Vitamins as Medicinal Products – Regulatory Considerations

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Dr. Frauke Hätzelt

aus Wolfenbüttel

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Betreuerin und 1. Referentin: Dr. Rose Schraitle

Zweite Referentin: Dr. Christine Mayer-Nicolai

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LIST OF ABBREVIATIONS

ADME	Absorption-Distribution-Metabolism-Excretion
AESGP	Association of the European Self-Medication Industry
AFC	Panel of Food Additives, Flavourings, Processing Aids and Materials in Contact with Food of EFSA
AGE	Advanced Glycosylation End Products
ASMF	Active Substance Master File
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
BMG	Bundesministerium für Gesundheit (Federal Ministry of Health, Austria)
CEP	Certificate of Suitability of Monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CoA	Coenzyme A
CP	Centralised Procedure
DACH	D-A-CH Nutrition Societies of Germany – Austria – Switzerland (DGE, ÖGE, SGE/SVE)
DCP	Decentralised Procedure
DGE	Deutsche Gesellschaft für Ernährung (German Nutrition Society)
DMA	Danish Medicines Agency
EC	European Commission
ECJ	European Court of Justice
EFSA	European Food Safety Authority
EMEA	European Medicines Agency
ENTR	Directorate-General Enterprise & Industry
EPAR	European Public Assessment Report
EU	European Union
EVM	Expert Group on Vitamins and Minerals, Food Standards Agency, UK
FAD	Flavin Adenine Dinucleotide
FMN	Flavin Mononucleotide
FPNU	Food for Particular Nutritional Uses
FSMP	Food for Special Medical Purposes
GMP	Good Manufacturing Practice
IMB	Irish Medicines Board
INS	EMEA Inspections Sector
IPEC Europe	International Pharmaceutical Excipients Council Europe
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Mutual Recognition Product Index
MRP	Mutual Recognition Procedure
NAD(P)	Nicotinamide Adenine Dinucleotide (Phosphate)
NAM	National Agency of Medicines (Finland)

NDA	Panel on Dietetic Products, Nutrition and Allergies of EFSA
NtA	Notice to Applicants
PALP	Pyridoxal-5'-Phosphate
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetic
RDA	Recommended Daily Amount
SANCO	Directorate-General Health & Consumers
SCF	Scientific Committee on Food
SPC	Summary of Product Characteristics
TDP	Thiamine Diphosphate
THF	Tetrahydrofolate
TTP	Thiamine Triphosphate
UL	Tolerable Upper Levels of Intake

1 Introduction

Vitamins are essential nutrients and as such they have to be ingested as part of the diet to ensure the normal functioning of the body.

Nutrition is a field of increasing public (and political) discussion. The relationship between health and a well-balanced diet is recognised more and more together with the increase of the so-called diseases of civilisation which are often caused or worsened by malnutrition. The public awareness of good nutrition also led to the development of nutrient-enriched food (fortified food) or of food supplements which contain nutrients, i.e. vitamins or minerals, in dose form to supplement the normal diet. The same trend can bee seen to a certain extent in the development of new cosmetics containing diverse additives, among them vitamins. The second national study on alimentary habits in Germany (Nationale Verzehrstudie II) revealed that about one third of all Germans take food supplements and not only with the intention to supplement nutritional deficits but also to prevent diseases (Max-Rubner-Institut, 2008), although the variety of food available in the industrial nations is sufficient to satisfy the vitamin needs of average healthy people with the normal diet (DGE, 2003). This is supported by the second national study on alimentary habits which showed that the vitamin supply of the majority of Germans according to the recommended daily amount (RDA) is covered (Max-Rubner-Institut, 2008).
There are, nevertheless, risk groups, either because they suffer from impaired resorption or because they have an increased need of vitamins, for whom supplementation of the nutrition is recommended (Bässler et al., 2002, Chapter 7; Hahn, 2009; Elsner, 2005).

The applications of vitamins mentioned above fall in the category of maintaining health, while medicinal products aim at preventing or treating diseases. As vitamins are essential for the normal functioning of the body, a lack of vitamins might cause diseases or diseases might inhibit the normal uptake or metabolism of vitamins. Vitamins might therefore be administered as medicinal products exerting their normal metabolic actions to restore the physiological functions of the body. And, further to that, vitamins can also exert pharmacological activities.

The aim of this thesis is to describe under which conditions products containing vitamins are considered medicinal products, discussing especially borderline aspects, and the particularities and consequences thereof. The thesis focuses on the European Union and Community legislation. When national aspects are to be considered, Germany is typically taken as example and compared, as appropriate, to other Member States.

The first part of the thesis deals with the demarcation of medicinal products from food, specifically food supplements, and cosmetics. The second part discusses selected aspects of the application of EU rules on marketing authorisations to medicinal products containing vitamins and evaluates them in the light of the current practice.

Finally, it shall be concluded from the discussions of the thesis which strategic options the special characteristic of vitamins of having nutritional and medicinal properties offers with regards to the development and marketing of a vitamin product.

2 Results and Discussion

2.1 Demarcation of Vitamin Containing Products

Vitamins are contained in food, cosmetics or medicinal products. Classification in one of these legal categories is important for the development of a new product, as the classification requires to follow very different regulations before and during commercialisation of the product, e.g. with regards to allowed ingredients, labelling, advertising, authorisation procedures or monitoring in the market. Food/cosmetics' law and pharmaceutical law differ fundamentally with regards to marketing. Marketing of food/cosmetics is generally allowed with certain exemptions described in the legislation and guidelines, while marketing of medicinal products is generally prohibited unless an authorisation has been granted by a competent authority. Commercialisation of a product as food which is classified by competent authorities as medicinal product would therefore be a criminal act.

To distinguish between medicinal products and food or cosmetics, the definitions in the respective EU laws need to be consulted. All three kinds of products represent important fields of Community law in the European Union. The national laws often differ significantly depending on the respective traditions in nutrition or medicine, and EU-wide harmonisation of laws aims at protection of public health and/or improving quality of life and at ensuring the functioing of the internal market.
The most recent examples of harmonised food legislation are Regulation (EC) No 1924/2006 of the European Parliament and of the Council on nutrition and health claims made on foods and Regulation (EC) No 1925/2006 of the European Parliament and of the Council on the addition of vitamins and minerals and of certain other substances to food.

Products containing vitamins can often be considered "borderline products" since classification is ambiguous and more than one definition seems applicable. Vitamins are on the one hand clearly recognised as nutrients as they are essential for the healthy functioning of the body and have to be ingested regularly. On the other hand they are recognised as medicinal products because diseases might be caused by lack of vitamins or diseases (combined with fever and enhanced metabolism, stress and catabolism) might influence the normal uptake and metabolism of vitamins (Bässler et al., 2002, chapter 1.5) requiring therapeutic intervention. Vitamins furthermore may exert pharmacological actions unrelated to their metabolic role (please refer to chapter 2.1.3.4). Borderline products exist in the grey area between both clearly recognised intentions, when vitamins are taken to reduce risk factors of a disease or to prevent a disease.

Legislaton requires clear allocation of products, it is not possible that more than one classification applies at the same time. Regulation (EC) No 178/2002, Art. 2 states that food does not include medicinal products. The recital of Directive 76/768/EEC on cosmetics states that "this Directive is not applicable to the products that fall under the definition of a cosmetic product but are exclusively intended to protect from disease". Directive 2001/83/EC, Art. 2(2) even prioritises the applicable laws as "the provisions of this Directive shall apply", if under consideration of all properties a

product falls within the definition of a medicinal product and within definitions of other Community legislation, e.g. food or cosmetic, because Directive 2001/83/EC provides for the highest level of measures to safeguard public health.

In the following the definitions are given and the demarcation of borderline products (medicinal product – cosmetics, medicinal product – food) is discussed.

Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use, as amended by Directive 2004/27/EC, provides the definition of medicinal products. Medicinal products are defined as "any substance or combination of substances presented as having properties for treating or preventing disease in human beings" (Art. 1(2)(a)) or as "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" (Art. 1(2)(a)). Thus, products can be defined as medicinal either by virtue of "presentation" or of "function". This terminology is used as from now to refer to either of the two aspects of the definition.

2.1.1 Legal Aspects of Demarcation of Medicinal Products and Cosmetics

Cosmetic products are regulated in Council Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products.
The definition given in Art. 1 of that directive mentions two conditions: the product must be placed in contact with external parts of the body, with the teeth or the mucous membranes of the oral cavity and it aims at "exclusively or mainly cleaning them, perfuming them, changing their appearance and/or correcting body odours and/or protecting them or keeping them in good condition". These last two aims are close to the purposes of medicinal products, the medicinal claim of "preventing disease" or the restoring/correcting/modifying of physiological functions, when thinking of e.g. hair growth, elasticity of skin or intact dental enamel. But, as the main or exclusive aim of cosmetics should be cleaning, perfuming, or changing appearance, these may only be secondary purposes for cosmetics. This intention is clarified in the recital of Directive 76/768/EEC on delimiting cosmetics and pharmaceuticals, saying that products with the sole purpose of protecting from disease are not covered by Directive 76/768/EEC.
Thus, cosmetic and medicinal products can be distinguished by the *purpose*. Medicinal products applied e.g. as ointments, gels, sprays or patches are also "placed in contact with various external parts of the human body" but with a medicinal purpose, e.g. Mirfulan® Spray N, Merckle Recordati GmbH, containing among others vitamins A and D to support healing of wounds (Package Leaflet Mirfulan® Spray N, 2006).
But also the location of application might suffice for demarcation, e.g. a gel to deliver vitamin A to the eye, which is excluded for cosmetics, Oculotect® mono A Augengel, Novartis Pharma GmbH (SPC Oculotect® mono A Augengel, 2005).

The European Commission has published several guidance documents on demarcation of cosmetics to other sectoral legislation, among them a guidance document on the demarcation between the Directives 76/768/EEC and 2001/83/EC (Guidance Document on the Demarcation between the Cosmetic Products Directive 76/768 and the Medicinal Products Directive 2001/83 as agreed between the Commission services and the competent authorities of Member States) which expresses the same interpretation of the definitions in both directives, of the purpose being the key parameter of classification. The demarcation of cosmetics is well covered by this guidance document, and shall therefore not be further investigated.

2.1.2 Legal Aspects of Demarcation of Medicinal Products and Food

2.1.2.1. EU Provisions

Regulation (EC) No 178/2002 of the European Parliament and of the Council laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety provides the framework for the EU food law. There are further laws regulating food in the EU, which have to be considered with regards to the demarcation:
Council Directive 89/398/EEC on substances that may be added for specific nutritional purposes in food for particular nutritional uses,
Commission Directive 1999/21/EC on dietary foods for special medical purposes,
Directive 2002/46/EC of the European Parliament and of the Council on the approximation of laws of the Member States relating to food supplements,
Regulation (EC) No 1924/2006 of the European Parliament and of the Council on nutrition and health claims made on foods,
Regulation (EC) No 1925/2006 of the European Parliament and of the Council on the addition of vitamins and minerals and of certain other substances to food.
General provisions on labelling of foodstuffs and on nutrition labelling are given in Directives 2000/13/EC and 90/496/EEC respectively, if the above mentioned directives and regulations do not provide for exemptions or additional requirements.

Types of Food and Demarcation Aspects thereof

Regulation (EC) No 178/2002 Art. 2 defines food as “any substance or product, whether processed, partially processed or unprocessed, intended to be, or reasonably expected to be ingested by humans” and excludes products which are in principle ingested but do not belong to food, among others medicinal products.

Directive 89/398/EEC on foodstuffs intended for particular nutritional uses defines dietary foods and lists those kinds of dietary foods which require specific provisions in separate directives, among them food for special medical purposes. It also demands “a list of substances with specific nutritional purposes such as vitamins, mineral salts, amino acids and other substances intended to be added” to these dietary foods (Art. 4(2) of Directive 89/398/EEC). Directive 2001/15/EC lists these substances. Further directives originating from Directive 89/398/EEC which have to be considered in the context of demarcation of foodstuffs and medicinal products are

Directive 2006/141/EC on infant formula and follow-on formula which gives details on vitamins in the composition of baby food and specifically Directive 1999/21/EC on dietary foods for special medical purposes.

There are certain types of food, as defined in the respective laws, which lie in the borderline area between nutrition and medicines, particularly for preventive purposes:

Food Supplements
⇓
Food for Particular Nutritional Uses
⇓
Food for Special Medical Purposes
⇓
Medicinal Products

Food supplements, acc. to Directive 2002/46/EC Art. 2, belong to food but are distinguished from other foodstuffs by the following three properties:

- by the purpose to supplement the normal diet,
- by being concentrated sources of nutrients (vitamins and minerals),
- by being marketed in dose form.

Food supplements and medicinal products have in common the presentation in dose form. According to Art. 2(a) of Directive 2002/46/EC food supplements are foodstuffs "marketed in dose form, namely forms such as capsules, pastilles, tablets, pills and other similar forms, sachets of powder, ampoules of liquid, drop dispensing bottles, and other similar forms of liquids and powders designed to be taken in measured small unit quantities". Dose forms for food supplements are insofar limited as food is ingested (see definition above, Regulation (EC) No. 178/2002, Art. 2). This means, that e.g. injection, inhalation, implantation are means of administration limited to medicinal products (or medical devices).

Medicinal products containing vitamins and food supplements have in common that both represent concentrated sources of vitamins. Hence, concentrated vitamins in ingestable dose form have to be classified either as food supplements (or FNPU, discussed separately below) or as medicinal products by their *purpose*. Food supplements aim at adding to the normal diet. As described in the recitals 3 and 4 of Directive 2002/46/EC, a normal and balanced diet should provide all necessary nutrients for a healthy life, but there are particular lifestyles and groups of population for which this ideal diet is not achieved, at least not for all nutrients, so people may need to supplement their diet. This goes along with the growing public awareness of the correlation of health and nutrition and the corresponding growing markets of food supplements and fortified foods. Food supplements aim at "consumers" not patients, i.e. healthy people, to maintain in good health not to treat a disease. That is reflected

in Directive 2002/46/EC on food supplements which “shall not apply to medicinal products as defined by Directive 2001/83/EC”.

The clear purpose of nutrition represents the differentiation criterion to medicinal products, because the intake of food supplements could be seen as preventive only in the very broad sense of supporting good health in general.

Foods for particular nutritional uses (FPNU, dietetic or dietary foods) “are foodstuffs which, owing to their special composition or manufacturing process, are clearly distinguishable from food stuffs for normal consumption” (Directive 89/398/EC, Art. 1(2)(a)). Particular nutritional uses could apply for “persons whose digestive processes or metabolisms are disturbed”, or “persons who are in a special physiological condition and who are therefore able to obtain special benefit from controlled consumption of certain substances in foodstuffs” (Directive 89/398/EEC, Art 1(2)(b)). FNPU have a nutritional purpose but for conditions which deviate to a certain extent from the average healthy person.
The relevant directives (89/398/EEC and 2001/15/EC) do not set maximum amounts, but dietary foods shall be “safe products that fulfil the particular nutritional requirements of the persons for whom they are intended as established by generally accepted scientific data” (Directive 2001/15/EC Art. 1(3)). Regulation (EC) No 1925/2006 requires upper safe levels of vitamins added to food (as does Directive 2002/46/EC for food supplements, see below). The regulation also applies for FPNU, but without prejudice to specific provisions of FPNU, in particular concerning “compositional requirements of such products rendered necessary by the particular nutritional requirements of the persons for whom they are intended” (Directive 2001/15/EC Art. 1(3)). In conclusion, scientifically justified deviations from the general maximum (or minimum) levels for vitamins in food are allowed for FPNU.

Food for special medical purposes (FSMP) provides for several exceptions of general food provisions:
FSMP is “specially processed or formulated and intended for the dietary management of patients and to be used under medical supervision” (Directive 1999/21/EC Art. 2(2)(b)). It is exceptional because it is given to patients and it is used under medical supervision. For this food specific rules for labelling and vitamin content apply.
FSMP are “intended for the exclusive or partial feeding of patients with a limited, impaired or disturbed capacity to take, digest, absorb, metabolise, or excrete ordinary foodstuffs or certain nutrients contained therein or metabolites, or with other medically-determined nutrient requirements, whose dietary management cannot be achieved only by modification of the normal diet, by other foods for particular nutritional uses” (Directive 1999/21/EC Art. 1(2)(b)). The purpose of FSMP is nutrition as part of the overall treatment of a disease. These food preparations may either be nutritionally complete or incomplete and may contain a standard nutrient formulation or a nutrient-adapted formulation specific for a disease. They usually also contain vitamins and Directive 1999/21/EC lists minimum and maximum values for the respective vitamins but also allows for deviation if justified by the targeted disorder or disease.

The labelling is specific, as it links FSMP to the treatment of a disease, which is generally prohibited for food. The target disease or condition has to be labelled as well as precautions and contra-indications, where applicable (Directive 1999/21/EC Art. 4(4)), similar to the requirements for the labelling and product information of medicinal products (Directive 2001/83/EC Art. 11, 54, 55).

Demarcation by Presentation/Labelling

If a product is labelled to prevent or treat a disease it is by definition a medicinal product. This is given by the definition of presentation medicinal products in Art. 1(2)(a) of Directive 2001/83/EC as well as by Directive 2000/13/EC Art. 2(1)(b) and Directive 2002/46/EC Art. 6(2) which prohibit such labels for foodstuffs and food supplements. Labels for foodstuffs have to be carefully chosen to be in line with both provisions. Certain exemptions exist for the labelling of food for special medical purposes. This has been discussed before.
Allowed health-related claims on food are described in Regulation (EC) No 1924/2006 on nutrition and health claims. Health claims mean “any claim that states, suggests or implies that a relationship exists between a food category, a food or one of its constituents and health” while reduction of disease risk claim “means any health claim that states, suggests or implies that the consumption of a food category, a food or one of its constituents significantly reduces a risk factor in the development of a human disease” (Art. 2(2) No. 5 and 6). Health claims may describe or refer to “growth, development and the functions of the body”, to “psychological and behavioural functions” or to “slimming or weight control or reduction in the sense of hunger or an increase in the sense of satiety or to the reduction of the available energy from the diet” (Art. 13).

Health claims are prohibited unless they comply with the provisions of the regulation. Generally, health claims shall only be permitted for foods that comply with nutrient profiles for this category of food (Art. 4). As health claims will be perceived as positive by consumers it shall be avoided that food containing a high concentration of a vitamin is promoted if other properties of the food are unfavourable to the health, e.g. high content of salt or saturated fat. The European Commission is obliged to set up such nutrient profiles. Food supplements and FSMP will be exempted from complying with the nutrient profiles (SANCO, 2009). Furthermore, the Commission is obliged to set up a list of permitted health claims together with the conditions for their use, also referred to as Art. 13(2) claims. The regulation also describes an accelerated application procedure for new health, claims Art. 13(5) claims, not contained in this list.

Reduction of disease risk claims and claims referring to children’s development, Art. 14 claims, must be applied for individually through a different application procedure. Authorised claims will be listed in a Community register to avoid multiple applications and assessments. These authorisations are based on a scientific evaluation of the presented data by the European Food Safety Authority (EFSA). Scientific opinions of the EFSA have been issued and can be found on the EFSA homepage (www.efsa.europea.eu) or in the EFSA Journal; example: “calcium and

vitamin D are needed for normal growth and development of bone in children" (NDA Panel, 2008).

In summary, the Nutrition and Health Claims Regulation also reflects the general principle to distinguish between products for maintaining health and those related to diseases. Medicinal products and food get closest with regards to the label when prevention of a disease or reduction of a disease risk have to be differentiated. By the regulation's provisions the demarcation between a presentation medicinal product and health or reduction of disease risk claims shall be given, and it is the EFSA's responsibility to perform the scientific evaluations.

Homeostasis Model for Demarcation of Medicinal Products and Food Supplements

The Committee of Experts on Nutrition, Food and Consumer Health of the Council of Europe recently developed a model, based on homeostasis, to distinguish between food supplements and medicinal products which contain plant-based substances (Council of Europe, 2008). "Homeostasis can be defined as the status of a person whose physiological parameters function within the limits considered as normal". According to the model both aspects, intended use and nature of induced effect, have to be evaluated for a product in relation to "homeostasis". By this evaluation it shall be determined whether a product falls in the functional definition of medicinal products. The system can also be purposefully be brought out of homeostasis, which is also classified as medicinal. For plant-based food supplements the model provides also a quantitative approach to differentiate nutritional and medicinal functions. It is based on determining the concentration of the active ingredient at which a therapeutic effect, i.e. a measurable deviation in parameters defining the limits of homeostasis, is observed. This is not applicable to vitamins, as vitamins would, due to their nutrient nature, always have an effect, either when ingested with the normal diet, or when taken as food supplements or when administered as medicinal product.
Although the model was originally intended to derive a quantitative approach to classify plant-based food supplements and although the differentiation of disease prevention and reduction of disease risk was explicitly exempted from the aim of the model, it may nevertheless be applied for vitamins in such a way. Thus, for vitamins it could provide an understanding when their effects in the body are "normal". Vitamin products taken to support, optimise or maintain normal physiological functions are food supplements while those products which aim at bringing physiological function back into the limits of normality are considered medicinal products.

Upper Safe Levels of Vitamins in Food Supplements

Pre-requisite for the marketing of vitamin-containing products is the safety of the product. The relevant legislation (Directive 2001/83/EC for medicines and Directive 2002/46/EC and Regulation (EC) No. 178/2002 for food) provides the conditions for safe products. If food is "injurious to health" it shall not be marketed (Regulation (EC) No. 178/2002 Art. 14). Safety of medicinal products has to be shown in clinical trials

according to Directive 2001/83/EC Art. 8(3)(i) or according to the exemptions thereof described in Arts. 10-10c.

Directive 2002/46/EC limits food supplements with regards to the content of vitamins, which may eventually also be understood as means of demarcation to medicinal products containing vitamins. According to Art. 5 of this directive the European Commission is required to set maximum daily amounts of vitamins in food supplements which are safe for the consumer, since some vitamins have adverse effects at excessive intakes. Setting of maximum and minimum amounts of vitamins (and minerals) in foodstuffs is also required for fortified foods by Regulation (EC) No 1925/2006, Art. 9(2). The limits shall be based on a scientific risk assessment of safety of the consumer, taking into account upper safe levels (i.e. total intake) and the intake from other dietary sources and for that the reference intakes for the population. The SCF/EFSA performed the scientific evaluation on behalf of the EC (SCF/NDA Panel, 2006).
Several other scientific organisations have undertaken similar attempts to determine upper safe levels of vitamins for long-term, even lifelong, consumption without adverse health effects, e.g. the Expert Group on Vitamins and Minerals of the UK Food Standards Agency (EVM, 2003) and the Bundesinstitut für Risikobewertung in Germany (Federal Institute for Risk Management, BfR, 2004). The terms used for these limits vary, the EFSA term “tolerable upper levels of intake” (UL) shall be used here. The UL is the total daily intake which has to be matched to the average daily intake from the normal diet. The difference between these two amounts could be ingested from supplements and would represent the reference for manufacturers of food supplements for the maximum content of their products and for their recommendations on consumption. The report of the SCF and the Scientific Panel on Dietetic Food, Nutrition and Allergies (NDA Panel) contains ULs for only six vitamins, the EVM gave upper levels for three vitamins and for all other they gave only guidance levels. The main reason for this is that for the other vitamins sufficient scientific data are not available, or that for some of them extremely low or non-existent toxicity can be assumed from the available evidence. These are some of the questions the European Commission wished to discuss with the stakeholders in the “Discussion Paper on the setting of maximum and minimum amounts for vitamins and minerals in foodstuffs” (SANCO, 2006a). Evaluation of the 58 responses received is still ongoing (SANCO, 2006b), so harmonised maximum amounts are not available yet.

Case-Law on Demarcation of Medicinal Products and Food

Before the harmonisation of the legislation on food supplements in the EU by Directive 2002/46/EC and more recently by Regulation (EC) No 1924/2006 on health claims, the demarcation of food (supplements) and medicinal products was often a matter of case-law of national courts or the European Court of Justice (ECJ). Many of the principles of the case-law were incorporated in the harmonised EU food legislation, e.g. the clear nutritional purpose of food supplements and the dose form for foodstuffs, and also some amendments of Directive 2001/83/EC by Directive 2004/27/EC relate to the demarcation problems with borderline products. Specifically,

these are the description of the modes of actions of medicinal products as “pharmacological, immunological or metabolic” (Art. 1(2)(b)), and the clarification that if a product falls in the definition of a medicinal product and of any other product covered by Community legislation, the provisions of Directive 2001/83/EC shall apply (Art. 2(2)).

Case-law (in the EU and in Germany) regarding food supplements has been comprehensively discussed by K. Streso (K. Streso, 2005), only few examples relating to demarcation of vitamin-containing products as food or medicinal products should be briefly mentioned here.
In case C-227/82 “Van Bennekom” (ECJ, 1983) the ECJ stated that “it is impossible in the present state of scientific knowledge to state whether the criterion of concentration alone is always sufficient in order to be able to determine whether a vitamin preparation constitutes a medicinal product, still less therefore is it possible to specify the level of concentration above which such a vitamin preparation falls within the community definition of a medicinal product”. “Thus, the classification of a vitamin as a medicinal product within the meaning of the second part of the definition in the aforesaid directive [Directive 65/65, predecessor of Directive 2001/83/EC, the referred definition of a medicinal product by virtue of its function are consistent in both directives] must be *carried out case by case, having regard to the pharmacological properties* of each such vitamin to the extent to which they have been established in the present state of scientific knowledge”. With regards to presentation medicinal products the court defines the “averagely well-informed consumer” as benchmark for the classification based on the public perception of a product.

Cases C-387/99 and C-150/00 (ECJ, 2004) both deal with classification of vitamin preparations as medicinal products if the content of vitamins exceed the RDA or specified multiples of RDA. Both judgements state that an automatic classification related to RDA is against the law, “since it does not make a distinction by reference to the different vitamins added or, in particular, to the level of risk to public health which their addition could entail”. “There is no automatic link between the level of the recommended daily amount and the potential danger of a vitamin”. Both judgements also emphasize the conclusions of case C-227/82 that classification has to be done case-by-case based on the pharmacological properties.

A more recent judgement on demarcation of a vitamin containing product already relating to the new harmonised food legislation of Directive 2002/46/EC and Regulation (EC) No. 178/2002 is case C-211/03 (a judgement on five joined cases, ECJ, 2005). This judgement emphasizes in accordance with the judgements cited before that “the competent national authority must decide on a case-by-case basis, taking into account all the characteristics of the product”.

These characteristics are further detailed (same as in the former judgements):

- "its composition,
- its pharmacological properties […],
- the manner in which it is used,
- the extent of its distribution,
- its familiarity to consumers,
- the risks which its use might entail".

But the judgement also weighs the different characteristics with regards to their decisiveness, and clearly "the pharmacological properties of a product are the factor on the basis of which the authorities of the Member States must ascertain […] whether it may […] be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings". And furthermore, "the risk that the use of a product may entail for health is an autonomous factor that must be taken into consideration".

In conclusion, case-law clearly states that the concentration is one of the criteria to distinguish between food and medicinal products, but with a view to distinguish a normal physiological and a medicinal function of a vitamin, and therefore the limit is dependent on the individual pharmacological properties of each vitamin and cannot be linked automatically to food/nutrition-related values such as RDA. The potential medicinal function of a vitamin is the ultimate criterion to the extent as it can be judged from the current status of scientific knowledge.

2.1.2.2 National Provisions of EU Member States

Internet pages of the EU Health Authorities were searched for national provisions on the demarcation of food supplements and medicinal products. The research was not comprehensive. Countries were chosen, e.g. Austria, Denmark and Finland, due to the ECJ cases C-387/99 and C-150/00 described before, in which Finland and Denmark appeared as interveners. United Kingdom on the other hand is known for a liberal classification of vitamin and mineral preparations as food. Further researches on the Internet pages of the authorities in Belgium, Bulgaria, France, Germany, Hungary, Latvia, Poland, Portugal, Spain and the Netherlands were unsuccessful, although the research was somewhat limited as not all articles or search functions were available in English.

Austria

The Austrian Ministry of Health (Bundesministerium für Gesundheit, BMG) published recommendations for the maximum amounts of vitamins in food supplements as basis for the demarcation of food supplements and medicinal products (BMG, 2007). The amounts are in the range of the joined recommended daily intakes of the nutrition societies of Germany, Austria and Switzerland (DACH, 2000), only for a few

vitamins they are higher, about twice (vitamins B_1, B_2, B_6), threefold (vitamin C) and up to fivefold (biotin).

Finland

The Finnish Health Authority NAM (National Agency for Medicines) classifies products as medicinal or non-medicinal based on composition and intended use. Annex 3 of the decision list of medicines (1179/2006) lists threshold values for vitamins and minerals. Products which contain higher amounts than these threshold values are considered medicinal (NAM, 2006). They roughly correspond to the Finnish nutritional recommendations (National Nutrition Council of Finland, 2005), only for a few B vitamins the amounts are slightly higher, about 1.5-fold for vitamins B_1, B_6, B_{12} and folic acid.

Denmark

In Denmark there is a further product category for products containing vitamins and/or minerals in dosage form for oral ingestion by humans, translated to “strong vitamin and mineral products”. The categorisation of products as food supplements, strong vitamin and mineral products or medicinal products depends mainly on the desired marketing and content. There are maximum amounts for content in food supplements, which are valid until the EU harmonised ULs come into force. The currently valid limits have been extended by Danish Medicines Agency (DMA) in the light of the coming harmonised ULs, as it is possible to apply for exemptions of the limits, allowing for marketing as food supplements at higher concentrations than before. The classification as medicinal product depends also on the intended purpose (according to the functional definition of Directive 2001/83/EC) and in that view is independent from the content. The special authorisation type of strong vitamin and mineral products follows the authorisation procedure of medicinal products and can be applied for via national procedure. Apart from the restrictions mentioned above, marketed in dosage form for oral ingestion by humans, strong vitamin products are limited to the indication of “prevention and treatment of deficiency conditions”. As the indication is pre-defined, only a limited, typically bibliographic, clinical documentation is required. The DMA published a guidance document, in which the information given here and details on documentation and application procedure can be found (DMA, 2008).

United Kingdom

The Medicines and Healthcare products Regulatory Agency (MHRA) in UK issued a Guidance Note (MHRA, 2007) for the demarcation of borderline products. For the demarcation of food supplements according to Directive 2002/46/EC the MHRA states that the ultimate criterion for the classification as a medicinal product is the definition of medicinal products acc. to Directive 2001/83/EC Art. 1(2), either by presentation or by function at vitamin administration doses below or above the ULs.

Ireland

In Ireland “maximum daily doses without prescription” are defined for some vitamins (folic acid, vitamins A, D, B_6, B_{12}, K_1). In general, excess of such doses would automatically lead to a medicinal status of a product. For products containing these vitamins it was clarified by the Irish Medicines Board (IMB) that they might nevertheless be marketed as food supplements provided that no medicinal claims are made (IMB, 2008). This is in line with Directive 2002/46/EC on food supplements.

2.1.3 Scientific Aspects of Demarcation of Medicinal Products and Food

Demarcation related to the *functional* definition of medicinal products of Directive 2001/83/EC leads to a scientific differentiation. Medicinal functions may be exerted by pharmacological, immunological or metabolic actions. The action of vitamins in the body is *per se* metabolic. But it may only be considered as medicinal when it aims at restoring, correcting or modifying physiological functions according to the definition by function in Directive 2001/83/EC Art. 1(2)(b). This raises the following questions:

- Under which circumstances is the metabolic action of a vitamin considered medicinal?
- Can vitamins exert also immunological or pharmacological actions in contrast to metabolic actions?
- Is the medical classification linked to a threshold value of the amount of the respective vitamin?

To answer these questions the scientific understanding of the medical, biochemical, pathological processes is a prerequisite. It shall be investigated in this chapter with a view of the legal demarcation questions.

2.1.3.1 Definition of Vitamins

Vitamins are small organic molecules which are required for vital functions of the human metabolism which can not – at least not in sufficient amounts – be synthesised by the body itself. They are essential components which have to be ingested, directly or as precursors (so-called “provitamins”) with the diet. Vitamins have catalytic (as constituents of coenzymes) or hormone-like regulating functions. Therefore they are needed only in very small quantities. Vitamins are defined because of their activity not by chemical class. There are 13 vitamins or vitamin families, which belong to different substance classes. Vitamin families comprise several related chemical structures with the same (qualitatively, not necessarily quantitatively) biological activity.
Vitamins are grouped as water-soluble or liposoluble vitamins. The solubility determines their pharmacokinetic (absorption, distribution, metabolism, excretion) properties.
The liposoluble vitamins are: vitamins A, D, E, K.
The water-soluble vitamins are: B-vitamins B_1, B_2, B_6, B_{12}, niacin, folic acid, biotin, pantothenic acid and vitamin C.

"Vitamin families" exist for vitamin D, E, K and vitamin B_{12} (H.J. Roth, 2009, K.H. Bässler et al., 2002, Chapter 1.1-1.2, Mutschler et al., 2001).

2.1.3.2 Biochemical and Medical Properties of Vitamins

In the following well-established knowledge about vitamins from textbooks is summarised to give a brief overview on the biochemical functions of the vitamins in the human body and on medical properties of vitamins (Vitamin-Lexikon, Bässler et al., 2002; Mutschler – Arzneimittelwirkungen, Mutschler et al., 2001; Vitamine, Spurenelemente und Mineralstoffe – Prävention und Therapie mit Mikronährstoffen Biesalski et al., 2002; and Vitamine – Physiologie, Pathophysiologie, Therapie, Biesalski et al.,1997; additional references are cited separately in the respective context).

Vitamin B_1, thiamine, is physiologically active as thiaminediphospate (TDP), the cofactor of 2-oxoacid dehydrogenases of the carbohydrate metabolism. Furthermore, thiamine has neurophysiological functions, it seems to be involved in signal transmission in the peripheral nerves, most probably in its tri-phosphorylated form TTP. The mechanism has not been solved, so it is not known but likely that neuropathic vitamin B_1 deficiency symptoms are related to this function. Thiamine seems to also have a down-regulating function in the formation of AGEs (advanced gylcosylation end products), which are associated with the chronic complications of diabetes. Beriberi is a complex thiamine avitaminosis in which also other B-vitamins are lacking. Severe vitamin B_1 deficiency often arises from alcohol abuse, the Wernicke-Korsakow-syndrome.

Vitamin B_2, riboflavin, is a constituent of the coenzymes FAD (flavin adenine dinucleotide) and FMN (flavin mononucleotide), which are required by many oxidoreductases, so-called flavoenzymes, especially in the citric acid cycle and β-oxidation. Noteworthy, it is involved in the conversion of pyridoxine (vitamin B_6) and folate to their coenzyme forms. Isolated riboflavin deficiency is very rare. Symptoms are disorders of the skin and the eye and prolonged deficiency results in anaemia.

The B-vitamin "niacin" comprises the two physiologically active forms nicotinic acid and its amide. They are part of the coenzymes NAD and NADP (nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate) which act as coenzymes of many oxidoreductases. The avitaminosis of niacin is pellagra.

Vitamin B_6, comprising the active forms pyridoxal, pyridoxine and pyridoxamine, is active as pyridoxal-5'-phosphate (PALP), the cofactor of several enzymes of the amino acid metabolism. Isolated vitamin B_6 deficiency is uncommon, symptoms are seborrhoeic dermatitis, glossitis and conjunctivitis, and neurologic symptoms such as insomnia, confusion, irritability and neuropathy.

Pantothenic acid is a constituent of Coenzyme A (CoA). CoA is involved in numerous metabolic pathways, it acts as carrier of acyl-groups in acyl-transfer reactions. The corresponding alcohol dexpanthenol (a provitamin form) accelerates and improves

healing of epidermal wounds and is therefore often used in cosmetics and medicinal ointments. Isolated deficiency is very rare, symptoms as fatigue, insomnia, gastrointestinal complaints, neurological disorders have been described.

Biotin is another cofactor from the B-vitamin group. As prosthetic group of enzymes which catalyse carboxylation reactions biotin is the carrier (acceptor/donor) of the carboxyl-groups. Biotin deficiency has rarely been observed in adults. Symptoms are dematitis, loss of hair and neuromuscular diseases.

The biologically active form of folic acid is tetrahydrofolate (THF). THF is a coenzyme, it acts as acceptor and donor of hydroxymethyl- and formyl-groups. These C_1-residues are formed and transferred onto THF in various degradation reactions, e.g. degradation of serine or tryptophane-metabolism. The C_1-groups are then in turn incorporated in various synthetic reactions. One of them is the formation of methionine from homocysteine. Increased levels of homocysteine are a risk factor for arteriosclerosis. This reaction is an example of the linkage of vitamin actions because vitamin B_{12} is also part of this reaction. Methionine then enters into the choline synthesis and by that folate has an indirect effect on the nervous system functions. C_1-residues bound to THF are also required in the synthesis of nucleic acids. And folate is involved by further mechanisms in DNA replication. Therefore, folate deficiency primarily affects cell division and cell growth. This leads to megaloblastic anemia (production of red blood cells in the bone marrow is hindered), the deficiency symptom for folic acid, and it also increases the risk of neural tube defects in the unborn child in pregnant women. For the same reason (the close relationship to cell division processes) the regeneration of THF during nucleic acid synthesis is a target for cytostatic anticancer drugs (methotrexate). The inhibition of THF regeneration impedes proliferation of fast-growing tumour cells.

Vitamin B_{12}, is a “vitamin family” of several cobalamin derivatives, which are all metabolised to the active forms methylcobalamin or adenosylcobalamin. Both act as coenzymes in only three different reactions in the human body. One of them is the methyl-transfer reaction forming methionine from homocysteine. Folic acid is involved as 5-methyl-tetrahydrofolate in this reaction as methyl-donor (see above). Failure of this reaction leads to several medical conditions. Normally, THF is regenerated in this reaction from its methylated form. Therefore vitamin B_{12} deficiency leads to a functional THF deficiency, manifesting itself in megaloblastic anemia (see above). Furthermore, the homocysteine level in the blood increases, which is related to arterial damage, i.e. cardiovascular diseases, and the methionine level decreases. A lack of methionine, which is involved as S-adenosyl-methionine in several metabolic pathways in the nervous system, may result in defects of the myelin sheath if it is not supplemented from the diet.
Uptake of cobalamin from the diet is complex and diseases of the gastrointestinal system may easily lead to vitamin B_{12} deficiency. Important in this context is the transport protein Intrinsic Factor, which is responsible for the active resorption of vitamin B_{12}.

Vitamin C, ascorbic acid, is part of many biochemical redox systems. Important are also its enhancing effects in the immune system. The molecular mechanisms are not known. They might be related to the antioxidative effect of vitamin C. Furthermore, vitamin C inhibits the formation of nitrosamines, increases the resorption of iron and is involved in the regeneration of vitamin E. Scurvy is the avitaminosis of vitamin C.

Vitamin A is active in different forms, retinol and its esters, retinal or retinoic acid. Beta-carotene is its most important provitamin. Vitamin A is active in various physiological processes, the molecular mechanisms of its involvement are mostly unknown: in growth, in growth and differentiation of epithelial cells, in reproduction, in the visual system (as the chromophore of the visual pigments in the retina) and in the immune system. The earliest symptoms of vitamin A deficiency affect the eye, starting with night blindness eventually leading to comlpete loss of vision. Non-ophthalmologic symptoms include impaired immunity and epithelial dysplasia.

The physiological active metabolite of vitamin D is 1,25-dihydroxycolecalciferol (calcitriol). Calcitriol has a steroid structure and functions as a hormone, therefore, the classification as vitamin is sometimes questioned. Most often, vitamin D, in its most relevant forms ergocalciferol and colecalciferol, is therefore described as prohormone. It is furthermore specific because the body can synthesise vitamin D by itself. Calcitriol regulates the calcium- and phosphate homeostasis in the body. In the intestine it regulates the resorption of calcium and phosphate, in the kidneys the re-resorption and in the bones it controls the equilibrium of mineralisation and demineralisation. This equilibrium is needed for growth of bones, for adoption to changing strain and to liberate calcium for the system, if necessary. The regulation also involves two other hormones: calcitonin and parathyroid hormone. Furthermore, calcitriol seems to exert regulating activity on the immune system and on the secretion of insulin. Deficiency of vitamin D leads to decreased calcium levels. The body reacts with hyperparathyroidism. Clinical symptoms are disorders of the bones, known as rickets and osteomalacia.

Vitamin E, various tocopherols with differing levels of activity, are well-known antioxidative substances. Vitamin E protects unsaturated fatty acids in cell membranes against oxidative degradation. It also influences the fluidity of cell membranes. Additionally anti-inflammatory, immunomodulating, antiproliferating activities are described. Therapeutic and prophylactic effects in many degenerative diseases, such as rheumatoid arthritis, cancer, coronary heart disease, Parkinson's and Alzheimer's disease, are discussed, but the data available so far are inconsistent. Vitamin E deficiency causes neurological disorders including neuromuscular diseases and may also lead to anaemia due to increased oxidative damage of red blood cells.

Vitamin K is the cofactor in the post-translational γ-carboxylation of specific glutamic acid residues in various proteins. The most prominent of these are the coagulation factors, which are activated by this post-translational modification, e.g. thrombine. Osteocalcin, another γ-carboxylated protein, is involved in the bone metabolism.

Vitamin K deficiency leads to decelerated coagulation and to bleeding in various tissues.

The important biochemical functions of the single vitamins have been summarised. As already described for vitamin B_{12} and folic acid, the functions of the vitamins are often interconnected or dependent on each other via various metabolic pathways. Further examples are:

- All B vitamins are connected in the pentose phosphate pathway and the citric acid cycle.
- The formation of PALP from pyridoxine/pyridoxal or pyridoxamine requires niacin and vitamin B_2.
- Vitamin A, D and K function together in the bone metabolism.

As can be seen from the description of the physiological functions of vitamins above, many modes of actions of vitamins have not been solved yet.

2.1.3.3 Adverse Reactions of Vitamins

Since vitamins are usually discussed in the context of deficiency related clinical symptoms or diseases, it is often overlooked that also excessive doses of vitamins may cause severe adverse health reactions (Pietrzik et al., 2008, chapter 7). Hypervitaminoses are known for a few vitamins, i.e. diseases caused by overdoses of vitamins.

A comprehensive overview of general side effects, contraindications and warnings for vitamins authorised as medicinal products in Germany can be found in Golly, 2009. Some examples of more severe side effects of vitamins in high doses shall be given.

High doses of vitamin B_6 may cause peripheral sensory neuropathy, depending on dose and duration of administration. Due to the limited data available the ranges can not be clearly determined, the current consensus seems to be that below 50 mg/day there is no risk and at doses of 1 g/day for a few months there is a high risk (Pietrzik et al., 2008, chapter 7).

Acute or chronic intoxications may occur as adverse drug reactions of vitamin A. Vitamin A also has teratogenic properties, therefore for women who are pregnant or may become pregnant maximum daily doses have to be labelled.
Beta-carotene, provitamin A, is discussed for increasing the risk of lung cancer in smokers. The interpretation of the results of several studies is still heavily disputed by experts (Pietrzik et al., 2008, chapter 7) but the available evidence was considered as sufficient for the German Health Authority Bundesinstitut für Arzneimitel und Medizinprodukte (BfArM, Federal Institute for Drugs and Medical Devices) to perform a graduated plan procedure (Stufenplanverfahren) which resulted in a contraindication for heavy smokers for medicinal products with daily doses >20 mg and a warning for daily doses between 2 mg and 20 mg. Authorisations for medicinal

products with β-carotene as excipient resulting in >2 mg daily intake were revoked (BfArM, 2005).

A toxic effect of vitamin D excess is due to the increased mobilisation of calcium leading to high blood levels (hypercalcaemia) and increased levels in the urine (hypercalciuria) with harmful effects on kidneys, blood vessels, heart and lungs (Pietrzik et al., 2008, chapter 7, EVM, 2003).

2.1.3.4 Metabolic Actions of Vitamins and Demarcation

Bässler (1991) set up a categorisation of high dose administrations of vitamins distinguishing pharmacological and physiological functions from the scientific viewpoint. High doses of vitamins, when exerting their physiological functions, are needed (numbering refers to medical conditions discussed in the following):

- to replenish the body's vitamin reserves after depletion (A)
- to overcome malabsorption (e.g. passive absorption of vitamin B_{12}, if active transport with intrinsic factor is inhibited) (A)
- to compensate for increased usage (A)
- to shift the equilibrium between bound and unbound coenzyme by saturating cell compartments or enzymes (B)
- to treat inherited enzyme defects (C)
    - by compensating of reduced affinity for coenzymes,
    - by increasing the stability through bound coenzyme,
    - by inducing apoenzyme synthesis (so far only hypothetical)

These "physiological functions" correspond to "metabolic actions" in the legal understanding but they would not necessarily all fall into the functional definition of a medicinal product.

A) Vitamin Deficiency

Generally, vitamins are administered to prevent or treat vitamin deficiency or deficiency-related diseases. Typical causes of vitamin deficiency are (Vitamin-Lexikon, Bässler et al., 2002, Chapter 1.5, Hahn, 2009, DGE, 2003):

- malnutrition, e.g. nutritional habits of elderly, alcohol abuse, energy-reduced diet, veganism
- impaired intestinal resorption, e.g. after resection of the small intestine or because of chronic diarrhoea, atrophy of the gastric or intestinal mucosa
- increased needs, e.g. pregnancy and lactation, fever, stress, alcohol abuse, smoking
- intake of other drugs/interaction with other drugs
- haemodialysis
- genetic disposition

Insufficient supply with vitamins leads to increasing grades of undersupply. At the first stage undersupply causes a decrease of the vitamin concentration in the body. Depending on the body's storage capacities the undersupply can be coped without impairing the vitamin's function for a certain time, until the reserves are depleted. On the next level vitamin-dependent enzyme functions are impaired, followed by development of uncharacteristic symptoms, e.g. fatigue, restlessness, gastrointestinal discomfort. Characteristic symptoms are typically observed at an advanced stage, described as hypovitaminosis. The most severe deficiencies, avitaminoses, often cause irreversible damage, e.g. blindness due to vitamin A deficiency, and – untreated – lead to death.
There are a few "famous" vitamin deficiency diseases (avitaminoses) like scurvy, beriberi, pellagra and rickets/osteomalacia, which ultimately let to the discovery of the class of nutrients called "vitamins".

Products to treat hypovitaminoses or avitaminoses shall "replenish the body's reserves" according to Bässler. They are unambiguously classified as medicinal products: the malfunction of metabolic pathways because of a vitamin deficiency is restored or corrected by the administration of vitamins. The second and third category of Bässler, malabsorption or increased usage, may lead to hypovitaminoses or avitaminoses. Vitamins taken to *prevent these diseases*, are also classified as medicinal products.

Persons at risk of developing a vitamin deficiency disease, e.g. due to increased need during pregnancy or due to gastrointestinal disorders impairing resorption or due to increased elimination by haemodialysis, might manage these situations also nutrionally by ingesting the vitamins as food supplements or FPNU or even FSMP. The adequacy of medicinal products or of food supplements or FNPU/FSMP depends on the individual state of health.

B) Shift of Equilibrium of Enzyme Reactions

Dakshinamurti et al. (2001 and 2003) investigated the mechanisms of certain neuroprotective effects of high doses of pyridoxine unrelated to pyridoxine deficiency. Pyridoxine administered in advance or shortly after a neurotoxic substance attenuated several of the cellular reactions *in vitro* or symptoms - seizures – *in vivo* (in mice with normal pyridoxine balance). Pyridoxine, active as PALP, seems to exert its normal physiological functions, but at an increased rate (enhanced activity of a PALP dependent enzyme). Similarly, Speitling et al. (1986) showed that high doses of pyridoxine increased the activity of various PALP-dependent enzymes in rats and assumed that it might be caused either by saturation of the apoenzyme or by induction of *de novo* synthesis of apoenzyme. These effects are examples for shifting the equilibrium in the categorisation of Bässler (1991). A pyridoxine product developed based on this biochemical background would be a medicinal product intended to ameliorate seizures or other neurological symptoms in a related concrete pathological condition or disease.

C) Inherited Enzyme Defects

The amelioration of human genetic diseases due to defective enzymes with reduced coenzyme binding is an accepted application of the so-called megavitamin therapy (Ames et al., 2002) which is otherwise highly debatable in the approach of orthomolecular medicine. When vitamins are administered to a person with a diagnosed inherited enzyme defect to prevent the disease which this defect might otherwise cause, this is a medicinal intention. Depending on the medical condition and the remaining enzyme activity, it might be sufficient though, that the person regularly takes food supplements targeting the defective enzyme to maintain health.

2.1.3.5 Pharmacological Actions of Vitamins and Demarcation

Vitamins can exert pharmacological actions other than their metabolic actions which have been described in chapter 2.1.3.2, and medicinal products applying these actions fall into the functional definition of medicinal products. Bässler (1991) provided three examples of such actions of vitamins:

- to modulate hemoglobine by pyridoxal phosphate
- to detoxicate of cyanide with hydroxocobalamin
- to modify the lipid profile with nicotinic acid

In fact, there are medicinal products on the market based on the latter two pharmacological actions described (see table 2).

2.1.3.6 Periconceptional Administration of Folic Acid as Example for Demarcation of FNPU and Medicinal Products

The classification of vitamins with regards to preventive applications has been discussed in chapter 2.1.2.1. It comes down to the differentiation between medicinal products and food for particular nutritional uses (FPNU). Particular *nutritional* uses apply for “persons whose digestive processes or metabolisms are disturbed”, or “persons who are in a special physiological condition and who are therefore able to obtain special benefit from controlled consumption of certain substances in foodstuffs” (Directive 89/398/EEC, Art. 1 No. 2(b)).

Both nutritional applications need high doses of vitamins according by Bässler (1991) to overcome malabsorption or to compensate for increased usage (see chapter 2.1.3.4).

An interesting case of demarcation of FPNU and medicinal products is the periconceptional administration of folic acid. There are folic acid preparations on the market (in Germany) either as dietetic food (FPNU) or as medicinal products. Four examples were chosen and their characteristics are compared in table 1. The recommended daily doses of three of them are similar or identical (Femibion 800, Folio forte and Folsan 0,4 mg), thus, the same effect in the body can be assumed. The mode of action or dosage do not represent differentiation criteria here. The

difference clearly lies in the intended purpose and the corresponding labelling. The descriptions of the intended purpose or indication are different, in line with the respective classification. Accordingly, only the medicinal products, Folsan 0,4 mg and 5 mg, explicitly name the related disease "neural tube defect". Additionally, it is noteworthy, that the dosage of Folsan 5 mg would most probably (in future, when tolerable upper intake levels are set by the EC) preclude a classification as food, because the recommendation of the EFSA for folic acid is 1 mg daily (SCF and NDA Panel, 2006).

Table 1: Comparison of different folic acid products related to periconceptional intake of folic acid to prevent neural tube defects / to ensure a normal development of the unborn child (all marketed in Germany)

Trade name	**Femibion® 800 Folic Acid plus Metafolin®[1)]**	**Folio® forte[2)]**	**Folsan® 0,4 mg[3)]**	**Folsan® 5 mg[4)]**
Classification	Dietetic food	Dietetic food	Medicinal product	Medicinal product
Composition	Total 800 µg folic acid (400 µg folic acid plus 416 µg L-methylfolate, corresponding to 400 µg folic acid) further vitamins and minerals	800 µg folic acid 150 µg iodine 10 µg vitamin B_{12}	400 µg folic acid	5 mg folic acid
Recommended daily dose (from planning of pregnancy up to the end of the 12th pregnancy week)	0.8 mg	0.8 mg	0.4 mg, 0.8 mg if indicated by the doctor	5 mg (up to 15 mg for other indications)
Indication / use and related information	"nutritional research has revealed the positive effect of folic acid and food folate on the course of pregnancy and on the development and normal growth of the unborn child"; "allows you not only to prepare your body optimally for pregnancy, but also to promote the development and normal growth of your unborn child"	"according to recent scientific knowledge a folic acid reserve is built up which is optimal for the first trimenon"; "the healthy mental and physical development of the child"; "for the particular nutritional needs of women who wish to become pregnant and who are in the first three months of pregnancy"	Periconceptional folic acid supplementation for primary prevention of neural tube defects even with adequate nutrition; prevention of folate deficiency states when sufficient dietary folate intake is not possible	Prevention of neural tube defects of the newborn by prophylactic treatment of women with increased risk, even with adequate nutrition; therapy of folate deficiency states, which can not be remedied with the nutrition; treatment of increased blood levels of homocysteine which are caused by folate deficiency

[1)] Package leaflet of Femibion® 800 folic acid plus Metafolin®
[2)] Homepage, of Folio® product family, labelling of Folio® forte
[3)] SPC of Folsan® 0,4 mg
[4)] Package leaflet of Folsan® 5 mg

Femibion 800 and Folio forte represent good examples for the application of the "Health Claims" Regulation (EC) No. 1924/2006. A claim on the development of the child or of a reduction of disease risk on food falls into the group of Art. 14 claims which need individual assessment by EFSA. Scientific opinions on folic acid related Art. 14 claims or requests for them have not been published by EFSA. But there is a Art. 13(2) request to EFSA by the European Commission Directorate-General for Health and Consumers meaning that this request and the respective claims fall under the transitional measures for claims used in compliance with national provisions before entry into force of Regulation (EC) No. 1924/2006, Art. 28(6) of that regulation. The request on "Folate - Healthy development of unborn baby: cell division; developing neural tube; blood formation" (Request No. EFSA-Q-2008-876) has not been completed yet. This requested claim depicts the difference of health- and disease-related claims, as *developing of neural tube* rather than *preventing neural tube defect* is proposed.

Femibion® 800 Folic Acid plus Metafolin® does not only contain folic acid but also L-methylfolate. It is a naturally occurring monosubstituted form of folic acid, the only form usually found in plasma. The package leaflet of Femibion claims that folic acid is more directly available in this form. L-Methylfolate has been included in the lists of allowed substances in dietetic food or food supplements in 2006 (amending Directives 2006/34/EC and 2006/37/EC) based on the Opinion of the EFSA in 2004 (AFC, 2004).

2.2 Applicability of EU Rules on Marketing Authorisations to Medicinal Products containing Vitamins

Generally, all provisions on marketing authorisations of medicinal products according to EU pharmaceutical legislation (Directive 2001/83/EC and Regulation (EC) No. 726/2004 and all related laws) do apply for medicinal products containing vitamins as active substances. Vitamins may also be contained in medicinal products as excipients, e.g. antioxidants or colouring agents, but these shall not be considered here. In the following, the principle regulatory procedural and content-related (quality, safety, efficacy) aspects are discussed regarding their applicability to vitamins.

2.2.1 Procedural Aspects

In the EU there are three different procedures to obtain marketing authorisation (MA) for medicinal products, the national procedure (NP), the mutual recognition (MRP) and decentralised procedures (DCP) or the centralised procedure (CP). In principle, all three types are applicable to vitamin containing products, if the respective prerequisites are fulfilled. To investigate the regulatory pathways utilised for the authorisation of medicinal vitamin products, the number of medicinal products authorised in the EU through the centralised or decentralised procedure (including MRP) were determined. The results are presented in tables 2 and 3.

Table 2: Vitamin-containing medicinal products authorised in the EU through the centralised procedure (from EMEA listing of EPARs, status 1 June 2009, URL: http://www.emea.europa.eu/htms/human/epar/a.htm)

Name of the medicinal product	**Fosavance**	**Cyanokit**	**Tredaptive/ Trevaclyn/Pelzont**
Type of application	Complete and independent application acc. to Art. 8(3) Directive 2001/83/EC	Complete and independent application acc. to Art. 8(3) Directive 2001/83/EC	Complete and independent application acc. to Art. 8(3) Directive 2001/83/EC
Eligibility for the optional centralised procedure	Acc. to Part B of Annex of Regulation (EC) No 2309/93 (not further detailed)	Acc. to Art. 3(2)(b) of Regulation (EC) No 726/2004, based on interest of patients	Acc. to Art. 3(2)(a) of Regulation (EC) No 726/2004, new active substance
Active substance	Alendronic acid and colecalciferol (vitamin D_3)	Hydroxocobalamin (vitamin B_{12})	nicotinic acid and laropiprant
Pharmaceutical form and posology	Tablet containing 70 mg alendronic acid and 70 µg (2800 IU) colecalciferol, 1 tablet once per week	Powder for infusion, 2.5 g hydroxo-cobalamin per vial, initial dose for adults. 5 g, subsequent dose for adults 5 g, maximum daily dose 10 g	Modified-release tablet containing 1000 mg nicotinic acid and 20 mg laropiprant, starting dose: 1 tablet once daily, after 4 weeks 2 tablets once daily
Therapeutic indication	Treatment of postmenopausal osteoporosis in patients at risk of vitamin D insufficiency. Fosavance reduces the risk of vertebral and hip fractures	Treatment of known or suspected cyanide poisoning Cyanokit is to be administered together with appropriate decontamination and supportive measures	Tredaptive is indicated for the treatment of dyslipidaemia, particularly in patients with combined mixed dyslipidaemia (characterised by elevated levels of LDL cholesterol and triglycerides and low HDL cholesterol) and in patients with primary hypercholesterolaemia (heterozygous familial and non familial). Tredaptive should be used in patients in combination with HMG CoA reductase inhibitors (statins), when the cholesterol lowering effect of HMG CoA reductase inhibitor monotherapy is inadequate. It can be used as monotherapy only in patients in whom HMG CoA reductase inhibitors are considered inappropriate or not tolerated. Diet and other non pharmacological treatments (e.g. exercise, weight reduction) should be continued during therapy with Tredaptive.

A search of the listing of European Public Assessment Reports (EPAR) for products authorised through a CP for those with vitamins as active substances revealed only five MAs whereby three of them represent duplicate authorisations of the same product for the same MAH (included only once in table 2).

Fosavance is a fixed combination product of vitamin D_3 (colecalciferol) and a bisphosphonate for treatment of postmenopausal osteoporosis. Cyanokit contains hydroxocobalamin (vitamin B_{12}) to treat cyanide poisoning. Tredaptive/ Trevaclyn/ Pelzont contains nicotinic acid for treatment of dyslipidemia, in combination with the PGD_2 receptor antagonist laropripant to counteract the flushes which are a typical adverse reaction of high doses of nicotinic acid.

Similarly, the MRI Product Index of the Heads of Medicines' Agencies was searched to get an overview of MRP/DCP products with vitamins as active substances. Overall, 44 marketing authorisations were found (MR numbers for multiple strengths of one product were counted only once). Some entries in the MRI Product Index also contain information about the type of application, whether an application is an initial application or a copy/multiple application. From the available information it can be seen that the majority of applications were bibliographic (20), seven were classified as full dossier applications, six as generic and two as fixed combinations. Ten were "not defined". In table 3 the number of MAs per vitamin are listed. The largest number are vitamin D products (28), four of them contain only calcitriol, the other are combinations of colecalciferol with calcium, four of which additionally contain the bisphosphonate risedronic acid. There are nine folic acid preparations and one combination of folic acid with vitamins B_6 and B_{12}. Three vitamin C preparations, and one combination of vitamin C with B vitamins have been authorised. Furthermore, one MA for nicotinic acid and one multivitamin preparation of the B vitamins, vitamin C and the vitamins A, D and E were found. Almost all products were oral presentations (data not shown), only two folic acid products (containing folinic acid) were a solution for injection or infusion.

The SPCs or public assessment reports for 23 out of the 44 medicinal products authorised decentrally were available. With the exception of the MA of nicotinic acid, indicated for the treatment of dyslipidemia, all other indications are based on metabolic actions of the vitamins. Almost all of them fell in the group of prevention and treatment of deficiency. Noteworthy special cases were:

- four parallel generic medicinal products containing calcitrol indicated for the corrections of the abnormalities of calcium and phosphate metabolism in patients with renal osteodystrophy and for the treatment of established post-menopausal osteoporosis;
- combinations of colecalciferol and calcium indicated for prevention and treatment of calcium and vitamin D deficiency and as vitamin D and calcium supplement in adjunct to specific osteoporosis treatment of patients who are at risk of vitamin D and calcium deficiency, applied for either with full dossiers or with bibliographic dossiers;
- four marketing authorisations (two parallel each) based on full applications for a combination product of film-coated tablets containing risedronic acid and granules containing calcium carbonate and colecalciferol indicated for treatment of postmenopausal osteoporosis;

- two independent generic medicinal products containing folinic acid indicated to diminish the toxicity and counteract the action of folic acid antagonists, such as methotrexate, in cytotoxic therapy and overdose in adults and children and also indicated in combination with 5-fluorouracil in cytotoxic therapy;
- nicotinic acid for treatment of dyslipidemia authorised following a bibliographic application.

Table 3: Vitamin-containing medicinal products authorised in the EU through the mutual recognition/decentralised procedure (from MRI-Product Index, status of 1 June 2009, for details refer to text)

Active Substance	**Number of MRP/DCP MA**	**Search Terms ***
Vitamin B_1	none	thiamine, thiamine chloride, thiamine hydrochloride, thiamine nitrate, thiaminedisulfide, benfotiamine, bentiamine, allithiamine, vitamin B_1
Vitamin B_2	none	riboflavin, vitamin B_2
Vitamin B_6	none	pyridoxine, pyridoxal, pyridoxamine, vitamin B_6
Vitamin B_{12}	none	cobalamin, cyanocobalamine, hydroxocobalamine, methylcobalamine, aquocobalamine, nitrocobalamine, adenosylcobalamin, vitamin B12
Folic acid	9	folic acid, folate, tetrahydrofolate
Folic acid + vitamin B_6 + vitamin B_{12}	1	
Biotin	none	biotin
Nicotinic acid	1	niacin, nicotinamide, nicotinic acid
Pantothenic acid	none	pantothenic acid, panthenol, dexpanthenol
Vitamin C	3	ascorbic acid, sodiumascorbate, calciumascorbate, ascorbate, vitamin C
Vitamin C + B-vitamins	1	
Vitamin A + B vitamins, vitamins C, D, E and minerals	1	retinol, retinal, retinoic acid, vitamin A
Vitamin D	4	cholecalciferol, colecalciferol, ergocalciferol, calcitriol, vitamin D
Vitamin D + calcium	20	
Vitamin D + calcium + risedronic acid	4	
Vitamin E	none	tocopherol, vitamin E
Vitamin K	none	vitamin K
	Total: 44	

* The search terms are given in table 3 to judge the results, please note that also different spellings (cholecalciferol, colecalciferol) were tested. An additional search with the term “vitamin” did not result in any further hits.

For comparison, in Germany 1201 products are authorised for humans, which contain vitamins as active substances *and* are marketable (from AMIS database on 2 July 2009, search for “?vitamin?” in “Stoffname” (substance name) and “M” in “Zielgruppe” (for humans only), filter “arzneilich wirksame Bestandteile” (active substances) und verkehrsfähig – ja (marketable)). This number contains marketing authorisations of all three procedural types (NP, MRP/DCP and CP).

These findings clearly support that vitamin medicinal products are authorised mainly nationally. Two imaginable reasons for these findings are that, firstly, many companies produce vitamin medicinal products only for the market of their respective home country, and secondly, many marketing authorisations originate from a time before EU authorisations MRP/DCP or CP were introduced. Since introduction of these procedures MAs in more than one country for one product can only be obtained by one of these procedures.
The centralised procedure is intended for innovative products or for such of interest of EU-wide availability to patients. Thus, vitamin products indicated to prevent or treat deficiency diseases generally do not fall in this category. The three centrally authorised vitamin medicinal products were eligible but not mandatory for centralised authorisation according to Arts. 2 and 3 of Regulation (EC) No 726/2004. Tredaptive/ Trevaclyn/ Pelzont fell under Art. 3(2)(a), of an active substance not authorised at the time when the regulation came into force, as the fixed combination of nicotinic acid and laropiprant was new. Cyanokit in contrast was eligible for the CP based on interest of patients (Art. 3(2)(b)). Fosavance was applied for before coming into force of Regulation (EC) No 726/2004, and the reference to Regulation (EC) No 2309/93 does not specify the reason for eligibility. Interestingly, the medicinal function of two of the three products, namely Cyanokit and Tredaptive/ Trevaclyn/ Pelzont, in their respective indications, are brought about by pharmacological actions as described in chapter 2.1.3.5.
Commercialisation interests in more than one country is thus the likely reason for the MRP/CDP authorised vitamin products in the EU.

As vitamin medicinal products have been on the market for such a long time, the most obvious application type for new applications is the bibliographic application for well-established medicinal use of the active substance(s) according to Art. 10a of Directive 2001/83/EC, especially if typical indications like “prevention and treatment of vitamin deficiency” are sought. This can be seen from the search of the MRP/DCP authorised medicinal vitamin products, as the majority of the products with a known indication of prevention and treatment of vitamin deficiency were classified as bibliographical application.

As there is a large number of vitamin medicinal products authorised, a generic application according to Art. 10 of Directive 2001/83/EC is also thinkable. The general prerequisites for a generic application are (NtA, Volume 2A, Chapter 5.3, 2005):

a) the same qualitative and quantitative composition in active substances as the reference product,
b) the same pharmaceutical form as the reference product,
c) bioequivalence with the reference product,
d) the data protection period of the reference product has expired,
e) the authorisation of the reference product is based on Art. 6 in accordance with the provisions of Art. 8(3).

The first two points are a matter of the pharmaceutical development of the medicinal product which shall be submitted for authorisation. Demonstration of bioequivalence requires studies in human. Trials on vitamins in human are complex because vitamins are part of the normal diet. This has to be taken into account, usually by a preparatory diet of the volunteers, to achieve a certain baseline of vitamins in the blood, because especially the liposoluble vitamins have long half lives in the body (Hahn, 2009).

The requirement for a reference product to be authorised according to the provisions of the Community pharmaceutical legislation (e) and the expiry of the data protection period (d) have to be specifically considered for vitamins (Art. 10(2)(a), Directive 2001/83/EC). Only medicinal products may be referred to which are authorised based on complete dossiers which comply with the provisions of the current Community legislation, i.e. according to Arts. 8(3) or 10a, 10b, 10c, meaning that bibliographic well-established use applications, fixed combination applications and informed consent applications are suitable. But abridged applications according to Arts. 10(1)/(3)/(4) - generic/hybrid/similar biological applications – cannot be referred to. In this context two recent judgements need to be considered. The ECJ recently decided that the marketing authorisation of a designated reference product, authorised before coming into force of any Community pharmaceutical legislation, which has never been updated to fulfil the requirements of Art 6 in accordance with the provisions of Art. 8(3), was therefore not suitable as reference product (case C-527/07, ECJ, 2009). This might be applicable to “old” nationally authorised vitamin products, which have not undergone or not yet completed that update. These would therefore not be suitable as reference product. The Oberverwaltungsgericht Nordrhein-Westfalen decided similarly in case 13 B 345/08 (OVG Nordrhein-Westfalen, 2008), that reference could only be made to marketing authorisations in accordance with Community law. Furthermore, they judged that the data and market protection period started only with the granting of such a marketing authorisation in conformity with the Community law. For “old” marketing authorisations that are the “updates” of the respective dossiers usually in the context of specific renewal procedures, e.g. the German Re-registration (Deutsche Nachzulassung). This could result in data protection periods still running in Germany for “old” vitamin products, i.e. these products would not be suitable as reference products for generic applications either.

Due to these constraints a bibliographic application (Directive 2001/83/EC, Art. 10a) is favourable if well-established medicinal use of the active substances in the desired indication can be demonstrated by sufficient bibliographic documentation.

The information on the application types (information available on 34 products, two of them classified as fixed combination) of the MRP/DCP authorised products support the discussion above. The majority of them were bibliographic and only few were generic applications. The applications outside of the indication of treatment and prevention of vitamin deficiency were either full dossiers or generic applications. Hence, for these indications the procedure of well-established use based on

bibliographic data was not applicable but the indications had to be supported by non-clinical and clinical data.

Applications according to Art. 10b of Directive 2001/83/EC “fixed combinations” are of special importance in the context of vitamin-containing medicinal products, because vitamins are often provided as so-called fixed combinations. Fixed combinations are combinations of two or more active substances in a single pharmaceutical form for administration (NtA, Volume 2A, Chapter 5.5). “In the case of medicinal products containing active substances used in the composition of authorised medicinal products but not hitherto used in combination for therapeutic purposes, the results of new pre-clinical tests or new clinical trials relating to that combination shall be provided in accordance with Art. 8(3)i, but it shall not be necessary to provide scientific references relating to each individual active substance” (Art. 10b). Thus, this type of application relates to novel fixed combinations of known active substances. Well-established fixed combinations may be applied for by a bibliographic Art. 10a application. The documentation on the novel combination of the actives substances according to Art. 10b may comprise data only from own tests or trials but may also be a mixed application. The centralised authorisation of Tredaptive/ Trevaclyn/ Pelzont is an example of a mixed application for a fixed combination of substances not authorised in this combination before.

The specific requirements on the (non-)clinical data for fixed combinations are discussed in detail in the section on safety and efficacy aspects (see chapter 2.2.3).

2.2.2 Quality Aspects

2.2.2.1 Active Substance

Vitamins typically fall in the category of existing active substances, unless, another chemical form, e.g. a precursor or a derivative, of a vitamin would be utilised in medicinal products for the first time, according to the “Guideline on summary of requirements for active substances in the quality part of the dossier” (CHMP, 2005). There are different options how to provide the required documentation in the drug substance part of the quality dossier: as full documentation, as ASMF or with a CEP, if the chemical form of the vitamin is described in a monograph of the European Pharmacopoeia (Ph. Eur.). Ph. Eur. monographs exist for almost all vitamins (except for vitamin A and K), although not for all known chemical forms, e.g. thiamine disulfide is not included in the Ph. Eur., while thiamine nitrate is.

The majority of vitamins are produced for food and feed applications rather than medicinal products. Thus, vitamins as active substances belong to the so-called atypical actives, which are substances whose primary industrial use is not as an active substance in medicinal products but in other industrial sectors, e.g. in food and feed, in cosmetics, or as excipients in pharmaceuticals. Typical other examples are citric acid or iodine (Canali, 2008, IPEC Europe, 2008, INS, 2008a).

With Directive 2001/83/EC coming into force manufacturing authorisation holders are obliged to “use as starting materials only active substances which have been manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials”, Art. 46. This imposed the obligation on the suppliers of these substances, among them vitamin manufacturers, to implement GMP standards, while typically other quality standards and quality management systems are applied. This is often cost-prohibitive because the pharmaceutical actives usually account only for a small fraction of their business and therefore the requirement poses a risk to the business connection of the substance manufacturer and the pharmaceutical companies (Canali, 2008, IPEC Europe, 2008). The EMEA Inspections Sector (INS) proposed the following solution: “Alternative sources should normally be sought but in exceptional circumstances the manufacturing authorisation holder should assess and document to which extent GMP is complied with and provide a risk-based justification for the acceptance of any derogation”. When declarations by qualified persons on GMP compliance of active substances are to be given, it has to be explained in detail, why the standards applied by the active substance manufacturer provide the same level of assurance as GMP (INS, 2008b). The approach was welcomed as pragmatic by the International Pharmaceutical Excipients Council Europe (IPEC Europe) and the Association of the European Self-Medication Industry (AESGP), and AESGP specifically offered to support EMEA in collecting experience (IPEC Europe 2008, AESGP, 2009).

2.2.2.2 Finished Product

The limited stability of most vitamins against oxygen, light, elevated temperature or certain pH ranges (Pietrzik et al., 2008, chapter 1.4) poses challenges for the development of pharmaceutical forms of the vitamins to avoid losses during manufacture as well as during shelf-life. Furthermore, formulation of fixed vitamin combinations often require compromises with regards to the different stability optima or potential physico-chemical incompatibilities.

For finished medicinal products of vitamins, the general legal provisions and quality standards apply, however, the Ph. Eur. permits one exemption: multivitamin preparations are exempt from the general requirement for dose variation (Ph. Eur. Monograph 2.9.6. Uniformity of content of single-dose preparations, Ph. Eur. Monograph 2.9.40. Uniformity of dosage units, 2009).

2.2.3 Safety and Efficacy Aspects

2.2.3.1 General Considerations

Some general aspects on the conduct of any clinical study with vitamins have to be taken into account, particularly, when studying vitamin deficiency related diseases. Vitamins are essential constituents of the daily nutrition, and the body has very different storage capacities, ranging from 4-10 days for vitamin B_1 up to 3-5 years for vitamin B_{12}. Thus, dietary habits of volunteers before and during a study need to be considered.

Epidemiological studies show correlations but cannot provide for causal relationships. Furthermore, isolated deficiencies are rare nowadays, more often, combined deficiencies occur and these often at a sub-clinical level. But intervention studies can only investigate a limited number of factors at the same time. All these aspects may make clinical results related to vitamin treatments difficult to interpret (Pietrzik et al., 2008, chapters 4 and 8).

Vitamins are still of interest for clinical testing though, as can be seen from the large number of entries of studies on vitamins in the database *clinicaltrials.gov*, e.g. 88 for vitamin D/ colecalciferol or 64 for vitamin E/ tocopherol or 56 for vitamin C/ ascorbic acid or 678 for vitamin A (numbers are for studies in the status of recruiting or not yet recruiting). And many of the studies are on deficiency indications or other well-known indications such as osteoporosis for vitamin D. Several others target chronic progressive degenerative diseases for which the potential benefits of preventive or accompanying administration of vitamins, especially in high doses, are investigated. For investigations in these indications, e.g. cardiovascular diseases, Diabetes mellitus, Parkinson's, Alzheimer's disease, efficacy guidelines on the conduct of appropriate clinical study programmes exist, but they usually do not cover vitamin therapy. Overall, the currently available clinical evidence indicates that undersupply of vitamins - at a low level without development of specific deficiency symptoms - increases the risk for many of these diseases. But the converse argumentation that supplementation of certain vitamins still has a beneficial effect at already good supply has not been shown yet (Elsner, 2005, Hahn, 2009, Bässler, 2002, chapter 7).

A general problem of studies for chronic degenerative diseases are the long periods of time though, which would have to be monitored. This is methodically and financially difficult to realise, considering especially, that patent protection for vitamins is not possible.

2.2.3.2 Fixed Combinations

Fixed combinations are frequent for medicinal products containing vitamins. Therefore, the related guidance shall be discussed in more detail. There are two guidelines, one dealing with the non-clinical development and the other on the clinical development (CHMP, 2008a and 2009). The clinical guideline was recently reviewed, the revision will come into effect in September 2009. Initially, the requirements are summarised and then are evaluated for vitamins as active substances specifically.

The coverage of both guidelines is wider than the application type of fixed combinations according to Art. 10b, Directive 2001/83/EC. The particularities on the Art. 10b application documentation relate to a novel combination of active substances which have been authorised for therapeutic use before (see chapter 2.2.1). The guidelines cover such combinations, but well-known fixed combinations or fixed combinations which contain new active substances are also included.

To authorise fixed combination products in the EU, certain prerequisites have to be fulfilled. “Each substance of the fixed combination must have a documented therapeutic contribution within the combination” (CHMP, 2009). Substances with narrow therapeutic indices are generally not suitable for fixed combination products. The dosage regimen must be chosen to be safe and effective for a significant target population.

The following advantages may justify a fixed combination:

- improvement of the benefit/risk ratio, either by improved efficacy with a comparable safety profile, due to addition or potentiation of the therapeutic actions, or by an improved safety profile at comparable efficacy, due to a reduced dosage of the single compounds because of synergistic interactions or due to counteracting an adverse effect of one compound by the other one.
- “Simplification of therapy by decreasing the number of individual dose units”, the so-called substitution indication (CHMP, 2009).

The main aim of non-clinical studies on fixed combinations is to investigate “potential additive, potentiation or antagonistic effects of the compounds when used together” or a potential “toxicity unique to the combination” (CHMP, 2008a).

If the to-be-combined active substances are already approved as free combination therapy non-clinical studies are normally not required when there is enough experience in humans for the individual and combined use.

For the novel combination of known active substances a limited non-clinical development program is needed depending on the following considerations. If pharmacodynamic or pharmacokinetic interactions of the active substances are the rationale for the fixed combination, these may need to be supported by the appropriate non-clinical data. Even if the safety of the individual compounds is well-documented safety pharmacology and toxicology studies might be necessary for the combination, e.g. if the systemic exposure might be different due to the combined administration or the concentration ranges in the fixed combination are different. Another reason might be if the compounds target the same organ system.

If a combination contains new compounds either a full non-clinical development program for the new compound(s) and bridging studies to the combination (if the other active substances are known) or a more extensive development program of the combination and only a limited set with the new active substance alone is needed.

To plan the appropriate clinical trials for a fixed combination the similarity to existing fixed or free combinations and the rationale for this combination have to be considered.
Generic fixed combinations have to show bioequivalence to the reference product as usual. The guideline on the investigation of bioequivalence (CHMP, 2008b) covers fixed combination products.

For fixed combinations of known active substances in the substitution indication bioequivalence to the combination of the recognised reference formulations of the individual compounds has to be shown to cover pharmacokinetic aspects. If pharmacodynamic or pharmacokinetic interactions are the reason for the combination these have to be investigated in healthy volunteers.
Efficacy and dose-effect studies are needed when the combination is essentially new. If it is close to existing combinations (simultaneous use) a bibliographic analysis might be sufficient or might at least reduce the required clinical trials. Of special importance in this context is an authorised indication for the free combination of the substances.
For fixed combinations of or with new active substances the full investigation is necessary (see also above on the non-clinical study programme).
With regards to safety studies in human the same criteria as for the non-clinical test have to be considered.

Vitamins are well-known active substances. Most of them have broad therapeutic indices (exceptions are vitamin A and D and to a certain extent vitamin B_6) and are therefore generally suitable for fixed combinations (Bässler, 2002, chapter 4.1-4.3).

The justification for the fixed combination of vitamins often fall in the substitution indication of facilitating therapy and of enhancing patient compliance. Vitamin deficiencies often occur concomitantly for several vitamins, e.g. for the B vitamins or for all water-soluble or for all liposoluble vitamins, at least if the deficiencies are caused by malnutrition or malabsorption. Also conditions of increased need, e.g. pregnancy, often require a higher supply of several vitamins at the same time. Fosavance (see table 2) is another example for the substitution indication. In contrast, the combination of nicotinic acid and laropiprant in Tredaptive (see table 2) is justified, because laropripant is a PDG_2 inhibitor which counteracts the common adverse reaction of flushes of nicotinic acid.

Fosavance and Tredaptive are discussed as examples for study requirements for fixed combinations as described above (based on the EPARs, CHMP 2005 and 2008c). Fosavance is a novel fixed combination of well-known active substances. Both substances were authorised singly for the indicated effects. Thus, clinical or non-clinical data on the single substances were not required. A PK study was conducted showing bioequivalence of alendronate in the combination and in the single substance product and providing also necessary PK data for the second active substance colecalciferol. A pivotal efficacy study was conducted to support the simultaneous administration of both substances. The experience on the combination in humans clinical studies superseded the need for animal data (CHMP, 2005).
Tredaptive is a fixed combination of well-known nicotinic acid, authorised before for the treatment of dyslipidemia in combination with HMG-CoA reductase inhibitors (statins), and the new active substance laropripant. A standard non-clinical test program characterised the new substance. Information on nicotinic acid were provided bibliographically. A complete clinical program was performed with the combination, as required for fixed combinations containing a new active substance,

and extended to investigations on the single substance laropripant as appropriate (CHMP, 2008c).

With regards to the required study program, fixed combinations of only vitamins (or vitamins and minerals - as minerals are also nutrients, the considerations on pure vitamin combinations largely apply to them as well) for the prevention or treatment of deficiency have to be distinguished from combinations of vitamins with other active substances or from combinations for other indications.
In this setting usually non-clinical tests and efficacy trials should not be required. The fixed combination is justified by the substitution indication, therefore beneficial additive effects on the efficacy need not to be shown. Single vitamin medicinal products are usually not labelled for concomitant administration with other vitamins but from the dietary use combination of vitamins can be regarded as uncritical. PK studies in humans to show bioequivalence to the administration of the individual compounds (or to an already authorised fixed combination) might be necessary, if the rules are strictly applied. The benefit of such trials in humans seems questionable in the light of general medical practice of exchanging vitamin preparations with each other. Furthermore, oral vitamin preparations for prevention or treatment of deficiency are administered for a longer time and continuously to achieve (again) a steady-state-concentration of the respective vitamins or their metabolites in the body. For this aim the pharmacokinetic compatibility of the vitamins is of less importance, as the ADME for the various vitamins is regulated by the normal mechanisms in the metabolism due to the actual need or storage level (Pietrzik, 2009, chapter 5.1).

2.2.4. Legal Status of Vitamins containing Medicinal Products

The determination of the legal status of medicinal products either as subject to medical description or as not subject to medical prescription is part of the marketing authorisation procedure, performed by the competent authorities (the CHMP or by the national authorities of the Member States). Directive 2001/83/EC Art. 70 lists the criteria which determine the basic classification into prescription or non-prescription products. Further understanding of these criteria can be gained from the Guideline on changing the classification for the supply of a medicinal product for human use (ENTR, 2006). Optional sub-categories are available for medicinal products subject to prescription and their conditions are described (Arts. 70 and 71). Products for which the criteria do not apply are not subject to prescription. Further details on sub-categories are subject to national provisions, e.g. the differentiation into “free sale” or “pharmacy only” in Germany or the “General Sale List” and “Pharmacy” classification in UK. Certain differences in the legal status between Member States remain because of differences in the national medical practice and pricing, e.g. reimbursement; issues which are not part of EU-wide harmonisation.

Prescription shall ensure medical supervision of administration to various extents, to avoid or control the risks which are imminent to the product or which might arise from misuse or abuse of the product. Also, novel products for which any of the risks can not be excluded due to limited clinical experience are classified as subject to

prescription. Vitamin products are typically classified as non-prescriptive products with two main exceptions:

- parenteral administration, since this type of administration needs medically qualified personnel;
- vitamins at high doses, due to their potential for adverse reactions or long-term sequelae (see chapter 2.1.3.3), “are likely to present a danger directly or indirectly, even when used correctly, if utilised without medical supervision” (Art. 71(1) first indent).

Examples for the second exception are the toxic properties of high doses of vitamin A and D. In Germany, the legal status (free sale, pharmacy only and prescription only) of vitamin A and D products depends on the daily dose (Golly, 2009).

3 Conclusion

From the discussions so far, the key conclusions are drawn here. The viewpoint is that of the regulator, i.e. based on familiarity with the typical properties and requirements of medicinal products:

- when may a product containing vitamins fall out of the definition of a medicinal product?
- when are the requirements for medicinal products not fully applicable or have to be applied/interpreted differently due to the particularities of active substances which also are nutrients?

Finally, the question shall be discussed under which circumstances which class of product might be favourable when developing a new product.

3.1 Demarcation of Medicinal Products from Food and Cosmetics

For consumers/patients or caregivers/physicians the demarcation of vitamin products is often not clear or not of importance as long as the regimen and the intended purpose can be realised. But demarcation is a crucial factor for the company marketing vitamins as the provisions of commercialisation differ significantly.

The comparison of the legal definitions showed that the borderline aspects of vitamin containing products arise when food or cosmetics are presented in dose forms as medicinal products and when the purposes come close in the area of maintaining health and reducing disease risks or preventing diseases.

The legally defined purposes are the key criteria of demarcation of medicinal products to food/cosmetics. The purpose is of cosmetics is clearly defined and supportive demarcation guidance is available. Thus, the differentiation of both product categories is usually possible.
The legal definition of food does not contain a purpose, it is related to ingestion only. The common understanding though relates food to consumption and nutrition. The definitions of the specific types of food discussed here, i.e. food supplements, FPNU and FSMP, do contain a correlation with nutrition. From the viewpoint of modern nutritional science nutrition can be defined as ingestion of all nutritional components necessary for the functioning and well-being of the body. This is not limited to nutrients to avoid undersupply but comprises all components which have a positive effect on the body, implying that prevention, in the meaning of maintaining overall health, is not a side action but an integral part of nutrition (Hahn, 2006, chapter 2.8). This understanding of nutrition further underlines the smooth conversion from nutrition to therapy and complicates the demarcation to medicinal products.

The definition of medicinal products contains their purpose in the functional definition, “with a view to restoring, correcting, modifying physiological functions”, and the presentation part of the definition describes the same purpose as “preventing or treating a disease” (Art. 1(2) Directive 2001/83/EC). The definition has been

amended (by Directive 2004/27/EC) to facilitate demarcation. Unfortunately, new terms have been introduced (pharmacological, immunological and metabolic actions) without corresponding definitions. This is particularly difficult to interpret for vitamins, as they always affect physiological functions and always exert metabolic actions.

The homeostasis model for plant-based food supplements (Council of Europe, 2008) may provide understanding for the difference between a normal and a "medicinal" effect on physiological function of the human body. Vitamin products could be distinguished if either they are intended to act within homeostasis, to "maintain, support, optimise" (Council of Europe, 2008), classifying them as food, of if they are intended to bring a system which is out of homeostasis back into homeostasis or to intentionally bring it out of homeostasis, to "restore, correct, modify", classifying them as medicinal products. Such an approach should be fixed in a consolidated guidance document by DG SANCO and DG Enterprise & Industry similar to the demarcation guidance on cosmetics.

An important part of demarcation is the labelling and/or advertising of the product. Regulation (EC) No 1924/2006 provides for the allowed health or reduction of disease risk claims for foodstuffs. The practical implementation of the provisions has just started, it has to be awaited whether the regulation proves as a sufficient instrument to delimit food and medicines' presentations, but the clear assignment of a scientific authority to evaluate the submitted claims is a promising approach.

Food as well as medicinal products may only be marketed if they are safe, that is fixed in the respective laws. So, if a product is correctly classified, all necessary measures for ensuring safety of the consumers/patients should automatically apply. Nevertheless, the ECJ in case C-211/03 (ECJ, 2005) declares the risk to health as an "autonomous factor" to be considered. This should not be understood in a way that classification as a medicinal product is a risk mitigation measure for products otherwise likely to be sold as food. If a product is unsafe as food it may not be marketed as food.

Vitamin intake may at high doses pose a risk to health, depending on the nature of the vitamin. Directive 2002/46/EC requires upper safe limits for nutrients (from which allowed maximum amounts in food supplements can be derived) to avert a potential risk. But these upper concentration limits for food must not be understood as lower limits for a medicinal function of the vitamin. Medicinal actions may be exerted at lower concentrations. There is no such concentration from which on the action of a vitamin becomes medicinal and from which on *at the same time* health risks occur. Evaluation of a potential risk at the vitamin dose in question has to be considered from two separate viewpoints: firstly, would it make the product - when regarded as food – unsafe (the ULs define the limits for that), and secondly, would it be acceptable or not for a medicinal product in the light of its benefits. Thus, upper limits for nutritional intake are required to protect consumers. For medicinal products these risks may be acceptable in relation to the benefit of the therapy or in relation to the more serious health risks when not taking the vitamins. Furthermore, detailed

instructions for use on medicinal products and the control of the products through health care professionals mitigate the risks.

Although not intended as demarcation limit, EU-wide harmonised upper limits for vitamin concentrations in food supplements will nevertheless lead to “delimitation” insofar that newly developed food products will not contain more than the agreed limits. So, with regards to new products harmonised regulations and upper limits will be advantageous. But for the existing diversified market of food supplements influenced by the differing national legislation it could result in the withdrawal of many products with higher vitamin content from the market. For the UK, the Expert Group on Vitamins and Minerals of the UK Food Standards Agency recommended maximum safe values for vitamins and minerals in 2003. A following market survey revealed that about 12-15% of the UK market on vitamin and mineral products contain higher doses of vitamins. In the UK, these products are not withdrawn but have to carry advisory statements on the possible adverse effects (Food Standards Agency, 2006). As the EVM recommendations are similar or slightly below the recommendations of EFSA, a significant impact could also be expected for the EU vitamin market following the implementation of the ULs. It seems unlikely though that for such products authorisation as medicinal products might be sought, e.g. in the indication of deficiency prevention, as these require high regulatory efforts.

3.2 Marketing Authorisations for Medicinal Products Containing Vitamins

Generally, all provisions for medicinal products on Community level apply also for vitamins as active substances with only very few exemptions

The analysis (chapter 2.2) revealed that the rules completely apply for new chemical forms of active substances or novel indications. Only if known vitamin active substances are utilised and the indication falls in the field of prevention or treatment of deficiency, certain simplifications are possible. Generally, such vitamin medicinal products would be submitted as bibliographic applications instead of generic applications, avoiding the pharmaceutical restrictions of similarity of generic and reference product and avoiding even the human studies on bioequivalence which would be minimum requirement for generics. Furthermore, certain limitations on reference medicinal products and protection periods could be faced if a generic application is sought, due to recent case-law.

In Denmark, the particular character of these products is clearly recognised, as a sub-category of medicinal products called “strong vitamin products” exist. It is limited to oral presentation in dose form, application to humans and to the indication of treatment and prevention of deficiency. The application for such products follows the normal marketing authorisation procedures but is simplified in the requirements for the (non)-clinical documentation. Such a category on Community level would be advantageous as well, considering the regulatory efforts of the MAH and competent authorities. It would furthermore provide for a certain harmonisation of the vitamin market and of SPCs.

It might be tempting to assume that the future upper safe levels for vitamins might also be applicable in regulatory procedures to support safety of a vitamin product. But safety of medicinal products aims at safety for the target patient group while the ULs are considered for healthy consumers. Furthermore, safety of medicinal products considers the finished product in its composition, its presentation and its route of administration, while ULs are limited to the ingredient. Nevertheless, the evaluation by EFSA might be supportive or at least might serve as starting point for data collection for a bibliographic (non-)clinical documentation.

3.3 Considerations for Development of Vitamin Products

When a new vitamin product shall be developed, an important part of planning is to decide, if it is intended to be marketed as food or as medicinal product. Foods generally have the advantages of shorter time-to-market, as the time-consuming conduct of studies and the authorisation procedure are not necessary, of lower development and production costs, and of more flexible quality management requirements compared to GMP for pharmaceutical products. As food is limited to ingestion, the following considerations are for oral forms only.

To decide for a product class the following should be taken into account:

Active ingredients

The ingredients to be used in food supplements and dietary foods are restricted to the positive lists in the respective laws. For food supplements only vitamins and minerals are allowed as ingredients and only certain chemical forms of them. Furthermore, in future there will be EU-harmonised maximum amounts of daily intake.

For medicinal products there is no pre-set list of allowed active substances. If a certain chemical form of a vitamin shall be utilised, e.g. for stability reasons or due to its bioavailability properties, that would require a marketing authorisation dossier by which the efficacy and safety of the active substance is shown. In principle, the positive lists of allowed ingredients in food supplements are open to inclusion of new substances, but unfortunately not on direct initiative by manufacturers.

Another aspect on the ingredients to be considered is the GMP quality requirement for active substances used in the manufacture of pharmaceutical products. These actives are usually more expensive and availability on the market is limited as vitamins belong to the group of “atypical actives”.

Dosage

If certain doses shall be administered exceeding the (future) ULs for food supplements it may be checked if marketing as dietary food is appropriate. For FPNU justified deviations of the upper limits are possible. FSMP might also be an option but these are not usually available to a broad public of customers.

Otherwise a marketing authorisation application is possible by showing the beneficial effect and the acceptable risk of such a dose and by justifying the indication for such an administration.

Intended Use/Indication

The purpose (as discussed above) is a critical issue. If a medicinal purpose is intended, authorisation as medicinal product is mandatory. If a vitamin shall be developed for a novel indication this needs to be investigated as regulated for medicinal products and only then the corresponding medicinal claims may be made. If on the other hand the vitamin product is intended for prevention or compensation of undersupply, a medicinal claim might not be absolutely necessary from a commercial point of view, because this use of vitamins is well-known to patients and doctors. If a doctor advises a patient to regularly (and orally) take certain doses of vitamins, from the patient's and doctor's perspective the product taken may equally be a food supplement/dietary food or a medicinal product.
In this case, marketing as food might be a good option as it would reduce time and costs of development. It should also be evaluated if health claims or reduction of disease claims are available or may be applied for.

Targeted Markets

The decision of the optimal development strategy will also be influenced by the number of countries where the product shall be marketed. Food stuffs may be marketed in all EU countries without restrictions, if the EU food provisions are fulfilled. For medicinal products a DCP/MRP authorisation procedure is mandatory if marketing authorisation is sought in more than one EU country. Currently, the medical practice on vitamins in the Member States is still rather different, which might lead to a difficult harmonisation process of the SPC during the review of an application with regards to indication, posology, target group etc.

Further aspects, not discussed here, are the market prices and the opportunities or limitations of reimbursement, which is applicable to medicinal products only. This needs to be included in the overall cost estimate as well.

4 Summary

Vitamins are well-known essential nutrients, they need to be ingested regularly although in minimal amounts and prolonged lack of vitamins leads to serious diseases and eventually to death. Many of their biochemical functions are well-known. Still many other mechanisms of action are not yet fully understood, e.g. of the antioxidative vitamins C, A and E.
From a legal demarcation point of view, vitamins are special as they may fall in three legal product classes - medicinal products, cosmetics or food.

The three product classes overlap in some aspects of their legal definitions. Products containing vitamins often fall in these borderline areas. But demarcation of such borderline cases is crucial, as the consequences for development and marketing of these products are very different depending on the classification. Borderline situations occur, when food or cosmetics are presented in dose forms. In these cases the intended purpose represents the demarcation criterion. Only medicinal products are intended to treat or prevent diseases. The purposes of food (and cosmetic) products come closest to this when they are intended to maintain health and reduce disease risks. Food supplements (Directive 2002/46/EC), food for particular nutritional uses, i.e. for persons with disturbed digestion or metabolism or persons in special physiological conditions (Directive 89/398/EEC), and a sub-category thereof, food for special medicinal purposes (Directive 1999/21/EC) fall in this borderline area.
The claims allowed on food with regards to their health-related purpose, delimiting them to presentation medicinal products, have recently been regulated in the Nutrition and Health Claims Regulation (EC) No 1924/2006. The conditions and authorisation procedures of health-related claims have been defined and the EFSA was assigned as authority carrying out the scientific evaluations.
The demarcation of vitamin products with regards to the functional definition of medicinal products is more difficult, as the medicinal purpose is defined to be achieved through pharmacological, immunological or metabolic action. Vitamins exert such actions also when they act as nutrients. As the pharmaceutical law does not provide further definitions, the homeostasis model (Council of Europe, 2008) for differentiating plant-based food supplements and medicinal products might provide a common understanding for vitamins as well. The medically normal status of the body/ metabolism is described as homeostasis. Effects of vitamins which keep the body in homeostasis are nutritional functions while medicinal products aim at restoring the status when it is out of homeostasis or at intentionally bringing it out of homeostasis.
The future introduction of EU-harmonised maximum allowed daily amounts of vitamins in food supplements will provide for delimitation of food supplements by upper permissible values of vitamin concentration. These limits aim at safe nutritional intake and do not take potential medicinal effects of vitamins into account, which may occur below these limits. These limits are therefore not of relevance for the demarcation of a vitamin product as a medicinal product according to the functional definition of Directive 2001/83/EC.

For medicinal products containing vitamins two specific characteristics of vitamins in relation to EU pharmaceutical law should be considered.
Vitamins are so-called atypical actives, their main field of industrial utilisation is not in pharmaceuticals, the GMP quality requirements for pharmaceutical actives represent competitive disadvantage for pharmaceutical companies in the vitamin business.
When a product containing solely vitamins is intended for prevention and treatment of deficiency, certain simplifications of the required non-clinical and clinical documentation for marketing authorisation dossiers apply. Bibliographic documentation should - to a large degree if not even completely - be sufficient, for single compounds as well as for the prevalent fixed combinations of vitamins, according to Directive 2001/83/EC, Arts. 10a or 10b and according to the fixed combination guidelines.

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