“Impact of the Implementation of Directive 2004/24/EC: Development of Marketing Authorisations for Herbal Medicinal Products and Registrations for Traditional Herbal Medicinal Products in Germany in the European Regulatory Environment”

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Alexandra Kürzel
aus Pasewalk

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Betreuerin und 1. Referentin: Dr. Birka Lehmann

2. Referent: Prof. Dr. Werner Knöss

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List of abbreviations

AESGP	Association of the European Self-Medication Industry
AMG	Arzneimittelgesetz (Medicinal Products Act, Drug Law)
AMIS	Arzneimittelinformationssystem (Drug Information System)
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
BMG	Bundesministerium für Gesundheit (Federal Ministry of Health)
BGA	Bundesgesundheitsamt (Federal Health Office)
CHMP	Committee for Medicinal Products for Human Use
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures- Human
CMS	concerned member state
CP	centralised procedure
CPMP	Committee for Proprietary Medicinal Products
DCP	decentralised procedure
DIMDI	Deutsches Institut für Medizinische Information und Dokumentation (German Institute of Medical Documentation and Information)
EC	European Community
EDQM	European Directorate for the Quality of Medicines and Health Care
EEA	European Economic Area
EEC	European Economic Community
EMA	European Medicines Agency
EU	European Union
HMP	herbal medicinal product
HMPC	Committee on Herbal Medicinal Products
MR	mutual recognition
MRP	mutual recognition procedure
NP	national procedure
OTC	over the counter
RMS	reference member state
SGB	Sozialgesetzbuch (Social Security Code)
SMPC	Summary of the Product Characteristics
THMP	traditional herbal medicinal product
TMP	traditional medicinal product
TU	traditional use
WEU	well-established use

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1 Introduction

Herbal medicinal products (HMPs) are defined as *medicinal products which exclusively contain, as active substances, either one or more herbal substances, one or more herbal preparations or one or more such herbal substances in combination with one or more such herbal preparation* [1]. Traditional herbal medicinal products (THMPs) are a subcategory of HMPs and may contain vitamins and minerals that are ancillary to the THMP regarding the therapeutic indications [1].

The natural origin of herbal medicines[1] represents a complex composition of numerous biological constituents. Herbal substances are always mixtures of constituents that are determined by the manufacturing process, the starting material and the extraction solvents [2]. These mixtures of herbal substances together develop their action in their entirety [3]. Phytotherapy describes the treatment and prevention of human diseases using plants, parts of plants or preparations of plants and has been used since ancient times [4]. The therapeutic approach does not differ from that of conventional medicines with chemically defined substances, however phytotherapy is characterised by the use of their name-giving herbal substances, preparations and products thereof [5].

HMPs are marketed in each EU/EEA Member State, although their market importance and acceptance level in the public vary considerably among the Member States [6]. Since the first European pharmaceutical Directive 65/65/EEC [7] for harmonising the requirements of marketing authorisations, HMPs need to obtain a marketing authorisation by the competent authority in the respective member state before they may be placed on the market, if they fall into the definition of a medicinal product in accordance with Article 1(2) of Directive 2001/83/EC [1]. The applicant of a marketing authorisation needs to document the quality, safety and efficacy of his medicinal product [1]. He may choose between different types of procedure in order to receive a marketing authorisation. The purely national procedure (NP) according to German legislation leads to a marketing authorisation valid only in Germany [8]. In the current pharmaceutical European legislation different types of procedure are laid down in order to facilitate the medicinal products' access to the market of more than one Member State: The mutual recognition procedure (MRP) and the decentralised procedure (DCP) result

[1] The term „herbal medicines" is used for both HMPs and THMPs in this thesis

in a marketing authorisation in more than one Member State and the centralised procedure (CP) leads to a marketing authorisation in each Member Sate in the European Community [8]. In principle, the requirements regarding the evaluation criteria for safety and efficacy within the marketing authorisation procedures apply to HMPs in the same way as they apply to other medicinal products with comparable indications [9]. However, the complex composition of herbal active substances needs to be taken into account [9]. The "Ad hoc Working Group on Herbal Medicinal Products" which was established in 1997 at the European Medicines Agency (EMA) reviewed criteria to evaluate safety and efficacy for HMPs [6] but a consensus on medical questions on European level was far from being reached for more than 30 years [9]. In 1989, the Note for Guidance on "Quality of Herbal Remedies" was established [10], later revised as the "Guideline on quality of herbal medicinal products/traditional herbal medicinal products" published on 31 March 2011 [2]. That was an important step of the "Ad hoc Working Group on Herbal Medicinal Products" at the European level. Whereas evaluation criteria for the quality of HMPs were established in the European scientific area, the question of harmonised assessment criteria for safety and efficacy for HMPs became increasingly important in Europe, particularly because the MRP became compulsory on 1 January 1998 and clarification was needed with respect to HMPs [9].

In 1998, the study "Herbal medicinal products in the European Union" was initiated by the European Parliament and was conducted by the Association of the European Self-Medication Industry (AESGP) on behalf of the European Commission in order to investigate the regulatory situation for HMPs in Europe [6]. The results of the study demonstrated that although the legal requirements do not differ between herbal or any other medicinal product in European pharmaceutical legislation, the European requirements of Directive 65/65/EEC [7] were not implemented in a uniform manner in national laws in the Member States as required, particularly with regards to the evaluation criteria for safety and efficacy for HMPs [6]. The study further revealed that herbal products were classified in different categories in the Member States [6]. In some Member States the same herbal products were classified as medicinal product whereas other Member States considered them as food supplements or even as food with health claims [6]. The study also demonstrated that the MRP was chosen to low extent by the applicants to gain access to the market for HMPs in the European Community [6].

Among others, the results of the AESGP study led to the conception of Directive 2004/24/EC [11] *amending as regards traditional herbal medicinal products* the Directive 2001/83/EC [1]. This Directive was established in the European legislation as a further step in the process of harmonising the European market for medicinal products [11]. The aim was to remove the heterogeneous situation for herbal medicines between the Member States in order to promote the harmonisation process thereof and to enhance the free movement without discrimination and distortion of competition between manufacturers and to protect the public health since the necessary guarantees of quality, safety and efficacy have not always been provided in the past [11].

In Article 1 of Directive 2004/24/EC the terms herbal substance, herbal preparation, HMP and THMP are defined for the first time in the European legislation [11]. Hitherto, the definitions of HMP, herbal substance and herbal preparation were given in the European "Guideline on quality of herbal medicinal products/traditional herbal medicinal products" [2].

Furthermore, Article 1 of Directive 2004/24/EC introduced a substantially new type of application for simplified registrations for HMPs having regard to their long tradition (see chapter 2.2) with the aim to remove the existing heterogeneous procedures and provisions for these products between the Member States [11]. 'Simplified' means that the data submitted by the applicant must demonstrate sufficient safety and plausible efficacy, especially in view of their long traditional use (TU) [11]. This type of application takes into account that a significant number of medicinal products, despite their long tradition does not fulfill the requirements for receiving a marketing authorisation based on well-established medicinal use (WEU) with recognised efficacy and an acceptable level of safety (see also chapter 2.1) and is not eligible for a marketing authorisation based on preclinical tests and clinical trials the data of which have been gained by the pharmaceutical company's own investigations [11].

A major step introduced in Article 1 of Directive 2004/24/EC [11] in conjunction with Article 55 of Regulation (EC) No 726/2004 [12] was the establishment of the Committee on Herbal Medicinal Products (HMPC) as part of the EMA having regard to the particularities of HMPs and THMPs [11]. The HMPC replaced the "CPMP Working Party on Herbal Medicinal Products" and is responsible to advice the EMA and to prepare its opinion on herbal medicines [13], to strengthen the role of HMPs and THMPs and to integrate them in the European regulatory framework [14]. The HMPC assists and contributes to the harmonisation process by providing guidance documents for quality, safety and efficacy for herbal medicines as well as a draft Community list and HMPC monographs [14].

The draft Community list entries of herbal substances, preparations and combinations thereof for use in TU registrations for THMPs [14] are approved and published by the European Commission [15]. In this case a list entry is approved the applicant is in general not required to provide evidence on the safe traditional use of the THMPs he applied for, if he can demonstrate that the proposed THMPs comply with the information contained in the Community list [3].

The HMPC monographs on herbal substances and herbal preparations thereof are for the use in applications for WEU marketing authorisations for HMPs and TU registrations for THMPs. *A Community herbal monograph comprises the scientific opinion of the HMPC on safety and efficacy (WEU) and plausibility of efficacy (TU) concerning a herbal substance and preparations thereof intended for medicinal use* [16]. Therefore, the HMPC reviews all available information including non-clinical and clinical data as well as the documented long-standing use and experience in the Community regarding herbal substances and preparations thereof intended for medicinal use [16]. Each herbal preparation is assessed individually as information available may vary from one preparation to another [16].

The HMPC monograph has the same structure as the Summary of the Product Characteristic (SmPC) as laid down in Article 8(3)j of Directive 2001/83/EC [1]. It is divided into two columns covering well-established use (marketing authorisation) based on sufficient safety and efficacy data and traditional use (simplified registration) based on sufficient safety data and plausible efficacy [16] (see figure 2). According to the results of the review the herbal preparation appears in the well-established use section of the monograph and another in the traditional use section. Some preparations could not be included if data are insufficient respectively the neither the WEU (ten years) nor the TU (30 years, 15 in the EU) criteria are fulfilled [16].

Figure 1: Example of a HMPC monograph for Vitis vinifera [17]

1. Name of the medicinal product

To be specified for the individual finished product.

2. Qualitative and quantitative composition[1,2]

Well-established use	Traditional use
With regard to the marketing authorisation application of Article 10(a) of Directive 2001/83/EC as amended	With regard to the registration application of Article 16d(1) of Directive 2001/83/EC as amended
Vitis vinifera L., folium	*Vitis vinifera* L., folium
(grapevine leaf) [3]	(grapevine leaf) [4]
i) Herbal substance	i) Herbal substance
Not applicable.	Not applicable.
ii) Herbal preparation	ii) Herbal preparation
Dry extract (DER 4-6:1); extraction solvent water	a) Comminuted herbal substance
	b) Powdered herbal substance
	c) Soft extract (DER 2.5-4:1); extraction solvent water

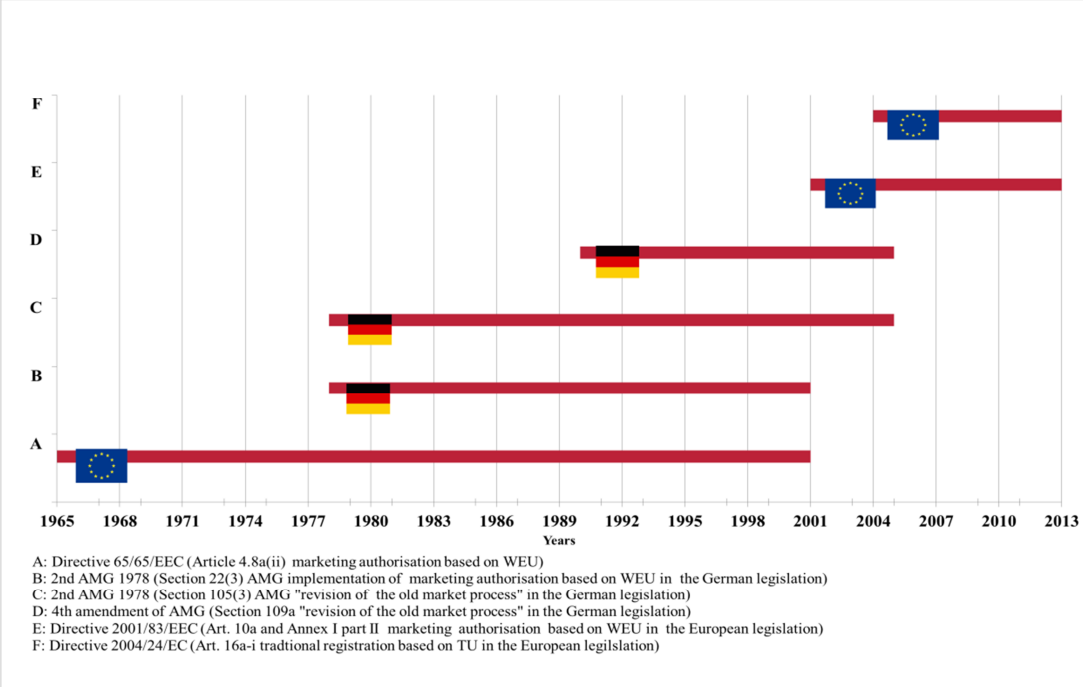
3. Pharmaceutical form

Well-established use	Traditional use
Herbal preparation in solid dosage forms for oral use.	Comminuted herbal substance as herbal tea for oral use.
	Herbal preparation in solid dosage forms for oral use.
	Herbal preparation in semi-solid dosage forms for cutaneous use.
	The pharmaceutical form should be described by the European Pharmacopoeia full standard term

The requirements of Directive 2004/24/EC [11] were implemented in Germany on 5 September 2005 by the 14th Act amending the Drug Law [21]. The implementation of Directive 2004/24/EC [11] led to a particular situation for herbal medicines in Germany for the following reasons. In Germany HMPs are highly recognised and have been played an important role of the German health care system for decades [3]. They are very well accepted by the population and are economically important in Germany [3]. As early as 1976, the German Parliament decided to follow the approach of pluralism in pharmacotherapy and expressively provided the integration of rules which respect the characteristics of 'particular therapeutic systems' [20] in the Medicinal Drug Law of 24 August 1976 which came into force on 1 January 1978 [20]. At this time the vast amount of approximately 51,500 herbal products was registered on the German market. In accordance with the AMG of 1978 medicinal products which were already on the market before 1978 needed to obtain a marketing authorisation based on proof of quality, safety and efficacy [20]. For the so called "revision of the old market process", in Germany special national legislation was set up which provided a framework for the evaluation of HMPs based on WEU [20] and of traditional medicinal products (TMPs) in Germany [21]. The evaluation of HMPs and TMPs was carried out by "Expert Commissions" in order to regulate the "revision of the old market process" in Germany [20]. The "revision of the old market process" was finalised by 31 December 2005.

In figure 2 a review of the key elements for herbal medicines in the European and German legislation is given.

Figure 2: Major steps for herbal medicines in the European and German legislation between 1965 and 2013



Additionally, in accordance with Section 36 of the AMG from 1978 a standard marketing authorisation was introduced as a national particularity of German legislation [20]. The standard marketing authorisation exempts medicinal products from the obligation to obtain a marketing authorisation because they are not expected to pose a direct or indirect risk [20]. Until the end of 2012, 20,023 standard marketing authorisations for herbal medicines are recorded in Germany.

In view of this nationally regulated market for herbal medicines in Germany, the impact of Directive 2004/24/EC [11] on the development of herbal medicines according to different criteria in Germany is examined in this thesis. As a basis for the discussion, a review of the requirements of the types of application based on WEU and TU in the current European legislation is given first. In the following, the results of a comprehensive data research which were performed by the Federal Institute for Drugs and Medical Devices (BfArM) is presented in order to analyse the following issues:

- The impact of Directive 2004/24/EC on the development of applications for WEU marketing authorisations for HMPs and TU registrations for THMPs in Germany.

- The impact of Directive 2004/24/EC on the development of applications for WEU marketing authorisations for HMPs and TU registrations for THMPs with regard to the types of procedure NP, MRP and DCP in Germany.

- The impact of Directive 2004/24/EC on the development of applications for WEU marketing authorisations for HMPs and TU registrations for THMPs with regard to the German involvement as RMS and CMS in MRPs and DCPs in Germany.

- The impact of Directive 2004/24/EC on the relevance of HMPC monographs in applications for WEU marketing authorisations and TU registrations in Germany.

2 The well-established and the traditional use approach

2.1. The well-established use approach according to Directive 2001/83/EC [1]

The WEU approach is based on bibliographic data [1]. It takes into account that the majority of medicinal products contain known substances and that their well-established medicinal use for years is confirmed by scientific literature [1]. Article 4.8(ii) of Directive 65/65/EEC allows omitting preclinical tests and clinical trials if the applicant has demonstrated recognised efficacy and acceptable safety level for a medicinal product by way of bibliographic data in order to receive a marketing authorisation [7]. Evaluation criteria for the quality, safety and efficacy are laid down in Directive 75/318/EEC [22] and 75/319/EEC [23]. *Because herbal medicinal products rely on long-term use and experience, bibliographic data can be used in the assessment* of herbal medicinal products [9].

The current definition and requirements of the type of application based on WEU were developed in the course of the European pharmaceutical legislation process on harmonisation of national laws in the 90ies [3]. The establishment of Commission Directive 1999/83/EC [24] amending the Annex of Directive 75/318/EEC [22] was supported by the efforts of the "Ad Hoc Working Group on Herbal Medicinal Products". This Directive defined the term "bibliographic applications" (and particularly the term "well-established use") more closely as well as gives details on the conditions for such applications [24]. Further, the Directive clarifies that "bibliographic reference" to other sources of evidence may demonstrate a valid proof of efficacy and safety if the applicant can explain and justify the use of these sources satisfactorily [24].

The WEU requirements of Directive 1999/83/EC [24] have been codified together with numerous other hitherto existing European Directives to one text in Directive 2001/83/EC [1][3]. The application type based on WEU was introduced in Article 10a of 2001/83/EC and specific requirements thereof were laid down in the Annex I part II of Directive 2001/83/EC [1]. In the German legislation the Section 22 (3) AMG has been added by the 14th Act Amending the Drug Law on 5 September 2005 [18] in accordance with Article 10a of Directive 2001/83/EC [1]. The Annex I part II of Directive 2001/83/EC [1] has been incorporated in the German legislation in the 3rd Chapter "well-established use" of the *Notice of the revision of general administrative regulations relating to the application of the Guidelines for the testing of medicinal products* on 11 October 2004 [25]. Today, the

European and German legislation are identical regarding the requirements of marketing authorisations based on WEU and are as follows:

Section 22 (3) of the 14th Act Amending the Drug Law [18]***:***

1. *in the case of a medicinal product which contains active substances that have been used for at least ten years in the European Union for general medical or veterinary purposes, the effects and side effects of which are known and evident from scientific data* [18]
2. *in the case of a medicinal product which, in its composition, is comparable to a medicinal product pursuant to number 1* [18]
3. *in the case of a medicinal product which is a new combination of constituents which are already known; however, other documents containing scientific findings may also be presented for the combination as such, if the efficacy and safety of the medicinal product according to its composition, dosage, pharmaceutical form and therapeutic indications can be determined by these documents* [18]

3th Chapter "well-established use" of the "Notice of the revision of general administrative regulations relating to the application of the Guidelines for the testing of medicinal products"[25]***:***

a) The following factors need to be considered in order to establish a well-established medicinal use of medicinal products [25]
   - *the time over which a substance has been used* may not be less than one decade from the first systematic and documented use, different periods of time may be necessary for establishing well established use for different substances [25]
   - *quantitative aspects of the use of the substance* [25]
   - *the degree of scientific interest in the use of the substance (reflected in the published scientific literature) and*
   - *the coherence of scientific assessments* [25]

b) *The documentation (…) should cover all aspects of the safety and/or efficacy assessment and must include or refer to a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies (…) it is in particular necessary to clarify that 'bibliographic reference' to other sources of evidence (post marketing studies, epidemiological studies, etc.) and not just data related to tests and trials may serve as a valid proof of safety and efficacy of a product if an application explains and justifies the use of these sources of information satisfactorily* [25].

c) *Particular attention must be paid to any missing information and justification must be given why demonstration of an acceptable level of safety and/or efficacy can be supported although some studies are lacking* [25]

d) *The non-clinical and/or clinical overviews must explain the relevance of any data submitted which concern a product different from the product intended for marketing. A judgement must be made whether the product studied can be considered as similar to the product, for which application for a marketing authorisation has been made in spite of the existing differences* [25]

2.2 The traditional use approach according to Directive 2004/24/EC [11]

The TU approach is based on the existence of corresponding products and takes into account empiric and bibliographic data that allow references to traditional use as a criterion for the safety and efficacy of a medicinal product in order to receive a traditional registration for a THMP [11]. The type of application based on TU is referred to as simplified registration because the data submitted by the applicant must demonstrate only sufficient safety and only plausible efficacy especially in view of their long traditional use [11].

The current requirements of the type of application based on TU are laid down in Article 16a-i of Directive 2004/24/EC [11] and were implemented in Section 39 a-d AMG in German legislation [18]. In the German legislation TMPs have already been authorised in accordance with Section 109 a AMG [21] in the "revision of the old market process". Section 141(14) AMG introduced national transitional rules for such 'Section 109a TMPs' containing herbal substance(s) in order to adapt them to the new requirements [18] of Directive 2004/24/EC [11]. Section 141 (14) AMG specifies that a transitional application pursuant to Section 39 a-d AMG has to be submitted for already authorised TMPs by 31 December 2008 [18]. If this was neglected, the corresponding marketing authorisations ceased being valid by 30 April 2011 [18]. The transitional rules are only applicable for TMPs which *exclusively contain as active substances, either one or more herbal substances, one or more herbal preparations or one or more such herbal substances in combination with one or more such herbal preparations* and also for HMPs containing vitamins and mineral the action of which is ancillary to the herbal active ingredients [18]. Today, the European and German legislation regarding the requirements of applications based on TU are identical and are as follows:

Section 39 a AMG contains the definition of THMPs: *(…) herbal medicinal products and medicinal products within the meaning of Section 2 sub-section 1, may be placed on the market as traditional herbal medicinal products only if they are registered (…)* [18]. The specification of Section 39 a AMG *(…) also apply to herbal medicinal products containing vitamins or minerals (…)* [18].

Section 39 b AMG contains the requirements of registration documents with regard to quality, safety and efficacy [18]. Regarding the quality *the results of analytical tests referred to in Section 22 (2) sentence 1 no 1* AMG are required [18]. The results of physico-chemical, biological or microbiological tests for THMPs do not substantially differ from those for any other medicinal product [18]. With regard to safety *a bibliographic review of safety data*

together with an expert report (…) were required additional information and documents (…) for assessing the safety (…) [18]. Concerning efficacy, *bibliographic evidence of the traditional use or expert reports showing that the product in question, or a corresponding product has been in medicinal use by humans or in animals for at least 30 years preceding the date of the application, including at least 15 years within the European Union and that under the stated conditions of use, the medicinal product is safe and the pharmacological effects or efficacy of the medicinal product are plausible based on use and experience over many years* [18].

Section 39 c AMG states the decision criteria for the registration of THMPs while other procedural provisions for THMPs are given in Section 39 d AMG [18].

3 Results

The following presentation of data research demonstrates the development of applications and completions of applications for WEU marketing authorisations and TU registrations with regard to different regulatory criteria in the current legislation as well as a review of WEU and traditional marketing authorisations according to German legislation in the “revision of the old market process” in Germany (chapter 3.1, 3.2 and 3.3). The results of the comprehensive data query were obtained from the Drug Information System (AMIS) database. The AMIS database is a central information system for medicinal products, active substances and tissues as well as their manufacturers or importers. In accordance with Section 67 a AMG the federal authorities in the portfolio of the Federal Ministry of Health (BMG) continuously generate and update information for medicinal products in collaboration with the German Institute of Medical Documentation and Information (DIMDI) [18]. The DIMDI is also an institute also within the portfolio of the Federal Ministry of Health that develops and operates database-supported information systems for drugs and medical devices in Germany [26].

The data represents the state of information as of December 2013. The AMIS data query was performed by combining different criteria, e. g. the “date of submission” and “phytopharmaceutical product” each with the “type of application” or “type of procedure” or by “RMS/CMS”. The query was performed by the BfArM. The provided data that are not fully available as such from public sources.

The data presented regarding the relevance of HMPC WEU and TU monographs (chapter 3.4). is the result of the evaluation of an annual questionnaire prepared by the BfArM on request of the EMA. The data represent the state of information as of December 2012. As above the provided data are also not fully accessible from public sources.

3.1. The applications and completions of applications for WEU marketing authorisations for HMPs, traditional marketing authorisations for TMPs and TU registrations for THMPs in Germany

3.1.1 The applications for WEU marketing authorisations for HMPs between 1995 and 2012 and TU registrations for THMPs between 2005 and 2012 in Germany

In Germany, the WEU application type is applicable since the AMG of 1 January of 1978 [20]. The TU application type is applicable in Germany since the 14th Act amending the Drug Law of 5 September 2005 [18]. Table 1 shows the development of applications for WEU marketing authorisations in accordance with Section 22 (3) AMG [18] for HMPs between 1995 and 2012 and TU registrations in accordance with Section 39 a-d AMG [18] for THMPs between 2005 until 2012 in Germany.

Table 1: The applications for WEU marketing authorisations in accordance with Section 22 (3) AMG [18] for HMPs between 1995 and 2012 and for TU registrations in accordance with Section 39 a-d AMG [18] for THMPs between 2005 and 2012 in Germany.

Year	WEU in accordance with Section 22 (3) AMG [18]	TU in accordance with Section 39 a-d AMG [18]
1995	156	-*
1996	219	-*
1997	252	-*
1998	197	-*
1999	103	-*
2000	118	-*
2001	69	-*
2002	94	-*
2003	66	-*
2004	26	-*
2005	44	12
2006	47	12
2007	40	17
2008	38	297
2009	72	26
2010	37	31
2011	38	22
2012	42	21
Total	1658	439

*not applicable

In the German legislation transitional application provisions for TU registrations in accordance with Section 141(14) AMG [18] were introduced in order to adapt the traditional already granted marketing authorisations for TMPs containing herbal substances in the German legislations to the new European requirement of Directive 2004/24/EC [11]. The applications for transitional TU registrations had to be submitted by 31 December 2008 [18] and therefore do not appear after this date. In Table 2 the development of applications for TU registrations in accordance with Section 39 a-d AMG [18] between 2005 and 2012 and of TU transitional registrations in accordance with Section 141(41) AMG [18] for THMPs between 2005 and 2008 in Germany is presented.

Table 2: The applications for TU registrations in accordance with Section 39 a-d AMG [18] and in accordance with Sec. 141 (14) AMG [18] for THMPs in Germany between 2005 and 2012.

Year	TU in accordance with Section 39 a-d AMG [18]	TU in accordance with Section 141 (14) AMG [18]
2005	12	0
2006	11	1
2007	14	3
2008	42	255
2009	26	-*
2010	31	-*
2011	22	-*
2012	21	-*
Total	178	259

*not applicable

Table 3 shows the development of the completions of applications for WEU marketing authorisations in accordance with Section 22 (3) AMG [18] grouped by granted, refused, withdrawn and expired marketing authorisations in Germany between 1995 and 2012. The applications of WEU marketing authorisations in accordance with Section 22 (3) AMG [18] are granted in accordance with Section 25 (1) AMG [18]. They may only be refused by the BfArM, if the submitted documents demonstrate reasons for such a refusal pursuant to Section 25 (2) AMG [18]. They shall be withdrawn by the BfArM on grounds in accordance with Section 30 AMG and by the applicants in accordance with Section 31 (1) (3) AMG [18]. The marketing authorisations in accordance with Section 22 (3) AMG [18] expire as specified in Section 31 AMG [18].

Table 3: The completion of applications for WEU marketing authorisations in accordance with Section 22 (3) AMG [18] for HMPs grouped by granted, refused, withdrawn and expired in Germany between 1995 and 2012.

WEU in accordance with Section 22 (3) AMG [18]					
Year	**Granted**	**Refused**	**Withdrawn**	**Expired**	**Total**
1995	11	17	34	8	70
1996	4	14	30	11	59
1997	3	35	40	10	88
1998	10	24	21	5	60
1999	1	6	16	13	36
2000	5	18	35	20	78
2001	12	68	39	32	151
2002	15	39	22	63	139
2003	32	8	6	32	78
2004	26	11	20	25	82
2005	49	13	9	39	110
2006	23	3	0	48	74
2007	23	6	0	46	75
2008	13	0	6	212	231
2009	24	0	3	22	49
2010	25	2	20	25	72
2011	15	2	4	34	55
2012	24	3	14	21	62
Total	315	269	319	666	1569
%	21	17	20	42	100

In Table 4 the development of the completions of applications for TU registrations in accordance with Section 39 a-d AMG [18] and Section 141 (14) AMG [18] grouped by granted, refused, withdrawn and expired in Germany between 2005 and 2012 is presented. The applications of TU registrations in accordance with Section 39 a-d AMG [18] and Section 141 (14) AMG [18] are granted in accordance with Section 39 c (1) in conjunction with Section 25 subsection 4 and 5 (5) AMG [18]. They may only be refused by the BfArM, if the submitted documents demonstrate grounds for refusal in accordance with Section 39 c (2) AMG [18]. The applications for TU registrations in accordance with Section 39 a-d AMG [18] and Section 141 (14) AMG [18] shall be withdrawn by the BfArM pursuant to Section 30 AMG in conjunction with 39 c AMG [18]. They may also be withdrawn by the applicants in accordance with Section 31 (1)(3) AMG [18]. The applications for TU registrations in accordance with Section 39 a-d AMG and Section 141 (14) AMG [18] expire as specified in Section 39 c (3) in conjunction with Section 31 AMG [18].

Table 4: The completions of applications for TU registrations in accordance with Section 39 a-d AMG [18] and Section 141 (14) AMG [18] for THMPs grouped by granted, refused, withdrawn and expired in Germany between 2005 and 2012.

	TU in accordance with Section 39a-d AMG[18]					TU in accordance with Section 141(14) AMG[18]				
Year	**Granted**	**Refused**	**Withdrawn**	**Expired**	**Total 39a-d**	**Granted**	**Refused**	**Withdrawn**	**Expired**	**Total 141(14)**
2005	1	0	0	0	1	0	0	0	0	0
2006	0	0	4	0	4	0	0	0	0	0
2007	4	10	0	0	14	1	0	0	0	1
2008	0	1	3	0	4	1	0	1	0	2
2009	4	2	4	0	10	4	4	7	0	15
2010	16	8	4	1	29	24	9	3	0	36
2011	17	2	3	0	22	42	27	6	0	75
2012	14	3	2	1	20	30	14	8	0	52
Total	56	26	20	2	104	102	54	25	0	181
%	54	25	19	2	100	56	30	14	0	100

3.1.2 The applications and completions of applications for WEU marketing authorisations for HMPs and traditional marketing authorisations for TMPs according to the German legislation in the "revision of the old market process" between 1978 and 2005

In accordance with Directives 65/65/EEC [7], 75/318/EEC [22] and 75/319/EEC [23] all medicinal products which were already on the market needed to be evaluated according to the requirements for the proof of quality, safety and efficacy by the Member States in order to keep them on the markets. In 1978, the AMG introduced transitional rules for the evaluation of these "old" medicinal products in Germany [20]. Table 5 presents a review of WEU renewal applications and completions of renewal applications for "fictively" granted marketing authorisations in accordance with Section 105(3) AMG [20] for HMPs and renewal applications and completions of renewal applications for "fictively" granted traditional marketing authorisations for TMPs containing herbal substances in accordance with Section 105(3) in conjunction with Section 109a AMG [21] in Germany in the "revision of the old market process" between 1978 and 2005 is presented. The "revision of the old market process" was finalised in December 2005.

Table 5: The renewal applications (up to 2005) and completions of renewal applications (up to 2012) for WEU marketing authorisations in accordance with Section 105 (3) AMG [20] for HMPs and for traditional marketing authorisations in accordance with Section 105 (3) in conjunction with Section 109 a AMG [21] for TMPs in Germany in the "revision of the old market process".

WEU in accordance with Section 105 (3) AMG [20]	Renewal applications by 30 April 1990 for WEU marketing authorisations for HMPs	8458
	Positive marketing authorisations for renewal applications by 31 December 2012	652
	Expired marketing authorisations for renewal applications by 31 December 2012	7564
	"Fictive" marketing authorisations by December 2012	95
TU in accordance with Section 105 (3) AMG in conjunction with Section 109a AMG [21]	Renewal applications by 31 December 2005 for traditional marketing authorisations for HMPs	905
	Positive marketing authorisations for renewal applications by 31 December 2012	167
	Expired marketing authorisations for renewal applications by 31 December 2012	682
	"Fictive" marketing authorisations by December 2012	34

During the "revision of the old market process" different provisions were laid down in the German legislation [20]. This has led to the expiry of the "old" marketing authorisations (see chapter 4.1). Table 6 shows a review of the expiry dates for WEU marketing authorisations in accordance with Section 105(3) AMG [20] and for traditional marketing authorisations for HMPs in accordance with Section 105(3) in conjunction with Section 109a AMG [21] for TMPs in the "revision of the old market" in Germany between 1990 and 2012.

Table 6: The expired WEU marketing authorisations in accordance with Section 105 (3) AMG [20] for HMPs and traditional marketing authorisations in accordance with Section 105 (3) in conjunction with Section 109 a AMG [21] for TMPs in Germany in the "revision of the old market process" between 1990 and 2005.

Expiry Year	WEU in accordance with Section 105 (3) AMG [20]	TU in accordance with Section 109 a AMG [21]
1990	28	0
1991	120	0
1992	237	0
1993	615	0
1994	255	0
1995	79	0
1996	89	0
1997	293	1
1998	233	0
1999	59	1
2000	176	2
2001	3236	31
2002	200	18
2003	171	16
2004	409	24
2005	379	30
2006	84	41
2007	70	24
2008	294	122
2009	63	22
2010	68	34
2011	319	280
2012	87	36
Total	7564	682

3.2 The applications for WEU marketing authorisations for HMPs and TU registrations for THMPs with regard to types of procedures (NP and MRP between 1995 and 2012, DCP between 2005 and 2012) in Germany

In 1995, the MRP was introduced in the European legislation, the DCP in 2005. The requirements of MRPs and DCPs are laid down in Article 28 (1) and 28 (2) of Directive 2001/83/EC [1], respectively and are implemented in Section 25(2) AMG [18] and in Section 25(3) AMG [18] in the German legislation [18]. Table 7 shows the development of applications for WEU marketing authorisations in accordance with Section 22 (3) AMG [18] and TU registrations in accordance with Section 39 a-d AMG [18] according to the type of procedure MRP between 1995 and 2012 and to DCP between 2005 and 2012 in Germany.

Table 7: The applications for WEU marketing authorisations in accordance with Section 22 (3) AMG [18] for HMPs between 1995 and 2012 and TU registrations in accordance with Section 39 a-d AMG [18] for THMPs with regard to types of procedure NPs and MRPs between 1995 and 2012 and DCPs between 2005 and 2012 in Germany.

	WEU in accordance with Section 22 (3) AMG [18]			**TU in accordance with Section 39 a-d AMG [18]**		
	NP	**MRP**	**DCP**	**NP**	**MRP**	**DCP**
1995	156	0	-	-*	-*	-*
1996	219	0	-	-*	-*	-*
1997	250	2	-	-*	-*	-*
1998	195	2	-	-*	-*	-*
1999	102	1	-	-*	-*	-*
2000	117	1	-	-*	-*	-*
2001	66	3	-	-*	-*	-*
2002	93	1	-	-*	-*	-*
2003	65	1	-	-*	-*	-*
2004	26	0	-	-*	-*	-*
2005	44	0	0	12	0	0
2006	47	0	0	11	0	0
2007	39	0	1	14	0	0
2008	37	0	1	42	0	0
2009	24	1	48	26	0	0
2010	37	0	0	31	0	0
2011	33	0	4	22	0	0
2012	39	0	3	21	0	1
Total	1589	12	57	178	0	1

*not applicable

3.3 The applications for WEU marketing authorisations for HMPs and TU registrations for THMPs with regard to the involvement of Germany as RMS and CMS in MRPs (between 1995 and 2012) and DCPs (between 2005 and 2012) in Germany

Table 8 presents the development of applications for WEU marketing authorisations in accordance with Section 22 (3) AMG [18] and TU registrations in accordance with Section 39 a-d AMG [18] according to the German involvement as RMS and CMS in MRPs between 1995 and 2012 and DCPs between 2005 and 2012 in Germany.

Table 8: The applications for WEU marketing authorisations in accordance with Section 22 (3) AMG [18] between 1995 and 2012 and TU applications in accordance with Section 39 a-d AMG [18] with regard to German involvement as RMS and CMS in MRPs between 1995 and 2012 and DCPs between 2005 and 2012 in Germany.

	WEU in accordance with Section 22 (3) AMG [18]				**TU in accordance with 39 a-d AMG [18]**			
	MRP		**DCP**		**MPR**		**DCP**	
	RMS	**CMS**	**RMS**	**CMS**	**RMS**	**CMS**	**RMS**	**CMS**
1995	0	0	-*	-*	-*	-*	-*	-*
1996	0	0	-*	-*	-*	-*	-*	-*
1997	0	2	-*	-*	-*	-*	-*	-*
1998	2	0	-*	-*	-*	-*	-*	-*
1999	1	0	-*	-*	-*	-*	-*	-*
2000	1	0	-*	-*	-*	-*	-*	-*
2001	3	0	-*	-*	-*	-*	-*	-*
2002	1	0	-*	-*	-*	-*	-*	-*
2003	0	1	-*	-*	-*	-*	-*	-*
2004	0	0	-*	-*	-*	-*	-*	-*
2005	0	0	0	0	0	0	0	0
2006	0	0	0	0	0	0	0	0
2007	0	0	1	0	0	0	0	0
2008	0	0	1	0	0	0	0	0
2009	0	1	48	0	0	0	0	0
2010	0	0	0	0	0	0	0	0
2011	0	0	4	0	0	0	0	0
2012	0	0	3	0	0	0	1	0
Total	8	4	57	0	0	0	1	0

*not applicable

In addition, one application in accordance with Section 21 AMG [18] was submitted via MRP and also one application in accordance with Section 21 AMG [18] was submitted via DCP in Germany between 2005 and 2012. These applications are not included in the discussion in chapter 4.2.

3.4 The relevance of HMPC monographs in Germany between 2005 and 2012

Table 9 reviews the applications for WEU marketing authorisations in accordance with Section 22 (3) AMG [18] and TU registrations in accordance with Section 39 a-d AMG [18] with regard to the reference to WEU and TU HMPC monographs in Germany between 2005 and 2012.

Table 9: The applications for WEU marketing authorisations in accordance with Section 22 (3) AMG [18] and TU registrations in accordance with Section 39 a-d AMG [18] with reference to WEU and TU HMPC monographs in Germany between 2005 and 2012.

	WEU in accordance with Section 22 (3) AMG [18]	**TU in accordance with Section 39 a-d AMG [18]**
Based on HMPC monograph	15	22
Make reference to relevant HMPC monograph(s)	22	51
Monographs used in the assessment by the competent authority	23	86

4 Discussion

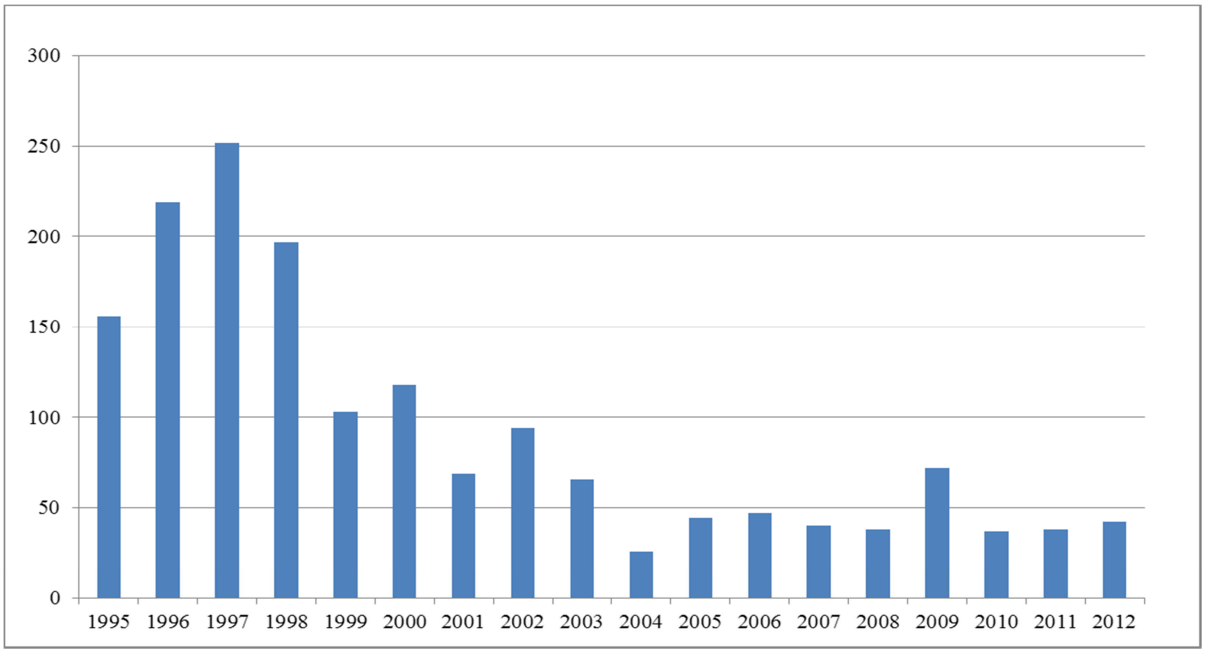
4.1 The development of applications and completions of applications for WEU marketing authorisations for HMPs and TU registrations for THMPs in Germany

In the following chapters (4.1.1- 4.1.4) the development of applications and completions of applications for WEU marketing authorisations in accordance with Section 22 (3) AMG [18] for HMPs between 1995 and 2012 and for TU registrations in accordance with Section 39 a d AMG [18] and 141 (14) AMG [18] for THMPs between 2005 and 2012 are discussed. In this context, the particular situation in Germany of the nationally regulated market for HMPs since 1978 and for TMPs since 1994 is especially taken into account.

4.1.1 The development of applications for WEU marketing authorisations in accordance with Section 22 (3) AMG [18] for HMPs in Germany between 1995 and 2012

A total of 1658 applications for WEU marketing authorisations pursuant to Section 22 (3) AMG [18] was submitted in Germany between 1995 and 2012 (Table 1, chapter 3.1.1). This number reflects the large interest to use this type of applications of the pharmaceutical companies in placing HMPs on the German market and illustrates the importance of HMPs for the healthcare system and the population in Germany. However, the total number needs to be considered in more detail for different periods of time.

Figure 3: Applications for WEU marketing authorisations in accordance with Section 22 (3) AMG [18] for HMPs in Germany between 2005 and 2012



Between 1995 and 2000

The majority of 1300 applications for WEU marketing authorisations was submitted in Germany between 1995 and 2000 (Table 1, chapter 3.1.1, ranging from 102 to 250 per year) which expresses a makes clear the large interest of use this type of applications in gaining access to the German market within this period of time. This high number of applications for WEU marketing authorisations may be directly related to the activities in the "revision of the old market process".

The "revision of the old market process" had to be performed by the Competent Authorities in the Member States in accordance with Directives 65/65/EEC [7], 75/318/EEC [22] and 75/319/EEC [23]. All medicinal products which had already been on the market in 1978 had to be reviewed in order to receive a marketing authorisation based on the proof of quality, safety and efficacy [7][22][23] and to keep them on the markets. Pursuant to Section 105 (2) AMG medicinal products which had already been on the German market before 1978 had to be notified at the Federal Health Office (BGA) within a period of 6 months starting 1 January 1978 in order to keep them on the German market as so called "fictively" licensed medicinal products [20]. Altogether, approximately 51,500 herbal products were registered in Germany by 30 June 1978. In accordance with Section 105 (3)(1) AMG [20], "fictively" licensed medicinal products expired on 30 April 1990 unless an application for a renewal for the "fictively" marketing authorisation in accordance with Section 105 (3) AMG was submitted to BfArM prior to 30 April 1990 [20].

Until 30 April 1990 a total of 8458 applications for WEU marketing authorisations in accordance with Section 105 (3) AMG [20] for HMPs was submitted to BfArM (Table 5, chapter 3.1.2). This large figure indicates the vast market existing for HMPs in Germany and the high interest of the pharmaceutical companies to keep their HMPs on the German market.

The German legislation introduced special transitional rules in the AMG of 1978 regarding the evaluation of the huge amount of "old" medicinal products in order to regulate the "revision of the old market process" [20]. The establishment of the Expert Commission E pursuant to Section 25 (7) AMG [20] situated at the BGA (parts of which evolved to today´s BfArM) is of particular importance for the evaluation of WEU marketing authorisations for HMPs in Germany [27]. The Commission E had the task to prepare and publish Commission E monographs which contained systematically collected scientific material on herbal preparations and provided the basis for the evaluation of already existing WEU "fictively" marketing authorisations for HMPs in Germany [27]. The Commission E monographs

contained scientific information on efficacy and safety as well as risk-benefit ratio, recommendations for treatment, adverse reactions, contraindications, and interactions with other medicinal products as well as the recommended dosage [27]. From 1984 until 1994, the Commission E established a total of 330 monographs, 186 thereof received a positive benefit-risk evaluation [27].

The provided Commission E monographs allowed the pharmaceutical companies to refer to this scientific material in order to obtain a new WEU marketing authorisation in accordance with Section 22 (3) AMG in Germany [27]. This fact might explain this high number of new applications for WEU marketing authorisations in accordance with Section 22 (3) AMG [18] in Germany between 1995 and 2000.

In accordance with the 5th Act Amending the Drug Law of 1994 [28], pharmaceutical companies were obliged to demonstrate the proof of safety and efficacy of their medicinal products themselves in order to accelerate the "revision of the old market process" in Germany [27]. Thus, the Commission E discontinued its work of preparing monographs in 1994 [27]. An update of Commission E monographs was legally not required [27]. Today, the monographs are regarded as a comprehensive achievement demonstrating the state of scientific knowledge at the date of its notification in the Federal Gazette [27].

Between 2001 and 2004

The use of applications for WEU marketing authorisations in accordance with 22 (3) AMG decreased significantly to a total of 299 applications between 2001 and 2004 (Table 1, chapter 3.1.1, ranging from 26 to 94 per year). This decline can be directly explained by the strong involvement of the pharmaceutical companies in regulatory and scientific activities in the still on-going "revision of the old market process" due to different provisions by the German legislation. In this respect, the European Commission stipulated that the "revision of the old market process" in Germany had to be finalised by 31 December 2005 [29].

In accordance with Section 105 (5c) of the 5th Act Amending the Drug Law of 09 August 1994 [28], pharmaceutical companies were allowed to keep their medicinal products on the German market until 31 December 2004 ("rule of 2004") if they withdraw them by 31 December 1995 (this was later extended to 31 December 1999) [28]. The aim of this measure was to facilitate the applicants' withdrawal decision in cases where it was

foreseeable that their applications would have led to a negative BfArM decision due to insufficient data. A complaint of the European Commission [29] led to cancellation of the "rule of 2004" in accordance with the 10th Act Amending the German Drug Law of 12 July 2000 [30] with the result that the evaluation process of the already withdrawn "fictively" marketing authorisations according to the "rule of 2004" needed to continue [30].

Additionally, in accordance with Section 105 (4a) of the 10th Act Amending the Drug Law [30] in compliance with the European requirements of Directive 2001/83/EC [1] the submission of "ex-ante" (preclinical tests and clinical trials) documents was also required for "old" medicinal products by 1 February 2001 [1][30]. The "fictively" marketing authorisations expired if these documents could not be submitted by the applicants by 01 February 2001 [30]. This measure was intended to streamline the adaptation of the "old" medicinal products to the requirements of quality, safety and efficacy as required in the European legislation [27].

Parallel to the "ex-ante" rule, the pharmaceutical companies could renounce their marketing authorisations in accordance with Section 105 (3)(3) of the 10th Act Amending the Drug Law until 31 January 2001 [30].

The aim of these above mentioned measurements in the German legislation in the "revision of the old market process" was primarily done in order to facilitate and to streamline the evaluation of "old" medicinal products as well as to remove medicinal products with insufficient data from the German market [27]. As indicated by the number of 7564 the majority of applications for "fictively" WEU marketing authorisations in accordance with Section 105 (3) AMG [20] for HMPs is expired by the end of 2012 (Table 5, chapter 3.1.2).

As example, in 2001, the large number of 3236 expiries (Table 6, chapter 3.1.2) of the "fictively" WEU marketing authorisations was a consequence of the "rule of 2004", the "ex-ante" rule and the opportunity to renounce the marketing authorisations. The large number of expired "fictively" WEU marketing authorisations indicating that the majority of HMPs which had already been on the German market before 1978 either could not prove quality, safety and efficacy in order to obtain a renewal for marketing authorisation. Further, economic reasons by the pharmaceutical companies could have led to the decision not maintaining these HMPs on the German market.

Today, a total of 652 HMPs is authorised in accordance with Section 105 (3) AMG [20] (Table 5, chapter 3.1.2) for HMPs on the German market. This demonstrates the pharmaceutical companies' continuing interest in keeping these HMPs on the German market. However, the review of the "revision of the old market process" with regard to WEU

marketing authorisations in accordance with Section 105 (3) AMG [20] (Table 5, chapter 3.1.2) reflects that the aim to remove medicinal products with insufficient data from the German market in order to provide safe and efficient medicinal products for public health can be regarded as achieved.

These provisions to regulate the "revision of the old market process" and the pressure of the European Commission required increased efforts both on the side of the pharmaceutical companies and BfArM. At sides of pharmaceutical companies' this fact alone tied up many of the resources and could have led to the reluctance for submitting new applications for WEU marketing authorisations in accordance with Section 22 (3) AMG [18] in Germany between 2001 and 2004. In addition, the pharmaceutical companies that market HMPs are often small or medium sized companies. This could have additionally reduced the potential to invest resources in the preparation of applications for new WEU marketing authorisations in Germany.

Beside the strong involvement of the pharmaceutical companies in "revision of the old market process", further conditions could have led to the reluctance of pharmaceutical companies for submitting new WEU marketing authorisations in Germany between 2001 and 2004.
The introduction of the WEU requirements by Commission Directive 1999/83/EC [24] may have decreased the willingness of the pharmaceutical companies to obtain WEU marketing authorisations. Even if the WEU requirements of Directive 1999/83/EC [24] do not differ significantly from the existing national WEU requirements of the AMG of 1978 [20] in accordance with Directives 65/65/EEC [7] 75/318/EEC [22] and 75/319/EEC [23], it cannot be excluded that the status of EU compliant requirements caused some uncertainties among the companies, e. g. in the case of small companies with obviously less experience in the European pharmaceutical environment. Maybe pharmaceutical companies were also reluctant to obtain applications for WEU marketing authorisations because of the imminent establishment of Directive 2004/24/EC [11] and its consequences for the regulatory situation of herbal medicines in Germany.
The reform of the German health insurance system led to changes in the reimbursement conditions for OTC (non-prescription) products in 2003 [31]. In accordance with Section 34 SGB V non-prescription drugs were excluded from the obligation to be reimbursed by the public health insurance system in order to reduce the costs in public health [31]. The majority of HMPs is non-prescription drugs in accordance with Section 43 AMG [18] and

was thus subject to these changed reimbursement conditions. Thus, it can be assumed that the applicants' decision to apply for new WEU marketing authorisations for HMPs was influenced by this fact.

Between 2005 and 2012

A total of 358 applications for WEU marketing authorisations in accordance with 22 (3) AMG was submitted to BfArM between 2005 and 2012 (Table 1, chapter 3.1.1, ranging from 42 to 72 per year). It would have been conceivable that the use of applications for WEU marketing authorisations decreased with the introduction of a new type of application for TU registrations by Directive 2004/24/EC [11] in Germany in 2005. But it could be demonstrated that the use of applications for WEU marketing authorisations between 2005 and 2012 remained at the similar level in relation with the number of applications between 2001 and 2005 in Germany so far.

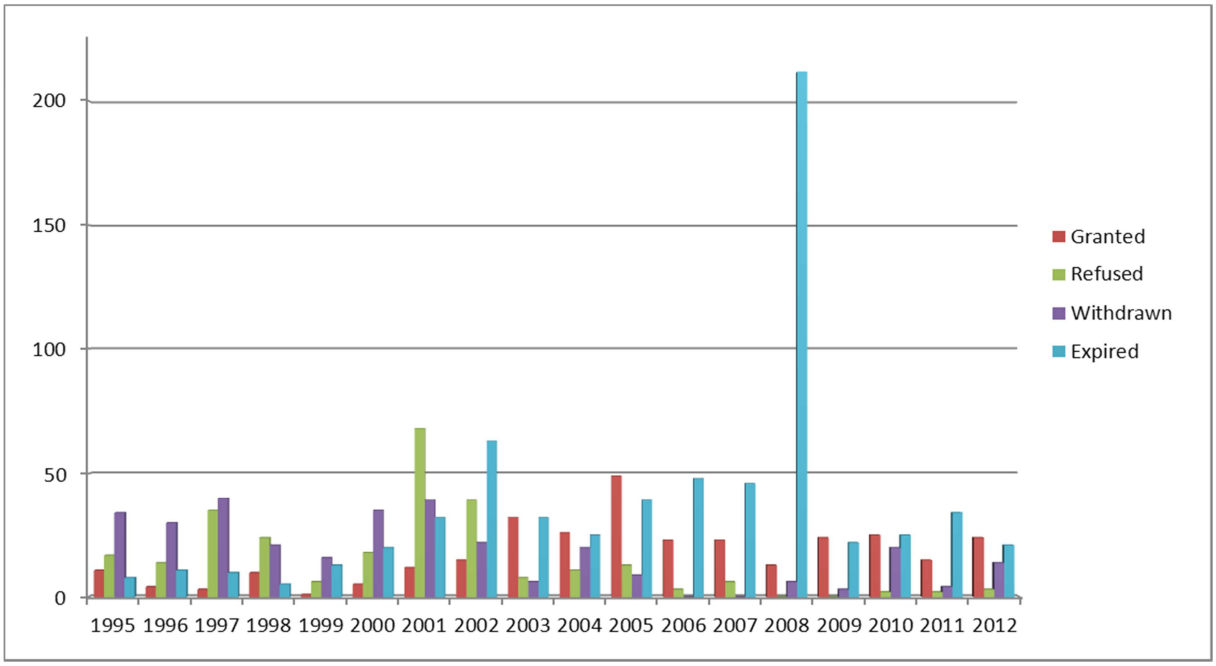
The development of new applications for WEU marketing authorisations in accordance with Section 22 (3) AMG [18] between 1995 and 2000 as well as the development of "fictively" marketing authorisation for HMPs in the "revision of the old market process" reveals the existing market for HMPs in Germany (see above). Therefore, it can be assumed rather, that the on-going low level of applications for WEU marketing authorisations obviously strongly related with the already existing market for HMPs and influenced the number of new applications for WEU marketing authorisation in accordance with Section 22 (3) AMG [18] between 2005 and 2012. Changed conditions in the German health insurance system for herbal medicines might be also the reason for the low number of applications for WEU marketing authorisations in Germany between 2001 and 2012.

Even if the number of the new applications for WEU marketing authorisations between 2001 and 2012 is on a lower level than between 1995 and 2000, the constant level of new applications for WEU marketing authorisations in this period of time reflects the current interest of the pharmaceutical companies to gain access to the market for WEU marketing authorisations in accordance with Section 22 (3) AMG [18]. However, it cannot be excluded that an increasing relevance of TU registrations (see chapter 4.1.3) in the future will lead to a decrease of the use of WEU applications in Germany.

4.1.2 The development of the completions of applications for WEU marketing authorisations in accordance with Section 22 (3) AMG [18] for HMPs in Germany between 1995 and 2012

In Germany a total of 1569 applications for WEU marketing authorisations in accordance with Section 22 (3) AMG [18] was completed from 1995 until 2012 (Table 3, chapter 3.1.1). The majority of the completed marketing authorisations has expired (42%), while the granted, refused and withdrawn marketing authorisations are distributed almost in equal proportions (about 20%). In general, the number of completions of applications of WEU marketing authorisations reflects the common regulatory situation of the BfArM's decisions on marketing authorisations and is not discussed in detail (see figure 3).

Figure 4: Completions of applications for WEU marketing authorisations in accordance with Section 22 (3) AMG [18] for HMPs in Germany between 2005 and 2012



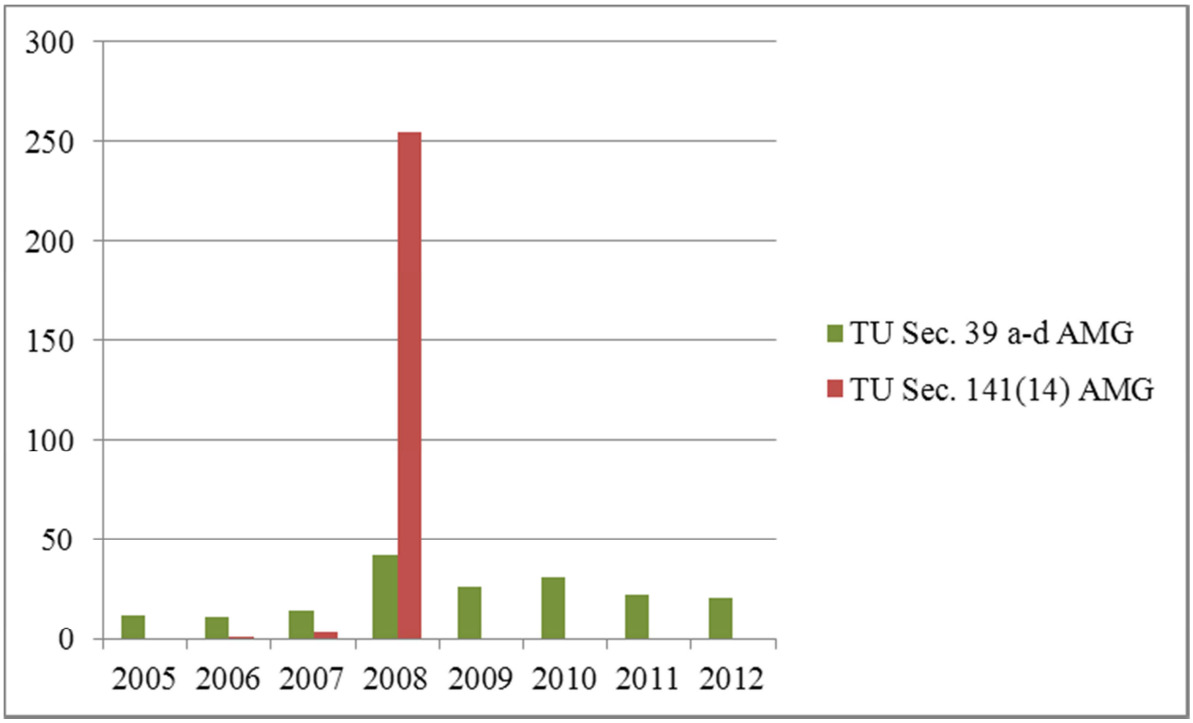
However, the large number of 212 marketing authorisations which expired in 2008 needs to be taken into account. This number may be associated with the introduction of the "sunset clause" rule by the 14th Act Amending the Drug Law [18] in accordance with Directive 2001/83/EC [1] in 2005. The "sunset clause" rule extended the notification requirements for medicinal products to include marketing and discontinuation of marketing by the holder of the marketing authorisations [18][33]. In accordance with Article 24 of Directive 2001/83 [1], transposed to Section 31 subsection 1(1) AMG *the MA shall expire if the authorised medicinal product is not placed on the market within three years of the granting of the MA, or*

if the authorised medicinal product that was placed on the market in accordance with the MA is not placed on the market for three successive years [18]. If no such notification was made by 5 September 2005, the marketing authorisation of the medicinal product expired on 5 September 2008 [18]. Obviously, as the number of expired WEU marketing authorisations demonstrates, the pharmaceutical companies were not interested in placing part of their authorised HMPs on the market. This may be explained by e. g. the economic situation of the pharmaceutical companies or by the changed reimbursement conditions for OTC medicinal products in Germany as mentioned above.

4.1.3 The development of applications for TU registrations in accordance with Section 39 a-d AMG [18] and Section 141 (14) AMG [18] for THMPs in Germany between 2005 and 2012

A total of 439 applications for TU registrations in accordance with Sections 39 a-d AMG [18] and 141 (14) AMG [18], respectively, have been submitted in Germany between 2005 and 2012 (Table 1, chapter 3.1.1). This demonstrates the importance of the use of this type of application on the German market. However, the applications pursuant to Section 39 a-d AMG [18] and those pursuant to Section 141 (14) AMG [18] need to be considered separately.

Figure 5: Applications for TU registrations in accordance with Section 39 a-d AMG [18] and in accordance with Section 141 (14) AMG [18] in Germany between 2005 and 2012



Applications in accordance with Section 39 a-d AMG [18]

178 applications for new TU registrations in accordance with Section 39 a-d AMG were submitted in Germany between 2005 and 2012 (Table 2, chapter 3.1.1). This figure reflects on a first glance reluctance of the pharmaceutical companies to use applications of TU registrations for new THMPs in gaining access to the German market.

However, it can be assumed that in Germany the pharmaceutical companies were strongly involved in the preparation of applications for transitional TU registrations in accordance with Section 141 (14) AMG [18] in this time period (see below). In view of small or medium size companies in this field, this fact obviously tied up resources and may explain the number of new applications for new TU registrations. Furthermore, due to the "revision of the old market process" a regulated national market for the majority of TMPs authorised in accordance with Section 109 a AMG [21] existed in Germany.

It must be also taken into account that the introduction of TU registrations applications for THMPs is a young provision in the European legislation. Thus, it can be assumed that the pharmaceutical companies have lower experience in this field. This can be reasoned the current reluctance by the pharmaceutical companies to use applications for TU registrations in order to gain access to the market in Germany between 2005 and 2012.

However, there was a gradually increasing of the use of TU monographs by 2012 (see chapter 4.4). Furthermore, out of all Member States, the first TU registration ever was granted in Germany. Moreover, out of all Member States in Germany the most applications for TU registrations were submitted between 2005 and 2012. [32]. Thus, an increasing use of TU registration applications seems foreseeable, currently.

Applications in accordance with Section 141 (14) AMG [18]

With the introduction of the new application type for TU registrations according to Directive 2004/24/EC [11] transitional national provisions had to be introduced in the German legislation in order to adapt the already "fictively" granted traditional marketing authorisations for TMPs containing herbal substances in accordance with Section 105 (3) AMG in conjunction with Section 109 a AMG [21] in the "revision of the old market process" on the new requirements according to the European legislation. In accordance with the transitional provisions of Section 141 (14) AMG [18], a TU registration application pursuant to Section 39 a-d AMG [18] or a marketing authorisation application had to be submitted for these existing traditional marketing authorisations by 31 December 2008 [18]. If it was not made the "old" herbal TMPs ceased to be valid on 30 April 2011 [18].

In the "revision of the old market process" the 4th Act Amending the Drug Law of 11 on April 1990 [21] . In accordance with Section 105 (3) AMG in conjunction with Section 109a AMG special rules for medicinal products derived from chemical, herbal and animal origin substances with traditional use were introduced into German legislation [21]. This purely German provision was only applicable for medicinal products which had already been on the market in Germany since 1978 with the aim to further accelerate the "revision of the old market process" and to keep those medicinal products on the German market that could not demonstrated efficacy and safety either by scientific bibliographic literature or by preclinical test and clinical trials [21][27].

In accordance with Section 25 (7) AMG the "109 a AMG Expert Committee" was established at the BfArM in order to evaluate the quality, safety and efficacy of TMPs [20]. The efficacy of the TMPs was deemed to be met when the substances or combinations of substances claimed efficacy in therapeutic indications which were recognised in a list of the therapeutic indications compiled after hearing the applicants by the 109 a AMG Expert Commission [21]. A position on the so-called "109 a AMG list of therapeutic indications" was mandatory in order to receive a renewal of the marketing authorisation in accordance with Section 105 (3) in conjunction with Section 109 a AMG [21].

The quality was deemed to be met if the documents and the analytical expert opinion had been submitted and the applicants had made a statutory declaration. The labeling of TMPs *shall be accompanied by the additional remark: "Traditionally used":…to strengthen and fortify the..., to improve the state of health..., to support the functioning of the ...or prevention against…, as a mild-action medicinal product for use in…[109 a]* [21].

In 2005 a total of 905 granted traditional marketing authorisations for HMPs in accordance with Section 105 (3) AMG in conjunction with Section 109 a AMG [21] (Table 5, chapter 3.1.2) could have been transferred in accordance with Section 141 (14) AMG [18] to the new requirements of the European legislation.

Out of 905 "fictively" granted traditional marketing authorisations for HMPs a total of 259 applications for transitional TU registrations in accordance with Section 141 (14) AMG [18] was submitted between 2005 and 2008 (Table 2, chapter 3.1.1). This indicates the interest of the pharmaceutical companies in keeping these TMPs already granted in "the revision of the old market process" on the German market.

However, it is demonstrated that out of 905 the majority of 646 granted traditional marketing authorisations for HMPs in accordance with Section 109 a AMG [21] had not submitted

applications for transitional TU registrations in accordance with Section 141 (14) AMG by 31 December 2008 and thus have been expired on 30 April 2011 [18] (Table 6, chapter 3.1.2).

This indicates that these traditional HMPs in accordance with Section 105 (3) AMG in conjunction with Section 109 a AMG [21] could obviously not be to comply with the new European requirements of TU registrations. In general, new introduced pharmaceutical legislation has led the pharmaceutical companies to consider about the maintenance of their existing marketing authorisations, e. g. with regard to the economic situation. This can also explain the number of transitional TU registrations of pharmaceutical companies to submit transitional TU registrations in accordance with Section 141 (14) AMG [18]. In addition, it must be taken into account that in several cases the same marketing authorisations of "old" TMPs were distributed by a group of pharmaceutical companies in the past. Today, in cases of the same marketing authorisations the distribution channels are regulated within the group of companies via different co-distributors. Therefore, only one application for transitional TU registration was required by the group of companies to keep the "old" TMPs on the German market. This could distort the number of transitional for TU registrations applications submitted in accordance with Section 141 (14) AMG [18].

If an application for TU registration in accordance with Section 141 (14) AMG [18] was submitted, the corresponding "old" traditional marketing authorisations for TMPs already granted in accordance with Section 105 (3) AMG in conjunction with Section 109 a AMG [21] expired if the evaluation of the corresponding transitional TU registrations in accordance with Section 141 (14) AMG will have to be completed [18]. Due to the on-going process of evaluation of the transitional TU registrations in accordance with Section 141 (14) AMG [18] at the BfArM, 167 marketing authorisations in accordance with Section 109 a AMG are still valid so far (Table 5, chapter 3.1.2) today.

4.1.4 The development of the completions of applications for TU registrations in accordance with Section 39 a-d AMG [18] and 141 (14) AMG [18] for THMPs in Germany

A total a total of 285 applications for TU registrations in accordance with Section 39 a-d AMG [18] and 141 (14) AMG [18] was completed in Germany between 2005 and 2012 (Table 4, chapter 3.1.1). 30% of the TU registrations in accordance with Section 141 (14) AMG [18] between 2005 and 2012 were refused because they could obviously not fulfill the new requirements of Directive 2004/24/EC [11] even if the corresponding TMPs

had already been authorised in accordance with Section 109 a AMG in German legislation [21].

The majority of the completed TU registrations have been granted (about 55%) and only few have expired. This reflects that the requirements of Directive 2004/24/EC [11] for THMPs could be fulfilled by the pharmaceutical companies in applications for new TU registrations and for a major part "old" TMPs in order to gain access or to maintain the access to the German market, respectively.

Figure 6: Completions of applications for TU registrations in accordance with Section 39 a-d AMG [18] for THMPs in Germany between 2005 and 2012

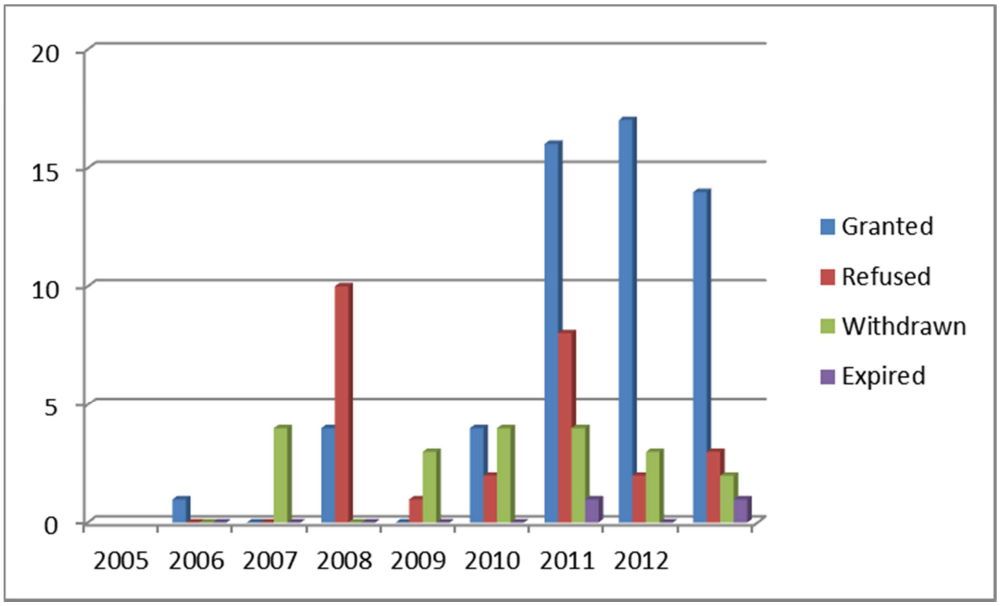
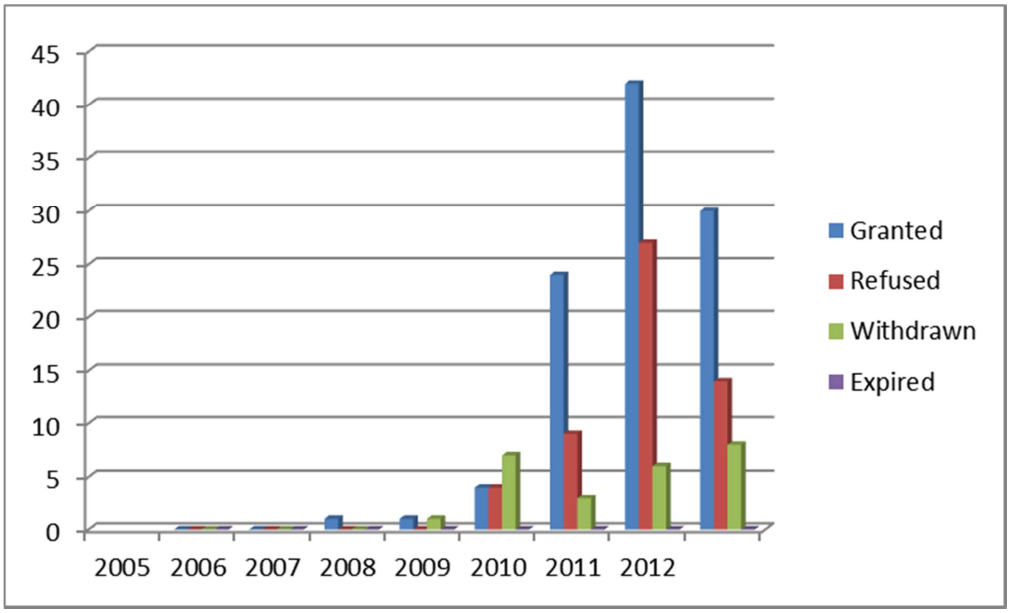


Figure 7: Completions of applications for TU registrations in accordance with Section 141 (14) AMG [18] for THMPs in Germany between 2005 and 2012



4.2 The development of the type of procedures NP, MRP and DCP in applications for WEU marketing authorisations and TU registrations in Germany

In the following chapters (4.2.1- 4.2.2) the development of applications and completions of applications for WEU marketing authorisations in accordance with Section 22 (3) AMG [18] between 1995 and 2012 for HMPs and for TU registrations in accordance with Section 39 a d AMG [18] and 141 (14) AMG [18] between 2005 and 2012 for THMPs with regard to the type of procedures NPs, MRPs and DCPs are discussed.

According to the current legislation, NPs, MRPs and DCPs are applicable for gaining access to the market for HMPs and THMPs in Germany [8]. In accordance with Regulation (EC) 726/2004, the CP is equally applicable for herbal medicines [12]. The CP is mandatory, if HMPs would fall into the scope of the Annex of Regulation (EC) 726/2004 (e. g. new active substance, intended for the treatment of special life-threatening diseases, e. g. cancer, diabetes, manufactured by biotechnological processes etc.) [12]. The CP may also be chosen, if the applicant stated that the medicinal product means a significant therapeutic, scientific or technical innovation [12].
The CP leads to a marketing authorisation in each Member State of the European Community with only one application submitted to the EMA [34]. Due to the fact that most HMPs contain known herbal substances and are indicated for the treatment of minor diseases [6], no CP for a HMP has been performed in the European Community until today. Thus, the CP is not included in this investigation.

4.2.1 The development of applications for WEU marketing authorisations in accordance with Section 22 (3) AMG [18] and TU registrations according Section 39 a-d AMG [18] with regard to NPs in Germany

1589 applications for WEU marketing authorisations of a total of 1658 were submitted via NP in Germany between 1995 and 2012 (Table 7, chapter 3.2). All but one (178/179) applications for TU registrations were submitted via NP between 2005 and 2012 (Table 7, chapter 3.2). The NP may be chosen by the applicants in order to receive a marketing authorisation or registration by the competent authority in the individual Member State in the EU/EEA in which the application has been submitted [8].
The large number of applications for WEU marketing authorisations and TU registrations via NP reflect the applicants' high interest in receiving marketing authorisations for HMPs and

TU registrations for THMPs via NP. As mentioned above herbal medicines are traditionally highly accepted by the German population and have been an important part of the healthcare system in Germany for decades [3]. The high use of NP illustrates the on-going importance of HMPs and THMPs for the German market. Further, the long-term experience in the evaluation of herbal medicines of the BfArM and the pharmaceutical companies in Germany, especially due to the "revision of the old market process" may be explained the high use of NPs in applications for WEU marketing authorisations and TU registrations in Germany between 2005 and 2012.

On the other hand the high number of applications for HMPs and THMPs submitted via NP indicates on a first glance a large uncertainty for submitting European procedures to gain access to the markets for HMPs and THMPs in Germany. But it must be taken into account that a NP in Germany can be used by the pharmaceutical companies as a starting point for following European or even international procedures to gain access to the European or global market.

4.2.2 The development of applications for WEU marketing authorisations in accordance with Section 22 (3) AMG [18] and TU registrations according Section 39 a-d AMG [18] with regard to MRPs and DCPs in Germany

12 of 1658 applications for WEU marketing authorisations were submitted via MRP between 1995 and 2012 and 57 via DCP between 2005 and 2012 in Germany (Table 7, chapter 3.2). Only one of 179 applications for TU registrations was submitted via DCP between 2005 and 2012 (Table 7, chapter 3.2). In comparison, 348 applications for marketing authorisations for medicinal products containing chemical substances were submitted via DCP (DE=RMS) to BfArM in 2011. However, the first TU registration application via DCP in which Germany acts as RMS was submitted in Germany in 2012.

The number of MRPs demonstrates the low use of MRPs for applications for WEU marketing authorisations and TU registrations while the number of DCPs indicates a greater use in accessing the market for WEU marketing authorisations. All applications for WEU marketing authorisations via DCPs were submitted in 2009 and are based on applications for one herbal preparation in different strengths and with different sets of CMSs involved.
The use of DCPs reflects the higher relevance and acceptance for HMPs than the use of MRPs to gain access to the European market.

In general, according to Directive 2004/24/EC [11] a registration for a THMP already granted by a Member State shall be recognised by another Member State in MRPs and DCPs based on HMPC monograph or consisting of substances, preparations or combinations thereof contained in a Community list adopted by the European Commission [18]. If neither a Community list entry nor HMPC monograph exist, MRPs and DCPs are possible but clarification and discussion with the proposed involved RMS and CMSs are recommended before an application for TU registrations for THMPs are submitted [35]. This "hurdle" could have influenced the decision by the applicants to submit a TU registration application via MRP or DCP for THMPs in Germany.
Additionally, as mentioned above the pharmaceutical companies were obviously strongly involved in regulatory and scientific activities with regard to applications for TU registrations in accordance with Section 141 (14) AMG [18] after the Directive 2004/24/EC [11] came into force (see chapter 4.1.3). Thus, it can be assumed that resources of pharmaceutical companies were focused on these transitional TU registrations and were restricted for MRPs and DCPs, especially in view of small or mediums size companies.

The MRP was introduced by Directive 93/39/EEC [36] and *"is to be used in order to obtain a marketing authorisation in more than one Member States where the medicinal product in question has already received a marketing authorisation in any Member State at the time of application"* [37].
During the MRP, the marketing authorisation already granted by the RMS should be recognised by the CMSs unless the medicinal product in question *presents serious risk to public health with regard to quality, safety and efficacy* [37]. If a consensus is reached the RMS closes the MPR and a national phase for granting the national marketing authorisation follows [37]. If the *serious risk to public health* cannot be resolved during the evaluation process between the CMSs and RMS, an arbitration process is initiated at the CMDh and/or CHMP at the EMA [37]. In practice, a negative decision at the end of the arbitration procedure could result in the loss of the granted national marketing authorisation in the RMS [37]. Therefore, the potential of loosing the already granted marketing authorisation or registration in the RMS could be the reason for the low use for submitting applications for WEU marketing authorisations and TU registrations via MRP, especially in view of Germany with the most important market for herbal medicines between the Member States in the European Community. The potential of losing a marketing authorisations already granted before Directive 2004/24/EC came into force, is increased due to fact that the medicinal

product in question do not comply with the harmonised evaluation criteria of WEU and TU monographs established by the HMPC. This fact could have further hinder the pharmaceutical companies to decide for applications via MRPs.

The DCP was introduced by Directive 2004/27/EC [38] because an *evaluation of the operation of marketing authorisation procedures has revealed the need to revise the mutual recognition procedure in order to improve the opportunities for cooperation between Member States"* [37]. The DCP *"is to be used in order to obtain a marketing authorisation in more than one Member States where the medicinal product in question has not yet received a marketing authorisation in any Member State at the time of application* [37].
During the DCP the RMS and CMSs involved have to evaluate the application. If a consensus is reached, the RMS closes the DCP and it is followed by a national phase for granting the national marketing authorisation or registration [37] However, the DCP provides two clock-stop periods in order to give the applicant an opportunity to resolve the deficiencies raised by the RMS and CMSs [37]. If the applicant cannot resolve the deficiencies, the clock-stop periods may be extended [37]. This contradicts the aim for both the BfArM and the pharmaceutical companies to approve applications for marketing authorisations as fast as possible. If no consensus is reached at the end of a DCP an arbitration process is initiated [37] with the risk of a negative decision and consequently no access to the market for the medicinal product [37]. The potential to lose a marketing authorisation already granted as like in MRP due the above mentioned reasons is not present in DCP. This may explain the higher interest in submitting an application via DCP than via MRP. Additionally, in most cases the DCP is potentially faster than the MRP. This might be an important benefit for the applicants and could be reasoned the higher number of DCP than MRP.

Both MRPs and DCPs rely on the principle of mutual recognition between the Member States [37]. The development of harmonised evaluation criteria for herbal medicines by the HMPC (see chapter 4.4) has been established by Directive 2004/24/EC [11] as a prerequisite to apply for MRPs or DCPs [37]. The HMPC established both a draft Community list to use in THMPs and WEU and TU HMPC monographs to use in HMPs and THMPs [14]. The applicants may refer to these published documents and the Member States take them into account accordingly when examining the applications (see chapter 4.4) [14].
However, the Directive had come into force only eight years ago. Before Directive 2004/24/EC [11] came into force, herbal products were regulated nationally in different ways,

e. g. as food, food supplement or pharmaceutical legislations [6]. Furthermore, different criteria for evaluations also existed between the Member States in the past [6]. In contrast, the European harmonisation process for the evaluation criteria for chemically defined substances was already initiated in the 90ies [3]. Thus, the heterogeneous situation and low experience with harmonised evaluation criteria for herbal medicines in the European pharmaceutical field might explain the reluctance of the applicants to submit their applications via MRPs or DCPs.
Furthermore, different conditions for herbal medicines in the Member States [6] can have influenced the applicants' interest and the decision to gain access to the market in more than one Member State. There are still different traditions regarding the therapeutic use of herbal medicine[6]. For example, Garlic (Allium sativum) is used for the treatment of cough and cold in UK and for the prevention of arteriosclerosis in Germany [6]. Traditions are based on long-term experience in therapeutic use and are well-known by the population [6] and may have a non-negligible influence on the evaluation of herbal medicines.
As compared to chemically defined substances, among the Member States herbal products are accepted and appreciated in different ways both by scientists and the population [6]. Even if the acceptance of herbal medicines has increased in the last decades [39] and harmonised evaluation criteria were introduced in the European legislation the economic interests of the applicants is strongly influenced by the acceptance level in the Member States and may have decrease the willingness to submit applications via MRP or DCP, regardless of harmonised evaluation criteria laid down in European legislation.
Furthermore, the classification of herbal products as medicinal products is not harmonised by European legislation and remains the decision of the national competence [40]. As an example Senna pods can be marketed as food in Belgium and as a medicinal product in Germany [6]. Heterogeneous classifications of herbal medicines can lead to unforeseeable consequences during a MRP and DCP which also can have a negative impact on the applicants' decision to choose these types of procedure.

Even if the BfArM and the pharmaceutical companies in Germany have long- term experience in regulatory and scientific handling herbal medicines, it can be assumed that the sum of different conditions for herbal medicines in the Member States has decisively influenced the willingness of the applicants to submit applications for WEU marketing authorisations and TU registrations via MRPs and DCPs in Germany. Finally, it must be taken into account that not only in Germany but also in other Member States, e. g. in France and Poland herbal medicines have already been regulated [6] before Directive 2004/24/EC [11] came into force.

This is a general limitation which has obviously been influenced the economic interest to use MRPs and DCPs for submitting applications for WEU marketing authorisations and TU registrations.

4.3 The development of the German involvement as RMS and CMS in MRPs and DCPs in applications for WEU marketing authorisations for HMPs and TU registrations for THMPs in Germany

In the following chapter the development of applications for WEU marketing authorisations in accordance with Section 22 (3) AMG [18] and TU registrations in accordance with Section 39 a-d AMG [18] (Table 8, chapter) with regard to the German involvement as RMS and CMS in MRPs between 1995 and 2012 and in DCPs between 2005 and 2012 are discussed.

Only 12 MRPs was submitted in Germany, in eight of them Germany acted as RMS and in five as CMS between 1995 and 2012. In total, 57 DCPs were submitted, in all of them Germany acted as RMS between 2005 and 2012 (Table 8, chapter 3.3).

The RMS is the Member State which evaluates the marketing authorisation dossier and prepares the assessment report on behalf of the CMS in MRP and DCP [41]. The RMS acts as a central point between the CMSs, the applicant and if applicable the CMDh and CHMP, as well [41]. He also gives advice and recommendations regarding regulatory and scientific issues to facilitate the planned procedures, e. g. the agreement of the timetable of MRPs and DCPs or a discussion of the legal basis of the application prior to the start of procedure [41]. If the applications and the dossier have been submitted in MRPs or DCPs, the RMS informs the applicant about any deficiencies in the validation phase notified by the CMSs and does not start the procedure until the CMSs agree with the RMS that the issue has been resolved [41].
During MRPs and DCPs, the RMS should describe the properties of the medicinal product objectively in the assessment report and should discuss the reasons for granting the marketing authorisation in MRPs and DCPs. All contacts between the applicant and CMSs should be channeled via the RMS in order to facilitate the communication and to come to an agreement that ensures the granting of a marketing authorisation with a safe and rational therapeutic use of the medicinal products [41].
In MRPs, the Member State in which the medicinal product is already authorised, acts as RMS. Together with the CMSs that are chosen by the applicant the assessment report, the summary of product characteristics, the package leaflet and the labeling have to be approved during the MRP [41]. The marketing authorisation already granted by the RMS should be recognised by the CMSs unless the medicinal product in question *presents serious risk to public health with regard to quality, safety and efficacy* [37]. If a consensus is reached the

RMS closes the procedure and the national phase for granting the national marketing authorisation follows [37].
In DCP, the RMS and the CMS also have to approve the assessment report, the summary of product characteristics, the package leaflet and labeling in line with the task of the RMS in the MRP [41]. If a consensus is reached during the DCP, the RMS closes the procedure and the national phase for granting the national marketing authorisation follows [37].

In the majority of MRPs and DCPs for herbal medicines Germany involved, Germany acted as RMS. As mentioned above, the BfArM has a long-standing expertise in the regulatory and scientific field regarding herbal medicines. Furthermore, Germany is very experienced in MRPs and DCPs and in acting as RMS ever since these procedures were established in European legislation. This might explain the preference of the applicants to choose Germany as RMS in MRPs and DCPs for herbal medicines. It is a rational and strategic decision and hence common practice for the applicants to choose a RMS in DCP with long-term regulatory and scientific experience. Additionally, the majority of pharmaceutical companies that market herbal medicines are located in Germany. Thus, it can be beneficial for handling the regulatory and scientific activities during a MRP and DCP which may have influenced the decision to choose Germany as RMS. Finally, there are no language barriers between the BfArM and the applicants.

4.4 The development of the relevance of WEU and TU HMPC monographs in Germany

The review of the relevance of WEU and TU HMPC monographs in applications for WEU marketing authorisations in accordance with Section 22 (3) AMG [18] and TU registrations in accordance with Section 39 a-d AMG [18] and 141 (14) AMG [18] was categorised according to the type of reference (Table 9, chapter 3.4). Between 2005 and 2012 a total of 15 applications for WEU marketing authorisations was based on WEU HMPC monographs, 22 referred to relevant HMPC monograph(s) and 23 were used in the assessment by the BfArM.
Between 2005 and 2012 a total of 22 applications for TU registrations was based on TU HMPC monograph(s), 51 referred to relevant HMPC monograph(s) and 86 were used in the assessment by the BfArM.

The use of the HMPC monographs reflects the relevance and the acceptance of the pharmaceutical companies of the establishment of WEU and TU HMPC monographs in applications for WEU marketing authorisations and TU registrations in Germany between 2005 and 2012. In Germany, the introduction of HMPC monographs by Directive 2004/24/EC [11] replaced the former Commission E monographs in Germany in the “revision of the old market process” as mentioned above. Thus, the HMPC monographs are particularly important for WEU marketing authorisations and TU registrations applications in Germany.
The establishment of HMPC monographs is still a rather young element of the harmonised evaluation for HMPs and THMPs at the European level. The first HMPC monograph was published in 2006. It will probably take at least a decade to transfer legislation into the market situation and allow a final statement on the impact of such an instrument.

However, the establishment of HMPC monographs is an on-going process. Until present 114 final HMPC monographs covering different therapeutic areas have been finalised and published [42]. Currently, out of all HMPC monographs, about 80% include a TU while about 20% include a WEU [16]. Based on the priority list by AEGSP and further interested parties the HMPC has established a priority list of herbal substances for which monographs should be prepared. For 2013 the HMPC plan to prepare 30 draft or final monographs in which the majority will include a TU [42]. Thus, it can be assumed that due to the on-going preparation of TU HMPC monographs and increasing experience of pharmaceutical companies in this

field, the use and the relevance of TU HMPC monographs in applications for TU registrations might be increased in Germany.

5 Conclusion and Outlook

Directive 2004/24/EC [11] is a milestone for herbal medicines in the European pharmaceutical legislation process. The objective was to harmonise the national laws of the Member States in order to protect public health since in the past the guarantees of quality, safety and efficacy [22] were not equally provided among the Member States. That is particularly demonstrated by the establishment of the HMPC as part of the EMA having regard to the particularities of HMPs and THMPs in the European Community [11] and the introduction of a simplified TU registration procedure for THMPs by Directive 2004/24/EC [11].

In Germany, the implementation of Directive 2004/24/EC by the 14th Act Amending the Drug Law of 5 September 2005 [18] has led to a particular situation in German legislation in view of the nationally existing regulated market for HMPs before Directive 2004/24/EC came into force [11].

The acceptance and relevance of WEU and TU monographs established by the HMPC for the harmonised evaluation of applications for WEU marketing authorisations and TU registrations, is an important result of Directive 2004/24/EC [11] in Germany. The establishment of HMPC monographs by Directive 2004/24/EC [11] replaced the Commission E monographs established in Germany in the "revision of the old market process".
The instrument of harmonised evaluation criteria in the form of HMPC monographs of Directive 2004/24/EC is still a rather young provision in European legislation [11]. Thus it shall be noted that the first HMPC monograph was published in 2006. It will probably take at least a decade to transfer legislation into the market situation and to allow a final statement on the impact of such an instrument.
Even if Directive 2004/24/EC [11] has not been into force for a sufficiently long period of time, the current use of the HMPC monographs suggests an on-going development of the relevance and acceptance of HMPC monographs as a basis for the evaluation of applications for WEU marketing authorisations and TU registrations of HMPC monographs in Germany. Currently, out of all HMPC monographs, about 80% include a TU while about 20% include WEU [16]. For 2013 the HMPC plan to prepare 30 draft or final monographs in which the majority will include a TU [42]. Thus, the on-going relevance of the use of TU monographs and a decrease of the use of WEU monographs might be expected.

A further impact of Directive 2004/24/EC [11] is the adaptation of TMPs which have already been authorised in the German legislation in the "revision of the old market process" with the European requirements of Directive 2004/24/EC [11]. Thus, it can be concluded that these transitional TU registration applications submitted in accordance with Section 141 (14) AMG [18] by 2008 are fully compliant with the European requirements of Directive 2004/24/EC [11].

Simultaneously, the development of applications for new TU registrations in accordance with Section 39 a-d AMG [18] for THMPs demonstrate some reluctance of the pharmaceutical companies to gain further access to the German market for THMPs by 2012.

However, in Germany the pharmaceutical companies were strongly involved in the preparation of applications for transitional TU registrations after the Directive 2004/24/EC came into force [11]. Further, due to the "revision of the old market process" a regulated national market for the majority of TMPs existed in Germany [20][21].

Because of the short period since the introduction of the option of TU registrations into legislation, pharmaceutical companies have had only limited experience in this field. Thus, a final statement on the impact of Directive 2004/24/EC [11] on the development of TU registrations cannot be given so far.

Nevertheless, it shall be noted that the first TU registration ever in the European Community was granted in Germany. Moreover, out of all Member States the most applications for TU registrations were submitted in Germany between 2005 and 2012 [32]. Furthermore, there was a gradually increasing of the use TU monographs by 2012. This suggest the on-going development of TU registration applications, particularly in view of the on-going work of the preparation of TU monographs by the HMPC and the growing experience by the pharmaceutical companies in this field. Thus, even if Directive 2004/24/EC [11] has not been in force for a sufficiently long period of time, the impact of Directive 2004/24/EC [11] on the development of TU registrations will probably continue to increase in Germany.

The development of applications for WEU marketing authorisations in accordance with Section 22 (3) AMG [18] for HMPs indicates a high relevance for gaining access to the market in Germany before 2001. Since 2001, the WEU applications decreased significantly but remained on a constant level until 2012. Thus, an on-going interest of the pharmaceutical companies in gaining access to the market for WEU marketing authorisations between 2005 and 2012 in Germany has been ascertained in this time period.

Since 2005, after Directive 2004/24/EC came into force [11], a decrease in the development of WEU marketing authorisations due to the introduction of a new type of application for simplified TU registrations in Germany might have been expected. However, no such impact of Directive 2004/24/EC [11] on the development of applications for WEU marketing authorisations has been ascertained in Germany between 2005 and 2012 so far.
The current use of WEU monographs is on a lower level than the use of TU monographs. Furthermore, only about 20% of the HMPC monographs include a WEU, currently. Thus, even if Directive 2004/24/EC [11] has not been in force for a sufficiently long period of time, the current use of WEU monographs so far does not suggest a negative influence of Directive 2004/24/EC [11] on the development of applications for WEU marketing authorisations in Germany. However, a decrease of applications for WEU marketing authorisations might be expected in Germany. Furthermore, in view of the existing nationally regulated market for WEU marketing authorisations in Germany before Directive 2004/24/EC came into force [11], a saturation of the German market can influence the further development of applications for WEU marketing authorisations in Germany.

There is a strong preference for using the NP in order to gain access to the German market before and after Directive 2004/24/EC came into force in Germany [11] which underlines the importance and the appreciation of HMPs and THMPs for the German market. This preference also reflects the uncertainty of the pharmaceutical companies with regard to submitting European procedures for placing HMPs on European markets.

Although Directive 2004/24/EC introduced the establishment of WEU and TU HMPC monographs [11] as a prerequisite for the harmonised evaluation of HMPs and THMPs in MRPs and DCPs the MRP has been used to minor extent after Directive 2004/24/EC came into force. Thus, an impact of Directive 2004/24/EC [11] on the development of MRPs cannot be clearly ascertained so far. Due to the risk of losing an already granted marketing authorisation as a consequence of a negative decision in the MRP, (especially in view of the fact that Germany in the most important market for herbal medicines of the Member States) the conclusion can be drawn that the impact of Directive 2004/24/EC [11] on the use of the MRPs will remain possibly on a low level in this field. Especially, due to the fact that the marketing authorisations which were already granted before Directive 2004/24/EC came into force, do not comply with the harmonised evaluation criteria of WEU and TU monographs established by the HMPC, the limited use of applications via MRPs seems foreseeable.

The DCP was used to greater extent for WEU applications and therefore a higher importance for Germany can be inferred. Moreover, the first DCP of a TU registration for a THMP in Germany of which Germany acts as RMS was submitted in Germany in 2012. It was discussed that special conditions, e. g. different acceptance level and traditions for herbal medicines among the Member States may influence the decision of pharmaceutical companies to submit applications via DCPs even if harmonised evaluation criteria were established at the European level. Because of the short time since harmonised evaluation criteria in form of HMPC monographs has been established, a final statement of the impact of Directive 2004/24/EC [11] on the development of DCPs also cannot be given so far. However, due to the current development of applications via DCPs, an on-going increase of the relevance of DCPs for HMPs and THMPs can be expected, even if Directive 2004/24/EC [11] has not been in force for a sufficiently long period of time.

In almost all MRPs and DCPs for herbal medicines in which Germany was involved, Germany acts as RMS. It can be concluded that due to its long- term experience in the scientific evaluation and dealing with regulatory issues regarding herbal medicines in German legislation, Germany is preferred as RMS. However, so far no impact of Directive 2004/24/EC [11] on the development in the German involvement of RMS and CMS can be ascertained. In view of the increasing experience of the pharmaceutical companies in submitting DCPs based on the on-going work of preparation of harmonised evaluation criteria in the form of HMPC monographs, a positive influence on the involvement of Germany as RMS in DCPs can be expected in Germany in the future.

In conclusion, a major impact of Directive 2004/24/EC [11] on different issues investigated was demonstrated. Especially, its impact on the relevance of the use of WEU and TU HMPC monographs and on the adaptation of TMPs already authorised in German legislation in the "revision of the old market process" with the European requirements of Directive 2004/24/EC [11] was shown. Due to the regulated national market for HMPs in German legislation before Directive 2004/24/EC [11] came into force, its positive impact will obviously continue to be supported by the long- term experience in regulatory and scientific handling of HMPs by the BfArM and pharmaceutical companies in order to achieve a harmonised market for herbal medicines on European level. However, it has to be taken into account that the process is still on-going and further impacts shall be analysed in the future.

6 Executive Summary

Directive 2004/24/EC [11] is a milestone for herbal medicines in the European pharmaceutical legislation process. The objective was to harmonise the national laws of the Member States in order to protect public health since in the past the guarantees of quality, safety and efficacy were not equally provided among the Member States [22]. That is particularly demonstrated by the establishment of the HMPC as part of the EMA having regard to the particularities of HMPs and THMPs in the European Community and the introduction of a simplified TU registration procedure for THMPs by Directive 2004/24/EC [11].

The implementation of Directive 2004/24/EC [11] by the 14th Act Amending the Drug Law of 5 September 2005 [18] has led to a particular situation for herbal medicines in Germany because a nationally regulated market for herbal medicines has already been established in German legislation since 1978 [20][21].

In this context, the impact of Directive 2004/24/EC [11] on different regulatory criteria for HMPs and THMPs in Germany was investigated (the development of WEU and TU applications, the development of the use of NPs, MRPs and DCPs, the involvement of Germany as RMS/CMS in MRPs and DCPs and the relevance of HMPC monographs). A comprehensive presentation of data research on the regulatory development of herbal medicines in Germany between 1978 and 2012 is provided. The data for this research were obtained from the Drug Information System (AMIS) database and from the evaluation of an annual questionnaire prepared by the BfArM on request of the EMA. The data provided are not fully available as such from public sources.

The high appreciation of HMPs and THMPs was demonstrated by a total of 439 applications for TU registrations in accordance with Section 39 a-d AMG and 141 (14) AMG [18] and of 358 applications for WEU marketing authorisations in accordance with Section 22 (3) AMG [18] between 2005 and 2012.
The acceptance and relevance of WEU and TU monographs established by the HMPC as an instrument for the harmonised evaluation in applications for WEU marketing authorisations and TU registrations, is an important result of Directive 2004/24/EC [11] in Germany. Out of all HMPC monographs, about 80% include a TU while about 20% include a WEU [16].

Due to the current development of TU registrations and the on-going preparation of TU monographs by the HMPC, an increase of the relevance of TU registration applications might be expected in Germany.

A further impact of Directive 2004/24/EC [11] is the adaptation of TMPs which have already been authorised in the German legislation in the "revision of the old market process" with the European requirements of Directive 2004/24/EC [11].

A strong preference for using the NP by pharmaceutical companies in order to gain access to the German market was also shown. The MRPs were used to minor extent so far while the DCPs was used to greater extent for submitting WEU applications [11]. It was further demonstrated that in all applications via DCPs for herbal medicines in which Germany was involved, Germany acted as RMS. Moreover, the first DCP of an application for a TU registration in which Germany acts as RMS is under evaluation, currently.

For the majority of criteria investigated, a final statement on the impact of Directive 2004/24/EC cannot be given so far due to the fact that Directive 2004/24/EC has not been in force for a sufficiently long period of time.
However, the current development of the individual criteria (the use of TU applications, the use of DCPs, the involvement of Germany as RMS in DCPs and the use of TU monographs) suggests increasing the impact of Directive 2004/24/EC [11] on these criteria in Germany. Due to the nationally regulated market for HMPs in Germany this impact might be supported by the long- term experience in regulatory and scientific handling of HMPs by the BfArM and pharmaceutical companies in order to achieve a harmonised market for herbal medicines on European level.

However, it will probably take at least a decade to transfer this legislation to the market situation in Germany. Thus, it has to be taken into account that the process is still on-going and further impacts shall be analysed in the future.

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Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Alexandra Kürzel