can demonstrate a recognized efficacy and an acceptable level of safety, and for traditional use HMPs if medicinal use of at least 30 years, including 15 years in the European Union, can be documented and the therapeutic indication is considered safe for use without the supervision of a physician. Basic requirements for HMPs of the three categories in the EU are shown in Table 1.

It should be noted that currently, only two new HMPs, Episalvan® and Veregen®, have obtained marketing authorizations in the EU. The mainstream categories in the European market are traditional use and well-established use HMPs, as mentioned above.

According to article 16h in Directive 2004/24/EC, the HMPC was established as a part of the EMA's scientific committees. The work of this committee is to carry out legal tasks concerning guidance documents addressing quality, safety and efficacy issues in the applications of TURs and WEU-MAs, to establish EU monographs for well-established use and traditional use HMPs (see Section 3), and to prepare a list of herbal substances and preparations for traditional use HMPs after the scientific assessment of the available data about safety and efficacy. All the guidance documents and monographs developed by the HMPC were recommended and accepted by both pharmaceutical industries and NCAs.

The HMPC plays a key role in harmonizing the regulation and facilitating the marketing of HMPs among the Member States, whereby the EU monograph developed by this committee has a fundamental role. The opinions of the EU monograph were intended to create a standard for the safety and efficacy evaluation of the HMP application and were to be considered as a strong recommendation to Member States or legally binding. Together with the basic quality requirements defined by the monograph of the European Pharmacopeia, the two distinctive types of European official monographs are complementary and provide a system of complete technical standards for the regulation of HMPs in the EU market (fig. 1). In particular, as a rare legally binding monograph regarding the safety and efficacy aspects of herbal medicine, the EU monograph has a fundamental impact on the harmonization of scientific assessment among the EU Member States.

**3. The EU monograph: brief contents and evaluation procedure**

An EU monograph comprises the scientific opinion of the HMPC on safety and efficacy data concerning a specific herbal substance and its preparations intended for medicinal use with regard to the well-established use and traditional use categories（The European Parliament and the Council of the European Union, 2004). It reflects the HMPC's view on all information necessary for the use of a medicinal product containing the herbal substance/preparation(s) described in the monograph and comprises the sets of qualitative and quantitative composition; pharmaceutical form;

therapeutic indications; posology and method of administration; contraindications; special warnings and precautions for use; interactions with other medicinal products and other forms of interaction; use by women during fertility, pregnancy and lactation; effects on ability to drive and use machines; undesirable effects; overdose; pharmacodynamic and pharmacokinetic properties; and preclinical safety data.

To establish EU monographs, the HMPC evaluates all available information, including non-clinical and clinical data, documented long-standing use and experience in the EU and, if available, outside the EU, following a standard operating procedure（European Medicines Agency, 2016). One feature of this procedure is close communication with interested parties (IPs) in the stages of starting a monograph project and public consultation on a draft version. The IPs consist of scientific communities, pharmaceutical industries, governmental institutions, EU Member States and EEA-EFTA States. After this evaluation procedure, a monograph will be adopted if the herbal substance and its preparations fulfill the requirements defined by article 10a for well-established use and/or article 16a for traditional use HMPs laid down in Directive 2004/24/EC. If not, a public statement (PS) will be produced. Finally, a complete package of the monograph or PS, assessment report, overview of comments and list of references will be published on the EMA website. Another feature of the evaluation procedure is a revision process introduced to guarantee the sustainability, in which each monograph or PS will be regularly updated and modified every 5 years according to the needs of current scientific knowledge by the same evaluation procedure. By February 2017, 28 of 154 final monographs had completed the revision procedure. The process for establishing an EU monograph is shown in fig. 2.

## 4. Relationship between an EU monograph and safety and efficacy assessment in the application of a TUR or WEU-MA for an HMP in Member States

### *4.1 The meaning of legal provisions for an EU monograph to the TUR and WEU-MA of an HMP in Member States*

#### *4.1.1 Reference material and strong recommendation for the safety and efficacy assessment in the national procedure of a TUR or WEU-MA for an HMP*

If the marketing authorization or registration of an HMP is intended for a single Member State, the respective national procedure (NP) is applicable. The proof of efficacy (or traditional use) and safety is derogated for the categories of well-established use and traditional use HMPs considering their history of use. The proof can be demonstrated with scientific bibliographies, bibliographic evidence, expert reports and monographs developed by international or national bodies and scientific communities, in contrast to the results of non-clinical studies and clinical trials required by new HMPs. Monographs are the most commonly used form of scientific or historical evidence, as they often represent the scientific and official view

of herbal medicines. They include, for example, EU monographs and ESCOP monographs derived from Europe and WHO herbal monographs, monographs in the Pharmacopoeia of the People's Republic of China and monographs in the Ayurvedic Pharmacopoeia of India from outside the EU (European Medicines Agency, 2014). All these monographs can be part of the documentation used to demonstrate efficacy (or traditional use) inside or outside the EU within the dossier to support the application for an HMP. However, monographs from outside of Europe are not directly implemented into EU legislation, while the ESCOP monograph is dedicated to EU HMPs and is frequently used as the basis for establishment of the EU monograph. The EU monograph acts as a nearly legally binding set in contrast to the others because it reflects the opinion of the HMPC by evaluation according to article 10a and article 16a laid down in Directive 2004/24/EC. This directive also makes a clear provision about this condition in article 16h; when an EU monograph has been established, it shall be taken into account by the Member State when examining the application of a well-established use or a traditional use HMP. Where no such monograph has yet been established, other appropriate monographs mentioned above, publications or data may be referred to. However, when a new EU monograph is established, the registration holder shall consider whether it is necessary to modify the registration dossier accordingly (The European Parliament and the Council of the European Union, 2004). Accordingly, even though the Member States are not obliged to follow the monograph, any decisions not to accept its content should be duly justified, as the important role of monographs is to bring harmonization to the field of HMPs (Co-ordination group for Mutual recognition and Decentralised procedures-human, 2013).

*4.1.2 The precondition role of the EU monograph in the mutual recognition procedure and decentralized procedure of traditional use HMPs*

The mutual recognition procedure (MRP) and decentralized procedure (DCP) apply to an HMP where the application is intended for more than one Member State. However, there is a precondition for the category of traditional use HMPs. Article 16d laid down in Directive 2004/24/EC has made a clear provision that the DCP and MRP apply by analogy to a traditional use HMP provided that an EU monograph has been established or the HMP consists of herbal substances, preparations or combinations thereof contained in the list entry developed by the HMPC (The European Parliament and the Council of the European Union, 2004). Member States should recognize the registration of a traditional use HMP granted by another Member State based on an EU monograph or a list entry, while for other products, Member States should take due account of such registrations. Moreover, the use of the MRP and DCP for traditional use HMPs has been further clarified in a question and answer document by the Co-ordination group for Mutual recognition and Decentralised procedures-human (CMDh) in 2013 (Co-ordination group for Mutual recognition and Decentralised procedures-human, 2013). Apart from the mandatory scope mentioned above, the

CMDh agreed that the MRP/DCP is possible for the registration of a traditional use HMP on a voluntary basis even if neither an EU monograph nor a list entry exists provided that adequate and sufficient documentation for traditional use and safety is enclosed in the dossier submitted. However, it still emphasized that the use of the MRP/DCP was the decision of the Member State. Discussion with Member States intended to be included in any procedure before submission of an application was recommended. This nearly means that the EU monograph acts as a precondition for the DCP and MRP of traditional use HMPs.

*4.1.3 The EU monograph is coupled with the referral and arbitration procedure of a traditional use HMP*

The Directive 2004/24/EC has defined two types of referral procedures in article 16c (1) c and article 16c (4) specifically applicable to traditional use HMPs, which may be started at the request of the Member State where an application for traditional use registration has been submitted (The European Parliament and the Council of the European Union, 2004). In the first procedure, the Member State can refer the matter to the HMPC when there are doubts on the adequacy of historical evidence of the long-standing use for a traditional use HMP although the 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 in the EU. Namely, the HMPC is asked to draw up an opinion on whether the data on long-standing use and experience of the traditional use HMP are sufficient to demonstrate plausible efficacy and pharmacological effects. In the second procedure, the HMPC is asked to draw up an opinion on whether an HMP is eligible for traditional use registration, where the Member State has determined that this product is eligible for traditional use registration but has less than 15 years of medicinal use in the EU. These two types of referral procedures performed by the HMPC lead to a re-evaluation of the involved traditional use HMP. In addition to issuing the opinion, the HMPC also evaluates the possibility of establishing an EU monograph for the concerned product. When the monograph is established, it should be taken into account by the Member State when making its final decision to register the product by the same set of rules as in Section 4.1.1.

Furthermore, the referrals defined in articles 29 (4), 30 and 31 of Directive 2001/83/EC, in situations where the Member States involved in a DCP/MRP fail to reach an agreement, divergent decisions have been taken by two or more Member States in different NPs, and concerns result from the evaluation of data from pharmacovigilance activities, are also applicable to the traditional use HMPs (European commission, 2016). The HMPC is the competent Committee, assuming the tasks that are normally carried out by the Committee for Medicinal Products for Human Use (CHMP) according to article 16h(1)(c) of Directive 2004/24/EC. Among these cases, the HMPC shall perform the tasks to arbitrate the divergent positions

among different Member States. The arbitration procedure evaluates the possibility of establishing an EU monograph for the product involved as well.

*4.2 The relationship between the EU monographs and the safety and efficacy assessment in the applications of TURs or WEU-MAs for HMPs in Member States*

*4.2.1 Herbal substances and preparations included in the granted HMPs and HMPC priority list*

Good conformity between the HMPC assessment work and the evaluation of the applications of HMPs in Member States can be detected in the recent documents of the HMPC. The report published in April 2017 showed relevant statistics on the granted TURs and WEU-ARs grouped for mono-herbal component and combination products in Member States (European Medicines Agency, 2017c). The status of HMPC assessments for herbal substances used in mono-herbal component HMPs was listed separately (Table 2). For the TURs, 162 herbal substances were used in the 1066 mono-herbal component products granted by the end of 2016. Among these herbal substances, 121 were under the HMPC priority list, and 108 of the 121 herbal substances had been adopted for a monograph. Regarding the WEU-ARs, 61 herbal substances were involved in 694 mono-herbal component products; 52 of the 61 herbal substances were under the priority list, among which 47 herbal substances had been adopted for a monograph.

*4.2.2 The use of EU monographs to the TURs and WEU-MAs for HMPs*

As mentioned before, an EU monograph can be used either as a fundamental material in the dossier for an application of a TUR or WEU-AR by a company or as an assessment standard of an HMP by the NCAs. This phenomenon has also been verified in practice in the EU Member States. The pharmaceutical companies and NCAs are increasingly exploring and accepting the benefits of EU monographs in the applications of the NP and DCP/MRP for HMPs.

More enterprises have successfully used the existing EU monographs in the marketing procedures. Phytovein capsules, which contains Butcher's Broom rhizome (*Ruscus aculeatus* L.), was approved by the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom in 2011. The EU monograph for Butcher's Broom rhizome was used to support the traditional use and safety. Consequently, the applicant did not have to provide further data to support the application (Medicines and Healthcare Products Regulatory Agency, 2011). Wieland Peschel (Wieland Peschel, 2014) made a survey of all the TURs and WEU-ARs granted via the NP up to 31 December 2012. Taking the TURs as an example, most applications of mono-herbal component products were based on a monograph (41%) or referred to a monograph (6%) or the relevant monographs were used by the NCAs during the assessment (9%). The other 44% of applications were granted without the use of a

monograph; the most common reason was that such a monograph was not yet available. The same trend was found in the category of well-established use. As the number of EU monographs grew from 120 in 2012 to 140 in 2016, a higher proportion of the use of monographs in HMP applications can be expected.

In addition, with the growing number of EU monographs, more cases of DCP/MRPs for traditional use HMPs have emerged. Under such circumstances, the EU monograph acts like a precondition, as demonstrated in Section 4.1.2. The number of applications of DCP/MRPs for traditional use HMPs according to the application type based on article 16a in Directive 2004/24/EC increased from 0 in 2010 to 21 by August 2017 (http://mri.cts-mrp.eu/Human). These 21 DCP/MRPs included 17 mono-herbal component and 4 combination products. Of the 17 mono-herbal component products, there were 11 herbal substances involved, and all of them had the relevant EU monographs adopted before the DCP/MRPs. For the rest of the combination products, none of the monographs on combinations are established, whereas each herbal substance included in the combinations has the relevant EU monograph published. The herbal substances used in the DCP/MRPs of traditional use HMPs grouped by mono-herbal component are listed in Table 3.

*4.2.3 The supporting role of EU monographs for the TURs and WEU-MAs of HMPs in Member States*

Substantial achievements have been made under the European HMP regulatory framework since the implementation of Directive 2004/24/EC in 2005 in the evaluation by Member States of applications submitted by companies and the assessment of EU monographs by the HMPC. From the current data published by the HMPC (European Medicines Agency, 2017c; European Medicines Agency, 2017b), we can see that the number of granted HMPs and the number of relevant EU monographs have undergone substantial growth in recent years (Table 4). The numbers of granted HMPs in the categories of traditional and well-established use have risen between 2004 and 2016 from 0 to 1719 and from 7 to 859, respectively. Similarly, the numbers of EU monographs relevant to the categories of traditional and well-established use have also gradually increased between 2005 and 2016 from 0 to approximately 140 and from 0 to 26, respectively. Moreover, a significant correlation between the number of annual granted HMPs in Member States and the number of relevant EU monographs (accumulated) published by the HMPC was observed in the categories of both traditional use ($r=0.666$, $p=0.013$) and well-established use ($r=0.850$ $p=0.000$). Although the number of applications is also affected by other factors, these data show that the EU monograph has contributed significantly. Therefore, the EU monographs could be considered to have a supportive function and a promoting role for the marketing authorizing and marketing registration of HMPs.

## 5. Conclusion

The evaluation of applications by NCAs at the national level and the assessment of EU monographs by the HMPC at the European level constitute the European regulation framework of HMPs. As the scientific opinion about the safety and efficacy of HMPs from the HMPC, the EU monograph has given a nearly legally binding meaning to the TURs and WEU-MAs of HMPs. The relationship between the EU monograph and the safety and efficacy assessment of HMPs in the marketing procedure in Member States and the supportive function of the EU monograph for facilitating the marketing were systematically demonstrated in this article. Based on the history of medicinal use, indications and data on safety and efficacy, a product may follow the route of a new HMP, a WEU HMP or a TU HMP (see figure 3). In the application of a new HMP, all preclinical and clinical data are required. In the application of a WEU-MA, the bibliographic data of safety and efficacy for the HMP can be replaced with the well-established use herbal monograph if it has been adopted by the HMPC. Similarly, if there exists a traditional use herbal monograph, historical evidence demonstrating a medicinal use of at least 30 years, including 15 years in the European Union, is no longer needed in the simplified registration for the traditional use HMP, although necessary data such as genotoxicology may also be requested by the NCAs for this category. In addition, although not specifically addressed in the EU monograph, good agricultural and collection practices (GACP), current good manufacturing practice (cGMP) and quality control of HMPs must be monitored to ensure the safety and efficacy of a product. Whether from the EU or non-European areas, HMPs intended for EU marketing authorization or registration should be compliant with standards and existing guidelines on quality and acceptable manufacturing practices. The safety-efficacy-quality triangle is the main driver for registration and acceptance of non-European traditional use HMPs (Liping Qu, et al, 2014).

Furthermore, it is worth noting that after the assessment of an herbal substance and its preparations, a PS document reflecting the opinion of disagreement by the HMPC can be published in contrast to an EU monograph if this herbal substance and its preparations cannot fulfill the requirements defined by article 10a and/or article 16a laid down in Directive 2004/24/EC. Similarly, on such occasion, NCAs could use the opinion in the PS document in the same way as an EU monograph in the evaluation of national applications to deny a TUR or WEU-AR for reasons of safety, lack of scientific or historical evidence, etc. However, divergent views from a few of the monographs or PS documents may arise on a case-by-case analysis in the evaluation of applications in Member States. Table 2 shows that 5 of the 162 traditional use herbal substances and 2 of the 61 well-established use herbal substances used in granted mono-herbal component HMPs have published PSs. Considering visci albi herba (*Viscum album* L.), for example, there are 12 TURs and 8 WEU-ARs of corresponding applications granted in Member States despite the PS document published by the HMPC. Such a situation shows the spirit of seeking common ground

while preserving differences in the EU regulation framework and gives the policy and legal “green light” to national decision as well.

In conclusion, the European framework has provided a powerful regulation model for harmonization of scientific assessment and facilitation of product marketing for HMPs with a history of medicinal use. For the pharmaceutical industries particularly those outside the EU, optimal use of the EU herbal monograph in their marketing procedure in Europe could be of great benefit. Furthermore, this model is well worth learning from for other countries and regions outside the EU. Regulatory authorities and policy researchers from non-European area with less understanding about EU legislation may benefit from this systematical and in-depth analysis. Consequently, it may help the establishment of legislation in countries with strong traditional use of herbal remedies and contribute to the safe use of traditional herbal medicine worldwide which might be benefit for all patients/consumers, health care stakeholders as well as herbal pharmaceutical industries.

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**Conflict of interest**

The authors declare they have no conflict of interest.

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**Table legends**

Table 1: Basic requirements for HMPs of the three categories in the EU regulation

Table 2: Number of herbal substances used in mono-herbal component HMPs at different stages of HMPC assessment by 31 December 2016

Table 3: Herbal substances used in the DCP/MRPs of traditional use HMPs grouped by mono-herbal component according to the application type based on article 16a until August 2017

Table 4: Number of granted HMPs in Member States and number of herbal substances adopted for an EU monograph by 31 December 2016

**Figure legends**

Fig. 1: Assessment of HMPs in the European regulatory framework at national and European levels.

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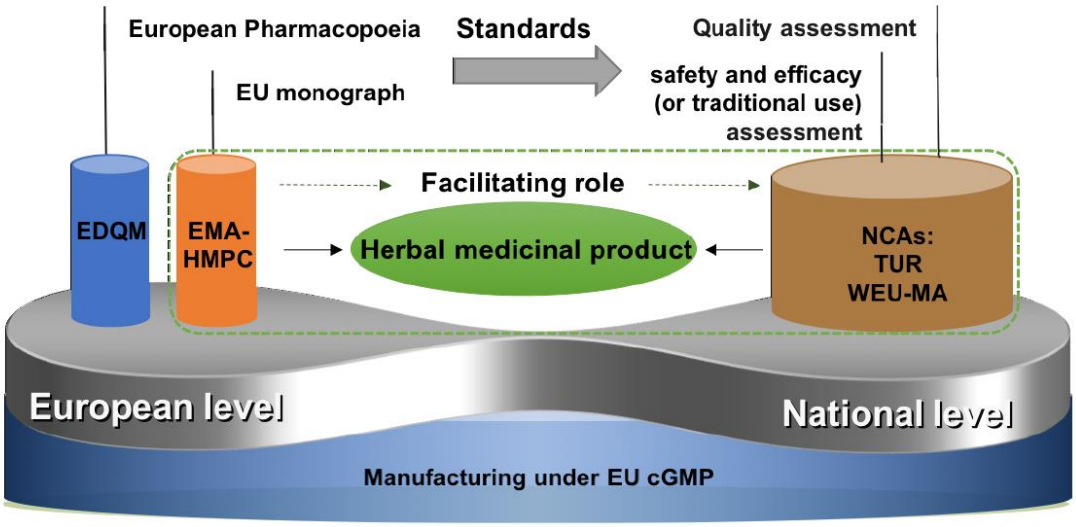
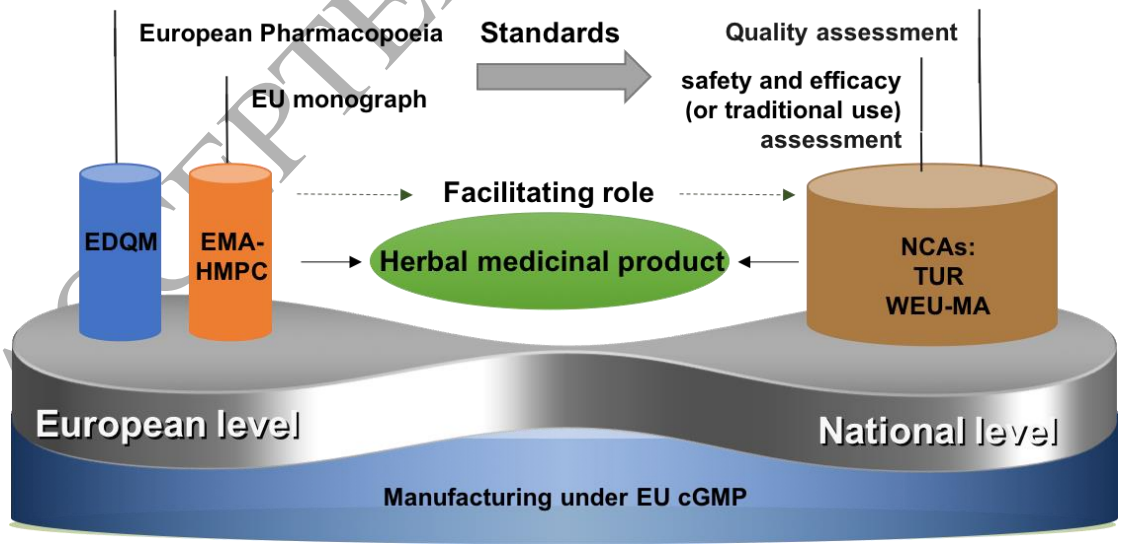
Fig. 3: Requirements of HMPs in the dossier for an application of a TUR or WEU-AR and the application of an EU monograph

Graphical Abstract




## Figures

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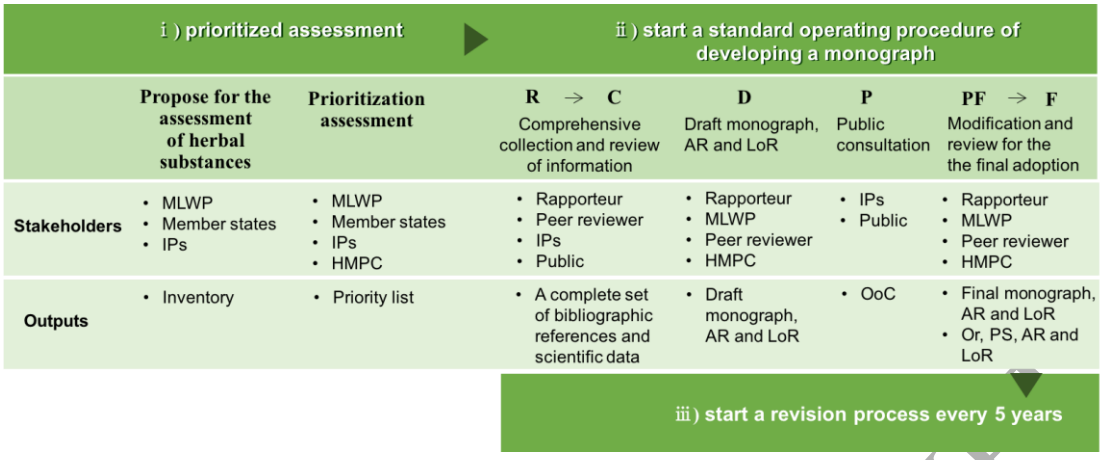


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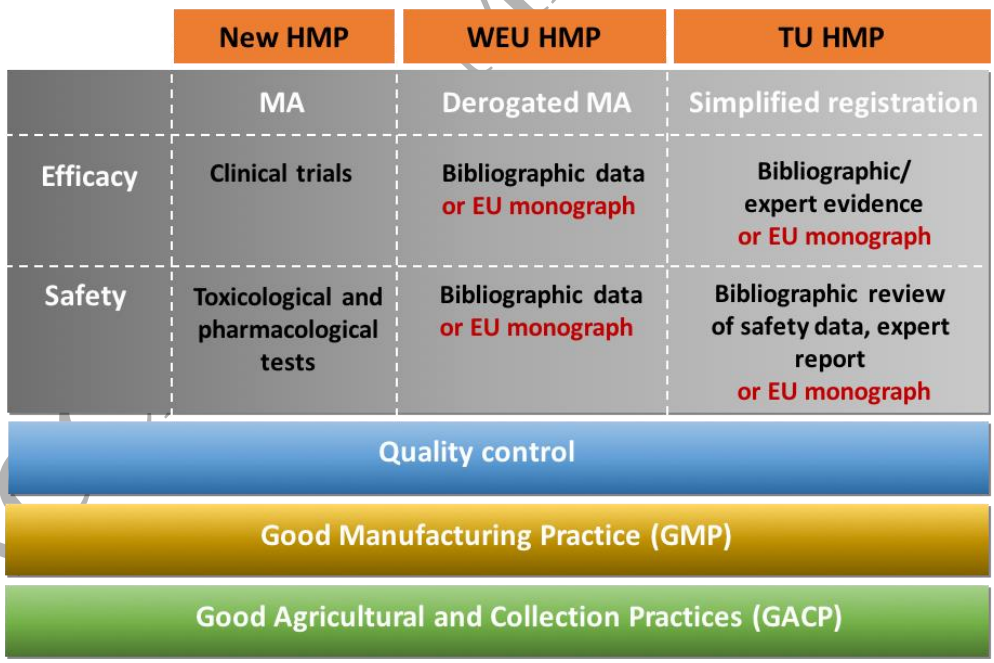


Fig. 3: Requirements of HMPs in the dossier for an application of a TUR or WEU-AR and the application of an EU monograph

## Tables

Table 1: Basic requirements for HMPs of the three categories in the EU regulation

| | New HMP | Well-established use HMP | Traditional use HMP |
|---|---|---|---|
| Quality | Comply with all requirements* | Comply with all requirements* | Comply with all requirements* |
| Safety | Non-clinical and clinical safety data | Bibliographic data on acceptable level of safety in the EU | Bibliographic review of safety data; expert report; necessary data that the NCAs requested |
| Efficacy | Data from Clinical trials | Bibliographic data on recognized efficacy in the EU | Bibliographic/expert evidence (efficacy or pharmacological effects must be plausible on the basis of long-standing use and experience) |
| History of medicinal use | Not applicable | At least 10 years of proven medicinal use in the EU | To be in medicinal use for at least 30 years, including a minimum of 15 years in the EU |
| Indications | No restriction | No restriction | To be used without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment |
| Route of administration | No restriction | No restriction | To be administered only by oral, external and inhalation routes |

* defined in the amended Directive 2001/83/EC and Directive 2003/63/EC and complemented with several scientific guidelines produced by the HMPC

Table 2: Number of herbal substances used in mono-herbal component HMPs at different stages of HMPC assessment by 31 December 2016

| Categories | Total number | Not on the priority list | On the priority list | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | R | C | D | P | PF | F [a] | F [b] |
| TU | 162 | 41 | 0 | 3 | 2 | 1 | 2 | 108 | 5 |
| WEU | 61 | 9 | 0 | 2 | 1 | 1 | 1 | 45 | 2 |

R, rapporteur assigned; C, on-going call for scientific data; D, draft under discussion; P, draft published; PF, assessment close to finalization (pre-final); F[a], final adopted for an EU monograph; F[b], final published a public statement.

Table 3: Herbal substances used in the DCP/MRPs of traditional use HMPs grouped by mono-herbal component according to the application type based on article 16a until August 2017

| Herbal substances | Number of DCPs/MRPs | Year | |
|---|---|---|---|
| | | DCP/MRP | Monograph |
| Uvae ursi folium | 2 | 2016; 2017 | 2011 |
| Arnicae flos | 1 | 2017 | 2014 |

| | | | |
|---|---|---|---|
| Harpagophyti radix | 3 | 2015; 2016; 2017 | 2008 |
| Hamamelidis cortex | 1 | 2016 | 2009 |
| Lupuli flos | 1 | 2013 | 2008 |
| Lavandulae aetheroleum | 1 | 2016 | 2012 |
| Passiflorae herba | 2 | 2011; 2015 | 2007 |
| Passiflorae herba | 1 | 2015 | 2012 |
| Vitis viniferae folium | 1 | 2013 | 2010 |
| Rosmarini aetheroleum | 1 | 2016 | 2010 |
| Thymi herba | 3 | 2014; 2015; 2016 | 2007 |

Table 4: Number of granted HMPs in Member States and number of herbal substances adopted for an EU monograph by 31 December 2016

| Year | Traditional use | | | Well-established use | | |
|---|---|---|---|---|---|---|
| | EU monograph (per year) | EU monograph (accumulated) | TUR | EU monograph (per year) | EU monograph (accumulated) | WEU -AR |
| 2004 | 0 | 0 | 0 | 0 | 0 | 7 |
| 2005 | 0 | 0 | 2 | 0 | 0 | 57 |
| 2006 | 2 | 2 | 5 | 6 | 6 | 44 |
| 2007 | 12 | 14 | 15 | 6 | 12 | 52 |
| 2008 | 16 | 30 | 33 | 1 | 13 | 46 |
| 2009 | 17 | 47 | 95 | 3 | 16 | 71 |
| 2010 | 18 | 65 | 223 | 4 | 20 | 73 |
| 2011 | 20 | 85 | 374 | 1 | 21 | 67 |
| 2012 | 15 | 100 | 270 | 1 | 22 | 100 |
| 2013 | 9 | 109 | 296 | 0 | 22 | 85 |
| 2014 | 11 | 120 | 125 | 0 | 22 | 75 |
| 2015 | 13 | 133 | 140 | 3 | 25 | 94 |
| 2016 | 7 | 140 | 141 | 1 | 26 | 88 |