DEMARCATION OF HERBAL BORDERLINE PRODUCTS – MEDICINAL PRODUCTS OR FOOD SUPPLEMENTS?

Wissenschaftliche Prüfungsarbeit

zur Erlangung des Titels

„Master of Drug Regulatory Affairs“

der Mathematisch-Naturwissenschaftlichen Fakultät

der Rheinischen Friedrich-Wilhelms-Universität Bonn

vorgelegt von

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Bonn 2006

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GLOSSARY

AIMD	Active Implantable Medical Devices
AMG	Arzneimittelgesetz
AMGVwV	Allgemeine Verwaltungsvorschrift zur Durchführung des Arzneimittelgesetzes
BGH	Bundesgerichtshof
BgVV	Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmedizin
EC	European Community
ECJ	European Court of Justice
EEC	European Economic Community
EU	European Union
LFBG	Lebensmittel-, Bedarfsgegenstände- und Futtermittelgesetzbuch
LMBG	Lebensmittel- und Bedarfsgegenständegesetz
MDD	Medical Device Directive
NemV	Verordnung über Nahrungsergänzungsmittel
NRW	Nordrhein-Westfalen
OLG	Oberlandesgericht
OVG	Oberverwaltungsgericht

1 INTRODUCTION

The demand for products that have a beneficial effect on human health is growing. Many food supplements with herbal ingredients promise to have this effect. But for quite a long time, there was no specific legal definition for this kind of products in Germany. Food supplements belong to foodstuffs and in Germany they were defined by the general definition of foodstuffs in §1 LMBG [1] (in September 2005 the LMBG has been replaced with the LFBG [2]). This situation caused many problems, since the specific characteristics of food supplements were not considered in this definition, e.g. the presentation in dose forms, which classify these products almost as medicinal products. Often different opinions existed between manufacturers and authorities in terms of the classification of a specific product as food supplement or as medicinal product. In many cases these problems had to be clarified by the national jurisdiction.
Furthermore, there was no harmonised definition for foodstuffs and food supplements in the European Union, although for medicinal products a harmonised definition already existed for some time (see Directive 65/65/EEC [3]). Therefore it was possible that a product was classified as food supplement in one member state and as medicinal product in another. This caused problems for manufacturers and suppliers who wanted to distribute a product in more than one member state and hampered the free movement of goods.
In 2002, the laws for foodstuffs and food supplements were harmonised in the European Union with Regulation (EC) No. 178/2002 [4] and Directive 2002/46/EC [5], resp.
In Germany, Directive 2002/46/EC [5] was implemented into national legislation with the "Verordnung über Nahrungsergänzungsmittel – NemV" [6].

In this thesis should be discussed if the problems of different classifications of products are solved with these provisions. It will be examined if definite criteria exist for the classification using the example of the so-called "herbal borderline products". These are products that contain herbal extracts and they are often located in a grey area since they show attributes of medicinal products as well as of food supplements.
At first, the relevant legal framework and criteria for the demarcation developed by jurisdiction are presented. As regards national jurisdiction, only German decisions were taken into account.
Afterwards, three examples of herbal products are analysed. All of them were classified as food supplements by their vendors. It should be discussed if it is possible to come to a clear decision about the character of these products by means of the existing legislation and criteria defined by jurisdiction.

2 BACKGROUND

2.1 CONSEQUENCES OF A CLASSIFICATION AS MEDICINAL PRODUCT OR FOOD SUPPLEMENT

Since medicinal products and food supplements are regulated by different legal areas in the EU legislation, there are extensive consequences for the marketing of a product if a product is classified as a medicinal product or a food supplement.

It is prohibited to introduce a medicinal product into the market, unless a marketing authorisation is granted by the relevant competent authority (e.g. see §21 AMG [7]). For this

purpose, the quality, efficacy and safety of the medicinal product have to be proven (see preamble to Directive 2001/83/EC [8]).

In contrast, it is allowed to sell foodstuffs and food supplements, unless there is a specific provision, which prohibits the distribution in certain cases (e.g. see §5 LFBG [2]). After launching, the product will be observed by the relevant authorities and if there are problems with the safety of the product, the product has to be taken off the market.
If a product is sold as a food supplement, but the relevant authority classifies this product as a medicinal product, the supplier would sell the product without a marketing authorisation. However, this is prohibited by law and the vendor has to take the product immediately off the market.

Furthermore, there are different rules for the advertising of medicinal products and foodstuffs/ food supplements. For medicinal products, advertising is strictly regulated in Title VIII of Directive 2001/83/EC [8]. In addition, Member States may have additional rules concerning misleading advertising of medicinal products. In Germany, this is the "Heilmittelwerbegesetz" [9].
Advertising for foodstuffs is regulated in Directive 2000/13/EC [10]. The rules are not as strict as for medicinal products, but misleading statements are also prohibited.

Labelling is regulated for medicinal product as well as for food supplements. §10 AMG [7] and Title V in Directive 2001/83/EC [8] state the rules for medicinal products. §4 NemV [6] and Directive 2002/46/EC [5], resp. in conjunction with Directive 2000/13/EC [10] give the rules for food supplements. But the labelling for medicinal products has to be authorised by the relevant competent authority.

2.2 RESPONSIBILITY FOR THE CLASSIFICATION OF MEDICINAL PRODUCTS IN GERMANY

The responsibility for the categorisation of a product as medicinal product is determined in § 11 AMGVwV [11] as follows:
Anfragen zur Zulassungs- oder Registrierungspflicht eines Arzneimittels beantwortet die zuständige Behörde des Landes, in dem der pharmazeutische Unternehmer seinen Sitz hat oder begründen will. Bei grundsätzlichen Fragen soll das Benehmen mit der zuständigen Bundesoberbehörde hergestellt werden. In diesen Fällen unterrichtet die zuständige Behörde des Landes auch die anderen Länder sowie die Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten über die ergangenen Entscheidungen. Hat der pharmazeutische Unternehmer seinen Sitz nicht im Geltungsbereich des Arzneimittelgesetzes, aber in einem anderen Mitgliedstaat der Europäischen Union oder in einem anderen Vertragsstaat des Abkommens über den Europäischen Wirtschaftsraum, beantwortet die zuständige Bundesoberbehörde Anfragen nach Satz 1.
This means that for companies, which have their registered office in Germany, the competent authority of the respective "Bundesland" is responsible; but companies that have their registered office in a foreign country should address their requests to the competent Federal authority, e.g. the "Bundesinstitut für Arzneimittel und Medizinprodukte".
According to § 21 section 4 AMG, the competent Federal authority also decides about the classification if the competent Länder authority applies for it:
Die zuständige Bundesoberbehörde entscheidet ferner unabhängig von einem Zulassungsantrag nach Absatz 3 auf Antrag einer zuständigen Landesbehörde über die Zulassungspflicht eines Arzneimittels.

2.3 LEGAL FRAMEWORK

In the following, the legal framework for the classification of products as medicinal products or foodstuff and food supplements, resp., is compiled and definitions of important criteria for demarcation are given.
All product categories are covered by European legislation.

2.3.1 Medicinal product

European Union
Medicinal products are defined in Art. 1 paragraph 2 of Directive 2001/83/EC as amended by Directive 2004/27/EC [8, 12]. Directive 2004/27/EC had to be implemented in national legislation by the member states since 30. October 2005, but not all member states realised this duty within the time limit.
A medicinal product is
(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or
(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

For the terms “pharmacological, immunological or metabolic action”, however, there is no legally binding definition up to now.

According to the above mentioned definition, medicinal products can be divided into two groups: “medicinal products by presentation” as stated in paragraph 2a and “medicinal products by function” as defined in paragraph 2b.
However, it is possible that a product is a medicinal product by function and by presentation.

The ECJ has explicitly ruled that the second paragraph of Article 1 paragraph 2 applies to all products which alter physiological functions and which thus may have an effect on health in general, even in absence of a disease [13]. For the definition of a medicinal product by function the ECJ has defined the following relevant criteria:

- The pharmacological properties of the product to the extent to which they have been established in the present state of scientific knowledge;
- The composition of a product and the way in which it is used;
- The risks which may be associated with consumption of the product;
- The extent to which it is sold and the consumers familiarity with it [14].

The existence of health risks is traditionally one of the criteria employed by the ECJ for classifying a product as medicinal [15]. It originates from the aim of health protection pursued by the Community pharmaceutical legislation that products creating health risks should be covered by the rigorous requirements of that legislation in any case of doubt as to their classification.

Medicinal products by presentation the ECJ has defined as follows: A product explicitly indicated or recommended as having therapeutic or prophylactic properties has to be regarded as a medicinal product by virtue of its presentation even if it has no known therapeutic effect. A product is deemed to be presented for treating or preventing disease within the meaning of Directive 2001/83/EC not only when it is explicitly indicated or recommended as such, but also, whenever any averagely well-informed consumer gets the

impression that the product in question should have such an effect [13]. This refers also to the product's form and the way it is packed, and to the information provided to the consumer. Reference to research by pharmaceutical laboratories or to methods or substances developed by medical practitioners or even to testimonials from medical practitioners commenting on the quality and properties of the respective product can lead to a classification of the product as being medicinal [16].

For products, which fall into the definition of two or more regulated products, the following provision was introduced with the review in Art. 2 paragraph 2 of Directive 2004/27 [12]:
In cases of doubt, where, taking into account all its characteristics, a product may fall within the definition of a "medicinal product" and within the definition of a product covered by other Community legislation the provisions of this Directive shall apply.
The rationale is given in the preamble in section no. 7:
With the same objective of clarifying situations, where a given product comes under the definition of a medicinal product but could also fall within the definition of other regulated products, it is necessary, in case of doubt and in order to ensure legal certainty, to state explicitly which provisions have to be complied with. Where a product comes clearly under the definition of other product categories, in particular food, food supplements, medical devices, biocides or cosmetics, this Directive should not apply.

This provision should lead to a change in jurisdiction, at least in Germany. Before introducing this provision, the predominant purpose based on objective characteristics for an averagely well informed, attentive and judicious consumer was decisive for the classification of a product. That means if the medicinal and the nutritional purpose were of equal value, the product was classified as foodstuff [17].
Now a product will be classified as a medicinal product if the medicinal and the nutritional purpose are of equal value.

Germany
The definition of medicinal products is implemented in German legislation in a different manner. According to § 2 (1) AMG [7] medicinal products are
…Stoffe und Zubereitungen aus Stoffen, die dazu bestimmt sind, durch Anwendung am oder im menschlichen oder tierischen Körper

1. *Krankheiten, Leiden, Körperschäden oder krankhafte Beschwerden zu heilen, zu lindern, zu verhüten oder zu erkennen,*
2. *die Beschaffenheit, den Zustand oder die Funktionen des Körpers oder seelische Zustände erkennen zu lassen ….*

§ 2 (3) AMG defines products, which are not medicinal products, e.g.

1. *Lebensmittel* (foodstuff) *im Sinne des § 2 Abs. 2 des Lebensmittel- und Futtermittelgesetzbuches,*
2. *kosmetische Mittel* (cosmetics) *im Sinne des § 2 Abs. 5 des Lebensmittel- und Futtermittelgesetzbuches, …*
7. *Medizinprodukte* (medical devices) *und Zubehör für Medizinprodukte im Sinne des § 3 des Medizinproduktegesetzes, es sei denn, es handelt sich um Arzneimittel im Sinne des §2 Abs. 1 Nr. 2, …*

In contrast to European legislation in German law the term "Fertigarzneimittel" is defined. According to § 4 (1) AMG [7] "Fertigarzneimittel"
…sind Arzneimittel, die im Voraus hergestellt und in einer zur Abgabe an den Verbraucher bestimmten Packung in den Verkehr gebracht werden oder andere zur Abgabe an Verbraucher bestimmte Arzneimittel, bei deren Zubereitung in sonstiger Weise ein

industrielles Verfahren zur Anwendung kommt oder die, ausgenommen in Apotheken, gewerblich hergestellt werden. Fertigarzneimittel sind nicht Zwischenprodukte, die für eine weitere Verarbeitung durch einen Hersteller bestimmt sind.

A related definition was included in Directive 2001/83/EC [8]; here proprietary medicinal products were defined as
Any ready-prepared medicinal product placed on the market under a special name and in a special pack.
But this section has been revoked by Directive 2004/27/EC [12].

In practice, there should not arise any consequences from the different definitions of medicinal products between European and German law. In the legislative procedure for the implementation of the Review into German law the government stated:
Eine Änderung des § 2 Abs. 1 AMG ist aus Sicht der Bundesregierung nicht erforderlich, weil man bei Anwendung der deutschen Legaldefinition in § 2 Abs. 1 AMG bei der Feststellung der Arzneimitteleigenschaft eines Mittels zu den gleichen Ergebnissen gelangt wie bei dem in Artikel 1 Nr. 2 Buchstabe b der Richtlinie 2001/83/EG und bei Artikel 1 Nr. 2 der Richtlinie 2001/82/EG geregelten europäischen Arzneimittelbegriff. Die Übernahme der europäischen Definition des Arzneimittelbegriffs würde somit die Bearbeitung von Abgrenzungsfragen nicht erleichtern [18].

Switzerland
In Switzerland, as an example for a non-EU country, medicinal products are defined as (Chapter 1, article 4 of the Federal Law on Medicinal Products and Medical Devices (Law on Therapeutic Products – LTP) [19])
Products of chemical or biological origin, which are intended to have, or are presented as having, a medicinal effect on the human or animal organism, in particular in the diagnosis, prevention or treatment of diseases, injuries and handicaps; blood and blood products shall also be considered as medicinal products.

In summary, legislation for medicinal products in Europe allows the classification of products as medicinal because of their function, i.e. mode of action, and/or their presentation.
Furthermore, a rule was introduced for the European Union to prioritise the law relating to medicinal products over other product categories, e.g. food and food supplements, in cases of doubt.

2.3.2 Foodstuffs

European Union
The definition of foodstuffs is given in Article 2 of the basic food Regulation (EC) No. 178/2002 [4]. The definition states:
For the purposes of this Regulation, 'food' (or 'foodstuff') means any substance or product, whether processed, partially processed or unprocessed, intended to be, or reasonably expected to be ingested by humans.
'Food' includes drink, chewing gum and any substance, including water, intentionally incorporated into the food during its manufacture, preparation or treatment. It includes water after the point of compliance as defined in Article 6 of Directive 98/83/EC and without prejudice to the requirements of Directives 80/778/EEC and 98/83/EC.
'Food' shall not include:

(a) feed;
(b) live animals unless they are prepared for placing on the market for human consumption;
(c) plants prior to harvesting;
(d) medicinal products within the meaning of Council Directives 65/65/EEC and 92/73/EEC;
(e) cosmetics within the meaning of Council Directive 76/768/EEC;
(f) tobacco and tobacco products within the meaning of Council Directive 89/622/EEC;
(g) narcotic or psychotropic substances within the meaning of the United Nations Single Convention on Narcotic Drugs, 1961, and the United Nations Convention on Psychotropic Substances, 1971;
(h) residues and contaminants.

This definition is very general and there is no specific purpose indicated. The terms "intended to be" and "reasonably" need to be interpreted. "Ingestion" is usually regarded as oral intake [20]. For a restriction of the wide scope of this definition, a list of excluded products is incorporated. But this list is not complete, e.g. medical devices are missing.
Furthermore, as there is a reference to the legislation for medicinal products (Directives 65/65/EEC and 92/73/EEC which are consolidated within Directive 2001/83/EC [8]), every change to the definition of medicinal products will automatically influence the definition of foodstuffs.

Germany
For Germany the definition of foodstuffs in the "Lebensmittel-, Bedarfsgegenstände- und Futtermittelgesetzbuch" (LFGB) [2] is the same as in the European legislation. § 1 LFBG gives a reference to Art. 2 of Regulation (EC) No. 178/2002 [4].
This definition is applicable to all EU member states since a Regulation is directly binding. Therefore it can be concluded that there exists a European concept of foodstuffs.

The definition of foodstuffs in the former LMBG [1] was more precise, because a specific purpose was included. §1 (1) stated: *Lebensmittel im Sinne dieses Gesetzes sind Stoffe, die dazu bestimmt sind, in unverändertem, zubereitetem oder verarbeitetem Zustand von Menschen verzehrt zu werden; ausgenommen sind Stoffe, die überwiegend dazu bestimmt sind, zu anderen Zwecken als zur Ernährung oder zum Genuss verzehrt zu werden.*
But this definition was not in accordance with EU-legislation; therefore the law had to be revised.

Switzerland
The definition of foodstuffs in Switzerland is given in the „Bundesgesetz über Lebensmittel und Gebrauchsgegenstände" (Lebensmittelgesetz, LMG) [21]. In Chapter 1 article 3 foodstuff is defined as
1 …Nahrungs- und Genussmittel.
2 Nahrungsmittel sind Erzeugnisse, die dem Aufbau oder dem Unterhalt des menschlichen Körpers dienen und nicht als Heilmittel angepriesen werden.
3 Genussmittel sind alkoholische Getränke sowie Tabak und andere Raucherwaren.

In contrast to EU legislation, the Swiss law includes a specific purpose for food – analogue to the old definition of foodstuff in Germany. In accordance to the EU law for foodstuff, medicinal products (in Switzerland called "Heilmittel") are excluded from this definition.

Because of the wide scope of the definition of foodstuff in the basic food regulation [4], nearly everything which is intended to be (orally) ingested by humans could be classified as food. Only the incorporated exclusions restrict the scope of this law. As medicinal products are part

of these exclusions (furthermore in Germany foodstuffs are excluded of the scope of the law of medicinal products, the AMG), it can be recorded that a product is never a foodstuff and a medicinal product at the same time. Consequently for a specific product applies either the legislation for food or the legislation for medicinal products.

2.3.3 Food supplement

European Union

The first time a definition for food supplements was given on a European level was Directive 2002/46/EC [5]. This directive has to be implemented into national law by the member states already since 31. July 2003.

According to Article 2 (a)

'food supplements' means foodstuffs the purpose of which is to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, marketed in dose form, namely forms such as capsules, pastilles, tablets, pills and other similar forms, sachets of powder, ampoules of liquids, drop dispensing bottles, and other similar forms of liquids and powders designed to be taken in measured small unit quantities.

In Article 2 (b) nutrients are specified as vitamins and minerals. This list will be completed further as stated in the preamble under section no. 8:

Specific rules concerning nutrients, other than vitamins and minerals, or other substances with a nutritional or physiological effect used as ingredients of food supplements should be laid down at a later stage, provided that adequate and appropriate scientific data about them become available.

Directive 2002/46/EC includes positive lists in Annex I and II containing allowed vitamins and minerals and their allowed forms to be added to food supplements.

The Directive is only applicable for *…food supplements marketed as foodstuffs and presented as such. These products shall be delivered to the ultimate consumer only in a pre-packaged form* (see Article 1.1); medicinal products as defined by Directive 2001/83/EC [8] are excluded from the scope of this Directive (see Article 1.2).

This provision precludes the possibility that a product is a medicinal product and a food supplement at the same time.

Since food supplements are meant "to supplement the normal diet", and, in addition, medicinal products are excluded from the scope of this Directive, it can be concluded that they are intended to be consumed only by healthy persons.

Germany

Directive 2002/46/EC [5] is implemented into German law with the "Verordnung über Nahrungsergänzungsmittel" (NemV) [6] dated 24. May 2004.

Food supplements are defined in § 1 section 1:

Nahrungsergänzungsmittel im Sinne dieser Verordnung ist ein Lebensmittel, das
1. dazu bestimmt ist, die allgemeine Ernährung zu ergänzen,
2. ein Konzentrat von Nährstoffen oder sonstigen Stoffen mit ernährungsspezifischer oder physiologischer Wirkung allein oder in Zusammensetzung darstellt und
3. in dosierter Form, insbesondere in Form von Kapseln, Pastillen, Tabletten, Pillen und anderen ähnlichen Darreichungsformen, Pulverbeuteln, Flüssigampullen, Flaschen mit Tropfeinsätzen und ähnlichen Darreichungsformen von Flüssigkeiten und Pulvern zur Aufnahme in abgemessenen kleinen Mengen, in den Verkehr gebracht wird.

In this definition is a discrepancy to the definition in European law, where the "normal diet" should be supplemented; the German legislator alludes to the "common diet". Since the content of the definition is equal, this should have no implications in practice [22].

Switzerland

There is also a definition for food supplements in Swiss legislation. Food supplements belong to the so-called „Speziallebensmittel" which are defined as follows (Verordnung des EDI vom 23. November 2005 über Speziallebensmittel [23], chapter 1 article 2):

1 … Lebensmittel, die für eine besondere Ernährung bestimmt sind und auf Grund ihrer Zusammensetzung oder des besonderen Verfahrens ihrer Herstellung:
a. den besonderen Ernährungsbedürfnissen von Menschen entsprechen, welche aus gesundheitlichen Gründen eine andersartige Kost benötigen; oder
b. dazu beitragen, bestimmte ernährungsphysiologische Wirkungen zu erzielen.

Food supplements are defined in this Directive in chapter 2, article 22:

1 Nahrungsergänzungsmittel sind Erzeugnisse, die Vitamine, Mineralstoffe oder andere Substanzen in konzentrierter Form enthalten und zur Ergänzung der Nahrung mit diesen Stoffen dienen.
2 Sie werden in Form von Kapseln, Tabletten, Flüssigkeiten oder Pulvern angeboten.

This definition has many similarities to the definition of food supplements in the EU and Germany. Therefore, the decisions about the classification of products should be analogous between Switzerland on the one hand and EU and Germany on the other hand.

To sum up, food supplements are a specific kind of foodstuff. They are intended for the supplementation of the normal diet of consumers, i.e. healthy persons with concentrated sources of nutrients or other substances. In contrast to medicinal products, they have no pharmacological effect, and they do not aim at the prophylaxis or the treatment of diseases.

2.3.4 Case Law from the European Court of Justice and National Jurisdiction

The review by the courts referring to the classification of products as medicinal products or food supplements has established significant case law that influenced the policy in the authorities and also the revision of the legislation.
Some important judgements, which introduced new significant criteria for demarcation are summarised below.
A detailed overview about the demarcation of medicinal products and food in the European Union and Germany in the jurisdiction before and after the introduction of the harmonised foodstuff definition in 2002 is presented in the Master Thesis of Dr. Karin Streso [24].

BGH I ZR 97/98 – "L-Carnitine" – Judgement of 10.02.2000 [25]

With this decision the BGH established the concept of the averagely well-informed, attentive and judicious consumer. The relevant factor for demarcation is how this consumer will appreciate the objective purpose of the product. For this purpose the following factors should be taken into account:

- The purpose of comparable products and their task;
- The opinion of pharmaceutical and medicinal science;
- Indication and instructions of the packaging;
- Promotion.

If there is no objective purpose ascertained, the complete product has to be assessed and the decisive factor is whether the product has a proven pharmacological effect.

BGH 2 StR 374/00 – "Vitamins" – Judgement of 25.04.2001 [26]

The pharmacological effect as a criterion for demarcation was confirmed with the BGH-penalty about vitamins. Here, the court decided that the excess of the recommended daily dose of more than threefold is not sufficient for the classification as a medicinal product. A pharmacological effect has to be demonstrated.
Furthermore it was stated that the presentation as capsules or tablets, the type of packaging or the intake recommendations are no indications for a medicinal product as these are also common for food supplements.

BGH I ZR 273/99 and BGH I ZR 34/01 – "Nutrition for sportsmen" – Judgements of 11.07.2002 [27]

With these judgements the jurisdiction of the "L-Carnitine"-Judgement was continued [25].
In BGH I ZR 273/99 it was decided that a group of products advertised in a catalogue as being capable of building up muscles cannot be classified as medicinal products in general, but must be assessed case by case. The relevant factors are the purpose from an objective point of view, the presentation of the package and if it has a pharmacological effect.
With BGH I ZR 34/01 it was stated that with the implementation of Regulation (EC) No. 178/2002 [4] no changes for the demarcation of medicinal products and foodstuff were introduced. According to BGH, the relevant factor for classification is the definition of medicinal products in EU-legislation. This definition was not changed. Furthermore the ECJ also uses the criterion "pharmacological effect" for demarcation. Therefore, the judgements of the national courts and of the ECJ are concurrent according to the court.

Joint cases C-211/03, C-299/03, C-316/03, C-317/03, C-318/03 – "HLH, Orthica" – Judgement of 09.06.2005 [15]

The OVG NRW forwarded several discussion points to the ECJ concerning the demarcation of medicinal products and foodstuffs or food supplements.
As response, the ECJ argued

- For the classification of a product all characteristics, including the ready-for-use-presentation, have to be taken into account.
- Directive 2002/46/EC relating to food supplements [5] as specific law takes priority over Regulation (EC) No. 178/2002 relating generally to food stuffs.
- If a product fulfils the conditions of a medicinal product as well as the conditions for being classified as a foodstuff, the provisions for medicinal products apply.
- The pharmacological properties of a product are essential for the classification as a function medicinal product. The possible risk to public health in connection with the use of the relevant product is an independent factor that must also be taken into consideration in the context of the classification as medicinal product.
- The import of a medicinal product into another member state is only possible if it is appropriately authorised. This provision applies also, if the product is legally marketed as foodstuff in the country of origin.
- The concept of "upper safe levels" is of no importance for the purpose of distinguishing between medicinal products and foodstuffs.
- In the context of an evaluation by a member state of the risks that foodstuffs or food supplements may constitute for human health, the criterion of the existence of a nutritional need in the population of the member state may also be taken into

consideration. However, the absence of such a need does not in itself suffice to justify a complete ban on marketing foodstuffs or food supplements lawfully manufactured or placed on the market in another member state.

- The scope for judgment evaluation of the national authorities for the establishment of an absence of nutritional need is subject to only limited review by the courts. This is compatible with Community law, on condition that the national procedure for judicial review of the decisions in that regard taken by those authorities enables the court or tribunal seized of an application for annulment of such a decision effectively to apply the relevant principles and rules of Community law when reviewing its legality.
- Novelty in the meaning of Regulation (EC) No 258/97 concerning novel foods and novel food ingredients [28] is to be interpreted that a food or a food ingredient has not been used for human consumption to a significant degree within the Community if, when all the circumstances of the case are taken into account, it is established that that food or that food ingredient has not been consumed in a significant quantity by humans in any of the Member States before the reference date.
- And finally: a national court cannot refer questions on the classification of products to the European Food Safety Authority. An opinion delivered by that Authority, possibly in a matter forming the subject-matter of a dispute pending before a national court, may constitute evidence that that court should take into consideration in the context of that dispute.

OVG NRW 13 A 463/03 – "Tibetan herbal tablets" – Judgement of 10.11.2005 [29]
The product which was subject in this case is assessed in section 3.1 as an example for borderline products. This judgement is of particular importance because the court discussed in detail the new legislation. It was concluded that the priority of the law relating to medicinal products over the law relating to foodstuffs is also applicable to the national legislation. If in one member state a product is classified as medicinal product in conformity with European legislation, this classification is not influenced by the classification as food supplement in another member state.

OVG NRW 13 A 1977/02 – "Lactobact. omni FOS" – Judgement of 17.03.2006 [30]
(Judgement resulting out of the Joint cases C-211/03, C-299/03, C-316/03, C-317/03, C-318/03 from the ECJ – not legally binding, in revision)
With this decision the court introduced a new characteristic for the demarcation of medicinal products and food supplements. The decisive factor here is the "therapeutic purpose"; the court stated that the pharmacological effect is no suitable criterion for the classification of a product.

2.3.5 Further Demarcation Criteria

Some significant criteria for the classification of medicinal products and foodstuff or food supplements were established by judgements of the European Court of Justice or national courts. In the meantime some of them became established in the legislation of medicinal products and food supplements. There is no universally valid definition for these criteria so far. In the following, an overview about descriptions in science and jurisdiction is given.

Pharmacological Effect/ Pharmacological Properties

An important criterion for the demarcation of medicinal products and food supplements is the pharmacological effect or the pharmacological properties of a product. The ECJ introduced this criterion into jurisdiction in 1991 [14]. However, it is debatable if there is a generally applicable definition of this attribute.

In the "Pschyrembel", a medicinal encyclopaedia the term "Pharmakon" (drug) is defined as follows:

Körperfremder oder körpereigener Stoff (chem. Element oder Verbindung), der nach Aufnahme im Körper oder an dessen Oberflächen erwünschte (Arzneimittel) oder schädliche (Toxine) Wirkung hervorruft; viele Pharmaka wirken dosisabhängig entweder als Arzneimittel oder als Gift [31].

For the term „Pharmacology" in the same reference book the following definition is given: *Wissenschaft von den Wechselwirkungen zwischen Arzneistoffen und Organismus* [31].

In textbooks for pharmacology a definition for „pharmacological effect" cannot be found, either. In the textbook "Levine's Pharmacology" e.g. pharmacology is defined as *the unified study of the properties of chemicals and living organisms and all aspects of their interactions*; and a drug is*, in broad terms, any chemical agent other than food that affects living organisms, in its medicinal sense a drug is any chemical agent used in the treatment, cure, prevention or diagnosis of disease* [32].

In the "Mutschler", an important textbook for pharmacology in Germany, there are two definitions of pharmacology: *die Lehre von den Wechselwirkungen der Arzneimittel an gesunden oder kranken Organismen*, or in a broader sense: *die Lehre von den Wechselwirkungen zwischen chemischen Substanzen und biologischen Systemen* [33]. The term „Arzneistoff" is defined as follows: *Wirkstoffe, die zur Vorbeugung, Linderung, Heilung oder Erkennung von Erkrankungen dienen können* [33].

In the Demarcation Guideline between medical devices and medicinal products the definition of pharmacological effect is as follows:

The action of a medicinal product is generally achieved by pharmacological, immunological means or by metabolism. […] "Pharmacological means", in the context of the MDD and AIMD, is understood as an interaction between the molecules of the substance in question and a cellular constituent, usually referred to as a receptor, which either results in a direct response, or which blocks the response to another agent. Although not a completely reliable criterion, the presence of a dose-response correlation is indicative of a pharmacological effect [34].

These definitions illustrate that the term „pharmacological effect" can be understood on the one hand as effects with medicinal properties, but on the other hand generally for physiological effects.

The ECJ itself describes the pharmacological properties of a product as the factor that provides a product for the use in human beings for performing a medical diagnosis or for restoring, correcting or modifying physiological functions [15]. This explanation traces back to the definition of medicinal products in Directive 2004/27/EC [12].

German courts also characterised the attribute pharmacological effect. The BGH stated that a pharmacological effect exists if the effect of a product exceeds the physiological effect caused by ingestion [27]. The OVG NRW concluded that the existence of a therapeutic effect indicates a pharmacological, immunological or metabolic action according to Directive 2001/83/EC as amended [29].

All these explanations demonstrate that a clear and generally accepted definition for the criterion pharmacological effect does not exist until now. So the concept of the pharmacological effect as distinguishing mark for the demarcation between medicinal products and other product classes such as food (supplements), medical devices and cosmetics is still under discussion [34].

Physiological effect

According to Directive 2002/46/EC [5] food supplements are characterised by a nutritional or a physiological effect. The nutritional effect is easier to be defined, since this effect is limited to the sustainment of body functions. But there is a smooth transition between physiological and pharmacological effect and this is, therefore, a crucial criterion for the demarcation of medicinal products and food supplements.

In the "Pschyrembel", the term „Physiology" is defined as follows:

Wissenschaft und Lehre von den normalen Lebensvorgängen, insbesondere von den physikalischen Funktionen des Organismus [31].

Another definition of „Physiology" and the mechanism of action of food supplements can be found in the Guidelines on Plant-based Supplements of the Council of Europe [36]:

Physiology is the science that studies the generally normal functions, organ properties and tissues of living beings. Physiological activities in the context of a healthy individual are the normal functions in the body which keep it working. Contrary to medicines that concern disease, food supplements must therefore be designed with the beneficial aim in mind of ensuring the maintenance and metabolic and physiological functioning of an individual in good health. This is the principle of homeostasis. As a matter of fact, homeostasis is defined as the bodily situation of a healthy individual in whom his/her physiological activities are functioning between the limits considered as normal.

Therapeutic purpose

It has to be discussed if the newly introduced term "therapeutic purpose" [30] is a better defined criterion for the demarcation between medicinal products and food (supplements).

In the Pschyrembel, the term "Therapy" is defined as follows:

Behandlung von Krankheiten, Heilverfahren [31].

In the judgements of the OVG NRW to „Lactobact. omni fos", "OPC-85" and "Vitamin E 400" the court stated that a therapeutic purpose is given *[…] wenn ein in einem Produkt enthaltener Stoff oder eine Stoffzusammensetzung nach dem aktuellen Stand der Wissenschaft geeignet sein kann, eine Verhütung, Heilung oder Linderung bestimmter Krankheiten zu erreichen, ferner dann, wenn mit dem Stoff oder der Stoffzusammensetzung entweder im Wege der Veränderung der normalen physiologischen Funktionen ein sonstiger Nutzen oder Vorteil erzielt oder eine medizinische Diagnose erstellt werden kann* [30].

With this new term the criterion for a medicinal product is closely linked to the existence and the treatment of diseases. The question remains if for the proof of the therapeutic purpose only clinical studies are acceptable. For many products only animal experiments or laboratory tests exist. This argumentation is currently under discussion since the definition of function medicinal products in Directive 2001/83/EC as amended alludes to the characteristic of a pharmacological, immunological or metabolic action of a substance [12].

This judgement is not legally binding at the moment; it has been appealed on a point of law.

The Council of Europe also talks about a "therapeutic effect" and points out that a food supplement *should in no case seek to deal with a pathological state, which belongs exclusively to the field of therapy* [36]. An exact definition of "therapeutic effect" and the discrimination to the physiological effect, however, is not given.

3 HERBAL BORDERLINE PRODUCTS

Three borderline products will be examined in this chapter. They all contain herbal extracts, but their origin, development and purpose are different.
The first example product derives from the Tibetan traditional medicine. A similar product exists in Switzerland where it is registered as a phytotherapeutic medicinal product. This product is presented as an example for a function medicinal product, which has been marketed as a food supplement.
The observation of fewer menopausal complaints in Asia led to the development of the second example product. A possible explanation of this effect may be the different diet in Asia using soy. A product with soy isoflavones should therefore adjust this deficiency in the Western world. This one is an example of products that may fall under the newly introduced provision for cases of doubt.
Before its first distribution, the third example product was relatively unknown in Germany. Therefore there was no perception about the status of the product and the position of customers and authorities was significantly formed by the presentation and promotion of the first suppliers. This product is a typical presentation medicinal product.

3.1 TIBETAN HERBAL TABLETS – PADMA 28

The product „Padma 28“ contains a mixture of herbals, which is offered in the form of tablets. This mixture of herbals originates in the Tibetan traditional medicine. It was distributed from Tibet to Mongolia, then to Siberia and Russia. Here the formula was adapted to the European circumstances, e.g. change of plants to European plants of the same species. The receipt then came to Poland and Western Europe, e.g. to Switzerland. Now Padma 28 is manufactured in Switzerland and registered there as medicinal product since 1978.
The registration as medicinal product required more changes in the composition in the course of the examination of quality and safety [37]. The actual product contains besides camphor a mixture of various herbs, e.g. Lichen islandicus, Valerianae radix etc. Some of the ingredients are components of traditionally authorised medicinal products in Germany. The indication authorised in Switzerland is disturbances of the blood supply with symptoms as itching, formication, spasm of the calf muscles etc [38].

Furthermore there is another version of Padma 28 on the EU market with a slightly different composition [39]. This product contains no aconite. Many suppliers offer this version as a food supplement in the Internet (search in the Internet e.g. via Google: “Padma 28”). In Austria e.g. the product is marketed under the name “Padma Basic” as food supplement [40, 41]. According to the supplier the product should give supportive information in terms of the immune system (*“…werden für die Gesamtheit der Abwehrfunktionen unterstützende Informationen bereitgestellt“*) [42].

Padma 28/ Padma Basic

Composition
For the decision about the classification of a product, the ingredients and their effects have to be examined.

The composition of 1 tablet of the product „Padma 28“ as registered as medicinal product in Switzerland is as follows [38]:

Aegle sepiar fructus	20 mg	Lichen islandicus	40 mg
Amomi fructus	25 mg	Liquiritiae radix	15 mg
Aquilegiae vulgaris herba	15 mg	Meliae tousend fructus	35 mg
Calcii sulfas pulvis	20 mg	Myrobalani fructus	30 mg
Calendulae flos cum calycibus	5 mg	Plantaginis herba	15 mg
Cardamomi fructus	30 mg	Polygoni avicularis herba	15 mg
Caryophylli flos	12 mg	Potentillae aureae herba	15 mg
Costi amari radix	40 mg	Santali rubri lignum	30 mg
D-Camphora	4 mg	Sidae cordifoliae herba	10 mg
Hedychii rhizoma	10 mg	Aconiti tuber	1 mg
Lactucae sativae folium	6 mg	Valerianae radix	10 mg

The resembling product on the market with the similar name (“Padma Basic”, but formerly marketed as “Padma 28” [40]) which is marketed as food supplement e.g. in Austria [43] has a slightly different composition.
1 tablet contains:

Aegle sepiar fructus	40 mg	Lichen islandicus	80 mg
Amomi mod. fructus	50 mg	Liquiritiae radix	30 mg
Aquilegiae viridi folia	30 mg	Meliae tousend fructus	70 mg
Calendulae flos	10 mg	Myrobalani fructus	60 mg
Cardamomi fructus	60 mg	Plantaginis lanc. herba	30 mg
Caryophylli fructus	24 mg	Polygoni avicularis herba	30 mg
Costus amaradus radix	80 mg	Potentillae aureae herba	30 mg
Camphora	8 mg	Santali rubri lignum	60 mg
Hedychii spic. hizoma	20 mg	Sidae cordifoliae herba	20 mg
Lactucae sativae folium	12 mg	Valerianae radix	20 mg

The main differences between the two products are the different amounts of the ingredients and the missing component “Aconiti tuber”. The component “calcium sulphate” is declared as filler on the labelling without quantity. For a preliminary analysis the products will be regarded as equal.

Mode of action

Some of the ingredients are components of herbal medicinal products in Germany and have been evaluated by the “Kommission E”, a commission for the assessment of herbals with therapeutic value in Germany.
The following herbals are specified in a monograph of this commission:

- Calendulae flos:
  This herb has anti-inflammatory properties and positive effects on wound healing and granulation by external application [44].

- Camphor:
  This drug has bronchospasmolytic effects, is an analeptic agent on the respiration and acts as a tonic on the circulation [45].

- Cardamomi fructus:
  The dried fruits have cholagogue and virostatic properties [46].

- Caryophylli fructus:
  This herb acts as an antiseptic, antibacterial, antifungal and antiviral agent and has local anaesthetic and spasmolytic properties. Some of these effects are only described for the local application e.g. on the oral and pharyngeal mucosa [47].

- Lichen islandicus:
  The moss has a slight antimicrobial and a palliative effect [48].

- Liquiritiae radix:
  Components of this herb have secretolytic and expectorant properties, furthermore the recovery of stomach ulcers will be supported. Adverse reactions like mineralocorticoid effects particularly with long term application and high dosage are also described as well as interactions, e.g. with diuretics [49].

- Plantaginis herba:
  This drug has antibacterial, astringent and palliative effects [50].

- Polygoni avicularis herba:
  This drug has astringent properties [51].

- Santali lignum rubrum:
  This drug is used for diseases of the gastro-intestinal tract, as diuretic, astringent agent and cough. But since the efficacy is not proven, the “Kommission E” advised against the use of this drug [52].

- Valerianae radix:
  The radix has sedative and soporific effects [53].

- Aconiti tuber:
  This drug has a negative assessment from the “Kommission E”. It has been applied in the therapy of neuralgia but because of the risk of intoxication at therapeutic doses this drug should not be used [54].
  This herb is an ingredient in the formulation of the medicinal product registered in Switzerland, but it is not contained in the product marketed as a food supplement (see above).

The herbs Potentilla aurea and Lactucae sativae are used in homoepathic therapy [55]. In India, Myrobalani fructus is traditionally used as astringent and against obstipation [55].

In the Swiss official product information of the approved medicinal product, Padma 28 is stated that the constituents of the product achieve their therapeutic effect in an additive, synergistic and antagonistic manner. Furthermore, several relevant ingredients are mentioned which have the following effects according to bibliographic data: Essential oil with camphor (in higher dosage a tonic on the circulation and rectifying on the labour tolerance) and eugenol (antibacterial and local analgetic); flavonoids (anti-inflammatory, anti-oxidant, metal chelate formation) and tanning agents (local anti-inflammatory, anti-oxidant) [38].

Thus it can be stated that the product contains substances that are accredited with pharmacological effects.

Database

In literature, several publications about experimental tests, clinical trials and case studies with Padma 28 can be found.

With *in vitro*- and *in vivo*-experiments e.g. anti-inflammatory properties and inhibition of immunobiological effects towards anti-atherosclerotic effects and therapeutic effect in peripheral circulatory disorders of Padma 28 were investigated [56, 57, 58, 59, 60, 61, 62, 63]. Apoptogenic and survival effects were examined in a leukaemia cell line [64] and effects on human dermal fibroblasts; epidermal keratinocytes and human skin in organ culture were assessed [65]. The antimicrobial activity of Padma 28 was also analysed and an antibacterial effect against Gram-positive bacteria *in vitro* was found [66]. Furthermore a protective effect against changes induced by prolonged appliance of ethanol was explored [67].

In clinical trials primarily the treatment of intermittent claudication with Padma 28 was investigated and an increase in the walking distance could be found [68, 69, 70, 71, 72]. This effect is also mentioned in the Swiss official product information besides the improvement of haemodynamically functional parameters [38]. An observational case study dealt with the treatment of chronic dental pulpitis and found a positive effect on this condition [73]. Moreover, the effect of Padma 28 on blood lipid oxidisability in subjects with mild hypercholesterolaemia was determined [74].

These publications show that the product Padma 28 is associated with pharmacological and curative effects – even though the database may not be exhaustive and the studies may not correspond to the standards of science.

Possible risks

According to the Swiss product information for Padma 28 the following undesirable effects can occur in very rare cases: gastrointestinal disturbances, nervous disturbances with cardiac palpitation and restlessness in predisposed persons, skin rashes or itching [38].

As stated above, in the monograph of the “Kommission E” for the drug Liquiritiae radix adverse reactions and interactions are described. These undesirable effects include mineralocorticoid effects with sodium and water retention, potassium depletion, oedema and in rare cases myoglobinuria [49]. In experimental tests it could be observed that liquorice affected isoenzymes of the Cytochrome-P-450-system in the liver [75]. Thus there is a potential for interactions with active substances, which are metabolised on this path.

It can be concluded that the intake of Padma 28 is not completely without risks. The probability of experiencing undesirable effects or interactions for the individual patient is indeed low, but cannot be ruled out.

Presentation/Promotion

The product “Padma 28” which is registered as a medicinal product in Switzerland is advertised with the statement in the internet: *“PADMA 28 wird verwendet bei Durchblutungsstörungen mit Beschwerden wie Kribbeln, Ameisenlaufen, Schwere- und Spannungsgefühl in den Beinen und Armen, Einschlafen von Händen und Füssen und bei Wadenkrämpfen*“ [76]. This statement is supported by the product information of the official “Arzneimittel-Kompendium” in Switzerland [38].

For the alternative product “Padma Basic”, which is marketed as a food supplement the following statements can be found: *“Eine zusätzliche Zufuhr von pflanzlichen Schutzstoffen kann bei Belastungssituationen zur Unterstützung der körpereigenen Schutzmechanismen sinnvoll sein. Die Inhaltstoffe der tibetischen Kräutermischung wirken Ameisenlaufen, Spannungsgefühl, Wadenkrämpfen, Einschlafen von Händen und Füßen entgegen. Studien*

belegen, dass PADMA BASIC die Durchblutung unterstützt. PADMA BASIC unterstützt die Funktion der Arterien. Ärzte empfehlen immer öfter Kräutermischungen aus Tibet für die Unterstützung des Immunsystems und der Durchblutung. Durch die Inhaltstoffe der tibetischen Kräutermischung (z.B. ätherische Öle, Polyphenole, etc.) kann die Regenerationszeit bei sportlicher Betätigung deutlich verkürzt werden. PADMA BASIC für geistige Beanspruchung. [40]

Similar statements can be found on other web sites, e.g. *PADMA BASIC Kräutertabletten unterstützen die Durchblutung, das Immunsystem, die Funktion der Arterien, bei geistiger Beanspruchung.* [77]

These statements are close to the indications given in the product information of the registered medicinal product “Padma 28”, but are stated in an alleviated form. They state that the effect of “Padma Basic” is supportive.

On the packaging of the product the following statements are given: *Stärkt die Gefäße und die körpereigenen Abwehrkräfte* and *Kräutertabletten nach tibetischer Rezeptur*. The required designation “Nahrungsergänzungsmittel” according to § 4 NemV is also stated [43].

Discussion

For the demarcation between medicinal products and food supplements an important factor in jurisdiction is how the product will appear to the averagely well-informed, attentive and judicious consumer. For this purpose the following factors should be taken into account: the purpose of comparable products and their task; the opinion of pharmaceutical and medicinal science; indication and instructions of the packaging and promotion and if there are pharmacological effects in the recommended dosage [25].
In the case of Padma 28 there is a comparable product with the same name, which is an authorised medicinal product in Switzerland [38]. If a potential customer is searching for information in the Internet, he will easily find many statements about this medicinal product; and since the ingredients of both products are similar it is difficult to differentiate between them.
Furthermore, in some studies effects e.g. on the blood circulation and anti-inflammatory properties were found. In clinical trials the effects of Padma 28 on different diseases were surveyed with positive results. So the conclusion can be suggested that the product has a pharmacological effect.
For the objective purpose of a product it is also important that the whole of the product is considered [26]. Therefore all components should be included in the assessment. In the case of Padma 28 most of the ingredients are known herbal drugs with established effects and they are often included in herbal medicinal products with various components; however, often in different composition and quantity.
The individual ingredients are contained in small amounts in the product. These amounts are assumed to be beneath the threshold of a pharmacological effect. The mode of action, however, is based on the unknown synergism of the various low dosed constituents. Therefore, pharmacological properties of the product cannot be excluded [29].
For the appearance of the product the advertisement and presentation are other important factors. In this context, however, particular statements must not only be reviewed, but also the whole promotion and the whole product [78]. As stated above, the advertising statements for Padma Basic are cautiously worded; they refer to a supporting effect to the physical health.

On the other hand, similar "indications" are advertised for the Swiss medicinal product Padma 28, e.g. "formication" and blood circulation; so there is little distinction between the two products.
The statement *„Kräutertabletten nach tibetischer Rezeptur"* implies to the consumer that the product contains traditional medicinal herbs from the Far East [29].
In summary, it can be stated that the product fulfils the conditions for a function medicinal product because of its pharmacological effects, which are described in scientific publications. Additionally, the presentation and promotion of the manufacturer and suppliers reveal no nutritive purpose, but indicates medicinal properties of the product.

3.2 PHYTOESTROGENS – SOY ISOFLAVONES

Since the hormone replacement therapy (HRT) with estrogens is under discussion because of its serious adverse reactions [79] there is an increasing interest for alternative treatments of menopausal complaints, e.g. hot flushes. One option are the so-called phytoestrogens, which could be extracted from Soya. This vegetable contains isoflavones, which interact with estrogenic receptors [80].
The concept of the positive effect of Soya on menopausal complaints results from the observation that Asiatic women have fewer problems with the climacteric period than women in the Western world. So in the last years many products with soy extracts have been placed on the market for the improvement of menopausal problems [80]. These products are mostly marketed as food supplements (search in the Internet e.g. via Google: "soja isoflavone"); it can be questioned if this classification is correct, since there is a smooth transition to the treatment of a disease that should be treated with medicinal products. This issue should be examined with one exemplary product.

„Alsifemin Klima-Aktiv-Kapseln mit Soja-Isoflavonen".

Composition
The composition of 1 capsule of this product according to one of the suppliers is presented in the following table [81]:

Soya extract therein soy isoflavones	125 mg 50 mg	Pantothenic acid *(as Calcium-D-Pantothenate)*	12 mg
Vitamin E, natural	18 mg	Folic acid	450 µg
Vitamin C	112,5 mg	Biotin	225 µg
Vitamin B_1	2,1 mg	Vitamin D	4,95 µg
Vitamin B_2	60 mg	Iron *(as Iron(II)-fumarate)*	5 mg
Vitamin B_3	24 mg	Zinc *(as Zinc oxide)*	5 mg
Vitamin B_6	80 mg	Lecithin *(as Soya lecithin)*	90 mg
Vitamin B_{12}	8 mg		

Vitamins and minerals, which may be used as nutrients in food supplements, are listed in Annex 1 of Directive 2002/46/EC. The compounds which are allowed for the production of food supplements are listed in Annex 2 of this Directive. Maximum or minimum quantities are not given until now; according to Article 5 these amounts should be established by the European Commission in the future [5]. The manufacturer, however, has to consider some criteria for the determination of maximum quantities. These are the Tolerable Upper Intake

Levels (UL), which are established on the basis of generally recognised scientific data and the intake by nutrition [82].
If these rules are considered, the vitamins and minerals contained in the product are not the determining factor for the classification as food supplement. Therefore only the ingredient Soya extract and its purpose will be taken into account for the assessment of the product.

Mode of action
Soybeans contain among other constituents isoflavones, mainly genistein and daidzein in the form of glycosides. They have a similar structure as the sex hormone estradiol and can interact with estrogenic receptors. The activity, however, is a 100 to 10.000 times lower than the effect of estradiol. These phytoestrogens are able to develop both estrogenic and antiestrogenic effects. The resulting effect depends on the hormone status and the concerned tissues. Furthermore phytoestrogens are accredited with the modulation of enzyme activity, antioxidative and antiandrogenic effects and antithyreoidale properties [80].

Potential intake of isoflavones from foodstuff
In literature the average amount of isoflavones from foodstuff in Asian countries is declared with 50 mg per day. Typical American and European foodstuff contains less than 5 mg per day [83].
Manufacturers and suppliers of food supplements with soy extract assume therefore a daily requirement of 50 mg isoflavones per day [84, 85].
Soy foodstuffs contain the following quantities of isoflavones (Daidzein und Genistein):
Mean value (Daidzein + Genistein) mg isoflavones/100 g foodstuff [83]:

Soybeans green, fresh	151,17 mg
Soybean flour	148,61 mg
Soy protein concentrate (extraction with water)	102,07 mg
Tempeh	43,52 mg
Soy protein concentrate (extraction with alcohol)	12,47 mg
Soy noodle	8,50 mg
Vegetarian Burger	8,22 mg

Database
Epidemiologic data indicate that Asian people have lower rates of osteoporotic fractures, cardiovascular diseases, postmenopausal symptoms and certain cancers than Western populations. These health effects are notably reduced when Asians adopt a Western lifestyle and eating habits [86]. These observations have led researchers to look at Soya as part of the traditional Asian diet for possible answers. An increasing number of researchers are investigating the relation between soy intake and the above mentioned diseases [87].
Many clinical studies of the effects of phytoestrogens on postmenopausal syndrome were conducted. The results are mixed: some studies report a modest benefit compared with placebo and others do not. There was also a wide range in the amount of total isoflavones used in these studies [87].
A review of randomised and controlled trials comes to the conclusion that Soya presumably has a moderate value in the treatment of hot flushes [88]. A meta-analysis, however, comes to a controversial result; the authors reason that a terminating conclusion cannot be drawn because of the heterogeneity of the studies [89].

These publications show that soy isoflavones are accredited with pharmacological effects – the North American Menopause Society states, however, that the results are insufficient to either support or refute efficacy for soy foods and isoflavone supplements [90].

Possible risks

Possible adverse reactions of Soya are allergenic reactions. This information has even to be given in the package leaflet of medicinal products [91].

Furthermore a procarcinogenic effect on estrogen-dependent tumours is under discussion. This effect is likely because of the affinity of isoflavones to estrogenic receptors. On the other hand, a protective effect on hormone-dependent tumours could also be found. Because of this contradictory data from *in vitro* and animal studies, a definite safety assessment of isoflavone intake cannot be made yet [80]. Long-term use of soy products should therefore be avoided.

Presentation/Promotion

According to § 4 NemV [6] the required designation "Nahrungsergänzungsmittel" is stated on the packaging of the product. As advertising statement the following information is given: "Fit und gesund in den Wechseljahren". These statements give no evidence about any medicinal properties of the product.

The information presented by suppliers in the Internet refers mainly to the properties of a foodstuff. On one website e.g. the following information is given:

„**Allgemeines über Alsifemin Klima-Aktiv-Kapseln:**

Der Weibliche Organismus reduziert ab dem 40. bis 45. Lebensjahr die Körpereigene Östrogenproduktion. Dies ist ein völlig natürlicher Vorgang im weiblichen Körper, überall auf der Welt. Die geringere Östrogenproduktion führt häufig zu unangenehmen Begleiterscheinungen wie lästigen Hitzewallungen, gelegentlichen Schweißausbrüchen, Erschöpfung, Müdigkeit und nachlassender Leistungskraft.

Untersuchungen haben gezeigt, dass diese typischen Begleiterscheinungen der Wechseljahre nicht bei jeder Frau gleich ausgeprägt sind und sich vor allem von Land zu Land unterscheiden. So sind diese Beschwerden vor allem in asiatischen Ländern kaum bekannt und nur gering ausgeprägt.

Ernährungswissenschaftliche Studien führen dies auf einen Unterschied in der Ernährung zurück. So wird in asiatischen Ländern im Vergleich zu Europa ein Vielfaches mehr an Soja im täglichen Essen verwendet. Soja ist die Pflanze, aus der die so genannten Isoflavone gewonnen werden. Diesen Soja-Isoflavonen wird der Unterschied im Wohlbefinden während der Wechseljahre zugeschrieben.

Alsifemin Klima-Aktiv-Kapseln mit Soja-Isoflavonen enthalten neben weiteren Nährstoffen eben diese Soja-Isoflavone. Diese gehören zur Gruppe der pflanzlichen Östrogene, auch Phyto-Östrogene genannt. Der verwendete Soja-Extrakt stammt aus nicht genverändertem Soja." [81] (Accentuation by the author)

Another supplier informs the customer as follows:

Nur 1 Alsifemin® Klima-Aktiv-Kapsel pro Tag enthält spezielle, auf den Bedarf der Frau in den Wechseljahren abgestimmte Nährstoffe mit Soja-Isoflavonen. Als Nahrungsergänzung trägt sie dazu bei, dem veränderten Nährstoffbedarf der Frauen in den Wechseljahren gerecht zu werden. Alsifemin® Klima-Aktiv-Kapseln enthalten Sojaextrakt, der reich an Isoflavonen (Phyto-Östrogenen) ist und in der Ernährung während der Wechseljahre nicht fehlen sollte. […]

Nur1 Alsifemin® Klima-Aktiv-Kapsel mit Soja-Isoflavonen pro Tag ist somit eine ideale Nahrungsergänzung für Frauen in den Wechseljahren. [92] (Accentuation by the author)

From these statements the purpose of the product as intended by the suppliers seems to be the supplementation of the nutrition.

On the other hand, the manufacturer gives the following information about the effect of isoflavones on the respective website:

„[Isoflavone] Haben eine östrogenähnliche Wirkung/ Haben einen schützenden Effekt auf Herz und Gefäße/ Wirken als Antioxidanzien und können freie Radikale entgiften/ Wirken auf den Calcium- und Knochenstoffwechsel. Kein lebensnotwendiger Nährstoff, daher treten keine direkten Mangelsymptome auf“ [84].
The statements „analogue effect to estrogens“ and “detoxication of free radicals” put the substance close to the effect of medicinal products just like the statement that this substance is no vital nutrient.

Other websites give more general information about the climacteric period and the treatment of possible complaints. One of them declares that the menopause is no disease but a natural physiologic process meanwhile the estrogen production is decreasing. Concomitantly natural complaints can occur as hot flushes, nocturnal sweating, sleep disturbances, dizziness, anxiety state, restlessness, low spirits and anergy. The different situation in East and Southeast Asia is addressed by implicating that the nutrition with larger amounts of soy is the reason for fewer complaints in the climacteric period [85]. These statements suggest the properties of soy and the contained isoflavones as foodstuff.
But then the same article relates to soy isoflavones as a *„wirksame Therapiealternative zur Linderung der Beschwerden“* and refers to clinical studies which document that „*Soja-Isoflavone Hitzewallungen und Schweißausbrüche reduzieren, sich positiv auf die Herz-Kreislauf-Funktionen und den Knochenstoffwechsel auswirken und zur Verminderung des Brustkrebsrisikos beitragen können“* [85]. This argumentation refers more to medicinal properties of the substance.

Discussion

It is not easy to reach a decision about the classification of products with soy isoflavones. On the one hand these products contain ingredients that are part of nutrition, particularly in East and Southeast Asia. The advertising addresses varying occurrence of menopausal complaints because of the different food pattern between the Western and the Eastern World. Furthermore the climacteric period is characterised as a natural event, which leads to different nutritional requirements.
This perception is supported by the judgement of the OLG Hamburg from May 2001 [93]. The court stated that complaints, which derive from a natural transposition of the body, cannot be defined as illness in general. A product can be classified as a food supplement if it is not intended for the alleviation of diseases but for symptoms which are below the threshold for an illness and which can be balanced with a sufficient supply of nutrients.
If the respective product is unambiguously designed with packaging, package information and promotion as a food supplement, the averagely well-informed customer will not get the impression that the product has pharmacological properties. The existence of medicinal products with similar indications will then not influence the customer, also [93].

But this concept of the OLG is contradicted by the ECJ. The ECJ has defined function medicinal products as “all products which alter physiological functions and which may thus have an effect on health in general, even in the absence of a disease” [13] (accentuation by the author). According to this definition the classification of a product as medicinal product is not influenced by the intention of the treatment of diseases.
In a medicinal encyclopaedia the disease climacteric syndrome is described with the following symptoms: hot flushes, dizziness and sweating, furthermore psychonervous and somatic disorders such as irritability, sleep disturbances, obesity and osteoporosis [31]. This shows that in the scientific literature the complaints which may accompany the menopause

are regarded as diseases. The promotion of products with soy isoflavones promise to improve at least the psychic complaints in the climacteric period.
Scientific literature also shows the probability of pharmacological effects and the possibility of health risks of soy isoflavones. These are other characteristics of medicinal products.

It can be concluded that the purpose of products with soy isoflavones as intended by the manufacturers and suppliers is the supplementation of the nutrition in a period of life with a different nutritional requirement. Therefore, they classify these products as food supplements.
But the probable existence of pharmacological effects and health risks and the treatment of complaints (which are also accredited in the advertising) classify these products as medicinal products.

Typical products with soy extract, e.g. the above cited "Alsifemin Klima-Aktiv-Kapseln" contain 50 mg soy isoflavones in a daily dose. This amount is usual for the Asian diet, but not for the diet of European people. A European would be required to consume an unusual portion of soy products to reach this amount of soy isoflavones with her normal food. This indicates that the purpose of such products exceeds the nutritional or physiological effect, at least for Europeans.

Since the medicinal and the nutritional purpose of these products are at least equivalent, with the introduction of the provision for cases of doubt with the Review [12], these products should be classified as medicinal products. However, since the judgement of the OLG Hamburg in 2001 classified one of these products as a food supplement [93] it is questionable if this product class will be re-evaluated.

3.3 MACA

The maca plant (*Lepidium meyenii Walp* or *Lepidium peruvianum Chacón*, resp.) comes from South America and is cultivated in the Andes since approximately 2000 years. The overground part of the plant is consumed as vegetable and the root tuber can be dried and pulverised. This powder contains proteins, fat, carbohydrates, minerals and vitamins. Furthermore, it is presumed that the powder contains hormone-like substances, which should support the pelvis region and influence the production of testosterone and estrogens. Since a few years food supplements with maca-powder are placed on the market in Europe with the designation *"Viagra der Natur"* [94]. Via search in the Internet (e.g. via Google: "Maca") many products with statements like "Kult-Aphrodisiakum der Inkas" [95] or "Maca: Verdreifachung der sexuellen Aktivität" [96] can be found.
This leads to the question if the classification of these products by the manufacturers and suppliers as food supplements is correct or if these products are medicinal products, which have to obtain a marketing authorisation before they can be placed on the market.

Capsules with maca root extract

Composition
One example product contains the following ingredients according to the supplier:
500 mg maca root extract per capsule, furthermore silica, magnesium stearate and gelatine [95].

Mode of action
The root powder contains mainly carbohydrates, fibres and proteins [97]. These ingredients are typical for foodstuff. Substances with pharmacological properties are not evidently identified in the product until now.

Database
Only few publications about the medicinal use of maca can be found in literature. One investigation found a noticeable increase of sexual activity in rats after ingestion of maca powder [98]. Other studies examined the effects of maca extracts on the sexual behaviour and spermatogenesis in rats and mice [99, 100].
In one investigation with humans no effect was found on the penile blood circulation of a standardized maca extract in men with mild erectile dysfunction [101].

These data give no scientific evidence for the support of a pharmacological effect of maca extract.

Possible health risks
The database for toxicological effects of maca extract is comparably low. A review states that maca has "a low degree of acute oral toxicity in animals and low cellular toxicity in vitro" [102].

Promotion
Many suppliers present capsules, which contain maca root extract in the Internet. They advertise their products with statements like:
"Natürliches Potenzmittel und Aphrodisiaka; Steigert die Libido; Fördert einen ausgeglichenen Hormonhaushalt; Steigert die Energie; Verbessert die männliche Potenz; Optimiert die Lebens- und Widerstandskraft und schützt gegen Stressfolgen; Erleichtert die ersten Symptome in der Menopause". They refer also to scientific studies, which should proof the efficacy of maca increasing sexual activity. A scientist is cited stating maca to be a natural alternative to Viagra® [95].
Other websites state the efficacy of maca against impotence and infertility; furthermore the product should have positive effects on sleep disturbances and menopausal complaints and should increase the physical and mental efficiency [103].
All these information can be easily found in the Internet and show that medicinal properties are accredited to products that contain maca.

Discussion
For the classification of this product the decisive factor is not the ingredient of the product but the main purpose [97]. The available scientific data gives no indication for a pharmacological effect or toxicological risks of maca extract. A nutritive purpose, however, is not apparent for capsules with maca extract.
The product is relatively new on the German market; the customer has not been familiar with this kind of product. Thus there is no established objective purpose of the product.
According to the advertisements in the Internet the product has an aphrodisiac effect and increases the potency. This would be an effect on the human body that exceeds the potential influence of foodstuff, i.e. it is more than a "normal" influence of the physiological function. Furthermore, promotion compares the efficacy of maca to the authorised medicinal product Viagra®. For the averagely well-informed, attentive and judicious consumer these statements lead to the impression that the product can influence designated functions of the body (here: virility) and is therefore a medicinal product.

Since the ingredients of the product have no established pharmacological properties, the product is considered as a medicinal product by presentation.
However, if a supplier clearly refrains from advertising the aphrodisiac and potency-increasing effects and limits the statements about his product to the nutritive purpose, a classification as a food supplement could be possible – if there is no new evidence for pharmacological properties and potential health risks.

4 CONCLUSION AND OUTLOOK

The legislation and consequently the definitions for medicinal products and food supplements have been harmonised throughout the European Union. The presented examples show, however, that classification of borderline products has not become easier. Furthermore there is a growing grey area with products for which it is unclear if they have to be classified as medicinal product or as foodstuff/ food supplement. There are still different views about the classification of specific products between authorities and distributors, but also between authorities and courts of justice, even between the authorities of the different member states.

According to the ECJ the classification of a product has to be performed on a case-by-case basis and the following criteria have to be taken into account [15]:

- ⇒ the qualitative and quantitative composition of the product
- ⇒ the purpose of the product as indicated by the manufacturer
- ⇒ the instructions for use, the distribution channel, the packaging
- ⇒ the pharmacological properties of a product according to the present state of scientific knowledge
- ⇒ the common objective view of the consumers or existing commercial practice, resp.
- ⇒ accompanying information, promotion, press releases, internet
- ⇒ the potential risks of the product
- ⇒ the provision for cases of doubt according to Article 2 (2) 2004/27/EC

Since the decision about the classification of a specific product has to be taken case by case, it is likely that different persons with diverse backgrounds (profession and/or employment) may come to different conclusions. On the one hand, food supplement producers and suppliers have the desire to retain as broad a product base as possible. On the other hand, regulators need a sufficiently broad definition of a medicinal product to allow all products that require control to be classified accordingly.

This situation is also caused by the current legislation since there are a lot of possibilities left for interpretation. The definition for food in the basic food regulation [4] is broad; a specific purpose is not included and it covers nearly all products that can be ingested by humans. This assumption is only restricted by an incomplete list of exclusions.
In Directive 2002/46/EC relating to food supplements [5] the purpose *[…] nutritional or physiological effect […]* is indicated for ingredients of food supplements. But these substances are not qualified until now except for vitamins and minerals, so there is a potential for different opinions about suitable constituents. Furthermore, the terms “nutritional or physiological effect” are not legally defined, thus their interpretation may also differ.

As a result of the broad notion of food in legislation, its definition is unsuitable for the demarcation of medicinal products and food. Therefore for classification of borderline products it has to be examined if the respective product fulfils the criteria of a medicinal product. The introduction of the rule for cases of doubt also supports the priority of the provisions for medicinal products [29].

The ECJ and consequently the national courts established the attribute “pharmacological effect” as an important criterion for the classification of a product as a medicinal product. However, this term is not easy to determine as shown in section 2.3.5. Although the definition of medicinal products was extended in Directive 2004/27/EC [12] utilising the mode of action “pharmacological, immunological or metabolic action”, the criteria are not defined legally.
According to current legislation and case law, a proposal for the procedure of the classification as medicinal product or foodstuff/ food supplement of a specific herbal borderline product is made:

Does the respective product have pharmacological effects or does it contain ingredients with pharmacological effects?
Criteria:
- The ingredients are identical to those of authorised medicinal products.
- Publications about clinical studies, *in vitro*- or *in vivo*-experiments can be found in the literature which prove pharmacological effects of the product or of its ingredients.
- The intake of the respective product induces adverse reactions or there is a potential for health risks.

yes → Medicinal product (by function)

no
↓

How is the respective product presented/advertised?
Criteria:
- The presentation/promotion is characteristic for medicinal products.
- A medicinal purpose is indicated.
- According to the common objective view the product is a medicinal product.
- There is no transparent nutritive purpose or purpose for consumption.

⇨The consumer gets the impression, the respective product is a medicinal product.

yes → Medicinal product (by presentation)

no
↓

foodstuff/ food supplement
(with misleading statements)

In the judgement of the OVG NRW concerning Tibetan herbal tablets [29], the court also declared that demarcation is still a national decision. This position is also acknowledged by the ECJ who stated that the classification of specific products as medicinal product or as foodstuff might be divergent between member states with the current state of Community

law [15]. Therefore, it is possible for a member state to classify a product as a medicinal product if this decision is in accordance with European legislation even though the same product is sold as a foodstuff or food supplement, in another member state.

This situation is rather unsatisfying since it leads to the following problems: There is no legal certainty for suppliers of herbal food supplements, and the free movement of goods is hampered between member states. Furthermore, pharmaceutical companies cannot use European procedures like the Mutual Recognition or the Decentralised Procedure for licensing of medicinal products if some member states do not accept the status of a specific product as medicinal.

A first step for an improvement of the present situation is announced in the frame of the new health and nutrition claims Regulation of the European Commission [104] which is meant to solve the question of promotion of food (the formal adoption by the Council is expected for autumn 2006). With this regulation, clear rules for statements about the health value of a product will be introduced. If suppliers of food supplements follow these rules in terms of advertising their products, they clearly present their products as a non-medicinal one and they avoid the risk to cross the border to presentation medicinal products.

However, there is still potential for optimisation of the current legislation. An amendment of the positive lists in Annex I and II of Directive 2002/46/EC relating to food supplements [5] with specific herbal extracts and statements about their quantitative amounts is required as well. If manufacturers use substances, which are included in those lists in the allowed amounts only, the status of their products as food supplements is ensured.

It should also be discussed if the attribute “pharmacological action” or “pharmacological effect” should be legally defined within the next revision of the legislation for medicinal products. The development of a more suitable criterion for the demarcation would be an alternative reasonable task, since the qualification of this criterion is discussed in the literature [34] and no solution has been found yet.

Although the above mentioned measures would improve the situation for producers and suppliers as well as for regulators, there are still products left which have to be assessed individually on a national level. For these products the development of a guideline for the demarcation of borderline products on a European level would be a reasonable target. At present guidelines or checklists are only present on a regional level. E.g. for Germany, there exists a Guidance document of the “Arbeitsgemeinschaft Lebensmittelchemischer Sachverständiger der Länder und BgVV” [105]. This document is currently under review, because of the recent revision of the legislation. Many local authorities therefore have to develop their own appraisal factors for the classification of products.
In the preparation phase for a European document, the perception of the authorities of the member states and industry would be discussed and harmonised. After finalisation of this guideline some well-defined criteria for the classification of borderline products for the European Union would exist.
Such a guideline would enhance the legal certainty for producers and suppliers since criteria to be considered for the development of food supplements marketable in all member states of the European Union would be established. Furthermore, the work of the regulators in the competent authorities would be facilitated because the classification of a specific product in one member state would be sufficient and the authorities of the other member states would be able to rely on this decision.

5 SUMMARY

The demand for products that have a beneficial effect on human health is growing. Many food supplements with herbal ingredients promise to have this effect. These herbal products are often located in a transitional area since they can have attributes of medicinal products as well as of food supplements. The demarcation of these products is unambiguous and often different opinions exist between producers and authorities in terms of the classification of a specific product as food supplement or as medicinal product. Furthermore it is possible that a product is classified as a food supplement in one member state and as a medicinal product in another.
In 2002, a harmonised definition for food supplements was introduced into European legislation with Directive 2002/46/EC. In addition, the definition of medicinal products was amended with Directive 2004/27/EC.

In this thesis it is examined if the classification of borderline products has become easier with these new provisions. The qualification of existing criteria for the classification has been analysed using the example of three herbal products. All of them were classified as food supplements by their vendors.
The first example product derives from the Tibetan traditional medicine. A similar product exists in Switzerland where it is registered as a phytotherapeutic medicinal product. This product is presented as an example for a function medicinal product that has been marketed as a food supplement.
The observation of fewer menopausal complaints in Asia in relation to the typical diet with plenty of soy led to the development of the second example product. This product is an example for products, which fall under the newly introduced provision for cases of doubt.
Before the first distribution, the third example product was relatively unknown in Germany. Therefore there was no perception about the status of the product and the position of customers and authorities was significantly formed by the presentation and promotion of the first suppliers who promised medicinal effects. This product is an example for a presentation medicinal product.
The presented examples show that the classification of borderline products has not become easier with the introduction of a harmonised legislation for medicinal products and food supplements in the European Union.

According to current legislation and case law, the classification of a specific product has to be conducted case by case. For demarcation, the identification of pharmacological properties of a product is an important criterion. However, this criterion is difficult to determine since a legal definition does not exist.
Furthermore the current state of Community law still allows that the classification of specific products as medicinal product or as foodstuff may be divergent between the member states.

A first step for an improvement of the present situation is announced in the frame of the new health and nutrition claims Regulation of the European Commission, which will bring clarity for the promotion of food in relation to statements about the health value of products.

For a further improvement of the current situation some proposals are made:

- The positive lists in Annex I and II of Directive 2002/46/EC relating to food supplements should be amended through extension of the positive lists with more substances suitable for food supplements. Furthermore maximum amounts for these substances should be given.

- The criterion “pharmacological properties”/”pharmacological action” should be legally defined or a more suitable criterion for the demarcation should be evolved.
- A guideline for the demarcation of borderline products on a European level should be developed.

With these measures the legal certainty for producers and suppliers would be enhanced and the work of the regulators in the competent authorities could be facilitated.

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ACKNOWLEDGMENTS

Bei Frau Dr. Schraitle bedanke ich mich herzlich für die Betreuung dieser Arbeit. Ihre Unterstützung hat meine Arbeit sehr gefördert und positiv beeinflusst.

Frau Dr. Wachenhausen danke ich für ihre bereitwillige Übernahme des 2. Referates.

Frau Dr. Stephan danke ich für ihre Anregungen und Denkanstöße, die mir beim Schreiben dieser Arbeit sehr geholfen haben.

Bei meinen Vorgesetzten und Kolleginnen im „alten“ und „neuen“ Fachgebiet bedanke ich mich vielmals für die Unterstützung, durch die die anstrengende Zeit der Seminare, Hausaufgaben und Masterarbeit leichter zu bewältigen war.

Frau Dr. Annette Münzenberg danke ich sehr herzlich für das Korrekturlesen der Arbeit und den „Blick von außen“.

Den Organisatoren und Referenten des Studiengangs danke ich für die organisatorische Unterstützung und die vielen interessanten und informativen Seminarstunden. Bei meinen Kommilitonen bedanke ich mich für die angenehme Atmosphäre während der Seminartage.

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

Bonn, den 12.11.06