Comparison of the requirements in the registration and marketing authorisation procedure of human homoeopathic medicinal products within the EU with regard to specific requirements in Germany, Austria, the Netherlands and Switzerland as a Non-EU-country

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List of Abbreviations

AMG: Gesetz über den Verkehr mit Arzneimitteln -Arzneimittelgesetz- German Drug Act

Austr. AMG: Bundesgesetz über die Herstellung und das Inverkehrbringen von Arzneimitteln-Arzneimittelgesetz- Austrian Drug Act

BfArM: Bundesinstitut für Arzneimittel und Medizinprodukte der Bundesrepublik Deutschland – Federal Institute of Drugs and Medical Devices (of the Federal Republic of Germany)

BHP: British Homoeopathic Pharmacopoeia

BMGF: Bundesministerium für Gesundheit und Frauen (der Republik Österreich)- Federal Ministry of Health and Women (of the Republic of Austria)

BMGS: Bundesministerium für Gesundheit und Soziale Sicherung (der Bundesrepublik Deutschland)- Federal Ministry of Health and Social Security (of the Federal Republic of Germany)

CTD: Common Technical Document

GHP: German Homoeopathic Pharmacopoeia

HMG: Bundesgesetz über Arzneimittel und Medizinprodukte- Heilmittelgesetz (der Schweiz)- Federal Law on Medicinal Products and Medical Devices (of Switzerland)

Ph.Eur.: European Pharmacopoeia

Ph.F.: Pharmacopée Française

VAM: Verordnung über Arzneimittel (der Schweiz)- Ordinance on medicinal products (of Switzerland)

VAZV: Verordnung über die vereinfachte Zulassung und die Meldepflicht von Arzneimitteln (der Schweiz)- Ordinance on the simplified marketing authorisation procedure and notification procedure of medicinal products (of Switzerland)

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1 Introduction

The founder of the homoeopathic treatment was the German medical doctor Samuel Hahnemann (1755-1843) who developed this therapy about 150 years ago. His main principles are still valid. These main principles are: “Similia similibus curentur” (Like cures like), the drug study of substances on healthy human beings in order to investigate the so-called homoeopathic “drug picture” and a special manufacturing process of the medicinal products which regulates the treatment of the starting material as well as its potentisation which is a special dilution procedure.

In Germany, homoeopathic medicinal products were not recognized as complementary and alternative medicines before the year 1976. The recognition, along with phytotherapy and anthroposophy came following the second German Drug Law in 1976.

The commission D at the former Federal Institute of Health [now: Federal Institute of Drugs and Medical devices (BfArM)] was assigned with the preparation of the homoeopathic scientific documents. At the same time, work was started on an official Homoeopathic Pharmacopoeia which defines the general rules and provides detailed requirements on the quality of the substances by monographs. The Homoeopathic Pharmacopoeia is now a binding part of the German Pharmacopoeia.

In 1995, the European Pharmacopoeia was enhanced by the general monograph “Homoeopathic Preparations” (Praeparationes homoeopathicas) [1], to be followed by the monographs regarding “Herbal Drugs for Homoeopathic Preparations” [2] as well as “Mother Tinctures for Homoeopathic Preparations” [3]. Meanwhile, these general monographs have been supplemented by special monographs of several chemical and herbal substances.

Consequently, homoeopathic medicines have been established as complementary and alternative medicines in Europe, too.

This thesis aims to describe and compare the different requirements in the registration and marketing authorisation procedure of homoeopathic medicinal products in Europe as well as specific requirements in the selected countries.

Furthermore, proposals shall be made with a view to a harmonisation or rather the establishment of consistent regulations of the registration- and marketing authorisation procedures of homoeopathic medicinal products.

2 Regulatory Requirements of EU-Law concerning the Simplified Registration Procedure of Homoeopathic Medicinal Products

2.1 Definitions

The Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use [4], last amended by the Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 [5] and the Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 as regards traditional herbal medicinal products [6], defines that within the EU medicinal products may only be placed on the market prior to a marketing authorisation at the competent authority.[1]

A medicinal product is defined as any substance or combination of substances presented for treating or preventing disease in human beings.[2] Thus, homoeopathic medicinal products are subject to a marketing authorisation.

Amongst numerous others, the Community code [4] consists of the Directive 92/73/EC which determines additional regulations on homoeopathic medicinal products.

The Directive 2001/83/EC [4] also provides a definition of a homoeopathic medicinal product in its article 1 no. 5 which has been amended by the Directive 2004/27/EC [5]. Hereby a homoeopathic medicinal product is defined as "any medicinal product prepared from substances called homoeopathic stocks in accordance with a homoeopathic manufacturing procedure described by the European Pharmacopoeia, or in the absence thereof, by the pharmacopoeias currently used officially in the member states. A homoeopathic medicinal product may contain a number of principles."[3] The given definition of homoeopathic medicinal products means that mother tinctures- in contradiction to the German homoeopathic tradition- are not regarded to be active substances in homoeopathic medicinal products.

According to the provisions of the Directive 2001/83/EC [4], there are two possibilities of obtaining the marketability of a homoeopathic medicinal product:

1. Through a simplified registration procedure. Its requirements are described in the following.
2. Through a marketing authorisation procedure. Basically, the requirements are those which apply to allopathic medicinal products. In contrast to the simplified registration procedure,

[1] Art. 6 [4]
[2] Art. 1 no.2 [4]
[3] Art. 1c [5]

the clinical documents must be submitted in the marketing authorization procedure. However, the specialities of the homoeopathic treatment system shall be regarded. The requirements of the marketing authorisation procedure of homoeopathic medicinal products are described in chapter 3 of this thesis.

2.2 Common Requirements of the Simplified Registration Procedure

No. 17 of the reasons for consideration of the Directive 2001/83/EC [4] defines that "it is necessary to adopt specific provisions for immunological-, *homoeopathic medicinal products*, radiopharmaceuticals and medicinal products based on human blood or human plasma" [4]. Furthermore it is determined that the "particular characteristics of these medicinal products, such as the very low level of active principles they contain and the difficulty of applying to them the conventional statistical methods relating to clinical trials, it is desirable to provide a special, simplified registration procedure."[4] For the applicability of the simplified registration procedure, the homoeopathic medicinal products must comply with the following requirements as laid down in Chapter 2, article 14 of the Directive 2001/83/EC [4].

2.2.1 Permitted Dosage Forms in the Simplified Registration Procedure

The permissible dosage forms in the simplified registration procedure are restricted to orally or externally applied medicinal products as only in these cases can an acceptable level of safety be supposed. Therefore, the simplified registration procedure is not applicable for parenteral preparations (method 11, GHP) [7]. Also dosage forms like suppositories (method 14, GHP) [7], eye and nasal drops (methods 15,25 GHP) [7] which are commonly used in the homoeopathic therapy may not be registered.

2.2.2 Permitted Potencies in the Simplified Registration Procedure

In order to guarantee the required safety of the medicinal product, the contained potencies of the homoeopathic ingredients are restricted as described in the Directive 2001/83/EC [4]. According to its article 14 clause 1, all homoeopathic ingredients of a registered medicinal product must not be of a higher concentration than one part per ten thousand of the mother tincture. This means no ingredient must be more highly concentrated than D4. Additionally, the concentration of any ingredient which would have a prescription status when used as an allopathic medicine has to be below $1/100^{th}$ of the smallest allopathic dose.

[4] No. 21 of the reasons for consideration of [4]

2.2.3 Labelling Requirements

Registered homoeopathic medicinal products must not be marketed with indications neither on the labelling nor in any other information on the medicinal product. Brand names are permitted for registered homoeopathic medicinal products in case they are composed of two or more stocks[5].

Article 69 of the Directive 2001/83/EC [4], amended by the provisions of the Directive 2004/27/EC [5], provides precise instructions regarding the labelling of the homoeopathic medicinal product registered according to article 14. Aside from the note "Homoeopathic medicinal product" the labelling has to include the following statement: "Homoeopathic medicinal product without approved indications". The patient shall also be given a warning statement to consult a doctor in case symptoms persist.

2.3 Pharmaceutical Quality Documentation

Provided that the homoeopathic medicinal product fulfils the above mentioned requirements, the necessary documentation is reduced as described in article 15 of the Directive 2001/83/EC [4]. The common use of the substances in the homoeopathic therapy has to be proven by bibliographic documentation. Furthermore, the applicant is obliged to prove the requested quality and batch uniformity in quality documentation. Basically, the provisions of module 3 CTD shall also apply to homoeopathic medicinal products. The revised Annex 1 [8] provides in its part III "Particular medicinal products", no. 3, specific provisions that need to be taken into account regarding the terminology, control of starting material, control tests on the finished medicinal product and on the stability tests to be performed.

2.3.1 Tests on Special Impurities

For homoeopathic mother tinctures made from plant material the drugs must have been tested regarding the presence of pesticide residues according to the common monograph Ph.Eur. 2.8.13 "Pesticide residues"[9]. The difficulties of this test, especially in the case when fresh plant material has been used in the production of the mother tincture, will be pointed out under 5.1.6. Additionally, the performance of tests regarding a possible contamination with heavy metals and aflatoxins may be demanded. In special cases, the risk of a possible radioactive contamination shall be considered.[6]

[5] Art. 69 as amended in [5]
[6] all requirements laid down in [2]

2.3.2 Viral Safety

The presence of infectious agents in starting material of animal or human origin must be minimized according to the Ph.Eur.-monograph "Homoeopathic Preparations" [1]. The applicant is obliged to prove the absence of pathogenic agents by detailed documentation that does not only include the evidence of origin and the production of the animal starting material, but also a detailed documentation of the manufacturing procedure. A risk limitation may be achieved through the manufacturing process and, if possible, through the exclusive use of animals and tissues which comply with the requirements of the law relating to food processing and distribution on animals that are intended for human consumption.

The donors of material of human origin must comply with the guidelines for blood donors and donated blood.

Starting material of animal origin must comply, if applicable, with the requirements of the common monograph "Products with the risk of transmitting agents of Animal Spongiform Encephalopathies" [10], the production has to be performed according to the requirements of the common Ph.Eur. monograph 5.2.8 "Minimising risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products" [11].

2.4 Pharmacological-Toxicological Documentation

The information on module 4 defined in the revised Annex I is also applicable in the simplified registration procedure.[7] Thus, the applicant is generally obliged to present documents regarding the pharmacological-toxicological properties of the homoeopathic medicinal product. In case this information is lacking, the applicant shall give an explanation and substantiate why an acceptable level of safety may be assumed.

2.5 Time for Assessment

Article 14 clause 2 of the Directive 2001/83/EC [4] determines that the duration of the registration procedure shall be the same as for marketing authorisation procedures- namely 210 days.

[7] Art. 14 clause 1 [8]

2.6 Validity of a Simplified Registration

As it applies to authorisations, the granted registration shall also be valid for five years if the registration holder does not submit an application of renewal at least six months before the ending of this five-years-period.[8]

2.7 Discussion

Compared with the marketing authorisation procedure, the registration procedure is a simplified procedure for obtaining the marketability of the product. Apart from this, it should be considered if the common restriction to D4 or higher dilutions, irrespective of the substance, makes sense. This regulation could possibly be replaced by a system which evaluates the toxicological potential of each substance and defines the permissible safe potency level. This system would have the advantage that the registration procedure would become applicable for numerous homoeopathic medicinal products containing low potencies that currently require a marketing authorisation procedure. Especially homoeopathic preparations which are traditionally used in low potencies like Crataegus or Echinacea and are related to a low toxicological potential should become applicable in a registration procedure. Additionally, once the permissible potencies for the substances in the registration procedure are defined, this system would be a relief for the authority as the documentation to be assessed in registration procedures is less extensive compared to those in marketing authorisation procedures. For the pharmaceutical manufacturers a single case assessment of the toxicological potential of substances would mean that the registration procedure could be performed in more cases and fees could be saved as the fees to be paid in registration procedures are in general lower than those in marketing authorisation procedures.

[8] Art. 24 clause 1 [4]

3 Regulatory Requirements of EU-law concerning the Marketing Authorisation Procedure of Homoeopathic Medicinal Products

3.1 Common Requirements

Revised Article 16 of the Community code defines that homoeopathic medicinal products that do not fulfil the requirements described in article 14 clause 1 or that are intended to be marketed with therapeutic indications or in dosage forms that are regarded to be related to potential risks- such as parenteral preparations- must be authorized and labelled according to the provisions of the articles 8, 10, 10 a-c and 11 [5]. The common requirements of the marketing authorisation procedure also apply to homoeopathic medicines. The homoeopathic ingredients are not restricted to certain potencies, meaning that all different homoeopathic substances in all different potencies may be authorized, provided they are manufactured according to a homoeopathic manufacturing process as defined by the official pharmacopoeias. It has not yet been clarified whether a mother tincture is also regarded as a homoeopathic preparation. Contrary to the definition of a homoeopathic medicinal product provided by the Directive 2004/27/EC[9], this is the point of view in Germany. In France, only dilutions, made from "souche" (= mother tincture), are considered to be homoeopathic preparations. The differences in the production and the traditional use are described under chapter 5.2.6.

3.2 Clinical Documentation

Aside from the documents on quality and safety, documents regarding the clinical properties (module 5 CTD) of the homoeopathic medicinal product must be submitted to the authority. Basically, the common requirements of the Directive 2001/83/EC [4] apply as defined in article 8. As the quality and safety of the product are concerned, the requirements are the same as in the simplified registration procedure. Annex 1 provides simplifications in its part II "Specific marketing authorisation dossiers and requirements" for well- established medicines [4]. Instead of own investigations bibliographic scientific documents may be used. The common use of the substance as a medicinal product must be documented at least for a period of ten years. The documentation has to be presented as described in Annex 1 [4,8]. All aspects necessary for the assessment of safety and efficacy must be covered by the documentation. The applicant is obliged to give a precise explanation on the reasons why an acceptable level of safety and efficacy may be assumed even though trials are lacking.

[9] Art. 1c [5]

Pursuant to the provisions of article 16 clause 2 of the Directive 2001/83/EC [4] member states with a long homoeopathic tradition may adopt specific rules for the assessment of results obtained from safety and efficacy tests. In these cases, the respective member states are obliged to inform the European commission thereof. The regulations of title IX "Pharmacovigilance" [4] apply to authorized medicinal products, but not to registered medicinal products.

3.3 Time for Assessment

The same legal respites apply as described for simplified registered medicinal products (chapter 2.5).

3.4 Validity of a granted Marketing Authorisation

The same applies as described in chapter 2.6. Once renewed, an approval shall be valid indefinitely.[10]

3.5 Discussion

The applying regulations of EU-law provide simplifications concerning the clinical documentation of homoeopathic medicinal products. However, the question is not yet answered whether a mother tincture is regarded as a homoeopathic preparation.

Pursuant to article 39 of the Directive 2001/83/EC [4], the mutual recognition procedure is not applicable for homoeopathic medicinal products. This should be changed at least for known homoeopathic substances as soon as the regulations of the countries are harmonized with view to the clinical documentation. The special characteristics of the homoeopathic treatment have to be considered. How this may be achieved, show the criteria on the assessment of scientific material published by the commission D at the German BfArM. These are described in detail in chapter 6.1.2. As outlined in chapter 6.4.2 the Swiss authority has also formulated detailed requirements on what clinical tests are to be performed on homoeopathic medicinal products. These depend on the number of homoeopathic ingredients (single or complex homoeopathic medicinal products) and take account of the special characteristics of homoeopathic medicinal products.

[10] revised Art. 24 [5]

4 Tabular Overview

Table 1: Comparison of the requirements in the simplified registration procedure and the marketing authorisation procedure as defined by applying EU-Directives [4, 8]

	Simplified registration procedure	Marketing authorisation procedure
Permitted dosage forms	**Restricted**: Orally and externally applied homoeopathic medicinal products only	**No restrictions**
Labelling/therapeutic indications	Homoeopathic character of the product to be outlined; Warning statement to seek doctor's advice required; Brand name only accepted for products derived from two or more stocks **Therapeutic indications not permitted**	Homoeopathic character to be outlined; Warning statement required; Brand name accepted (no special provisions) **Therapeutic indications permitted**
Permitted potencies of homoeopathic ingredients	**Restricted**: General "D4 and higher" rule applies to all homoeopathic ingredients; For those substances that are prescription drugs when used as an allopathic medicine, the acceptable concentration must be below 1/100th of the smallest allopathic dose that is subject to doctor´s prescription	**No restrictions, all dilutions are applicable**
Quality documentation	Required General provisions of module 3 CTD shall apply; several modifications thereof as defined in revised Annex 1 to be taken into account	Same requirements as defined for registration procedure
Pharmacological-toxicological documentation	Required, general provisions of module 4 CTD shall apply Missing information to be justified	Required, see "registration procedure"
Clinical documentation	Not required	**Required**, general provisions of module 5 CTD shall apply

5 National Regulatory Requirements concerning Simplified Registration Procedures in selected EU-Member States and Switzerland

5.1 Registration Procedure of Homoeopathic Medicinal Products in Germany

5.1.1 Common Requirements

The requirements of the simplified registration procedure are defined in the 5th chapter of the German Drug Act in its articles 38 and 39 [12]. Details can be found in the "Verordnung über homöopathische Arzneimittel vom 15.03.1978" (Ordinance on homoeopathic medicinal products) [13] which is in accordance with § 39 clause 3 AMG. This ordinance provides the obligation of notifications, the premises in which cases a new registration has to be obtained as well as the prerequisites of a cancellation and the renewal of a registration.

Only finished homoeopathic medicinal products as defined in § 2 clause 1 or clause 2 no.1 AMG [12] may be registered. Pursuant to § 39 clause 2 AMG [12], the competent authority shall grant the registration unless one of the reasons for a refusal as defined in § 39 AMG [12] applies. In principle, the applicant has to submit the documents required in the marketing authorisation procedure as defined in §§ 22 till 24 AMG [12]. In compliance with EU-law, registered homoeopathic medicinal products must not be marketed with indications, consequently the documentation does not consist of any information regarding the efficacy or indications of the medicinal product.

The pharmacological-toxicological and the clinical documentation as well as their expert reports need not be submitted to the authority in the German simplified registration procedure. As the pharmacological-toxicological documentation is concerned, this general exemption is not compliant with the provisions of the revised Annex 1 [8]. Accordingly, these documents may only be omitted in case the applicant provides a sufficient explanation why an acceptable level of safety may be assumed without presenting test results. An acceptable level of safety may for example be assumed in case the homoeopathic ingredients are diluted to high dilution grades. However, pursuant to EU-law the applicant is obliged to provide an explanation.

The authority shall refuse the registration in case "there is a good reason to suspect that, if used in keeping with its designated purpose, the medicinal product has harmful effects which exceed the bounds considered justifiable in the light of knowledge available to medical science."[11] Meanwhile, the German BMGS has issued a new version of the "Bekanntmachung

[11] § 39 clause 2 no. 2 AMG [12]

der Neufassung der Allgemeinen Verwaltungsvorschrift zur Anwendung der Arzneimittelprüfrichtlinien vom 05.05.1995" (Medicinal product testing directives) [14], accordingly a specific pharmacological- toxicological document may only be lacking in case the acceptable level of safety is proven. When the German Drug Act is revised, this will form the legal basis for the revised "Arzneimittelprüfrichtlinien" [15]. There exists since October, 2004, a consultancy document for revision of the German Drug Act. The requirements of EU-law, that is to say the revised Annex 1 [8] will then be implemented into German national law.

In line with the definition of a homoeopathic medicinal product as given by the Directive 2004/27/EC [5], homoeopathic medicinal products containing more than one active principle may also be registered. Contrary to EU- law, the use of brand names is in Germany also permitted for homoeopathic medicinal products containing only a single principle. The trade name used must not stipulate any indication of the medicinal product.

The competent authority may refuse an application for registration only due to the reasons defined by § 39 clause 2 AMG [12]. Some of them are specific to the German registration procedure. In the following a few essential reasons for a refusal shall be outlined.

5.1.1.1 Limitation of Acceptable Dosage Forms

The EU-requirements as specified in article 14 of the Directive 2001/83/EC [4] are implemented into § 39 clause 2 no. 5a AMG [12], whereas the registration shall be refused if the medicinal product is not intended for oral or external use. Therefore, other dosage forms of the GHP like parenteral preparations are subject to a marketing authorisation procedure.

5.1.1.2 Permitted Potencies

Also in conformity with EU- law is the demand that only non- prescription homoeopathic medicinal products may be registered. All substances or combinations of substances may be registered irrespective of the contained potency, meaning that also mother tinctures are applicable in the German registration procedure which is a deviation from EU-law. This is to say that in the German registration procedure permitted dilutions are not, as defined by EU-law, restricted to potencies "D4 and higher". The so-called "D4-rule" applies in Germany only in the case of prescription drugs which are listed according to the "Verordnung über verschreibungspflichtige Arzneimittel in der Fassung der Bekanntmachung vom 30.08.1990 mit ihren Änderungsverordnungen" (Ordinance on Prescription Drugs) [16]. This list is currently being changed by decisions of an expert committee on prescription drugs.

Additionally, the substances used in the homoeopathic therapy are subject to a single case assessment through votes of the commission D at the BfArM. § 25 clause 7 AMG [12] defines that the competent authority shall establish expert committees on non-prescription medicinal products of the several therapies. The task of the commission D is, amongst others, to assess the safety and efficacy of homoeopathic substances. The commission D in its function as an authorisation commission must also be consulted in case of a possible refusal of a registration.

5.1.1.3 Labelling Requirements

The naming of indications is not allowed for registered homoeopathic medicinal products[12], neither on the label nor in the package information leaflet nor in any other information related to the medicinal product. As aforementioned, the brand name, if used, must not include an indication. Registered homoeopathic medicinal products have to carry the notice "Homoeopathic medicinal product"[13] close to the designation on the label and in the package information leaflet. Instead of indications, the registration holder is obliged to provide the information "Registered homoeopathic medicinal product, and therefore without declaration of a therapeutic indication."[14] It is furthermore obligatory to inform the patient of the necessity of consulting a doctor by the notice "In case symptoms persist, seek doctor´s advice."[15] With regard to this, EU-law concerning the labelling of registered homoeopathic medicinal products is implemented in German national law.

5.1.2 Pharmaceutical Quality Documentation

According to § 39 clause 2 no. 2 and 3 AMG [12], the homoeopathic medicinal product must have undergone adequate analytical tests and must be of a sufficient quality. Therefore, the applicant is obliged to submit documents regarding the analytical tests that have been performed as well as the proof of adequate quality. The provisions of the "Allgemeine Verwaltungsvorschrift zur Registrierung homöopathischer Arzneimittel vom 18.12.1992" (Ordinance on the registration of homoeopathic medicinal products) [17] set out the requirements for the analytical tests of registered homoeopathic medicinal products. These will be no longer valid in the near future. As outlined above the new version of the "Arzneimittelprüfrichtlinien" [15], which implements the revised Annex 1 of the Directive

[12] §§ 10 clause 4 s.3, 11 clause 3 s.2 AMG [12]
[13] § 10 clause 4 s.1 AMG [12]
[14] § 10 clause 4 s.4 AMG [12]
[15] §§ 10 clause 4, 11 clause 3 AMG [12]

2001/83/EC [8] will apply. The named ordinance on the registration of homoeopathic medicinal products will then only apply to veterinary homoeopathic medicinal products.
The complexity of the analytical tests on the substances is due to the respective monographs of the GHP. A GHP-monograph consists of two parts. The first part determines the quality of the starting material through a detailed description and tests of specific identity and purity, e.g. mineral material is characterized by a detailed description of the crystal structure and its hardness. Identity and purity tests as well as at least one determination of content are obligatory. In the case of herbal starting material, a macroscopic description has to be conducted, for drugs an additional microscopic description is required. Besides purity tests the monograph is supplemented with test-tube-reactions which have to be specific, and with thin-layer-chromatography. For chemically defined starting material a determination of content must always be performed, while in the case of herbal-based material this is necessary only if toxic ingredients are present or when the content determination is required for the assurance of the sufficient quality of the starting material. The second part of a GHP-monograph describes the dosage forms by a master formula. Tests need only be performed on the lowest possible potency. The GHP does not include any provisions regarding the tests of further dilutions. In case a substance is not described in the GHP, the applicant is required to issue its own monograph that should be comparable to a GHP-monograph with regard to its structure and demands. In addition, control tests are to be carried out on the bulk material and the finished medicinal product according to the provisions of the above mentioned “Allgemeine Verwaltungsvorschrift zur Registrierung homöopathischer Arzneimittel” [17] . The control tests must in every case comprise of tests that are specific for each of the forms of administration. For complex homoeopathic medicinal products, several facilitations are possible that are due to the technical limitations in the performance of the analytical methods. Only in exceptional cases the quality of the medicinal product may be proven through a consistent documentation of the manufacturing process.

5.1.2.1 Stability Tests

Basically the provisions of the “Allgemeine Verwaltungsvorschrift zur Registrierung homöopathischer Arzneimittel” [17] apply to determining product stability. These determine that a homoeopathic medicinal product is stable as long as the requirements of the GHP-monograph are fulfilled. The mentioned ordinance which is also applicable for combinational products assumes for higher potencies a stability of five years assuming that interactions can be excluded. This regulation will probably not remain in the future. It is planned to be

changed in the way that the stability of the potentised dilutions are assumed to be dependant on the stability of the mother tincture and on the stability of the lowest possible dilution. As far as the stability tests on the finished medicinal products are concerned, the "Allgemeine Verwaltungsvorschrift zur Registrierung homöopathischer Arzneimittel" [17] only provides the regulation that the tests have to include the common and specific characteristics of the dosage form. The tests ought to be performed according to the requirements of the "Note for Guidance on Stability Testing: Stability Testing of existing active substances and related finished products" taking account of the homoeopathic character of the medicinal products as stated in a Guideline published by the BfArM [18]. The applicant is obliged to present the results of the stability tests on at least two pilot scale-or production scale-batches. The test schedule has to include testing of the fulfilment of the test requirements every three months during the first year, every six months within the second year and once yearly during the following years. As far as the storage conditions (temperature, relative humidity) are concerned, the provisions of the mentioned Note for Guidance as stated in the Guideline [18] are applicable. The test parameters depend on the composition of the homoeopathic medicinal product. In any case, the medicinal product must comply with the common attributes of the dosage form. In case the homoeopathic medicinal product consists of mother tinctures or other low potencies, additional tests and, if applicable, a determination of content has to be performed. For homoeopathic medicinal products that do not contain mother tinctures or low potencies, the obligatory tests depend on the contained potencies. If only higher potencies are contained, it is sufficient to test the compliance with the common attributes of the dosage form, provided that interactions can be excluded. This is in line with the provisions of the "Allgemeine Verwaltungsvorschrift zur Registrierung homöopathischer Arzneimittel" [17].

5.1.2.2 Tests on Special Impurities

According to the „Allgemeine Verwaltungsvorschrift zur Registrierung homöopathischer Arzneimittel" [17], the applicant is required to provide information on a possible contamination of the homoeopathic medicinal product with special impurities, such as pesticides, residual solvents, aflatoxins, ethylene oxide and heavy metals. Whereas just a few years ago the written confirmation of the applicant regarding the compliance with the regulations was regarded sufficient, the applicant is now obliged to provide proof by the presentation of test results performed on two batches of the homoeopathic medicinal product. Additionally, the proof is required of how the requirements are met for every batch.

In the case of heavy metals, it is not sufficient to perform the test according to the Ph.Eur.-monograph 2.4.8 [19], but it is obligatory to prove the compliance with certain limits for lead (5mg/kg), cadmium (0,2mg/kg) and mercury (0,1mg/kg) as defined by the "Bekanntmachung von Empfehlungen für Höchstmengen an Schwermetallen bei Arzneimitteln pflanzlicher und tierischer Herkunft- Arzneimittelkontaminanten- Empfehlung Schwermetalle" (Recommendation concerning heavy metal residues in medicinal products) [20].
Every batch of herbal starting material must comply with the "Aflatoxin-Verbots-Verordnung" (Ordinance on prohibition of a possible contamination with aflatoxins) [21] and the monograph "Pesticide residues" [9] of the European Pharmacopoeia. Test results of two batches have to be submitted.
With view to the required tests of heavy metal residues and aflatoxins, the German requirements are higher than forseen in the monograph "Herbal Preparations" of the Ph.Eur [2], whereas the tests are only to be performed in special cases.

5.1.2.3 Viral Safety

The requirements in Germany are the same as described under 2.3.2.

5.1.3 German-Specific Requirements

5.1.3.1 Exemptions from the Obligation to Register

5.1.3.1.1 Standard Registrations

In accordance with the provisions of the "Verordnung über die Freistellung homöopathischer Arzneimittel von der Registrierung (Verordnung über Standardregistrierungen) vom 03.12.1982" (Ordinance on standard registrations) [23], homoeopathic medicinal products are exempted from the obligation to register if certain requirements are met as outlined in the following. The homoeopathic ingredient must be described in a GHP- monograph and must comply with the requirements defined in the monograph. Apart from this, the ingredient must be listed in the Annexes of the named ordinance and the medicinal product must not be authorized. The requirements of the standard registration mainly apply to medicinal products with only one active ingredient.

5.1.3.1.2 Extended Dispensing

A very specific regulation in Germany is the so- called "extended dispensing" according to § 38 clause 1 s.3 AMG [12]. Accordingly, the pharmaceutical manufacturer is not obliged to obtain a registration provided that not more than 1000 packages of the homoeopathic medicinal product are placed on the market annually. For the applicability of this exemption

from the obligation to register, the homoeopathic medicinal product has to meet several conditions as described. The homoeopathic medicinal product has to be in line with all the requirements in the registration procedure, meaning that no reason for a refusal pursuant to § 39 clause 2 no. 2- 7a [12] applies. Moreover, the medicinal product must not contain any active substances derived from animals, microorganisms including viruses or metabolic products.[16] Furthermore, in line with EU- law, the medicinal product must not consist of more than 1/100 of the smallest doses of substances, which are in allopathic medicines subject to a doctor´s prescription.[17]

5.1.3.2 Degree of Common Knowledge

A further important requirement in the simplified registration procedure is that the use of the medicinal product has to be commonly known in the homoeopathic therapy. This applies when the medicinal product is described in the scientific homoeopathic literature and has been placed on the market before 1978.[18,19] For homoeopathic combinational products this rule becomes relevant, as in the view of the German authority, it is not regarded sufficient that each of the single homoeopathic ingredients are commonly known, but that the combination itself must be commonly known. The German authority states the view that only for medicinal products that have been on the market for a long time with a particular composition, dosage form and means of application, it is possible to assign a reasonable therapeutic use without claiming an indication. However, the legality of this German- specific rule is questionable. *Sander* considers this rule to be an infringement of EU-law as the EU-law does not provide any corresponding regulation. Thus he is of the opinion that an application for registration may not be rejected due to the lack of evidence of being commonly known.[20] *Rehmann* comes to the same conclusion with a different explanation: the proof of efficacy is difficult for homoeopathic medicines and concurrently the toxicological potential is negligible. If the simplified registration procedure is not applicable pursuant to § 39 clause 2 no. 7a AMG [12] and it is not possible to obtain a marketing authorisation due to failure of the proof of the efficacy this leads to a prohibition of marketing and, hence not in conformity with constitutional law.[21]

[16] § 38 clause 1 no. 1 AMG [12]
[17] § 38 clause 1 no. 2 AMG [12]
[18] Erl. §39 Nr. 10a [24]
[19] Erl. §39 Rdnr. 12 [25]
[20] Erl. § 39 Nr. 10a [24]
[21] Erl. § 39 Rdnr. 12 [25]

5.1.3.3 Posology

The commission D at the BfArM edited dosage instructions for homoeopathic medicinal products which were amended and extended by a new version of March 17th, 2004 [26]. These dosage instructions shall be binding in both a registration procedure and a marketing authorisation procedure if no preparation-specific documentation is submitted. Acceptable as preparation- specific documentation are clinical trial data that provide evidence for the superiority of the specific dosage instructions against the common dosage instructions issued by the commission D. The defaults of the dosage guideline are applicable for the adult patient. It differentiates between dosage instructions that apply to mother tinctures and low potencies (meaning potencies up to a D23) and medicinal products containing high potencies. A third part regulates the posology of LM- and Q-potencies.

These dosage instructions might not be in line with the requirements of article 14 of the Directive 2001/83/EC [4] due to the fact that the safety of a registered medicinal product is assumed by the acceptance of dilutions potentised at least up to a D4. Pursuant to EU-law, no other restrictions regarding the posology can be found. The applicant may select freely.

5.1.4 Time for Assessment

The German Dug Act does not provide a regulation regarding the legal respite, in which the authority is obliged to grant the registration. Nevertheless it may be assumed pursuant to the articles 28 clause 4, 27 AMG [12]- in compliance with article 14 clause 2 of the Directive 2001/83/EC [4] that a registration shall be granted within a period of seven months as it is obligatory for marketing authorisations.[22] In fact, this time-frame has rarely been met.

5.1.5 Validity of a Granted Registration

Provided a homoeopathic medicinal product complies with the requirements, i.e. no reason for refusal pursuant to § 39 clause 2 AMG [12] applies, the registration is to be granted. A registration is valid for a period of five years unless an application of renewal is submitted to the competent authority six to three months before the five-years-period expires. According to § 77 and § 28 AMG [12], the federal higher authority may grant the registration with additional conditions.

[22] Erl. § 39 AMG C, p.5 [24]

5.1.6 Discussion

The registration procedure consists of several national specific requirements. Compared to EU-law, some of them are facilitations and some are obstacles. The aforementioned extended dispensing facilitates the marketing of low quantities of a homoeopathic medicinal product, provided the requirements as defined in § 38 AMG [12] are met. In these cases, the marketing is permitted without having obtained a registration. Another facilitation is the possibility to make use of the above mentioned standard registration. In this case, the homoeopathic medicinal product may also be marketed without the obligation to have it registered at the competent authority.

An obstacle is the demand of § 39 clause 2 no. 7a AMG [12] that the medicinal product ought to be commonly known which leads to the fact that the simplified registration procedure is not applicable for numerous medicinal products, especially homoeopathic combinational products. In particular an enhancement of the homoeopathic therapy through the implementation of new active substances is not possible in the registration procedure. In these cases the pharmaceutical manufacturer has to apply for a marketing authorisation. The marketing authorisation procedure is in general more time-and money-consuming than a registration procedure.

It is worth discussing the required test on pesticide residues. The European Pharmacopoeia provides, in its monograph “Pesticide residues” [9], the test limits applicable for herbal drugs. If the test is performed on extracts, tinctures or other pharmaceutical forms, the named test limits of the Ph.Eur.- monograph ought to be adapted by using an extraction factor that has to be determined experimentally. For homoeopathic medicinal products the tests may be performed on the lowest possible potency.[23] In the manufacture of herbal extracts which results in a concentration of the starting material an enrichment of pesticides depending on the extracting agent might occur so that the determination of an extraction factor seems to be appropriate. However, this matter is different for homoeopathic mother tinctures: mother tinctures manufactured according to the GHP-methods 1 or 2 have a plant material- mother tincture ratio of 1:2, for method 3- mother tinctures the ratio is 1:3. In contrast to herbal extracts, a dilution and not a concentration of plant material takes place. Therefore it would certainly seem appropriate to permit the performance of the tests on the mother tinctures without demanding the extraction factor.

[23] Rdnr. 599 [22]

Mother tinctures that are manufactured according to method 4, GHP, are made from dried herbal material and, therefore, the test can be easily performed on the herbal material, while in the manufacture of mother tinctures according to the methods 1, 2 or 3 GHP fresh plant material is used. Fresh plant material has to be used up immediately after harvest, so in case it is of non- European origin, the pharmaceutical manufacturer based in Europe does not get the possibility to perform the tests. Furthermore the constituent potency of the substance in the finished medicinal product should be taken into account, for potencies greater than D6 a possible pesticide load is negligible.

Additionally, the authority may make an exception to the obligation to perform the mentioned tests if the mode of treatment with pesticides (type of pesticides, time of use during the cultivation and after the harvest) is known for every batch and an exact verification is possible. This applies, in particular, to proved organic cultivation.

5.2 Notification Procedure of Homoeopathic Medicinal Products in Austria

5.2.1 Common Requirements

§ 11 clause 2a austr. AMG [27] regulates that homoeopathic medicinal products are not subject to a marketing authorisation procedure if they exclusively consist of active ingredients that are described in the homoeopathic part of a pharmacopoeia of an EU- member state and manufactured according to a homoeopathic master formula. In these cases, a simplified notification pursuant to § 11 clause 2a austr. AMG [27] is sufficient.

First of all, the applicant has to be qualified in the notification procedure. According to § 14 clause 3 austr. AMG [27] a pharmaceutical manufacturer is a qualified person when he is based in a member state of the European Union and is, within this member state, allowed to place the medicinal product on the market. The proof of being qualified as an applicant is part of the documents to be submitted to the authority. In case the applicant holds a registration or marketing authorisation in another member state for the concerned medicinal product, this becomes binding part of the notification documents.[24]

In compliance with the EU- requirements as regards the simplified procedure, the permitted dosage forms in the notification procedure are reduced to orally or externally applied homoeopathic medicinal products. Therapeutical indications in the naming, labelling or in the package information leaflet are also not possible for a notified medicinal product according to § 11 clause 2a austr. AMG [27]. An important requirement in the notification procedure is the

[24] §16 a clause 1 no. 2 austr. AMG [27]

limitation of the permitted substances and potencies. § 11 clause 2a no. 4 austr. AMG [27] authorises the Federal Minister of Health to accept an ordinance that defines the potencies that are of an acceptable safety level, without being subject to a single case evaluation and, therefore, are applicable in the notification procedure according to § 11 clause 2a austr. AMG [27]. The permitted substances and their lowest admissible potencies are listed in two annexes of the "Verordnung des Bundesministers für Gesundheit, Sport und Konsumentenschutz betreffend anmeldepflichtige homöopathische Arzneispezialitäten" (Ordinance of the Federal Minister of Health, Sports and Consumer Care regarding notifiable homoeopathic medicinal products) [28]. Annex 1 consists of substances described in monographs of the GHP. Annex 2 lists substances described in the homoeopathic part of the Ph.F. Depending on the supposed toxicological potential, the acceptable potencies in the notification procedure are either low or medium potencies (in the range of D2 to D4), in case of chemical or mineral substances of the GHP potencies above D6 are allowed.

Furthermore, it is important in terms of the applicability of the notification procedure, that the manufacture of the Annex 1-substances is performed according to the methods of the GHP, while Annex 2- substances have to be manufactured according to the methods of the Ph.F.

In addition to single homoeopathic medicinal products, also combinational products are eligible for notification. The allowed potencies relate to their final concentration in the medicinal product. A restriction with regard to the choice of possible ingredients is that the applicant may only choose substances from one of the two annexes, meaning that it is only acceptable to specify with reference to one of the pharmacopoeias, either GHP or Ph.F. However, it is interesting that in case of fresh plant material is used as starting material for one homoeopathic ingredient, both annexes permit the same potency, even though the manufacturing methods of the pharmacopoeias are differing. This results in different concentrations of herbal material in the manufactured dilutions as will be demonstrated in chapter 5.2.6.

5.2.2 Labelling Requirements

In line with EU-law, the notified homoeopathic medicinal product must have the statement "Homoeopathic medicinal product without approved therapeutic indications" on the labelling and in the package information leaflet if it exists. Brand names are accepted; however the name of the medicinal product must not stipulate any indication. The patient has to be given the notice to seek doctor´s advice in case symptoms persist.

5.2.3 Pharmaceutical Quality Documentation

The required documents in the notification procedure are defined in § 16a austr. AMG and substantiated in § 15 austr. AMG [27]. The applicant is obliged to prove the quality of the medicinal product. The active ingredients must be adequately tested. The submission of the monographs of the homoeopathic pharmacopoeias is regarded sufficient for this proof. The same applies to the excipients being used; in this case a specification of the manufacturer is also regarded to be acceptable. Furthermore, the applicant is obliged to provide information on the manufacturing process and the performance of control tests during the manufacture of the medicinal product. The desired running time has to be documented with the results of the stability tests. The homoeopathic character of the contained substances must be demonstrated by appropriate homoeopathic literature which is part of the notification documents.

5.2.3.1 Tests on Special Impurities

Neither the results of tests on special impurities nor a written confirmation on the compliance with the regulations have been required so far. At the moment, the pharmaceutical manufacturer is only obliged to confirm the compliance with the requirements of the GHP or the Ph.F.

5.2.3.2 Viral Safety

No documentation has been required so far.

5.2.4 Time for Assessment

After the submission and verification of the documents by the BMGF, the homoeopathic medicinal product is entered with a given registration number into the register of proprietary medicinal products pursuant to § 27 austr. AMG [27]. A legal respite for the authority is not defined, but the granting of a registration should be possible within the seven-months-period which is defined for the granting of marketing authorisation applications.

5.2.5 Validity of Notifications

Very specific in the notification and registration process in Austria is that once the homoeopathic medicinal product is notified and registered according to §§ 11 clause 2a and 27 austr. AMG [27], the registration is of an unlimited validity. Nevertheless variations and withdrawals of granted registrations have to be recorded in the register.[25] The registration

[25] § 27 clause 2 austr. AMG [27]

holder is obliged to inform the BMGF of every variation regarding the registered homoeopathic medicinal product.[26] This obligation does not include changes in the designation of the product or in the content of the homoeopathic medicinal product. These cases require a complete new notification and registration procedure.

5.2.6 Discussion

In compliance with the requirements of the Directive 2001/83/EC [4] as concerns the simplified procedure, the acceptable dosage forms in the notification procedure are restricted to orally or externally applied medicinal products. The "D4-rule" of EU-law which generally applies to all homoeopathic substances, has not been transformed into Austrian law yet. In fact, as noted above, the permissible substances and its potencies are defined in two positive lists. Consequently, the permissible substances in the notification procedure are restricted by law.

In case of homoeopathic dilutions manufactured from fresh plant material both annexes permit the same potency not considering the fact that the respective manufacturing methods differ. This results in different concentrations of herbal material in the homoeopathic dilutions as to be shown in the following.

In the manufacture of mother tinctures, according to the specification of "Preparations homeopathiques" of the Ph.F. [29], the dry residue of the herbal material has to be determined and from this, the water free fraction of the plant must be calculated. If, for example, the averaged dry residue is 60 %, 100 kg fresh plant material consists of 60 kg water. Consequently, the water free part is 40 kg. According to the rules of the Ph.F., the plant material is spiked with the 10- fold amount of ethanol of a certain concentration, in this case with 400 kg ethanol. Provided the same plant material is used in the manufacture of a mother tincture according to the rules of the GHP [7], only 60 kg (method 2a) and 120 kg respectively (method 3a) of ethanol would be added. This means that only 1/6 and 1/3 respectively of the ethanol amount pursuant to the rules of the Ph.F. would be added.

Furthermore there are differences between the two pharmacopoeias in the manufacture of the first dilution. In compliance with the rules of the Ph.F., the mother tincture is diluted in the ratio 1:10, whilst the first potency subject to method 2a, GHP, is obtained through a dilution in the ratio 2:10, for the first dilution manufactured according to method 3a, the ratio is 3:10.

It is obvious that the differences in the manufacture result in great differences in the concentration of the herbal material in the dilutions which are not considered in the named

[26] § 24 clause 9 austr. AMG [27]

ordinance. This issue also applies to the simplified registration procedure as described in the Directive 2001/83/EC [4] and causes difficulties in the attempt to harmonise monographs of fresh herbal material for homoeopathic preparations to be incorporated in the Ph.Eur.

In contrast to the general "D4-rule" of EU-law, also lower potencies are applicable in the notification process in Austria provided the substance is listed in one of the annexes of the named ordinance. The notification procedure may be performed relatively fast and is cost-saving. The required documentation is little and the maintenance of registrations is easy as they do not need to be renewed. Only variations have to be recorded to the BMGF by taking account of the rules defined in § 24 clause 9 austr. AMG [27].

5.3 Registration procedure of Homoeopathic Medicinal Products in the Netherlands

5.3.1 Common Requirements

The requirements given by EU-law as regards the registration procedure of homoeopathic medicinal products are implemented into the Dutch Drug Act, and especially article 4 of the "Besluit houdende wijzging homeopathische farmaceutische producten dd. 12.12.1995" (Ordinance on homoeopathic medicinal products) [30] applies. In line with the named requirements of the Directive 2001/83/EC [4], the permissible dosage forms in the Dutch registration procedure are restricted to orally and externally applied medicinal products. Terming of an indication is neither allowed in the labelling nor in the package information leaflet or any other information on the product. As concerns the acceptable potencies in the simplified registration procedure, the requirement of the EU-law applies, that irrespective of the substance, all substances must be diluted at least to a ratio of 1:10.000. Regarding the documentation to be submitted to the authority, the applicant has to prove the adequate quality and safety of the homoeopathic medicinal product which is also required by the Directive 2001/83/EC [4,8].

Very specific in the registration process of homoeopathic medicinal products in the Netherlands is the dossier format. So far a Notice to Applicants [31], specific to homoeopathic medicinal products ought to be used. The competent authority planned to replace this dossier format by a Common Technical Document for homoeopathic medicinal products by January 2005, however still only module 1 is available.[27]

[27] as reflected on http://www.cbg-meb.nl/nl/docs/hpathica/homeo-ia.pdf on January,22,2005

5.3.2 Labelling Requirements

In compliance with the requirements of the Directive 2001/83/EC [4], regarding the labelling, the homoeopathic character of the medicinal product has to be outlined. Indications must not be named.[28]

5.3.3 Pharmaceutical Quality and Pharmacological-Toxicological Documentation

Especially compared with the requirements of the notification procedure in Austria, it is obvious that these are a lot tighter in the Netherlands.[29] In the control of the starting material, information has to be given and tests performed on the raw material, the mother tinctures and the dilutions being used. As concerns the raw material information regarding the supplier, the origin and the manufacture is necessary. Furthermore information on impurities and degradation products within the manufacturing- and cleaning- process is required, the results of a batch control must be presented. The described information must not only be provided for the homoeopathic mother tinctures, but also for the contained dilutions of the finished medicinal product. Compared with the requirements of the other described countries regarding the analytical tests the requirements in the Netherlands are high, e.g. it is required to perform the tests on impurities on the dilutions, too. Apart from the test on the common attributes of the finished medicinal product, a qualitative and quantitative determination of the active ingredients up to dilution grades D3 and D4 respectively (depending on the substance) have to be performed. This is, especially in the case of combinational products, rarely possible. However, the authority also accepts semi-quantitative thin-layer chromatography. Nevertheless the sense of such tests should be discussed as a validation is hardly possible.

As concerns the stability studies, there are also a few specific requirements in the Netherlands. Extensive stability studies have to be performed. Aside from the stability testing on the mother tincture and the finished medicinal product, tests on the starting material are required. This applies in case the starting material is a chemical substance or dried plant material. Additionally, the applicant is obliged to submit the results of the stability tests on the dilutions. This may be related with difficulties. If the results of the stability tests on the dilutions are not submitted, the manufacturer is obliged to manufacture them right before the processing.

The pharmacological- toxicological documentation must include a detailed assessment of the contained substances. The following information is to be given in the documentation: Single dose and repeated dose toxicity, reproductive function toxicity, embryo-fetal and perinatal

[28] article 5 [30]

[29] The dossier requirements as described are extracted from the Dutch “Notice to Applicants” [31]

toxicity, oncogenic and carcinogenic potential as well as allergy potential. This means that all the properties tested on an allopathic medicinal product are generally also to be tested on a homoeopathic medicinal product. However, based on experiences, the authority accepts the lack of data for certain aspects and does not demand the performance of tests. The data have to be evaluated with view to the contained potencies in the expert report.

5.3.3.1 Tests on Special Impurities

The required tests on special impurities are identical with those required in Germany. However, the tests are more extensive as tests are also required for the contained dilutions.

5.3.3.2 Viral Safety

The required documents are the same as determined by the provisions of the applying Ph.Eur-monographs (described in chapter 2.3.2.).

5.3.4 Time for Assessment

Like in the other selected countries and compliant with EU-law the legal respite for the authority is 210 days. Based on experiences the authority rarely meets this legal time frame.

5.3.5 Validity of a granted Registration

In contrast to the situation in the other selected countries the validity of a registration is not yet defined. The dossier has to be updated on request of the competent authority which is an ongoing process. It is expected that this will be changed to a formal five-years renewal.

5.3.6 Discussion

Compared with the requirements of the other listed countries in the simplified registration procedure, the requirements of the Netherlands are considerably higher, especially with regard to the quality documentation, e.g. the identity test on the finished medicinal product must also be performed on contained higher potencies and not only if the lowest possible dilution is contained. Furthermore quantitative tests are required for higher potencies as already mentioned above. In case this is technically not possible due to a high dilution grade, the compliance with the common attributes of the dosage form has to be tested, a requirement that does not provide any deeper insight into the shelf-life of the medicinal product. These higher requirements also apply to the stability tests, where more tests are necessary than in the other selected countries.

One can be anxious to see what the CTD for homoeopathic medicinal products will bring.

5.4 Notification Procedure of Homoeopathic Medicinal Products in Switzerland

5.4.1 Common Requirements

Finished medicinal products may only be marketed prior to a marketing authorisation at the competent authority.[30] Therefore homoeopathic medicinal products are basically subject to a marketing authorisation procedure, too. However, for special categories of medicinal products, a simplified marketing authorisation procedure is applicable, consistency with the requirements regarding the quality, efficacy and safety of the product provided.[31] This applies to medicinal products of the complementary medicine as defined in article 14 b HMG [32]. The requirements of the notification procedure are given in the "Verordnung des Schweizerischen Heilmittelinstituts über die vereinfachte Zulassung und Meldepflicht von Arzneimitteln (VAZV) vom 09.11.2001" (Ordinance on the simplified marketing authorisation procedure and notification procedure of medicinal products) [33]. Accordingly, homoeopathic medicinal products may be notified if they are used traditionally and manufactured pursuant to the methods of official homoeopathic pharmacopoeias. The notification procedure is only applicable for homoeopathic medicinal products that are marketed without having a trade name, an indication or dosage instructions.

A formal requirement as regards the applicability of the notification procedure is -as generally also applies to marketing authorisation procedures- that the notifying person is a resident of Switzerland and is justified to produce medicinal products or provide the wholesale trade with medicinal products. The authority provides information for the applicant regarding the requirements of the notification procedure and the simplified marketing authorisation procedure of a homoeopathic medicinal product by a detailed "Anleitung des Schweizerischen Heilmittelinstituts zum Einreichen von Zulassungsgesuchen für homöopathische und anthroposophische Arzneimittel der Humanmedizin vom 31.12.2002" (Guidance on the submission of applications for the marketing authorisation of homoeopathic and anthroposophic human medicinal products) [34].

The notification procedure differs in important points from the EU- Directives and the requirements of the other stated countries:

[30] Art. 9 HMG [32]
[31] Art. 14 HMG [32]

5.4.1.1 Permitted Dosage forms in the Notification Procedure

All dosage forms that are used in the Homoeopathic Therapy and manufactured according to a method described in an official homoeopathic pharmacopoeia (GHP, Ph.F. or BHP) are notifiable. This means, in contrast to the other listed countries, the notification procedure is applicable also for parenteral preparations, even though they are irrespective of their contained potencies, available on doctor´s prescription only.

5.4.1.2 Permitted Substances and required Potencies in the Notification Procedure

All substances described in an official homoeopathic pharmacopoeia or in a monograph of the commission D at the BfArM and manufactured according to the common methods of Homoeopathy, are permitted as starting material in the notification procedure. Also traditionally used homoeopathic substances that are not yet described in a monograph, are applicable in the notification procedure, provided the manufacturer submits their own monograph.

In principle, the potencies should be selected in a way that a harmful effect on the patient is impossible. This means that the permitted potencies of the constituents are not generally restricted to a certain potency as foreseen by the Directive 2001/83/EC [4]. The permitted dilutions depend on the substance, which seems reasonable and correct. The acceptable potencies given by the commission D-monographs (within the category “dosage forms”) must be taken into account. Currently the commission D are discussing the making of restrictions regarding the use of the substances. It would be desirable to have these discussions published soon so that a discussion would become possible.

In line with the rules in Germany, substances that are only available on a doctor´s prescription may only be notified above the potency D6.

5.4.2 Special Requirements for Sale within the Self- Medication Sector

Notified medicinal products are eligible for self- medication in case they exclusively consist of substances that are listed in the so- called List C or List D (according to the provisions of the articles 25 and 26 VAM [35]) or provided a positive monograph of the commission D exists.

These substances must be manufactured according to an official homoeopathic manufacturing method and must at least be diluted to a D4 relating to the finished medicinal product.

Annex 1 of the above mentioned guidance document [34] lists substances that may only be used as self- medication products in higher potencies, e.g. nosodes and products derived from animal organs. In the case of the requirements of Annex 1 regarding, when the potency

stipulations are not met, the medicinal products are available on prescription only. A second Annex of the above mentioned guidance document mainly consists of herbal substances that may also be used at low potencies including the mother tincture since their use is considered to be safe. Medicinal products containing substances that are not described in a commission D-monograph are available on prescription only unless the potency is D12 or higher.

5.4.3 Labelling Requirements

As in the other selected countries, the homoeopathic character must be outlined. Notified homoeopathic medicinal products must not be marketed with a trade name. In case of the product that consists of only one active ingredient, this ingredient forms the name of the product. The ingredient has to be denoted according to an official homoeopathic pharmacopoeia. If this differs, the short name of the official pharmacopoeia has to be stated in brackets after the name of the ingredient. Additionally, the contained potency is part of the name. For combinational products, the applicant may choose one of the following possibilities. If the product consists of one main ingredient, this may be the name of the product with a supplementary word, for example “plus”. Otherwise the name consists of all the contained active ingredients.

As concerns the name of the medicinal product, the requirements of the Directive 2001/83/EC are less stringent: the use of a trade name for combinational products is allowed. In line with the requirements of the other countries, the homoeopathic character of the medicinal product has to be outlined through the supplement “Homoeopathic medicinal product” close to the name of the product.

The claiming of indications or dosage instructions is not possible for notified medicinal products. The prohibition of having dosage instructions is very different from all the other listed countries, especially from Germany, where detailed guidelines regarding the posology exist and are difficult to deviate from.

5.4.4 Pharmaceutical Quality-and Toxicology Documentation

As in the authorisation procedures, the applicant in a notification procedure has to prove that the requirements of the appropriate quality are met. They do not differ from the quality documentation in marketing authorisation procedures. The required documentation is the same as in Germany. This refers to the starting material, the mother tinctures and the lowest possible potencies. The same applies to the finished medicinal product and the stability tests. Tests on higher potencies as required in the Netherlands are not obligatory in Switzerland.

Tests on the determination of the content as well as limit tests are only obligatory in the case of inorganic substances and herbal substances containing ingredients that have potent pharmacological properties. Contrary to EU- law and the soon valid new version of the German "Arzneimittelprüfrichtlinien" [15], documentation of the toxicological properties of the medicinal product is not required.

5.4.4.1 Tests on Special Impurities

Concerning special impurities, the requirements of the European Pharmacopoeia and of the official homoeopathic pharmacopoeias have to be met. It is obligatory to perform tests regarding pesticide- and heavy metal residues, the testing frequency is related to the incidence of a possible contamination.

5.4.4.2 Viral Safety

For starting material of animal origin the absence of pathogenic agents has to be proven.

5.4.4.3 Time for Assessment

Homoeopathic medicinal products may be placed on the market after the authority has accepted the notification and has issued a written confirmation thereof. A legal timeframe is not defined.

5.4.5 Validity of a Notification

The notification procedure has to be repeated every five years by the submission of a special notification form which lists, in its annex, all the finished medicinal products to be notified. Changes within the five-year-period are to be notified to the competent authority until December 31st of each year for the following year.

5.4.6 Discussion

In principle, all dosage forms that are commonly used in the Homoeopathic therapy and that are manufactured according to the rules of an official homoeopathic pharmacopoeia are eligible for notification. Consequently, the notification procedure is also applicable for parenteral preparations, but they are only available on prescription. Therefore, the notification procedure differs significantly from the requirements of the EU-law and the requirements of the simplified procedures of the listed EU-member states as the permissible dosage forms are always restricted to orally and externally applied medicinal products. Additionally, in contradiction to EU-law and the other member states being discussed, also homoeopathic

medicinal products that are subject to a doctor´s prescription are notifiable assuming the compliance with the aforementioned requirements. However, special regulations must be met if the homoeopathic medicinal products are intended to be used as self- medication products.
The regulations of the VAZV [33] currently being valid, are transitional provisions, as work has been started on a new ordinance that will provide regulations for the registration and marketing authorisation of homoeopathic medicinal products with and without acknowledged indications. According to the rules it is not possible for foreign manufacturers to be the applicant neither in marketing authorisation nor in notification procedures. In these cases, a distributor has to be the applicant.

5.5 Tabular Overview

Table 2: Requirements in the simplified procedures of the selected countries with special regard to differences

	Germany	Austria	Netherlands	Switzerland
Permitted dosage forms	Compliant with EU-law: only orally or externally applied homoeopathic medicinal products are permitted	Compliant with EU-law: only orally or externally applied homoeopathic medicinal products are permitted	Compliant with EU-law: only orally or externally applied homoeopathic medicinal products are permitted	All dosage forms commonly used in the Homoeopathic therapy are applicable
Permitted potencies	"General D4-rule" of EU-law not implemented into German national law. Basically, substances from mother tincture on applicable; "D4-rule" applies to prescription status drugs only	"General D4-rule" not implemented into Austrian national law Permitted substances and their potencies defined in two positive lists	EU-requirements implemented: "General D4-rule" applies- every ingredient must at least be diluted to a ratio 1:10.000; Ingredients that are available on prescription only when used as allopathic medicines, must not be higher concentrated than 1/100th of the smallest allopathic dose that is subject to a doctor´s prescription	Substance specific; restrictions of the Commission D-monographs to be taken into account
Labelling	EU-requirements implemented; but brand name is also accepted for medicinal products with only one active ingredient	EU-requirements implemented into national law	EU-requirements implemented into national law	Homoeoptahic character must be outlined; Brand names are not permitted at all
Dosage instructions	Very detailed binding provisions; Deviation only possible if prepara-tion specific material is submitted	No general provisions	No general provisions	Dosage instructions not permitted at all
Quality documentation	Still deviating from EU-law, but the new version of the "Arzneimittelprüfrichtlinien "[15] which will be enforced in the near future implements the revised Annex 1	Still deviating from EU-law, especially with regard to tests on special impurities, and viral safety (have not been required so far)	Very detailed requirements until now, formulated in the Dutch-NtA for homoeopathic medicinal products; partly higher requirements than scheduled by EU-law, e.g. stability tests required on diluted ingredients	Same as in Germany
Pharmacological-toxicological documentation	Not required so far; EU-provisions will be implemented into national law soon	Not required	Required	Not required in case the substance is positively assessed by the commission D at the German BfArM
Validity of a gran-ted registration/ notification	5 years	Unlimited	Not defined yet, ongoing process	5 years

6 National Regulatory Requirements concerning the Marketing Authorisation Procedure of Homoeopathic Medicinal Products in selected EU-member states and Switzerland

6.1 Marketing Authorisation Procedure of Homoeopathic Medicinal Products in Germany

6.1.1 Common Requirements

As concerns the marketing authorisation procedure of homoeopathic medicinal products, the common requirements apply as defined in the fourth chapter of the AMG, §§ 21 and 22 AMG [12]. Compared with the simplified registration procedure, the dossier to be submitted is more extensive, especially with regard to the requirement of the submission of pharmacological-toxicological and clinical documentation. In principle, the quality documentation to be submitted in the marketing authorisation procedure does not differ from the one required in the registration procedure. However, special characteristics of the dosage forms have to be taken into account. The Guideline regarding the applicability of the Note for Guidance on Stability Testing [18] requires that for critical dosage forms like parenteral preparations, tests ought to be performed on three instead of on two batches.

6.1.2 Pharmacological-Toxicological and Clinical Documentation

As concerns the pharmacological-toxicological and the clinical documentation, § 22 clause 3 AMG [12] applies. Hereby it is defined that the performance of trials may be replaced by other scientific documentation in case the effects and side-effects of the medicinal product are already known. The scientific documents must provide information on the effects and side-effects of the medicinal product.[32] Additionally, the medical experiences obtained in the homoeopathic therapy have to be taken into account. Pursuant to the provisions of the soon valid new version of the "Arzneimittelprüfrichtlinien" [15] which will implement the requirements of the revised Annex 1, scientific documents to be submitted may be

- trials and single case studies that allow a scientific evaluation
- scientific literature
- expert reports edited by professional associations
- knowledge obtained from the use of registered or authorized medicinal products according to § 67 clause 6 AMG.

[32] § 22 clause 3 no. 1 AMG [12]

For homoeopathic medicinal products, the scientific documents shall be assessed “according to homoeopathic experiences and the way the therapy defines itself”. This has also to be stressed in the wording of the indications.

As the commission D is now of the opinion that its monographs which describe the acknowledged indications, contraindications, side-effects, interactions, dosages, areas of application and dosage forms of a substance, are alone not sufficient for the proof of clinical indications, criteria on the assessment of scientific material concerning homoeopathic medicinal products were published [36]. These depend on the seriousness of the illness and they formulate the aim of the therapy (e.g. for the relief of symptoms, reduction of the incidence of symptoms which occur occasionally, treatment of an illness). They evaluate the scientific literature as well as the level of evidence. The named paper also makes provisions regarding the wording of the area of application in the package information leaflet (e.g. single application or combined with other medicinal products, declaration of information regarding a differential diagnosis). Additionally, a point system for the evaluation of scientific material is defined, whereas a certain score has to be achieved in the marketing authorisation procedure. This means that the type of scientific knowledge is evaluated by an assignment of points, whereas its quality shall be taken into account with regard to the design and performance of trials. The highest score may be achieved by a randomized, placebo- controlled double blind study, a medium score is attained by an observational study and the lowest score applies to commission D-monographs or demonstrated long-time use (meaning the medicinal product must have been marketed before 1978). A so-called homoeopathic drug study becomes mandatory in two cases: unless there is not enough homoeopathic literature available for the intended indication of a known substance or if a new substance shall be introduced into the homoeopathic therapy. It either aims to bring out a homoeopathic “drug picture” or shall enhance or specify existent homoeopathic “drug pictures”. A homoeopathic drug study is defined to be a clinical study on substances in the form of starting material, mother tinctures or dilutions. Also fixed combinations may be tested. The “Bekanntmachung über die Zulassung, Nachzulassung und Registrierung von Arzneimitteln- Empfehlungen der Kommission D nach § 25 Abs. 6 und 7 des AMG zur Planung und Durchführung homöopathischer Arzneimittelprüfungen vom 18.11.1998“ (Publication of the commission D regarding the design and performance of homoeopathic drug studies in the marketing authorisation and registration of medicinal products) [37] must be taken into account.

6.1.3 Time for Assessment

Compliant with EU-law, the authority is obliged to make a decision on a submitted application for marketing authorisation within seven months.[33] This period is not applicable when a letter of deficiencies is issued, but the applicant must eliminate the deficiencies within a period of not more than six months. According to § 28 AMG [12], the authority may grant an application with special conditions. In this case the mentioned respite of seven months is not applicable.

6.1.4 Validity of a granted Marketing Authorisation

In line with the EU-requirements, a marketing authorisation is valid for five years. To be maintained, the applicant has to submit an application of renewal at least three months before the five-years-period expires.

6.1.5 Discussion

Compared with the simplified registration procedure, the marketing authorisation procedure of a homoeopathic medicinal product, especially in case of a combinational product, is more complex and the fees are higher. The marketing authorisation procedure, however, provides the following advantages: First of all, therapeutic indications may be named. Secondly, the acceptable dosage forms are not restricted to orally and externally applied medicinal products. All dosage forms commonly used in the homoeopathic therapy may be authorized. Furthermore, the accepted substances are not restricted to commonly known substances[34] and commonly known combinations of substances respectively as in the simplified registration procedure. On the other hand there is the requirement for clinical trials and the greater associated expense. Worth mentioning is the fact that the fees in marketing authorisation procedures are much higher compared to the fees in registration procedures. The applicant has to pay 17.833 Euro for an authorized homoeopathic medicinal product with a known homoeopathic ingredient.[35] For a registered homoeopathic medicinal product, depending on the number of homoeopathic ingredients, a fee of 1.080 up to 3.550 Euro has to be paid [39]. The applicant has to be aware that not only new medical entities, but also new combinations of known substances are automatically only available on a doctor´s prescription pursuant to

[33] § 27 clause 1 AMG [12]
[34] as defined in 5.1.3.2
[35] Anlage zu § 1 AMG-KostV, Gebührenziffer 2 [38]

§ 49 AMG [12]. In this case, the fee to be paid is 62.314 Euro[36] (!).

A positive aspect is the fact that a commission on homoeopathic medicinal products exists at the German authority which must be consulted in the case of a possible refusal of a marketing authorisation. This ensures that the specifics of the homoeopathic therapy are considered. Due to the above mentioned consultancy document of October 2004, the requirements of Annex 1 of the Directive 2001/83/EC [4] will replace the previously valid "Arzneimittelprüfrichtlinien" [14] so that the German requirements of the marketing authorisation procedure of homoeopathic medicinal products will be in line with EU-law, after the German Drug Act has been amended. This is a further step in the European harmonisation process and leads to uniformity in the quality criteria of homoeopathic medicinal products.

6.2 Marketing Authorisation Procedure of Homoeopathic Medicinal Products in Austria

6.2.1 Common Requirements

The documents required in the Austrian marketing authorisation procedure are defined in § 15 clause 1 austr. AMG [27]. § 15 clause 2 austr. AMG [27] defines that irrespective of the required documents as defined by clause 1, commentarial and evaluative summaries on the quality, safety and efficacy of the medicinal product must be submitted. In contrast to the quality documentation to be submitted in the Austrian notification procedure, the quality documentation in the authorisation procedure must comprise, if applicable, a written confirmation regarding the compliance with the Ph.Eur.-monograph "Pesticide residues" [9] and the applying Ph.Eur.-monographs concerning viral safety [10,11]. The required documentation in the marketing authorisation procedure of a homoeopathic medicinal product is substantiated in § 16 austr. AMG [27]. Accordingly, information on the expedience of the dosage form, and clinical as well as nonclinical data may be omitted.

6.2.2 Pharmacological-Toxicological and Clinical Documentation

Pursuant to § 16 clause 1 austr. AMG [27], the applicant is obliged to submit documents that are relevant in the assessment of the toxicological properties as well as documents regarding the proof of the specific homoeopathic efficacy of the medicinal product. In this way, the authority shall be enabled to obtain knowledge about the safety and efficacy of the medicinal product for which the marketing authorisation shall be obtained. In order to prove the

[36] Anlage zu § 1 AMG-KostV, Gebührenziffer 1 [38]

toxicological safety of the medicinal product, documented literature and data base survey is appropriate. Additionally, the commission D-monographs of the BfArM are of high value.
The specific homoeopathic efficacy may be proven with the respective monographs of the homoeopathic pharmacopoeias or of the commission D as well as with common homoeopathic literature.
For the overall assessment of the clinical part, the competent authority denominates an external qualified person. The applicant has to bear the costs.

6.2.3 Time for Assessment

According to § 21 clause 1 austr. AMG [27], the competent authority is obliged to come to a decision within seven months. Basically, this is compliant with the provisions of EU-law.
For homoeopathic medicinal products an external qualified person must be consulted so that in fact this time frame has rarely been met.

6.2.4 Validity of a granted Marketing Authorisation

As for all other medicinal products, a granted marketing authorisation of a homoeopathic medicinal product expires after five years. To be maintained, the authorisation holder must demonstrate that the marketing authorisation requirements are still compliant with the actual level of scientific knowledge.[37]

6.2.5 Discussion

Having submitted a toxicological assessment and a bibliographical proof of the efficacy of the homoeopathic ingredients, the marketing authorisation procedure is feasible without any problems. Due to the fact that a permanent expert committee on homoeopathic medicinal products does not exist at the Austrian authority, an external qualified person has to be assigned by the authority which is a time-consuming process. Consequently, the marketing authorisation is rarely granted within the legal time frame. Moreover, the applicant is obliged to submit an application for the assignment of the qualified person. This should be done simultaneously with the submission of the application for marketing authorisation as otherwise the time-to-market is extended.
As it is the case in Germany, higher fees have to be paid for authorized homoeopathic medicinal products.[38]

[37] § 19 a clause 1 austr. AMG [27]
[38] 436 € for products with one active ingredient/ 1453 € for a combination product (Anlage [38] I.2 b.e), 145 € for a registered product (Anlage [38], VI.3)

Authorized homoeopathic medicinal products are subject to renewals which is not the case for notified medicinal products which is very specific to the Austrian notification process.

6.3 Marketing Authorisation Procedure of Homoeopathic Medicinal Products in the Netherlands

6.3.1 Common Requirements

The marketing authorisation procedure is performed according to the provisions of article 6 [30]. As for the simplified registration procedure, the Dutch Notice to Applicants has to be used. Concerning the quality- and the pharmacological-toxicological documentation, the same requirements apply as in the simplified registration procedure. It is worth mentioning that critical products and dosage forms as for nosodes or parenteral preparations have not been authorized yet.[39]

6.3.2 Pharmacological-Toxicological and Clinical Documentation

The pharmacological- toxicological documentation which also has to be submitted in the simplified registration procedure must consist of a detailed assessment of the contained substances. It is described under 5.3.3.

The clinical documentation has to evaluate the homoeopathic "drug pictures" of the ingredients with regard to the planned indications of the medicinal product. This information is to be supplemented with a detailed bibliographical documentation. The results from clinical trials shall also be submitted. In case the product has already been marketed in another country, acquired information must also be submitted. This should apply in numerous cases as the Netherlands is not a country with a long homoeopathic tradition. Furthermore, an expert committee on homoeopathic medicinal products comparable to the commission D at the German BfArM does not exist.

6.3.3 Time for Assessment

The EU- requirements apply. Based on experiences, they are rarely met.

6.3.4 Validity of a granted Marketing Authorisation

Compliant with EU- law, the authorisation is valid for a period of five years.

[39] as reflected on http://www.echamp.org/eu_guide.php

6.3.5 Discussion

In principle, the Dutch requirements in the marketing authorisation procedure are higher than those of the other selected countries. The homoeopathic character of the medicinal products is rarely taken into consideration. This applies in particular to the toxicological and clinical documentation, but also to the quality documentation. The applicant is obliged to present the data in a special scheme (the Dutch Notice to Applicants for homoeopathic medicinal products) which lists numerous points that are either not available for homoeopathic medicinal products or are not relevant due to the dilutions and the nature of the substances. Possibly this will be changed in the near future by the CTD for homoeopathic medicinal products.

6.4 Marketing Authorisation Procedure of Homoeopathic Medicinal Products in Switzerland

6.4.1 Common Requirements

The provisions of the VAZV [33] do not only regulate the notification procedure of homoeopathic medicinal products but also define the requirements of a simplified marketing authorisation procedure. This procedure applies to, amongst others, medicinal products which consist of known substances, to orphan drugs and to complementary medicines. Assuming that all the quality, safety and efficacy requirements are fulfilled, it is also necessary that obligations to Swiss and International laws are met.[40]

6.4.2 Pharmacological-Toxicological and Clinical Documentation

Basically, pursuant to article 8 VAZV [33], the submission of bibliographical documentation is regarded to be sufficient. The performance of new tests on animals may be required in cases, in which the evidence obtained from literature is not satisfactory. The toxicological documentation may be replaced by a positive monograph of the commission D at the BfArM, however the authority may require further documents.[41] Concerning new active substances and excipients, documents have to be submitted on the acute and chronic toxicity, on embryotoxic and teratogenic effects and on the possibility of allergic, carcinogenic and mutagenic effects. In case new active substances or excipients are contained in medicinal products that are intended for dermal use, used on mucosa or for parenteral application, single

[40] Art. 14 clause 1 HMG [32]
[41] Teil III: Toxikologische Dokumentation, p. 8 [34]

and repeated tests of local tolerance and sensitizing properties have to be performed. In any case the applicant is obliged to give good reasons in a summary of whether toxicological tests need not be performed. A literature reference list must also be submitted. If the new substance in the medicinal product is highly diluted, the applicant may explain the lack of toxicological studies by the very low concentration of the substance in the finished medicinal product.

Concerning the clinical documentation according to article 9 VAZV [33], clinical trials may be replaced by the results obtained from observational studies or by bibliographic documentation. An adequate proof of local tolerance is required in any case. The submitted documents are assessed by experts on homoeopathic medicines. The "Anleitung zum Einreichen von Zulassungsgesuchen für homöopathische und anthroposophische Arzneimittel" [34] clearly distinguishes between homoeopathic medicinal products containing only one active ingredient and complex homoeopathic medicinal products. The clinical documentation on products with only one active ingredient is mainly bibliographical. For combinational products, the applicant is obliged to provide an explanation on the choice of the contained potencies, as well as on the dosage instructions and the application route. In combinational products, the homoeopathic ingredients may only be contained as mother tinctures or in low and medium potencies. This means that only homoeopathic ingredients with a direct effect on organs may be used. Additionally, they must show a corresponding effect on the affected organs, and the properties of the contained substances have to complement another. Apart from this, only a small number of substances may be contained, however a maximum number is not defined. If applicable, an explanation must be given on the choice of different quantities of the ingredients.

The proof of the efficacy of the combination itself may be achieved by bibliographical documents, scientific evaluated clinical reports, observational studies and, of course, with the results from clinical trials. In the marketing authorisation procedure, the applicant is obliged to provide an appropriate proof of tolerance which depends on the dosage form of the medicinal product. Due to the toxicological potential of nosodes and preparations derived from animal organs, the proof of tolerance must be performed with special regard to possible allergic reactions. The summary must clearly define the therapeutical benefit and the tolerance of the medicinal product.

6.4.3 Time for Assessment

Neither the provisions of the HMG [32] nor those of the VAM [35] give a time frame, in which the authority is obliged to grant a marketing authorisation. Article 3 clause 3 VAM [35]

only defines that the authority may grant a respite of 120 days in case an incomplete dossier has been submitted or if other deficiencies in the dossier exist. The lacking legal time frame is the main difference between the regulations in Switzerland and the other described countries as concerns the time for assessment.

6.4.4 Validity of a granted Marketing Authorisation

As in all other countries, a granted marketing authorisation shall be valid for a period of five years.[42] In order to maintain it, the applicant must submit an application for renewal at least six months before its expiry.[43] The provisions of the Swiss law regarding the validity of marketing authorisations are the same as in the other described countries.

6.4.5 Discussion

In Switzerland, a simplified marketing authorisation procedure applies to homoeopathic medicinal products. The specialities of the homoeopathic treatment are taken into account and special regulations for these products are provided. Switzerland is alone amongst the described countries where precise and well substantiated guidance regarding the authorisation of homoeopathic medicinal products is given. These seem to be reasonable and appropriate. The toxicological potential of certain substances and dosage forms is especially considered. The "Anleitung zum Einreichen von Zulassungsgesuchen für homöopathische Humanarzneimittel" [34] is a clearly structured guidance for the applicant which simplifies the submission of the required documentation.

[42] Art. 16 clause 2 HMG [32]
[43] Art. 9 VAM [35]

6.5 Tabular Overview

Table 3: Dossier requirements in the marketing authorisation procedure concerning the pharm-tox. and clinical documentation

	Germany	Austria	Netherlands	Switzerland
Pharmacological-toxicological documentation *Known hom. active substances*	Bibliographical: assessment of possible risks required (the toxicological potential must be discussed, the daily intake to be calculated)	Bibliographical: documented literature and database survey	Performance of tests required on single dose/repeated dose toxicity, reproductive function, embryofetal and perinatal toxicity, mutagenic potential, oncogenic/carcinogenic potential, allergy potential	Bibliographical; Commission D-monographs accepted and of high value
Pharmacological-toxicological documentation *New active substances*	Full documentation required according to provisions of module 4 CTD	Full documentation required according to provisions of module 4 CTD	Full documentation required according to provisions of Dutch NtA for homoeopathic medicinal products- soon to be replaced by CTD for homoeopathic medicinal products	Performance of tests required on acute and chronic toxicity, embryotoxic and teratogenic effects, Allergy potential, carcinogenic and mutagenic effects
Clinical documentation *Known hom. active substances*	Published criteria of commission D evaluate scientific documents by an assignment of points Highest score may be achieved by a placebo-controlled double-blind-study; A certain score must be achieved in the proof of clinical indications in the m.a.procedure; Score to be obtained is due to severity of illness to be cured with the medicinal product	Bibliographical: Monographs of official homoeopathic pharmacopoeias; Commission D-monographs accepted; Common homoeopathic literature accepted	Bibliographical documents to be supplemented with observational studies	Clinical trials may be replaced by observational studies and/or bibliographic documentation Adequate proof of tolerance required
Clinical documentation *New active substances*	Performance of a homoeopathic drug study mandatory	Performance of a homoeopathic drug study mandatory	Performance of a homoeopathic drug study mandatory as defined by the provisions of Dutch NtA for homoeopathic medicinal products	Performance of a homoeopathic drug study mandatory
Assessment/expert committee at competent authority	Assessment to be carried out by internal experts on homoeopathic medicinal products at the BfarM (Section 2) Commission D must be consulted in case of a possible refusal	Assessment by external experts	Homoeopathic unit at the authority but homoeopathic character of the medicinal products is not adequately considered in assessment	Internal experts

7 Conclusion and Outlook

In all described countries the marketability of a homoeopathic medicinal product may be achieved through a simplified registration procedure. In compliance with the provisions of the EU-Directive 2001/83/EC [4] the naming of indications is not permitted for registered homoeopathic medicinal products. A marketing authorisation procedure becomes mandatory if the homoeopathic medicinal product shall be marketed with indications. The requirements of the registration procedure differ in main aspects from those of a marketing authorisation procedure. Additionally, the requirements of the procedures in the selected countries are not harmonised. The procedures and national-specific requirements are described and compared in detail in the presentation of each country; nevertheless this thesis is restricted to the most important aspects. In any case, complying with the EU- provisions, the homoeopathic character of the medicinal product must be outlined. This appears to be appropriate.

On the other hand the "D4-rule" for homoeopathic ingredients in the simplified registration procedure as required in the Directive 2001/83/EC [4] does not seem to be reasonable. The demand for a certain grade of dilution, irrespective of the substance and without consideration of the toxicological potential of its ingredients is not appropriate in the light of the traditional homoeopathy treatment. Until today, the "D4- rule" of the European law has only been transmitted into the national law of the Netherlands which is not a country with a long homoeopathic tradition and without an expert committee on homoeopathic medicinal products.

Austria, also a country without a long homoeopathic tradition has integrated the homoeopathic traditions of Germany and France using the monographs of both homoeopathic pharmacopoeias in the compilation of the lists of substances that are applicable in the simplified registration procedure. The European "D4-rule" is not implemented into Austrian national law yet.

In Germany, the commission D-monographs which are also relevant in other countries such as Switzerland have been modified through unpublished votes of the commission D. An international harmonisation would be sensible.

The establishment of a commission on homoeopathic medicinal products at the EMEA similar to the Herbal Medicinal Products Committee which had its constitutional session in September, 2004, would be conceivable.

In the future, the mutual recognition procedure should become a possible way to gain the marketability for homoeopathic medicinal products, too.

Not only herbal medicinal products, but also homoeopathic medicinal products belong to the group of complementary and alternative medicines. Therefore, the following possibility could be

taken into account: Concerning the marketing authorisation of traditional herbal medicinal products the Directive 2001/83/EC [4] was amended by the provisions of the Directive 2004/24/EC [6]. Accordingly, the results from the pharmacological- toxicological and clinical tests may be omitted if the applicant proves with a detailed documentation of published scientific literature that the ingredients of the medicinal product are of well- established use and have a recognised efficacy and an acceptable level of safety. For the proof of the traditional use the applicant is obliged to submit "bibliographical or expert evidence to the effect, that the medicinal product in question or a corresponding product has been in medicinal use throughout a period of at least 30 years preceding the date of the application, including at least 15 years within the European Community".[44] Homoeopathic medicinal products are explicitly excluded from this provision. Reasons are not provided. A simplified marketing authorisation procedure for homoeopathic medicinal products based on article 16 clause 1 a-c of the Directive 2004/24/EC would be desirable as numerous substances used in the Homoeopathic therapy would comply with these requirements. The entry to the market of these homoeopathic medicinal products with decades of therapeutic use could then be extremely simplified.

[44] Art. 16 clause 1c [6]

8 Summary

According to the provisions of the Directive 2001/83/EC on the Community Code relating to medicinal products for Human use marketability of a homoeopathic medicinal product may be achieved through either a simplified registration or through a marketing authorisation procedure.
The simplified registration procedure provides simplifications with view to the dossier requirements: documentation on the clinical properties of the respective homoeopathic medicinal product need not be submitted to the competent authority. The requirements regarding the quality and safety documents are basically the same as for authorized homoeopathic medicinal products.
To be applicable in the simplified registration procedure, the homoeopathic medicinal product must meet several requirements as defined in article 14 of the Directive 2001/83/EC. First of all, it is not possible to market a registered homoeopathic medicinal product with therapeutic indications neither in the naming nor in any other information related to the medicinal product. Secondly, only dosage forms that are intended for oral or external use are applicable. Additionally, no homoeopathic ingredient must be of a higher concentration than one part in ten thousand of the mother tincture. In the case of substances that would have prescription status when used in allopathic medicines, the concentration must not be higher than $1/100^{th}$ of the smallest allopathic dose.
This thesis aims to describe and compare both procedures with special regard to national-specific requirements. All selected countries (Germany, Austria, the Netherlands and Switzerland) have implemented simplified procedures. However, their requirements are still differing and inconsistent. The general restriction to"D4 and higher dilutions" of EU-law has not been transformed into German and Austrian national law. In both countries, as well as in Switzerland, the toxicological potential is assessed for each substance and due to this the permissible potencies are defined.
Harmonisation of the regulatory requirements in the registration procedure is still an ongoing process in Europe. The adoption of the general "D4-rule" of EU-law would not take account of national homoeopathic tradition, and therefore seems to be not reasonable.
This thesis makes proposals concerning a possible and sensible harmonisation.

9 References

[1] Monograph "Homoeopathic Preparations" of the European Pharmacopoeia, 4th edition 2002, 4th supplement, published by the Directorate for the Quality of Medicines of the Council of Europe, Strasbourg, 4379

[2] Monograph "Herbal Drugs for Homoeopathic Preparations" of the European Pharmacopoeia, 4th edition, 1st supplement, published by the Directorate for the Quality of Medicines of the Council of Europe, Strasbourg, 3258

[3] Monograph "Mother Tinctures for Homoeopathic Preparations" of the European Pharmacopoeia, 4th edition, 5th supplement, published by the Directorate for the Quality of Medicines of the Council of Europe, Strasbourg, 4643

[4] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (Official Journal of the European Union No. L 311 of 28.11.2001, 67 pp)

[5] Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use (Official Journal of the European Union No. L 136 of 30.04.2004, 34 pp)

[6] Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use (Official Journal of the European Union No. L 136 of 30.04.2004, 85 pp)

[7] H 5.4.4: Specific methods of production, German Homoeopathic Pharmacopoeia, Volume 1: General Part/Monographs A-D, issued in 2001, Medpharm scientific publishers, 2003

[8] Directive 2003/63/EC of the European Parliament and of the Council of 25 June 2003 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use (Official Journal of the European Union No. L 159, 46 pp)

[9] Monograph “Pesticide residues” of the European Pharmacopoeia, Ph.Eur. 2.8.13, 4th edition 2002, published by the Directorate for the Quality of Medicines of the Council of Europe, Strasbourg, 229

[10] Monograph “Products with the risk of transmitting agents of Animal Spongiform Encephalopathies” of the European Pharmacopoeia, 4th edition 2002, published by the Directorate for the Quality of Medicines of the Council of Europe, Strasbourg, 729

[11] Monograph “Minimising risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products”, Ph.Eur. 5.2.8, 4th edition 2002, published by the Directorate for the Quality of Medicines of the Council of Europe, Strasbourg, 616

[12] Gesetz über den Verkehr mit Arzneimitteln (Arzneimittelgesetz) in der Fassung der Bekanntmachung vom 11.12.1998, BGBl. I, 3586, zuletzt geändert am 09.12.2004, BGBl. I, 3214

[13] Verordnung über homöopathische Arzneimittel vom 15.03.1978, BGBl. I, 401

[14] Bekanntmachung der Neufassung der Allgemeinen Verwaltungsvorschrift zur Anwendung der Arzneimittelprüfrichtlinien vom 05.05.1995, BAnz Nr. 96a vom 20.05.1995

[15] Bekanntmachung des Bundesministeriums für Gesundheit und Soziale Sicherung: 2. Allgemeine Verwaltungsvorschrift zur Änderung der Allgemeinen Verwaltungsvorschrift zur Anwendung der Arzneimittelprüfrichtlinien vom 11.10.2004, BAnz Nr. 197 vom 16.10.2004

[16] Verordnung über verschreibungspflichtige Arzneimittel in der Fassung der Bekanntmachung vom 30.08.1990, BGBl. I, 1866, mit 53. Verordnung zur Änderung der Verordnung über verschreibungspflichtige Arzneimittel vom 17.12.2004, BGBl. I 2004, 3526

[17] Allgemeine Verwaltungsvorschrift zur Registrierung homöopathischer Arzneimittel vom 18.12.1992, BAnz Nr. 244 vom 30.12.1992, 9704

[18] Leitfaden des BfArM zur Anwendung der "Note for Guidance on Stability Testing: Stability Testing of existing active substances and related finished products, CPMP/QWP/122/02 corr.", Stabilitätsprüfung bei nach homöopathischen Verfahrenstechniken hergestellten Arzneimitteln, Stand: 22.09.2003, as reflected on the internet site:
http://www.bfarm.de/de/Arzneimittel/bes_therap/am_anthropo/Stabilitaetspruefung_hom_AM_22092003.pdf

[19] Monograph "Heavy metals" of the European Pharmacopoeia, Ph.Eur. 2.4.8, 4th edition 2002, published by the Directorate for the Quality of Medicines of the Council of Europe, Strasbourg, 105

[20] Bundesministerium für Gesundheit: Bekanntmachung von Empfehlungen für Höchstmengen an Schwermetallen bei Arzneimitteln pflanzlicher und tierischer Herkunft-Arzneimittelkontaminanten-Empfehlung-Schwermetalle. Entwurf vom 17.10.1991 (The draft has then not been published)

[21] Verordnung über das Verbot der Verwendung von mit Aflatoxinen kontaminierten Stoffen bei der Herstellung von Arzneimitteln (Aflatoxin-Verbots-Verordnung) vom 19.07.2000, BGBl. 1081, 1505

[22] Formulare und Erläuterungen zum Antrag auf Zulassung eines Arzneimittels beim Bundesinstitut für Arzneimittel und Medizinprodukte, 3. Auflage, Stand 31.10.1996, Bundesanzeiger Verlag

[23] Verordnung über die Freistellung homöopathischer Arzneimittel von der Registrierung-Verordnung über Standardregistrierungen vom 03.12.1982, BGBl. I, 1602

[24] Sander, A.: Kommentar für die juristische und pharmazeutische Praxis zum Arzneimittelgesetz mit Hinweisen zu Medizinprodukten und zum Betäubungsmittelgesetz incl. 41. Lieferung, Stand Dezember 2003, W. Kohlhammer Verlag

[25] Rehmann, W.A.: Arzneimittelgesetz (AMG) mit Erläuterungen, 2. Auflage, C.H. Beck Verlag, München 2003

[26] Neufassung der Dosierungsempfehlungen der Kommission D für homöopathische Arzneimittel, verabschiedet auf der 18. Sitzung der Kommission D am 12.06.2002, überarbeitet auf der 20. Sitzung der Kommission D am 25.06.2003, Stand am 17.03.2004, as reflected on the internet site:
http://www.bfarm.de/de/Arzneimittel/bes_therap/am_anthropo/kd21dos.pdf
on November 25,2004

[27] Bundesgesetz vom 02.03.1983 über die Herstellung und das Inverkehrbringen von Arzneimitteln (Arzneimittelgesetz), BGBl. Nr. 185/1983, in der Fassung BGBl. Nr. 748/1988, zuletzt geändert in Bundesgesetzblatt Nr. 25/2004

[28] Verordnung des Bundesministers für Gesundheit, Sport und Konsumentenschutz betreffend anmeldepflichtige homöopathische Arzneispezialitäten, BGBl. Nr. 1011/1994

[29] Préparations homeopathiques, monograph Preparations Homeopathiques, Jan. 1998, Pharmacopée Française, Xe édition, 2003, Redigee par ordre du gouvernement, Agence française de securité sanitaire des produits des santé

[30] Besluit houdende wijzging van het besluit homeopathische farmaceutische producten dd. 12.12.1995, Stb.1995, 654

[31] Notice to Applicants for homeopathic medicinal products (according to Council Directive 92/73/EEC), September 1999 as reflected on the internet site:
http://www.cbg-meb.nl/uk/hpathica/rgstr.htm ,
on February 1st, 2004

[32] Bundesgesetz über Arzneimittel und Medizinprodukte- Heilmittelgesetz (HMG) vom 15.12.2000, Bundesblatt Nr. 51 vom 28.12.2000- SR 812.21, Stand am 20.01.2004, as reflected on the internet site:
http://www.bag.admin.ch/heilmitt/gesetz/d/ , on November 22, 2004

[33] Verordnung des Schweizerischen Heilmittelinstituts über die vereinfachte Zulassung und Meldepflicht von Arzneimitteln (VAZV) vom 09.11.2001, Stand am 28.12.2001, as reflected on the internet site:
http://www.bag.admin.ch/heilmitt/gesetz/verord/d/vvza.pdf ,
on November 22, 2004

[34] Anleitung des Schweizerischen Heilmittelinstituts zum Einreichen von Zulassungsgesuchen für homöopathische und anthroposophische Arzneimittel der Humanmedizin vom 31.12.2002, as reflected on the internet site:
http://www.swissmedic.ch/files/pdf/Anleitung_Gesuch_Homoeopathika_Anthroposophika.pdf ,
on November 22, 2004

[35] Verordnung über die Arzneimittel- Arzneimittelverordnung vom 17.10.2001, Stand am 07.09.2004, as reflected on the internet site:
http://www.admin.ch/ch/d/sr/8/812.212.21.de.pdf ,
on November 22, 2004

[36] Kommission D beim Bundesinstitut für Arzneimittel und Medizinprodukte: Kriterien für Erkenntnismaterial zu klinischen Indikationen in der Homöopathie, Stand 09.10.2002 as reflected on the internet site:
http://www.bfarm.de/de/Arzneimittel/bes_therap/am_anthropo/AGKriterienEM209Tab3u.pdf , on November 22, 2004

[37] Bekanntmachung über die Zulassung, Nachzulassung und Registrierung von Arzneimitteln- Empfehlungen der Kommission D nach § 25 Abs. 6 und 7 des AMG zur Planung und Durchführung homöopathischer Arzneimittelprüfungen vom 18.11.1998 as reflected on the internet site:
http://www.bfarm.de/de/Arzneimittel/bes_therap/am_anthropo/Hom_AM_Pruefungen.pdf , on November 22, 2004

[38] Kostenverordnung für die Zulassung von Arzneimitteln durch das Bundesinstitut für Arzneimittel und Medizinprodukte und das Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (AMG- Kostenverordnung, AMGKostVO) vom 10.12.2003, BGBl. 2003 I Nr. 59 vom 16.12.2003

[39] Kostenverordnung für die Registrierung homöopathischer Arzneimittel durch das Bundesinstitut für Arzneimittel und Medizinprodukte und das Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmedizin vom 09.04.1997 (BGBl. I, 780), geändert durch Artikel 31 des Gesetzes zur Umstellung von Gesetzen und anderen Vorschriften auf dem Gebiet des Gesundheitswesens (Achtes Euro- Einführungsgesetz) vom 23.10.2001, BGBl. I, 2706

[40] Verordnung vom 20.04.2000 der Bundesministerin für Arbeit, Gesundheit und Soziales über den Gebührentarif gemäß dem Arzneimittelgesetz, zuletzt aktualisiert am 17.12.2003, as reflected on the internet site: http://www.bmgf.gv.at/cms/site/attachments/5/3/4/CH0008/CMS1071649134050/gebuehrentarif.pdf on January 17, 2005

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

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