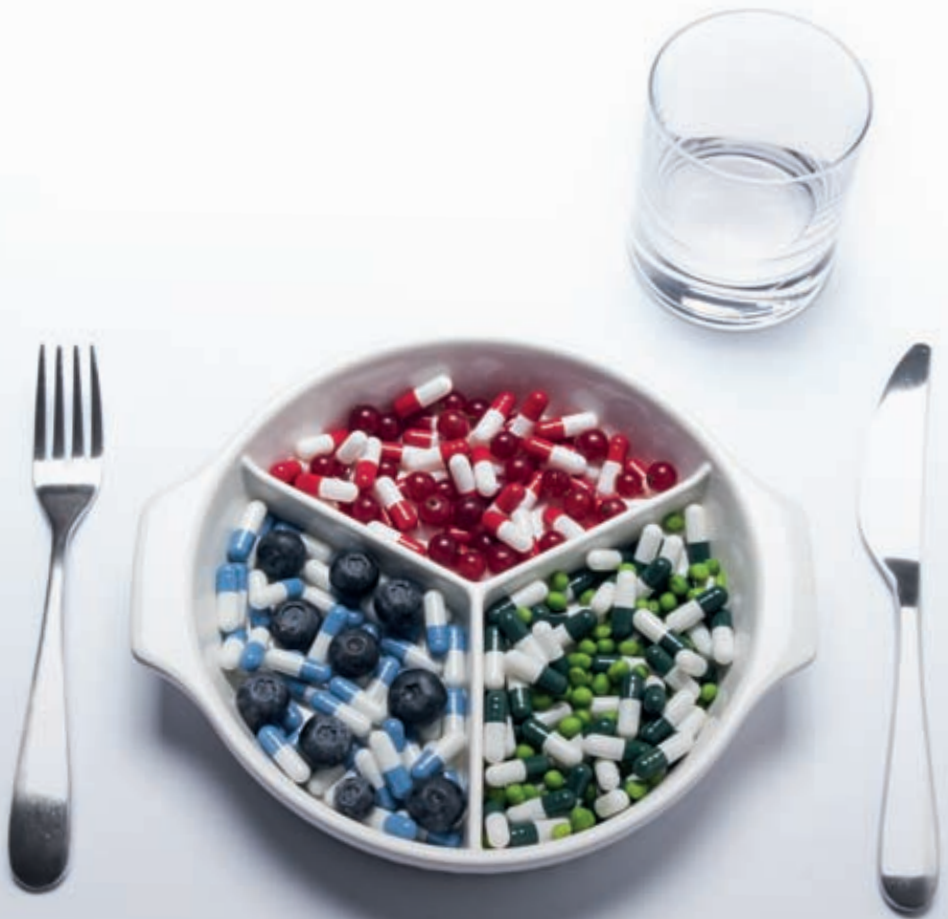


TAMAR CHEKA WEENEN

On the Origin and Development of the Medical Nutrition Industry



ON THE ORIGIN AND DEVELOPMENT OF THE MEDICAL NUTRITION INDUSTRY

On the Origin and Development of the Medical Nutrition Industry

*De oorsprong en ontwikkeling van de
medische voedingsindustrie*

DISSERTATION

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Erasmus University Rotterdam

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CHAPTER 1

INTRODUCTION

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1.1 SCOPE - THE FOOD-PHARMA INTERFACE

As the boundaries between many once-distinct industries are blurring and consequently combine, this process gives rise to new industries. This also holds true for the health and life science sector (4-6). In the past few years the gap between pharma and nutrition science is closing. One reason is the increasing scientific evidence regarding the potential of nutrition and the role in the prevention or treatment of diseases and/or risk factors for disease (7).

As a result of the re-discovered medical application of nutrition, the traditional boundaries between the pharmaceutical and food industries are fading. It is at this interface where the ideal set of conditions/environment is provided for the development of a new industry segment: pharmanutrition.

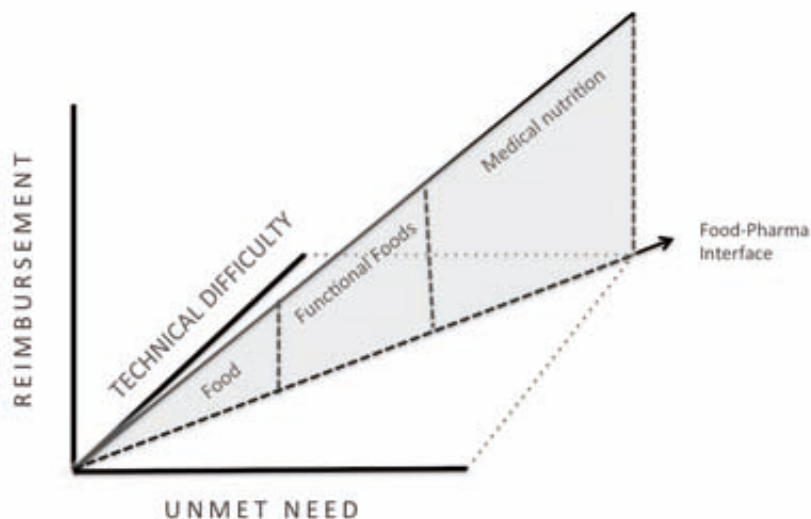
Convergence is taking place where (large) pharmaceutical, biotechnology and food companies are merging or forming strategic alliances to maintain long-term profitability (5, 6, 8). Consequently, the number of companies with multidisciplinary activities eligible to fall under the pharmanutrition industry has increased. Especially in an era where the pharmaceutical industry is facing both fewer product approvals in combination with block-buster patent expirations, such convergence trends offer profitable opportunities (8, 9). Food industry research programs slowly start resembling approaches used in the pharmaceutical world, while pharmaceutical companies realize the potential of nutrition slowing down disease progression or improving therapeutic outcome (7).

The resulting new industries present companies with both threats and opportunities. On the one end, industry convergence increases the risks for developing new knowledge and technologies. Inventors leave the comfort zone of their mono-disciplinary area of expertise to venture into unknown discipline-crossing activities. On the other hand, the early stages of industry convergence offer significant opportunities. One of them encompassing the first-mover advantage, and potentially setting the knowledge and technological industry standard in doing so (9).

Compared to the food industry, the pharmaceutical industry is relatively young. Ever since the pharmaceutical industry has developed into a cluster of industries concentrating on developing commercial applications for global health care markets (10).

Existing pharmaceutical and food companies realize that pharmanutrition is an area filled with opportunities for enhancing discovery, technological and development competencies. (8,11). Already during the past few decades, various boundary-spanning innovative pharmanutritional products have been granted market approval. These, so-called, pharmanutrition products claim to provide a form of specific health benefits beyond basic nutrition. Examples of pharmanutrition products resulting from the convergence between the food- and pharmaceutical- industries are functional foods and medical nutrition (Figure 1.).

Figure 1. Industries situated in the health and life science sector



Nevertheless, both pharmaceutical and food companies also recognize the disadvantages in funding inventions that lead to the commercialization of boundary-spanning products. Especially during the early stages of industry convergence, such products are perceived by the regulatory authorities and legal practices as entities with ambiguous identities. Consequently, the boundary-spanning product is generally misunderstood by the majority of risk-averse consumers and experienced as illegitimate. Additionally, the greatest distinction between food products and medicines is of great significance for legal practice, since medicines are more strictly regulated than foods (12). Therefore, carefully categorizing industries and identifying industry boundaries may lead to better consumer perception and higher market acceptance.

Disadvantages of boundary spanning products are that having an unclear and ambiguous identity decreases the chances of receiving attention as well as not being perceived as legitimate and trustworthy (11).

This introduction starts off by exploring the definitions and characteristics of the pharmanutrition industry in the European health and life science sector. At present, nonstandardized terminology describing pharmanutritional products is often perceived as confusing (7). The focus will be on defining the industry boundaries and illustrating industry convergence. By taking conventional foods at one end of the spectrum, and pharmaceutical products at the other, the pharmanutrition industry can

be split further into two categories falling within this spectrum: functional foods and medical nutrition.

In order to understand the blurring of lines between the conventional foods; functional foods; medical nutrition; and pharmaceuticals industries, it is useful to review each industry.

Table 1. Pharmanutrition industries' characteristics

Product term	Product type	Target population	Function	Purchasing	Reimbursement	Clinical trials	Estimated market size	Example
Conventional foods	Regular food	Healthy individuals // General population	Basic nutrition	Supermarket	No	No	€900-1000 billion	<ul style="list-style-type: none"> Regular margarine Yoghurt
Functional foods	Addition of nutrient to regular food	Healthy individuals // General population	Health promotion // Reduction of risk of disease	Supermarket	No	Required in case of a health claim	€7-9 billion	<ul style="list-style-type: none"> Butter fortified with omega 3 fatty acids. Yoghurt with probiotic cultures.
Medical nutrition	Specific combination of nutrients	Patients	To manage a disease state // Alleviate symptoms	Pharmacy	Country dependent	Required in case of a product claim	€1.5 – 2.5 billion	<ul style="list-style-type: none"> Oral liquid supplement enriched with extra proteins for patients with sarcopenia. Oral liquid supplement enriched with proteins, reduced mineral (phosphate) and liquid content for kidney patients.
Pharmaceuticals	Chemical entity	Patients	Disease prevention // curing	Pharmacy	In most cases	Required	€110-130 billion	<ul style="list-style-type: none"> Penicillin Aspirin

1.1.1 Conventional foods

The conventional foods industry (Table 1.) encompasses a broad range of nutritional products for consumption, ranging from natural sources to genetically, biologically and/or chemically modified food substances. It is considered to be at the opposite end of the industry spectrum, unrelated to the pharmaceutical industry. This product category is defined according to EU legislation as “*any substance or product, whether processed, partially processed or unprocessed, intended to be, or reasonably expected to be ingested by humans. Foods include drinks, chewing gum and any substance, including water, intentionally incorporated into the food during its manufacture, preparation or treatment.*” Food is consumed to provide nutritional support for the body. It is usually of plant or animal origin and contains essential nutrients, such as carbohydrates, fats proteins, vitamins or minerals (13). Foods do not include: live animals unless they are prepared for marketing for human consumption, plants prior to harvesting, medicinal products, tobacco and tobacco products, narcotic or psychotropic substances, and residues and contaminants. Both international trade and technological developments have contributed to a significant increase in the available foods and other edible ingredients.

With the increasing pace of developments in the food industry, EU regulatory bodies realized the need for a formalized safety assessment of new foods In the EU (14), the general policy on food safety has been laid down in the EU White Paper on Food Safety (15). This document outlines a comprehensive range of actions required to complement and modernize existing European food legislation, which in turn led to the introduction of the General Food Law (Regulation (EC) 178/2001). This regulation formed the basis for the establishment of the independent European Food Safety Authority (EFSA) in 2002. In summary, these regulations are necessary to ensure EU unified food safety standards.

Conventional foods are inherently linked to an individual’s health. As a result, conscious consumers seek out the health properties of natural food substances.

1.1.2 Functional foods

The term “functional food” was first introduced in Japan in the 1980’s as FOSHU (Food for Specified Health Uses) and has since developed into a successful and lucrative industry (16, 17). The Japanese interest in functional foods spread towards the Western world in the early 1990s. As a result, the Western functional food industry has evolved at the intersection of the pharmaceutical and food industries (9, 17). This product category consists of food products with added health benefits when compared to the regular nutritional value of the traditional food product(18). To date, most countries do not have a formal and legislative definition of the term *functional food*. Even for experts, delineating the boundaries between food and functional foods is challenging (17). According to the EU-project Functional Food Science in Europe (FUFOSE), functional foods are defined as: “*A food can be regarded as functional if it is satisfactorily demonstrated to affect beneficially one or more target functions in the body, beyond adequate nutritional effects...*” (19). The functional food industry is seen to have evolved from the convergence of the food industry and health and life science sector. Comparable to the pharmaceutical industry, which is based on

traditional healing experiences such as willow bark (aspirin), functional foods are based on traditional nutrition folklore such as fatty fish, at present often supplemented as a refined omega fatty acid.

As awareness and trust concerning food related health benefits is growing among the general public, consumer demands are changing. They collectively seek foods with added health benefits, which include functional foods. Most early developments of functional foods were food products enriched with vitamins and/or minerals. Soon, foods fortified with various essential micronutrients - such as phytosterol and soluble fiber - became more popular (20, 21).

Through functional foods, consumers aim to prevent diseases and improve their physical and mental well-being (22). The majority of functional food products are aimed at; optimizing health by increasing energy-levels, by boosting the immune system or through the prevention of chronic illnesses (including cancer, cardiovascular disease, Alzheimer's disease and osteoporosis) (18). Especially in the Western World, any innovation targeting those disease areas are considered valuable. combination of the following reasons; healthcare costs are increasing; people demand an improved quality of life; and there is a steady increase in life expectancy. Combined with the general saying that "an ounce prevention is worth a pound of cure", consumers are more actively pursuing healthy lifestyle and dietary choices.

Consumer perception of functional foods is strengthened by means of nutrition and/or health claims. A claim is defined by the Codex Alimentarius, as "*any representation which states, suggests or implies that a food has particular characteristics relating to its origin, nutritional properties, nature, production, processing, composition or any other quality*" (23). To ensure that claims on foods and food constituents are scientifically justified, the European Union published Regulation No 1924/2006 on nutrition and health claims made on foods (24). This regulation distinguishes two categories of claims on foods: health claims and nutritional claims. Nevertheless, functional foods are not regulated in the same way as pharma (EMA or FDA). According to functional food legislation, health claims state, suggest or imply, a relationship between food and health. Such claims include reduction of risk of disease claims, function claims, or claims referring to the growth and development of a child.

Nutrition claims state, suggest or imply that a food has particular beneficial nutritional properties due to the energy it provides or the nutrients it contains. Examples hereof are content claims or comparative claims, e.g. "this product contains calcium" or "this product is low in sugar". Explicit conditions are provided in EU legislation for claims such as "source of", "rich in", "reduced", "fat-free" (23). The European Food Safety Authority (EFSA) carries out the scientific assessments of these claims in Europe. The final approval is provided by the European Commission and member states but is strongly based on the scientific opinions of EFSA as to whether the claim is sufficiently substantiated (25, 26).

Since many applicants have encountered difficulties in submitting EFSA acceptable scientific evidence to be granted a health claim, they published in July 2007 its "scientific and technical guidance for the preparation and presentation of the

application for authorization of a health claim". This publication is pursuant to Article 14 of Regulation 1924/2006 in order to assist the applicant with submitting health and nutritional claims. As may be expected, the reactions from various stakeholders regarding this EFSA document differ considerably (27). Some stakeholders have brought up the issue that the current EFSA approach may hamper innovation. Others state that in the long term, Regulation 1924/2006 will improve the reliability and credibility of health claims on foods. According to yet other experts, this regulation will not empty the functional food shelves but solely change the look of those shelves.

1.1.3 Medical nutrition

Medical nutrition is perhaps the most confusing category, subject to different interpretations between, as well as within, geographical regions. Terms include; medical nutrition, clinical nutrition, medical foods, enteral nutrition, foods for special medical purposes, and dietary supplements (7, 12, 28, 29).

In Europe, medical nutrition is not regulated by the EMA (European Medicines Agency) but is governed by the Foods for Special Medical Purposes (FSMP) Directive. The design and production of medical nutrition is predominantly based on scientific knowledge. In this Directive, medical nutrition is defined as: "*foods that meet the particular nutritional requirements of persons affected by or who are malnourished because of a specific disease, disorder or medical condition*" (30). This category includes oral nutritional supplements as well as tube feeding, of which the latter is administered via nasogastric, nasoenteric or percutaneous tubes. There are three categories in medical nutrition: nutritionally complete foods that can serve as the sole source of nutrition for a patient; nutritionally complete foods with an adapted nutrient formulation which can also serve as the sole source of nutrition for a patient; nutritionally incomplete foods which are not suitable as the sole source of a patient's nourishment (30).

As a result of the patient specific needs, medical nutrition is often personalized in order to optimize the health-benefit effect. The European Union provided manufacturers with basic rules concerning the vitamin and mineral substances that are needed for covering particular requirements of intended users (30). The legislation of medical nutrition is harmonized on EU level, but in case of the Directives it is implemented in the individual Member States.

Medical nutrition spans both conventional food and pharmaceutical categories. Nevertheless, medical nutritional products are intended for patients suffering from a disease and are predominantly prescribed by a medical professional. Therefore, medical nutrition products are perceived to be more related to the latter category. As a consequence of this industry convergence, it is confusing for the regulatory authorities, medical nutrition companies and market, how to validate the safety, efficacy and quality of a medical nutritional product for example. In the pharmaceutical industry, clinical trials are an essential aspect in new product development. For the medical nutrition industry in Europe, clinical trials are optional. Companies may choose to carry out clinical trials to obtain sufficient evidence on the efficacy of a product to be able to substantiate a product claim.

These product claims are often important in the process of applying for reimbursement. The requirements for reimbursement are dependent on the health care system of the particular country and the reimbursement decision rests with the respective countries' advisory committees (31, 32).

Already in the last few decades, pharma-like clinical evidence concerning the effectiveness of medical nutrition has significantly enhanced its credibility (33). Medical nutrition is becoming a well-accepted form of nutritional support for patients suffering from disease-related malnutrition. Disease-related malnutrition is a highly underestimated condition, prevalent throughout hospitals, community health care centres (outpatients, care homes, general practice) and other community settings (34). Malnutrition is defined as *“a state of nutrition in which a deficiency, excess (or imbalance) of energy, protein and other essential nutrients causes measurable adverse effects on tissue/body form (body shape, size and composition) and function, and clinical outcome”* (35). There are many causal factors leading to disease-related malnutrition, yet in general; it is the underlying medical condition that affects the intake of essential micronutrients.

1.1.4 Pharmaceuticals

The pharmaceutical industry represents the other end of the health & life science sector spectrum, and in turn is highly unrelated to the conventional foods industry. During the 1980s, the pharmaceutical industry experienced an exponential growth-spurt, leading to the highest product turn-over and market approvals of new chemical entities (NCEs) known to history. Nevertheless, this growth has significantly slowed down at the start of the millennium, due to a number of reasons including, but not limited to; rising development costs; enhanced best-standard of care, blockbusters patent expiry and intensified global competition (36, 37). Pharmaceutical new chemical entities are defined by the EU legislation as: *“any substance or combination of substances presented for treating or preventing disease in human beings. Any substance or combination of substances which 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 is likewise considered as a pharmaceutical product”* (38)

Pharmaceutical new chemical entities are considered prescription medicines, used for therapeutic treatment or prophylaxis of a chronic or acute disease. They can only be obtained at a pharmacy with a prescription from a physician. The drug development value chain is considered as one of the most (inter-) nationally regulated processes, whereby the NCE has to demonstrate specific safety, efficacy, quality and ethical standards throughout the discovery, pre-clinical, clinical and market phases. As a result, the average clinical development phase of the value chain takes over 12 years, and requires an investment close to €0.6 Billion (39). Since 1995, the European medicines Agency (EMA) is responsible for the scientific evaluation and monitoring of the safety and efficacy of pharmaceutical products in Europe.

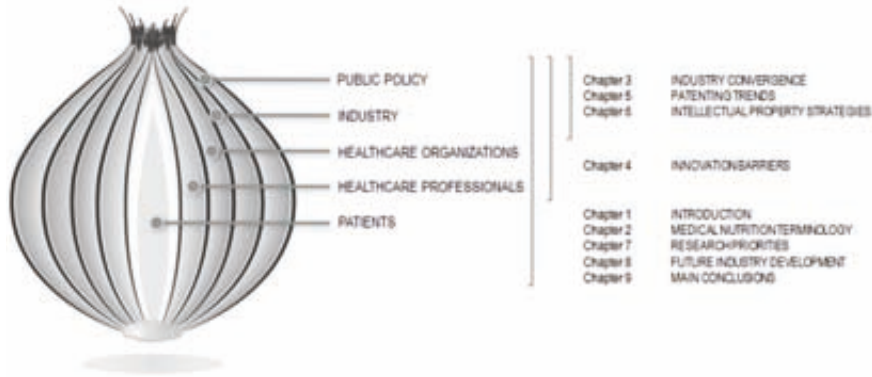
1.2 OBJECTIVES AND OUTLINE

The European medical nutrition industry is relatively new within the historical scope of the health and life sciences and represents one of the fastest growing segments within this sector. This industry finds itself on the interface between the food and pharmaceutical industry with its own Foods for Special Medical Purposes (FSMPs) regulations. Medical nutrition products are prescribed food compositions that consist of targeted nutritional compositions for intervention in disease progression and symptom alleviation. The European medical nutrition industry is dominated by 5 companies: Abbott Nutrition, B Braun, Danone (Nutricia), Fresenius Kabi and Nestle. This industry is perceived as an industry in an early development stage offering ample innovation opportunities. Its growth is most likely attributable to an increase in scientific advances and societal awareness on the functional health benefits of nutrition.

Medical nutrition affects multiple societal levels, making innovations within this field particularly valuable (Figure 2). The primary goal of medical nutrition is to fulfill the unmet patient needs of malnourished patients, representing the onion core. The second inner layer is represented by the health care professionals who prescribe medical nutrition products to their patients to provide nutritional support. At the industry level, successful medical nutrition innovation is considered the primary driver for economic development. The outer onion layer represents the policy level, medical nutrition products can enhance public health; thereby significantly reducing healthcare related costs. Therefore, by staying innovative, medical nutrition companies will be able to maintain their competitive niche and continue to accommodate the unmet medical needs of malnourished patients.

In this dissertation we tackle research topics addressing all societal levels, thereby stimulating the adoption of a holistic approach in developing medical nutrition products. This in turns may contribute to an innovation boost for the benefit of public health, academia and industry. Figure 2. depicts the outline of this dissertation according to the different societal levels.

Figure 2. Outline of dissertation according to different societal levels



Medical nutrition innovation takes place within a so-called technological innovation system, which is a concept developed to explain the nature and rate of technological change. It can be defined as a set of actors and rules that influence the speed and direction of technological change in a specific technological area (40) Since we are dealing with a relatively new industry, academic insights into medical nutrition innovation are lacking. Motivated by the multi-leveled societal importance of medical nutrition, this PhD dissertation aims to advance the understanding of the innovation dynamics of the European medical nutrition industry. It starts off by (1) delineating the boundaries of medical nutrition; (2) followed by an analysis of the medical nutrition innovation system and (3) concluding by proposing possible medical nutrition industry future scenarios.

(1) Delineating the boundaries of medical nutrition (Chapters 1, 2 & 3)

The concept of medical nutrition lacks universal coherence and therefore *Chapter 1* sets out to put clarity and continuity to the use of terms and definitions concerning the medical nutrition product category. *Chapter 2* describes the emergence and boundaries of the medical nutrition industry as a result of food-pharma convergence focusing on knowledge diffusion and consolidation. Through patent analysis we visualized and measured which distinct industry domains have converged to result in the medical nutrition industry as it is today.

(2) The medical nutrition innovation system (Chapters 2, 3, 4, 5 & 6 & 7)

Chapters 3, 4, 5 and 6 focus on analyzing the technological medical nutrition innovation system. The purpose of analyzing a sectoral innovation system is to study and evaluate the development of a particular technological field in terms of the structures and processes that support or hamper it.

Innovation is a necessity for survival in dynamic and complex industries such as the medical nutrition industry. Nevertheless, innovation is a difficult undertaking and companies must first overcome numerous barriers inhibiting innovation. *Chapter 3* sets out to qualitatively and quantitatively explore the barriers inhibiting medical nutrition innovation. Studying these barriers provides insight into the dynamics of innovation, which simultaneously is a first step in the process of overcoming them. Subsequently, *Chapter 4* analyzes medical nutrition market development and the innovation activities of the five players of the European medical nutrition industry by means of patent data analysis.

Since innovation does not only rely on the development of ideas but also on the ability to protect these ideas, *Chapters 4 & 5* evaluate intellectual property protection strategies within the medical nutrition industry. *Chapter 5* concludes with an intellectual property decision framework supporting both medical nutrition companies and academic research and development departments in their intellectual property strategy decision processes. Ultimately, *Chapter 6* evaluates the current involvement of key opinion leaders in the medical nutrition innovation process and provides a prioritization overview of unmet patient needs and innovation opportunities in the medical nutrition market.

(3) Medical nutrition industry future scenarios (Chapters 8 & 9)

Based on the results from the previous chapters, *Chapter 8* consists of a medical nutrition industry development forecast analysis proposing four different possible future scenarios for the development of the medical nutrition industry. *Chapter 9* concludes this dissertation by summarizing the key findings and implications of this research, and provides directions for future research.

1.3 GLOSSARY OF TERMS

Clinical trial / research	Any investigation in human subjects intended to discover or verify the clinical safety and efficacy of a health product and its effect on humans.												
Incremental innovation	Incremental inventions consist of minor improvements or adjustments to existing inventions or technologies.												
Industry convergence	The blurring of boundaries between distinct industries.												
Innovation	The process of turning opportunity into new ideas and of putting these into widely used practice.												
Inorganic growth	A growth in the operations of a business that arises from mergers or acquisitions, rather than an increase in the companies own business activity.												
Intellectual property	Intellectual Property (IP) refers to the protection of creations of the mind, which have both a moral and a commercial value. IP law typically grants the author of an intellectual creation exclusive rights for exploiting and benefiting from their creation. Internationally recognized IP rights for protecting inventions include: trade secrets, copyrights, brands/trademarks, and patents.												
Malnutrition	A state of nutrition in which a deficiency, excess (or imbalance) of energy, protein and other essential nutrients causes measurable adverse effects on tissue/body form (body shape, size and composition) and function, and clinical outcome.												
Medical nutrition	<p>Due to journal requirements, throughout this dissertation different terms for medical nutrition are used:</p> <table><tr><th>Chapters</th><th>Term</th><th>Nutrition type</th></tr><tr><td>1, 2.2, 3, 4, 5, 7, 8</td><td>Medical nutrition</td><td>Oral nutrition & Tube feeding</td></tr><tr><td>2.1</td><td>Medical nutrition</td><td>Oral nutrition, Tube feeding & Intravenous nutrition</td></tr><tr><td>6</td><td>Enteral nutrition</td><td>Oral nutrition & Tube feeding</td></tr></table>	Chapters	Term	Nutrition type	1, 2.2, 3, 4, 5, 7, 8	Medical nutrition	Oral nutrition & Tube feeding	2.1	Medical nutrition	Oral nutrition, Tube feeding & Intravenous nutrition	6	Enteral nutrition	Oral nutrition & Tube feeding
Chapters	Term	Nutrition type											
1, 2.2, 3, 4, 5, 7, 8	Medical nutrition	Oral nutrition & Tube feeding											
2.1	Medical nutrition	Oral nutrition, Tube feeding & Intravenous nutrition											
6	Enteral nutrition	Oral nutrition & Tube feeding											

	<p>Medical nutrition is defined as a specially formulated nutritional composition for the dietary management of patients with diseases, disorders or medical conditions that cause distinct nutritional requirements. It may consist of partial or exclusive feeding by means of oral intake, tube feeding and/or parenteral administration under healthcare professional supervision.</p>
Organic growth	<p>Organic growth represents the true growth from the core of the company.</p>
Patent	<p>A patent gives the inventor the right to exclude others from producing, using, selling, offering to sell, or importing the invention without permission and has a statutory duration of 20 years.</p>
Radical innovation	<p>Exhibits key characteristics that are inherently different from existing innovations or technologies and is considered to form a crucial basis from which subsequent incremental developments may evolve.</p>
Technology S-curve	<p>Describes successful industry development as an S-curve proceeding from the emerging, to the growth, to the saturation phase.</p>

CHAPTER 2

A CRITICAL LOOK AT MEDICAL NUTRITION TERMINOLOGY AND DEFINITIONS: A LITERATURE REVIEW

Weenen TC, Commandeur HR, Claassen E (Accepted) A critical look at medical nutrition terminology and definitions: a literature review

ABSTRACT

A plethora of terms and definitions for medical nutrition has resulted in an ambiguity in the way “medical nutrition” is termed and defined across various societal levels. The terms *medical nutrition*, *clinical nutrition*, *enteral nutrition*, *parenteral nutrition*, *oral nutritional supplements*, *medical foods*, *foods for special medical purposes*, *nutritional support*, *nutritional intervention* and *nutritional therapy* are used interchangeably. To date consistent terminology/nomenclature and definitions have not emerged from the US and European medical nutrition community. The current absence of clear medical nutrition product category boundaries makes it necessary to introduce medical nutrition terminology conformance in order to reduce widespread confusion at policy; industry; healthcare; and patient level. In order to end discussion, this literature review attempts to put quantitative and qualitative clarity and continuity to the use of these terms and definitions by: (1) addressing the terminology used; (2) discussing the distinguishing features of medical nutrition in various definitions and (3) proposing a single medical nutrition term and a clear pragmatic operational definition. A scientific literature-based comparison was conducted resulting in the selection of 22 publications, describing 8 different terms with 19 definitions.

Based on the terminology found in literature, the following medical nutrition terminology is proposed: medical nutrition comprises both parenteral (intravenous) as well as enteral nutrition (tube feeding and oral nutrition), which may be given via the oral route or via a tube into the gastrointestinal tract. The features found to be most important in describing medical nutrition are: *route of administration*; *disease*; *supervision*; *composition* and *support/management*. These features have been integrated into one operational clinical definition and resulted in the following definition: **MEDICAL NUTRITION:** specially formulated nutritional composition for the dietary management of patients with diseases, disorders or medical conditions that cause distinct nutritional requirements. It may consist of partial or exclusive feeding by means of oral intake, tube feeding and/or parenteral administration under healthcare professional supervision.

2.1 INTRODUCTION

Nutrition is moving towards more health-oriented innovation thereby creating a “food-pharma” interface of products with an emphasis on the interaction between pharmacology and nutrition science (Figure 1) (7, 12). Drawing boundaries between the different food-pharma markets is challenging for those not actively involved in the nutrition market since there are few legislative term definitions for nutrition. During the last decade, the functional food (FF) industry is considered as an interesting area of research and innovation within the food industry (41). Adjacent to the functional foods industry, another food-pharma industry has emerged at this interface: the medical nutrition (MN) industry (42). The MN industry has been characterized as a growth industry with ample innovation opportunities. Nevertheless, newly emerging industries are often fragile and are prone to collapsing, possibly leading to the metaphorical *innovation cliff* (3, 43). Two key factors that may contribute to this phenomenon include a lack of regulatory transparency and reduced innovation adoption. These two factors are undeniably interlinked; clear regulatory frameworks often create pressure that motivates innovation and progress which in turn may enhance profits and competitiveness (44, 45). The emergence of new food-pharma industries such as the MN industry and the resulting absence of clear product category boundaries make it necessary to introduce MN terminology conformance in order to reduce widespread confusion.

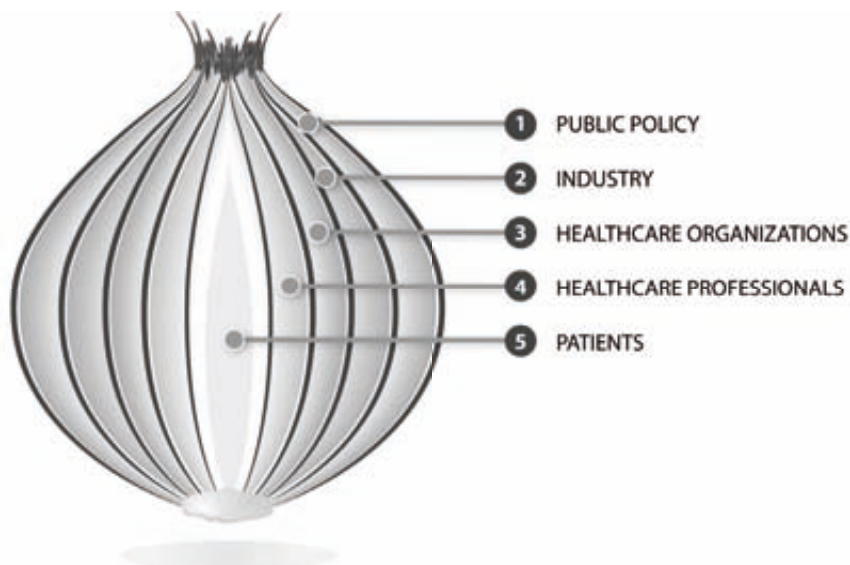
Figure 1. Food-Pharma Interface – From regular food to pharmaceuticals. Adapted from (12)



Although previous research has shown that the MN industry originates from food-pharma industry convergence, consensual product category boundaries have not been clearly delineated (46, 47). At the regulatory and clinical level, a plethora of MN terms are applied and used interchangeably. So far there is no unitary accepted terminology and definition for MN. Although this lack of conformance in defining MN has been recognized, there has been no embracement of a unitary accepted terminology and definition. A number of (inter)national authorities, academic bodies and the industry have proposed standardized terminology and definitions for aspects of medical nutrition. For example, in 2006, the European Society for Clinical Nutrition and Metabolism (ESPEN) attempted to implement a European terminology for this food type: *“enteral nutrition: all forms of nutritional support that imply the use of “dietary foods for special medical purposes” as defined in the European legal regulation of the commission directive 1999/21/EC of 25 March 1999, independent of the route of application. It includes oral nutritional supplements (oral nutrition) as well as tube feeding via nasogastric, nasoenteral or percutaneous tubes”* (48). Nevertheless, this description of enteral nutrition only comprises a share of all types of medical nutrition products.

Carefully categorizing MN product category boundaries can lead to an increase in healthcare professional awareness; resulting in higher patient acceptance and more targeted value-adding/safety-driven research and product development (3, 49-53). Currently, at the healthcare professional level, awareness concerning malnutrition and nutritional support is considered low (54). This directly influences patient awareness since patients are informed about nutritional support possibilities by their healthcare professional. Furthermore, reducing the uncertainty on product classification may also aid start-up enterprises at the front-end of the innovation process by enabling them to clearly define product innovation opportunities. At the public policy level, since MN is considered of high societal value, defining industry boundaries may have an indirect public health benefit thereby reducing healthcare costs (55). Agreement on terminology and definition for MN can therefore contribute to transparency at various societal levels (Figure 2). Such transparency can contribute to adopting a holistic approach in developing MN products. Creating holistic joined-up approaches across healthcare settings and communities may in turn stimulate innovation and prevent a possible MN innovation cliff (3, 54, 56).

Figure 2. Different societal levels affected by transparent MN terminology and definition



The objective of this review in order to reduce terminology and definition confusion and to end discussion is therefore to: (1) address the terminology used; (2) discuss the distinguishing features of MN in various definitions and (3) conclude with a proposition of consensual MN terminology and a pragmatic operational definition. A scientific literature-based comparison is presented, followed by a stepwise discussion on terminology and definitions.

Overview

Search terms

Fifteen ESPEN faculty members whom are considered MN key opinion leaders (KOLs) (practicing MD; dietitians; nurses; researchers; professors; and consultants) were asked to list all terms used to describe MN so as to create an overview of search terms applied in the literature search. The following 11 terms were stated: *medical nutrition (MN)*; *clinical nutrition (CN)*; *enteral nutrition (EN)*; *parenteral nutrition*

(PN); medical foods (MF); foods for special medical purposes (FSMP); oral nutritional supplements (ONS); tube feeding (TF); nutritional support ; nutritional intervention and nutritional therapy.

Literature search

The literature search was conducted using a combination of Metapress, Pubmed, Google Scholar and Sciencedirect public search engines, applying relevant search terms on the theme, including the terms MN, CN, EN, PN, MF, FSMP, ONS, TF, nutritional support, nutritional intervention and nutritional therapy. The search was restricted to publications in English. We primarily focused on MN oriented scientific journals such as *Clinical Nutrition*; *The American Journal of Clinical Nutrition*; *Nutrition in Clinical Practice*; *Journal of Parenteral and Enteral Nutrition*; *Journal of Human Nutrition and Dietetics*; *Journal of American Dietetic Association* and *Nutrition*. Furthermore, the online publications of US and European regulations were used as sources.

After reviewing 113 scientific publications from 1999 to 2013, 22 publications were selected on the basis of their representation of a definition of MN, describing 8 different terms with 19 definitions (Table 1.). Surprisingly, the terms *clinical nutrition*, *nutritional intervention* and *nutritional therapy* are not defined as such in regulatory or scientific publications. All other terms as mentioned by the KOLs were found in literature. In addition, the definitions predominately originate from scientific papers published by either governmental bodies and/or nutrition oriented societies.

The different MN terms are first discussed in a stepwise manner, followed by an analysis of the different MN definitions on the basis of distinguishing MN features. The definitions were analysed on the basis of the occurrence of six features: *route of administration*; *disease*; *malnutrition*; *supervision*; *composition*; *support / management* (Table 2.), and discussed below.

Table 2. Features defining MN mentioned in literature (definition numbers refer to table 1.

Feature	Definition Nr.
Nutrition type	All
Disease	1,2,3,5,6,10,11
Malnutrition	1
Supervision	5,10,14
Composition	3,12,13, 17
Support / management	1,4,5,7, 8, 10,11, 18
Region	All

Terminology

Although the terms *clinical nutrition*, *nutritional intervention* and *nutritional therapy* are often used in the medical field, these terms are not defined in scientific literature. These terms may refer to the use of nutrition in clinical settings and not as a product category on its own. These terms may also include dietary changes for patients in clinical settings in contrast to MN, which is defined here as *specifically formulated nutritional compositions*. This is confirmed by the definition of the *European Journal of Clinical Nutrition*: “.... an international journal providing essential scientific information on nutritional and metabolic care and the relationship between nutrition and disease both in the setting of basic science and clinical practice.”. Therefore, these terms are not discussed in this review. Furthermore, the term *nutritional support* was defined in the ESPEN guidelines on enteral nutrition. According to these guidelines, *nutritional support* encompasses oral nutrition products, tube feeding (TF) and food fortification. Since nutritional support is regarded as a generic way of applying MN to manage nutritional risk, it is further left out of scope in this review.

Further complicating the terminology is that *enteral nutrition (EN)* is applied both to describe solely TF as well as both oral nutrition and TF (48). Since *enteros* means *intestine*, and both TF and oral nutrition utilise the gastro-intestinal tract, we propose that the term *enteral nutrition* encompasses both TF as well as oral nutrition. Also commonly perceived as MN but regulated within the pharmaceutical scope, lies the concept of intravenous nutrition, or parenteral nutrition (PN). Since the purpose of PN is to meet the patients’ special nutritional needs, similar to the other types of MN, PN is included in this MN terminology and definition review

Geographic region – Europe and US

Both the United States (US) and European (EU) governments have mandated, through their regulatory bodies, that legislation be established to ensure the safety and truthful labelling of nutritional products (57). However, the regulatory approaches and terminology differ from each other. In the US, the oral and tube routes of administration of MN are regulated as a *Medical Foods (MF)*, whereas in the EU, these are regulated as *Foods for Special Medical Purposes (FSMPs)*. At present, regulatory changes are taking place within the European MN market with the goal to provide a better environment for businesses, better application of rules, better consumer protection on the content and marketing of MN and possibly inducing an innovation boost (46)..

The US FDA regulations define MN as a *medical food*, therefore logically, this term is only found in the definitions of US origin. Similarly, the European regulatory term *Foods for Special Medical Purposes* is only found in the definitions originating from Europe. Parenteral nutrition is regulated both in Europe and the US under the pharmaceutical regulatory framework. All other terms (*MN*; *EN*; *oral nutrition*) are used interchangeably in terminology and definitions originate both from the US and Europe.

Medical nutrition purposes

Within the concept of MN we propose that at present two types of medical nutrition purposes exist:

- (1) Management of disease-related malnutrition: these are often high protein / high energy, multi-nutrient dense products intended to manage disease-related malnutrition in patients who are unable to consume sufficient normal foods to meet their nutritional requirements as a result of a disease, disorder or condition, or its associated treatment e.g. stroke, oncology, surgery or chemotherapy
- (2) Disease-specific dietary management: these products are intended for the dietary management of a particular disease state. They can be considered to manage nutritional risk by omitting specific ingredients or nutrients which would cause problems if consumed as part of a normal diet by patients with specific diseases, e.g. avoidance of cow's milk protein in cow milk allergy, and avoidance of phenylalanine in phenylketonuria, or by providing nutrients in a specific amount or balance that might be difficult or impractical to achieve by means of normal foods, e.g. ketogenic diet for childhood epilepsy.

Route of administration

Three routes of application for MN exist: Oral Route = orally; Tube Feeding (TF) = through a gastrointestinal tube; and Parenteral Nutrition (PN) = intravenously. The different routes of administration are described separately.

Oral Route

Broadly, oral route products can be divided into two categories: (1) those intended for the dietary management of disease-related malnutrition, also known as oral nutritional supplements (ONS) and (2) specialised compositions designed to be used in a particular disease, termed here as disease-specific dietary management products. The first type, ONS products, may have a standard nutrient composition and are designed to be used to manage a state of malnutrition in a variety of different diseases. These are often high-protein / high-energy dense products containing macro- and micronutrients. Some ONS have a disease-specific composition, whereby the nutrient profile is adapted to make them particularly suitable for managing disease-related malnutrition in a certain disease, disorder or condition. The second category consists of disease-specific dietary management products which are designed to be used in the dietary management of a particular disease state, but where disease-related malnutrition is not the primary concern. In all cases, these products should be used under healthcare professional supervision after an evaluation of individual circumstances, to ensure that the right type of product is used at the right time to meet predefined nutritional goals (56).

Oral nutrition products are regulated as *medical foods* in the US, as part of the orphan drug act. In Europe, oral nutrition products are governed by the FSMP directive which is part of food legislation. These products are usually specifically designed for oral use and are generally only prescribed under supervision of a medical professional. These are not to be confused with food or dietary supplements in pill formats that solely provide vitamins, minerals, etc. and which can be purchased over

the counter / freely by consumers (56). Oral nutrition products are often used as a supplement to other food intake, but in many cases they are nutritionally complete and may be used as a sole source of nutrition (58). Oral nutrition products may be liquid, ready to use products, e.g. in a small bottle with a straw or may be available in powder form, to be added as a fortifier to other foods, or to be made up into a drink with water or milk. Some oral nutrition products are thickened for use in patient groups with swallowing difficulties (dysphagia).

Tube feeding (TF)

When the administration of nutritional support via the oral route is not possible, provided that the gastrointestinal tract is at least partially functional, feeding via a tube may be advisable. Similar to oral nutrition, TF may be supplementary to oral intake or can be the sole source of nutrition (56). TF may be administered through a nasogastric, nasoenteral or percutaneous tube (56, 59). In the US and Europe, oral nutrition and TF are regulated similarly, either as MF (in the US) or as FSMPs (in Europe).

Similar to oral nutrition products, the desired impact/effect of TF can be divided into: (1) managing disease-related malnutrition; (2) disease-specific dietary management.

Parenteral nutrition (PN)

The term parenteral originates from the Greek *para* meaning “besides” and *enteros* meaning “intestine”, because it bypasses the intestines. PN thus refers to a means of bringing nutrition into the body other than through the gastrointestinal tract, in other words, intravenously (56). PN is administered when other nutritional routes (regular diet/oral nutrition/TF) are not efficacious or when it is unsafe to use those other routes (59). It is delivered via a catheter inserted into a peripheral or central vein (venous access), and depending on the patient’s clinical situation, may be required as short-term nutritional support, for the longer term or even for life (56). The term total parenteral nutrition refers to the administration of nutrients and energy solely by the parenteral route, while supplemental parenteral nutrition complements either oral or TF supply (56). The purpose of PN is to reduce a patient’s nutritional risk by managing disease-related malnutrition. PN is part of the pharmaceutical regulatory landscape (covered by the FDA in the US and EMA in the EU), and as such must follow a clearly defined clinical research process (56).

2.2 Definition: distinguishing features

Disease

The feature *disease* (or similarly: illness, (medical) condition or disorder) can be found in 39% of all the MN definitions presented in this review. Dorland's Medical Dictionary for healthcare Consumers defines disease as: "*a definite pathological process having a characteristic set of signs and symptoms. It may affect the whole body or any of its parts, and its etiology, pathology, and prognosis may be known or unknown*" (60). In contrary to for example functional foods, which are predominantly intended for healthy consumers, MN is primarily intended for patients whose nutritional requirements cannot be met by normal foods, due to an underlying medical condition/disease/disorder or illness (61).

Malnutrition

Even though *malnutrition* is often overheard in the context of MN, the concept itself can only be found in one of the MN definitions in this review (62). Malnutrition can be defined as "a state of nutrition in which a deficiency, excess or imbalance of energy, protein and other nutrients causes measurable adverse effects on tissue/body form (body shape, size and composition) and function, and clinical outcome" (63). Malnutrition thus often arises due to the consequences of disease. In this review, we will only refer to *disease-related malnutrition*. Disease can result in under-nutrition due to different effects: decreased dietary intakes; impaired gastrointestinal functions reducing digestion and absorption; and an altered metabolism. The prevalence of disease-related malnutrition is high in patients in hospitals, care homes and other institutions, and those living in their own homes in industrialized regions such as Europe and the US (MNI, 2012). Not all MN products are intended to manage disease-related malnutrition; some types are intended for the disease-specific dietary management of patients (see section 1.2.2).

Supervision

Despite the fact that the term *supervision* is stated in both the US and European MN regulations, it remains poorly defined and under-debated in literature. The Miller-Keane encyclopedia & dictionary of medicine, nursing & allied health defines *healthcare supervision* as: "the management of the treatment plan by a healthcare professional" (64). This in turn leads to the question, what is a healthcare professional? Dorland's Medical Dictionary for Healthcare Consumers defines a *healthcare professional* as: "a person who by education, training, certification, or licensure is qualified to and is engaged in providing healthcare" (60).

In addition, in Directive 2011/24/EU on the application of patients' rights in cross-border healthcare, the following definitions are laid out: "health professional: means a doctor of medicine, a nurse responsible for general care, a dental practitioner, a midwife or a pharmacist within the meaning of Directive 2005/36/EC, or another professional exercising activities in the healthcare sector which are restricted to a regulated profession as defined in Article 3(1)(a) of Directive 2005/36/EC, or a

person considered to be a health professional according to the legislation of the Member State of treatment” (65).

Since MN is prescribed/recommended in clinical, dietetic and pharmacy settings, we propose to define physicians, dietitians, nurses and pharmacists as the supervising healthcare professionals.

Composition

Overall, MN aims for an increased and/or adapted intake of macro- and micronutrients and even though each MN composition differs, the European regulations define minimum and maximum levels of vitamins, minerals and trace elements. The maximum levels in the European FSMP directive are based to some extent on existing MN compositions and safety data (66). Ingredients used in MN in the US must be approved with a *Generally Recognized as Safe* (GRAS) status. With respect to the concept *composition*, the MN definitions in this review refer to: micro- and/or macro nutrients; nutritional compositions; high energy and/or high protein intake.

Support / management

Since the concepts *support* and *management* are found in 44% of all the MN definitions, they seem to be an important factor in defining MN. Despite the fact that the concepts *support* and/or *management* are stated in both the US and European MN regulations, it remains poorly defined. In 2009, Schrijvers proposed an overall definition for *disease management*: “Disease management consists of a group of coherent interventions designed to prevent or manage one or more chronic conditions using a systematic, multidisciplinary approach and potentially employing multiple treatment modalities. The goal of disease management is to identify persons at risk for one or more chronic conditions, to promote self management by patients and to address the illnesses or conditions with maximum clinical outcome, effectiveness and efficiency regardless of treatment setting(s) or typical reimbursement patterns” (67). In the case of MN, it is not only patients with chronic conditions who are prescribed MN; in some circumstances, e.g. after surgery, it may be a short-term solution to bridge a gap until a patient is able to resume normal food intake. Furthermore, MN is generally prescribed under supervision of a medical professional in contrary to the general definition of disease management which states: “*to promote self management by patients*”.

One barrier that can be encountered in the development of TF and oral MN is that it cannot be claimed to *treat* or *cure* a disease since it is considered as a food. The recognized therapeutic mode of action of substances may be used as a cut-off point to differentiate between a food item and a pharmaceutical substance. Pharmaceutical legislation only applies to a product if it is capable of modifying human physiological functions by exerting a pharmacological, immunological or metabolic action (12, 68). Nevertheless, delineating the boundaries clinically between the concepts *support/management* and *treat/cure* remains difficult. Delineating these boundaries could lead to an increase in MN development costs if certain MN

products would require more clinical research or follow pharmaceutical processes (54).

With the exception of *malnutrition*, all concepts are present in three or more MN definitions. We therefore propose that the remaining concepts should all be present in a clear clinical definition of MN.

2.3 Conclusions: operational terminology and definition

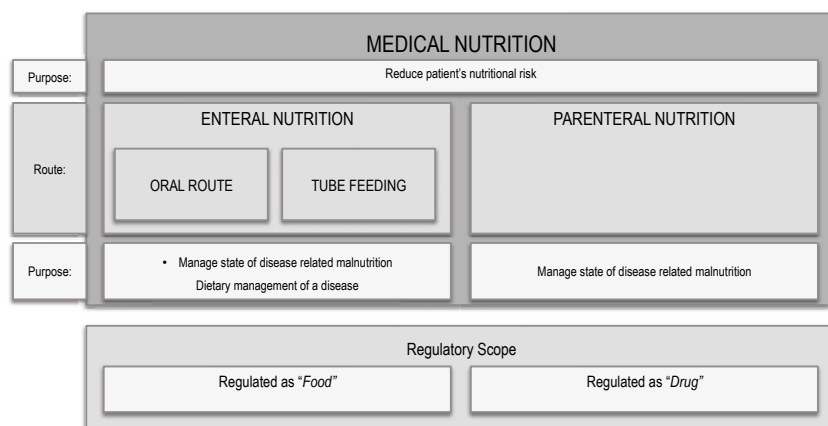
This literature review provides a qualitative and quantitative overview of MN terminology and definitions. It confirms that, comparable to previous research, market boundaries have not been clearly delineated (47). At present, a plethora of terms and definitions for MN are used interchangeably in the US and Europe. In practice, consistent terminology/nomenclature and definitions have not emerged from the US and European MN communities resulting in an ambiguity in the consensus on MN terminology and the absence of a pragmatic operational definition. Agreement on terminology and definition for MN can therefore contribute to transparency at various societal levels thereby increasing MN awareness and fostering innovative MN development. Faced with a potential innovation cliff, transparent terminology and a clear definition can hopefully stimulate development and contribute to an innovation boost in a market with such public health benefit.

In this review we have discussed two elements to foster this discussion: the first addressed the terminology used; the second dealt with the features considered in the definition. To conclude we would like to propose consensual terminology followed by a pragmatic operational definition.

Terminology

The terms *medical nutrition*, *clinical nutrition*, *enteral nutrition*, *parenteral nutrition*, *oral nutritional supplements*, *medical foods* and *foods for special medical purposes* are used interchangeably. Eight out of eleven terms are defined in the literature, and although the term *clinical nutrition* is often used/heard in the professional field, this concept is not defined in scientific literature and therefore excluded from the consensual the proposed MN terminology. The term *nutritional support* is left out of scope of this review due to the generic use of this term. Based on how the terminology from scientific literature describes different types of nutritional support, encompassing both enteral nutrition and parenteral nutrition, we propose the following terminology for MN: medical nutrition comprises both parenteral as well as enteral nutrition, which in turn is divided into oral route products and tube feeding (Figure 3). Whereas EN is regulated as a food, PN is regulated as a pharmaceutical product.

Figure 3. Categorization of the different types of medical nutrition in the US and Europe



Definition

The MN definitions from twenty-three selected and relevant literature sources were characterized by means of five distinguishing MN features. Due to the high prevalence of four of these features, we propose that the following four features should be included in a common and consensual clinical MN definition: *disease*; *supervision*; *composition* and *support/management*. These features are integrated into one operational clinical MN definition and presented in Box 1.

BOX 1. MEDICAL NUTRITION: specially formulated nutritional composition for the dietary management of patients with diseases, disorders or medical conditions that cause distinct nutritional requirements. It may consist of partial or exclusive feeding by means of oral intake, tube feeding and/or parenteral administration under healthcare professional supervision.

No.	Synonym	Region	Nutrition type	Definition	Government body / Society	Distinguishing Features				References
						Disease	Malnutrition	Supervision	Contents / Composition	
1.	Medical nutrition	EU	Oral nutrition & Tube feeding	Medical nutrition is a novel concept born with the recognition of the importance of malnutrition as a consequence, complication and cause of perpetuation and aggravation of several illnesses. Recent advances and progresses in the non-nutritional management and treatment of different disease states associated with malnutrition highlighted the need for a truly scientific appraisal of nutrition therapy.	European Society for Clinical Nutrition and Metabolism (ESPEN)	x	x			(63)
2.	Medical nutrition	US	Oral nutrition	Medical nutrition therapy is a specific nutrition service and procedure used to treat an illness, injury, or condition. It involves and in-depth nutrition assessment of the patient or client; nutrition diagnosis; nutrition intervention, which includes diet therapy, counselling, or use of specialized nutrition supplements; and nutrition monitoring and evaluation.	American Dietetic Association	x				(70)
3.	Medical nutrition	EU	Oral nutrition & Tube feeding	Medical nutrition products are prescribed food compositions that consist of targeted nutritional compositions for intervention in disease progression and symptom alleviation	N/A	x			x	(39)
4.	Medical nutrition	EU	Oral nutrition & Tube feeding & Parenteral nutrition	A term used to describe commercially available products for nutritional intervention, including OR, tube feeds and parenteral nutrition.	N/A				x	(56)
5.	Foods for Special Medical Purposes	EU	Oral nutrition & Tube feeding	Foods that are specifically formulated, processed and intended for the dietary management of diseases, disorders or medical conditions of individuals who are being treated under medical supervision. These foods are intended for the exclusive or partial feeding.	European Commission	x		x		(27)
6.	Foods for Special Medical Purposes	EU	Oral nutrition	FSMP can be regarded as a subcategory of functional foods which have, as primary target, diseases where a dietary impact has been demonstrated, such as non-insulin dependent diabetes mellitus or cardiovascular diseases.	N/A	x				(4) (26) (71)

7.	Enteral nutrition	EU	Oral nutrition & Tube feeding	All forms of nutritional support that imply the use of 'dietary foods for special medical purposes' as defined in the European regulation of the Commission Directive 1992/17/EC of 1999, depending on the mode of application. It includes oral nutritional supplements (OR) as well as tube feeding via nasogastric, nasenteral or percutaneous tubes.	European Society for Clinical Nutrition and Metabolism (ESPEN)	x	(47)
8.	Enteral nutrition	EU	Tube feeding	Enteral nutrition, generally defined by third party payers as tube feeding for patients who cannot take food orally	Nestle Nutrition Works hop Series: Clinical and Performance Program	x	(72)
9.	Enteral nutrition	US	Tube feeding	Nutrition provided through the gastrointestinal tract via a tube, catheter, or stoma that delivers nutrients distal to the oral cavity.	American Society for Parenteral and Enteral Nutrition (ASPEN)	x	(73)
10.	Medical foods	US	Oral nutrition & Tube feeding	The term medical food, as defined in section 51(b) of the Orphan Drug Act (21 U.S.C. 360ee (b) (3)) is "a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.	Food and Drug Administration (FDA)	x	(74)
		US					(75)
		US					(76)
		US					(77)
11.	Medical foods	US		Foods formulated to aid in the dietary management of a specific disease or health-related condition that causes distinct nutritional requirements different from the nutritional requirements of healthy individuals.	N/A	x	(44)
12.	Oral nutritional supplements	US	Oral nutrition	Oral nutritional supplements are intended for those individuals who have altered dietary requirements that cannot be achieved by conventional diet or food modification, or for management of distinctive nutrient needs resulting from a specific disease or condition that impairs ability to ingest, digest, absorb or metabolize nutrients.	Nestle Nutrition Works hop Series: Clinical and Performance Program	x	(78)
13.	Oral nutritional supplements	EU	Oral nutrition	Multi-nutrient liquid, semi-solid or powder products that provide macronutrients and micronutrients with the aim of increasing oral nutritional intake. In many cases OR are nutritionally complete and could also be used as a sole source of nutrition. OR are distinct from dietary supplements which provide vitamins, minerals and/or trace elements in a pill format (also known as food supplements) and they must comply with the labelling and compositional requirements of	Medical Nutrition International Industry (MNI)	x	(56)

Directive 1989/21 EC on Foods for Special Medical Purposes (FSMP).						
14.	Oral nutritional supplements	Ireland	Oral nutrition	High energy and/or high protein oral supplements in liquid, pudding or powdered form, commercially manufactured to be taken under medical or dietetic supervision only	x	(79)
15.	Parenteral nutrition	EU	Parenteral nutrition	General term used to describe nutrition through either a central or peripheral venous catheter. Parenteral nutrition represents an alternative or additional approach to enteral nutrition. It is used when other routes are not succeeding (not necessarily having failed completely) or when it is not possible or would be unsafe to use other routes (i.e. oral or tube).	x	(59) (56)
16.	Parenteral nutrition		Parenteral nutrition	Parenteral nutrition is an invasive therapy that provides nutrition support for persons who do not have adequate gastrointestinal functions; however, it does have inherent risks.	x	(80)
17.	Parenteral nutrition	EU	Parenteral nutrition	The term parenteral comes from the Greek para meaning "besides" and enteros meaning "intestine", i.e. besides the intestine. Parenteral nutrition thus refers to a means of bringing nutrition into the body other than through the gastrointestinal tract, in other words, intravenously.		(55)
18.	Parenteral nutrition	US	Parenteral nutrition	The administration of nutrients intravenously.	x	(81)
19.	Nutritional support	EU	Enteral nutrition & food fortification	Nutritional support includes food fortification, ONS, tube feeding and parenteral nutrition. It aims for increased intake of macro- and/or micronutrients.	x	(47)

Table 1. Medical nutrition terms and definitions found in literature

CHAPTER 3

FOOD-PHARMA CONVERGENCE IN MEDICAL NUTRITION – BEST OF BOTH WORLDS?

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Food-pharma convergence in medical nutrition: Best of both worlds? PloS One:
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ABSTRACT

At present, industries within the health and life science sector are moving towards one another resulting in new industries such as the medical nutrition industry. Medical nutrition products are specific nutritional compositions for intervention in disease progression and symptom alleviation. Industry convergence, described as the blurring of boundaries between industries, plays a crucial role in the shaping of new markets and industries. Assuming that the medical nutrition industry has emerged from the convergence between the food and pharma industries, it is crucial to research how and which distinct industry domains have contributed to establish this relatively new industry.

The first two stages of industry convergence (knowledge diffusion and consolidation) are measured by means of patent analysis. First, the extent of knowledge diffusion within the medical nutrition industry is graphed in a patent citation interrelations network. Subsequently the consolidation based on technological convergence is determined by means of patent co-classification. Furthermore, the medical nutrition core domain and technology interrelations are measured by means of a cross impact analysis.

This study proves that the medical nutrition industry is a result of food and pharma convergence. It is therefore crucial for medical nutrition companies to effectively monitor technological developments within as well as across industry boundaries. This study further reveals that although the medical nutrition industry's core technology domain is food, technological development is mainly driven by pharmaceutical/pharmacological technologies. Additionally, the results indicate that the industry has surpassed the knowledge diffusion stage of convergence, and is currently in the consolidation phase of industry convergence. Nevertheless, while the medical nutrition can be classified as an industry in an advanced phase of convergence, one cannot predict that the pharma and food industry segments will completely converge or whether the medical industry will become an individual successful industry.

3.1 INTRODUCTION

The Health & Life Sciences sector is currently undergoing significant change across all its industries. Boundary-crossing developments are occurring, especially between the food and pharmaceutical industries. The emergence of innovation at this intersection is blurring the clear boundaries between these two industries (69). Such boundary-blurring innovation leads to industry convergence, which in turn results in the emergence of new industries. Food-pharma products resulting from this convergence are known as Nutritional Supplements (NS), Functional Foods (FF), and Medical Nutrition (MN). NS include vitamins, minerals, herbs, amino acids, and other related products intended to supplement the nutritional content of the diet in tablet/capsule dosage (70). FF are conventional foods with added nutrients that claim to improve health beyond the basic nutritional functions (3, 71-75). MN products are specific nutritional compositions for disease intervention that effectively contribute to the therapeutic regimen by improving a patient's general condition (42, 76). MN can be divided into tube feeding and oral nutritional supplements (e.g. Nutridrink; Ensure; and Resource) and are primarily prescribed by healthcare professionals. NS, FF, and MN are food substances that are considered to improve health, and exist between conventional foods and pharmaceuticals at the so-called food-pharma interface (Figure 1) (77). Nevertheless, the individual pharmaceutical and food companies recognize the risks in developing food-pharma inventions(76, 78). They fear that the commercialization of boundary-spanning products (3) could result in a lower customer acceptance due to the ambiguous identity of the product (3).

Figure 1. Industries situated at the food=-pharma interface. Adapted from (3)



The present study focuses on the emerging MN industry, where industry boundaries are still relatively undefined. This is reflected by the terminology used to describe this product category, which is most often perceived as confusing. MN is just one term among many others to indicate the same product category (e.g. oral nutritional supplement, medical food, clinical nutrition, enteral nutrition).

The European (EU) MN industry comprises 5 leading companies and currently finds itself in the growth phase of the industry lifecycle (3, 79). It is difficult to predict the prerequisites for determining the future success of an emerging industry such as the MN industry, nonetheless: carefully categorizing industries and identifying industry boundaries is crucial and can lead to better consumer perception and higher market acceptance (3, 49-53). In the view that millions of patients are suffering from disease-related malnutrition, including a surprisingly high proportion living in the developed countries/high income economies (3, 58, 76) and many studies have proven that nutritional interventions prevent and/or support the development of disease-related malnutrition (58, 76), MN is considered of high societal value. Therefore, defining industry boundaries may also have an indirect societal impact. The first step in identifying industry boundaries is by determining the status of industry convergence and thereby investigating how and which distinct industry domains have contributed to establish an industry.

In this research the concept of MN industrial convergence is based upon the assumption that the phenomenon of industry convergence proceeds along an evolutionary trajectory consisting of four phases: Initialization; Knowledge Diffusion; Consolidation; and Maturation (Figure 2) (80-82). Such industry convergence has been observed in many industries such as telecommunications, computing and consumer electronics or cosmetics and pharmaceuticals (83-86). In the initial stage, R&D of two or more distinct industries segments remains independent. It is during the knowledge diffusion stage where cross-disciplinary citations may eventually result into joint research collaborations (consolidation stage). As the metaphorical distance between the two knowledge areas decreases, technology development follows, which in turn leads to technology convergence (82). It is believed that market convergence is also a consequence of the new technological combinations. Ultimately, sectors begin to merge with one another, completing the industrial convergence process.

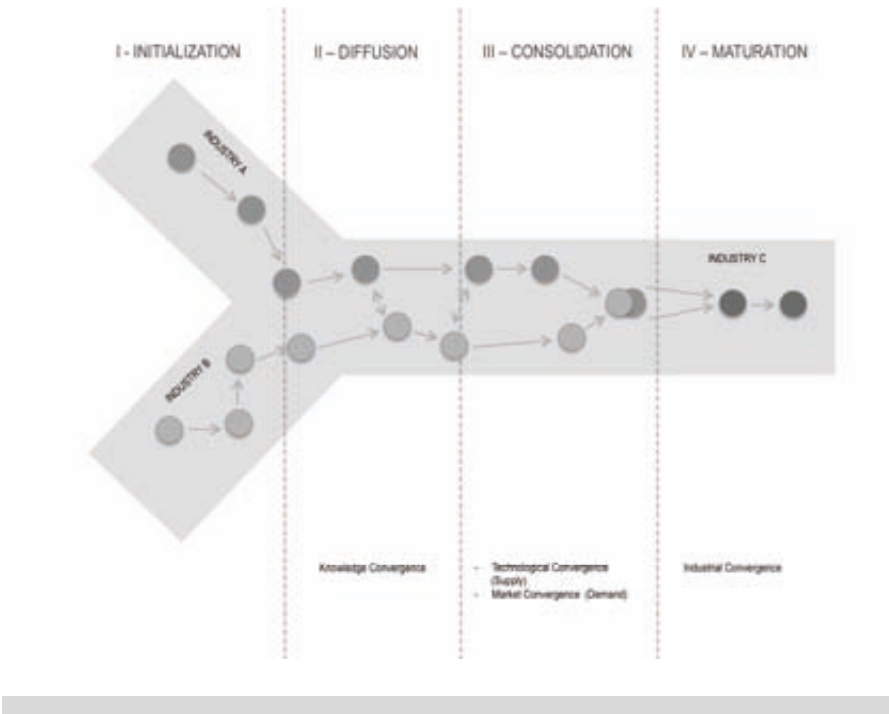
This study shows how and which distinct industry domains have contributed to establish the MN industry. First we determine the extent of knowledge diffusion within the MN industry, subsequently we define the consolidation into the MN industry on the basis of technological convergence (Fig. 2), and eventually we identify the MN core domains and chart the technology interrelation and its influence on the MN industry development. Both knowledge diffusion and technological convergence are two important drivers of innovation and recognized as crucial components for industry growth (86, 87). Specifically within the health and life science sector, both drivers contribute to the evolution of young and emerging industries such as the MN industry (88). Moreover, scientific advancements are the key ingredient in stimulating both knowledge diffusion and technological convergence. The former - knowledge diffusion - is defined as the process through which knowledge is spread along a specific path in a social system (89).

Technological convergence implies a technological change where inventions emerge at the intersection of established and clearly defined industry boundaries (90). The cumulative effect of both drivers ultimately leads to industry convergence (91).

The quantitative diffusion and consolidation results from this study will contribute to detailed insights in MN industry development and can help industry players to address specific innovation strategies for the future.

Patents have been proven to be a valuable source of information in mapping MN industry development (92, 93), they contain about 80% of all technological knowledge and are generally regarded as precursors of technological developments (82, 94). In addition, they can be independently accessed and analyzed through various types of comprehensive and open databases (95). Finally, in contrary to other knowledge sources, such as scientific literature, patents are categorized according to multiple technology classes according to their technological characteristics. This allows for accurate co-classification analyses to identify the interrelation between technologies (96). Therefore, in this study, patent data was used to identify the evolutionary (technological) development of the MN industry.

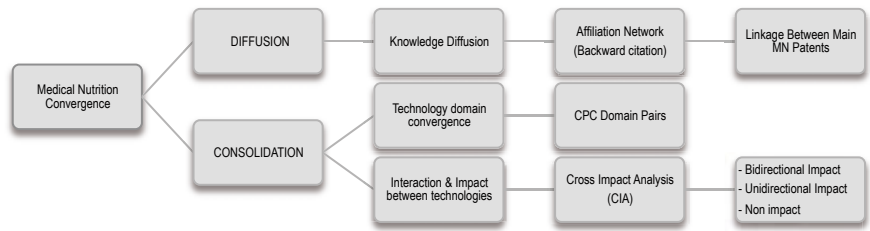
Figure 2. Linear model of convergence adapted from (80-82, 97) Linear model of convergence adapted from (80-82, 97)



3.2 METHODOLOGY

The methods applied in this study are based on research methods by Karvonen, Tseng, and Choi (90, 98, 99) and adapted to fit our research objective. To determine the stage of convergence in the MN industry, this study is divided into Knowledge Diffusion and Consolidation. Furthermore, the consolidation is divided into technological convergence, and CIA (Figure 3). Data on patents concerning MN was extracted from the Derwent Innovations IndexSM and Espacenet pertaining to the European published patent applications. In total, 274 patent applications were filed by the 5 leading EU MN companies from 1984 up to 2013 (so-called; main patents).

Figure 3. Research Framework



3.2.1 Knowledge diffusion

Since knowledge convergence is the first stage of convergence, the analysis of knowledge flow within the MN industry is an appropriate method for identifying possible current and future convergence between knowledge disciplines originating from different industries (100). Patent citation data is considered an important information source for analyzing science-based knowledge flows. Patent citations within the MN industry are indicative for the technological relationship between patents in the MN industry (101-105). Patent citations refer to the number of cited patents within the original patent application as an indicator of prior art. Such an analysis provides information of inter- industry competition and knowledge spillovers (90, 106).

In order to identify the knowledge diffusion within the MN industry, the backward citations of all main patents were extracted. Subsequently, we constructed an affiliation network visualizing the interrelations of all main patents of the European MN companies. This method is a powerful tool to analyze knowledge flows and within-industry competition (98). The mutual linkage between the main MN patents were explored and visualized using the statistical software programs Ucinet and

NetDraw (107). This network represents the knowledge flows between the European MN companies (anonymous) and gives an indication of within industry competition.

3.2.2 *Technological convergence*

In general, patents have multiple technology classifications depending on their claims. Since patents are classified into certain technological classes according to their technological characteristics, co-classification analysis identifies the interrelation between technologies (96). The co-classification analysis measures the frequency by which two classification codes are jointly assigned to a patent and can be interpreted as an indication of the strength of the technological relationships. Ultimately, this allows for calculating technological convergence (95, 108). The co-classification in this study is based on the Cooperative Patent Classification (CPC) codes (109). Since the MN industry is not yet assigned to one specific classification category, the co-classification of different technologies currently delineates this industry. This is in accordance with the fact that the MN industry is still in growth phase as described earlier (3).

The expert designated CPC codes from each patent were extracted to analyze science-based technological convergence within the MN industry. CPC is an extension of the International Patent Classification (IPC) and is a joint endeavor of the European Patent Office (EPO) and the United States Patent and Trademark Office (USPTO) to harmonize the classification systems into a single system. This jointly developed classification system is much more granulated than the IPC system.

The CPCs were extracted from the patent search and analysis software ACCLAIMiP and the Espacenet portal. Since patents can be classified into several CPC groups, the co-classification provides information concerning technological convergence. In order to reveal the technological convergence domains within the MN industry, the first two (converging) CPC codes were extracted from all main patents and grouped into various domain combinations (90, 110, 111). CPC codes are a hierarchical way of assigning the category to which every patent belongs (112). The MN patents are categorized into classes, which are divided into sub-classes, main groups and sub-groups. The main groups are merged into domain combinations as illustrated in Table 1. In this study we make no difference between the orders of category combinations (e.g. no difference between 1-2 and 2-1). Subsequently, the number of patents per domain combination was divided in time blocks of 5 years, showing the evolutionary development of the emerging MN industry.

There is a predicted lag in the convergent domains since patent applications are available in the public domain only 18 months after filing. As a result, the dataset is accurate to January 2012 and therefore by definition no 2013 patent applications could be included.

Table 1. Predominant CPC groups in MN patent literature

Nr.	CPC Code	Groups
1	A23K1	Animal feeding-stuffs
2	A23G1	Cocoa; Cocoa products
3	A23F5	Coffee; Coffee substitutes; Preparations thereof
4	A61K8	Cosmetic or similar toilet preparations
5	F24D19	Details
6	A23D7	Edible oil or fat compositions containing an aqueous phase
7	Y02B30	Energy efficient heating, ventilation or air conditioning
8	A61J15	Feeding-tubes for therapeutic purposes
9	A23V2002	Food compositions, function of food ingredients or processes for food or foodstuffs
10	A23L1	Foods or foodstuffs
11	C07K16	Immunoglobulins
12	A61K9	Medicinal preparations characterized by special physical form
13	A61K45	Medicinal preparations containing active ingredients
14	A61K2039	Medicinal preparations containing antigens or antibodies
15	A61K33	Medicinal preparations containing inorganic active ingredients
16	A61K35	Medicinal preparations containing materials or reaction products thereof with undetermined constitution
17	A61K31	Medicinal preparations containing organic active ingredients
18	A61K38	Medicinal preparations containing peptides
19	A61K36	Medicinal preparations of undetermined constitution containing material from algae, lichens, fungi or plants, or derivatives thereof
20	A23C9	Milk preparations; Milk powder or milk powder preparations
21	A23C11	Milk substitutes
22	A61K2300	Mixtures or combinations of active ingredients
23	A23L2	Non-alcoholic beverages; Dry compositions or concentrates thereof
24	A23J1	Obtaining protein compositions for foodstuffs; Bulk opening of eggs and separation of yolks from whites
25	A23D9	Other edible oils or fats
26	C07K14	Peptides having more than 20 amino acids; Gastrins; Somatostatins; Melanotropins; Derivatives thereof
27	A23J7	Phosphatide compositions for foodstuffs
28	C12P19	Preparation of compounds containing saccharide radicals
29	C12P17	Preparation of heterocyclic carbon compounds with only O, N, S, Se or Te as ring hetero atoms

30	A61Q19	Preparations for care of the skin
31	A23L3	Preservation of foods or foodstuffs, in general
32	C12R1	Processes using micro-organisms
33	A23G3	Sweetmeats; Confectionery; Marzipan; Coated or filled products
34	A23F3	Tea; Tea substitutes; Preparations thereof
35	A23C21	Whey; Whey preparations
36	A23J3	Working-up of proteins for foodstuffs

3.2.3 Cross impact analysis

The identification of the overall structure of technologies and interaction among them is essential to recognize the maturity of technological trends and discover technological possibilities through convergence between various fields of technologies (113). Cross Impact Analysis (CIA) is considered a reliable quantitative methodology to identify the core technologies and interrelations between technology domains (114-116) based on patent classification data (99). In our study, the technology impact between various MN technology domains is analyzed based on patent co-classification data as described in technological convergence section. The impact between technologies can be derived from the CPC codes of the patent. Moreover, the impact of (A, B) can be defined as conditional probabilities between two technologies (99). This means that the cross impact of technology A on technology B can be defined as follows:

$$\text{Impact (A, B)} = P(B|A) = (N(A \cap B)) / (N(A))$$

In this equation, N (A) refers to the total number of patents included in domain A, and N (A∩B) indicates the number of patents, which include both domain A and domain B. The patent-based cross impact between domains can be analyzed by calculating the conditional probability with the number of patents in the patent classes. The score of index ranges from 0 to 1. If the score is close to 1, then technology domain A has a high impact on technology domain B and when the score is approaching the 0, the impact is considered lower.

Technology pairs based on the cross impact scores can be classified into three groups. In case 1, the so-called bidirectional impact, most of the patents in technologies A and B overlap; hence, both Impact (A, B) and Impact (B, A) are high. Consequently, conditional probabilities are relatively high and the impacts of one technology on the other technology are both high.

In case 2, called one directional impact, a high number of patents in technology A is also included in technology B, however, the portion of patents in technology B that is also included in technology A is relatively small. This means that Impact (A, B) is high, but Impact (B, A) is low. In this case, the impact between technologies A and B is unidirectional.

In case 3, called nonimpact, technologies A and B are almost exclusive and there is little interaction between them. Basically, these two technologies can be said to be almost independent.

Moreover, the individual impacts between the domains are visualized by means of network analysis depicting the type of interaction (arrow) between the domains (node). The direction of the arrow indicates the direction of impact between two domains. It visualizes whether technologies are equally influencing one another (bidirectional) or whether the impact of the first technology on the second is different from the impact of the second technology on the first (unidirectional) (99, 117).

Patent data is a valuable source of information and is useful in the study of technological convergence and diffusion as well as in technology interrelation and development. Nonetheless, not all inventions are patented and changes in patent law over the years make it difficult to analyze trends over time (118). Since the protection afforded to patentees worldwide has been improved, the companies are more inclined to file for a patent than before (118). Additionally, since CPC is a joint endeavor of the EPO and USPTO, this classification system is more detailed, up to date, and dynamic (112). Subsequently, we have applied the quantitative patent-based CIA method of Choi (99) as opposed to the more conventional qualitative (CIA) approach, by means of literature surveys and expert interviews, aiming to overcome inconsistent outcomes. Furthermore, the citations lag between the application or grant year of the citing patent and that of the cited patents make it impossible to assemble all the main patents within the MN industry up until present time (119). To address this limitation, a prediction line was drawn (result section CIA).

3.3 RESULTS

In total, 274 patent applications were filed by the 5 leading European MN companies between 1984 and 2013. The MN patents can be assigned to 5 classes which are subsequently divided into 7 sub-classes, 37 main groups and 151 sub-groups.

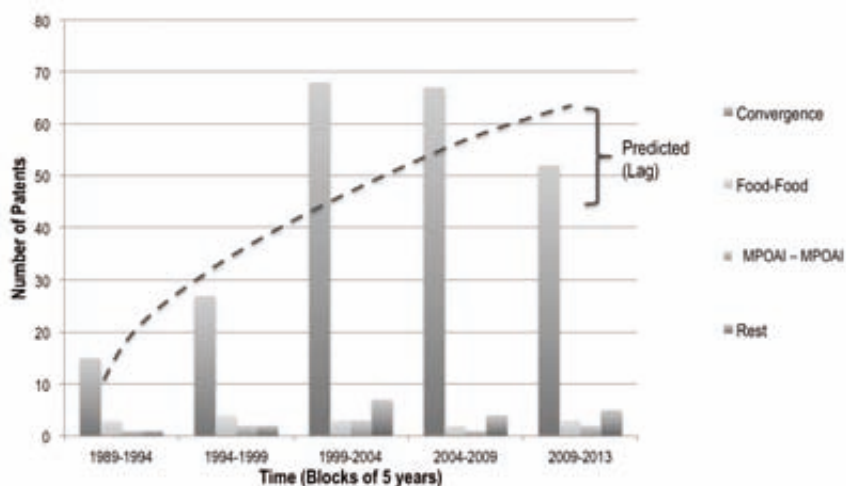
3.3.1 Knowledge Diffusion

The knowledge diffusion network shows that most patents (78%) are not interrelated within the MN industry by means of patent citations. Interestingly, figure 4 shows that the remaining 22% of the patents lead back to two patent precursors and the CPCs of the precursors indicate convergence between the *Food – Food Compositions* and the *Food – Pharmaceutical Organic Active Ingredients* industrial domain combinations (Figure 4). The remaining 78% of the main patents are not linked to patents within the MN industry domain and are therefore linked to patents from other industrial domains. The high occurrence of patent linkage beyond the industrial domain indicates boundary-spanning convergence is taking place in MN development.

3.3.2 Technological convergence

Figure 5 illustrates that between 1989 and 2013, 84% of all MN main patents show convergence between different industrial domains indicating technological convergence. Furthermore, figure 5 demonstrates that convergence of industry domains have played an essential role in the MN industry development since 1989, nevertheless, the importance of specific domain combinations varies over the course of time (Figure 6).

Figure 5. Evolution of single domains versus different domain convergence in MN – MN cannot be classified as a single domain but predominantly as a convergence between different domains.

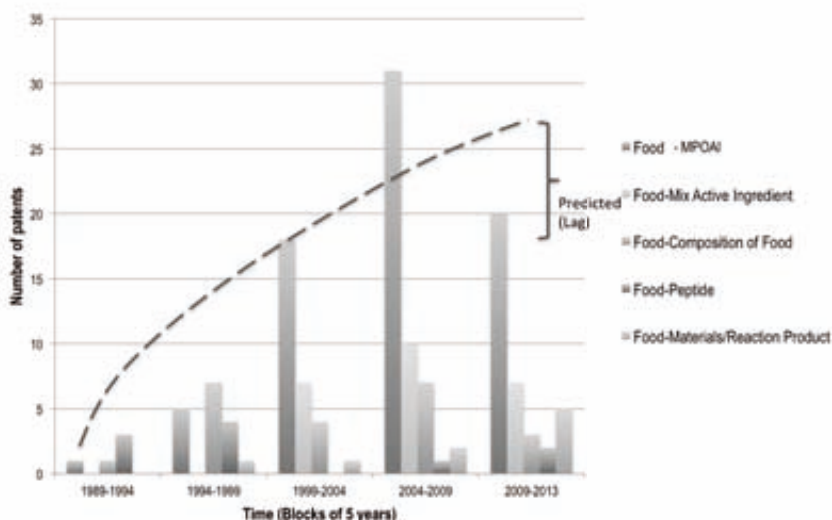


Further sub-categorization of the MN domains, indicating domain convergence, reveals the 5 most prevalent sub-groups: *Food – Medicinal preparations containing organic active ingredients*; *Food – Medicinal preparations containing peptides*; *Food – Food Compositions*; *Food – Medicinal preparations containing combinations of active ingredients (MPOAI)*; and *Food – Materials/Reaction Products* (Figure 6).

Figure 6 shows that from 1989 until now Organic Active Ingredients, Food Compositions, and Peptide Compositions have played an essential role in the development of MN industry. In 1994 a new domain combination emerged: *Food – Materials/Reaction Product*. Since 1999, another new domain combination emerged: *Food – Medicinal preparations containing peptides*.

The principal domain convergence has occurred between the *Food* domain and *MPOAI* domain. Examples of MPOAI are: carbohydrates; sugars; carboxylic acids; hydrocarbons; amino acids; vitamins; and medicinal plant derivatives.

Figure 6. Food-Pharma dominates the domain convergence in MN – Selection of top 5 converging domains from 1989 to 2013 in MN



3.3.3 CIA

The cross impact scores help classify each technology pair into three groups: Bidirectional, Unidirectional, and Non-impact. The CIA network illustrates that 22 out of 47 technology pairs can be classified as bidirectional- or unidirectional impact (Figure 7).

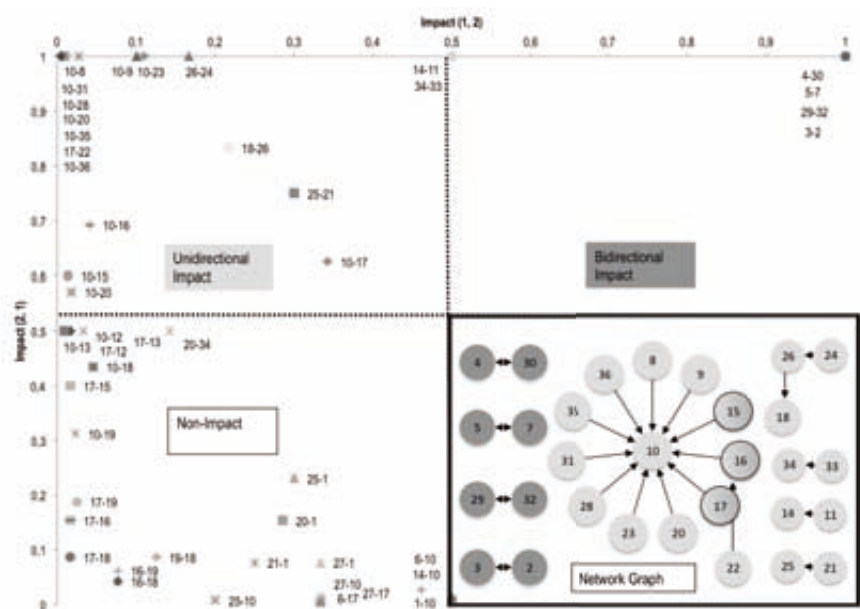
Furthermore, the bottom-right quadrant of figure 7 illustrates a network graph of the relationships between technology domains within the MN industry. Each node represents a technology domain and the color of the node indicates its corresponding score that classifies the impact between two technology domains. The bidirectional impact technology pairs are expressed as blue nodes and the unidirectional impact technology pairs as red nodes. Furthermore, the direction of the arrows indicates the direction of impact. The network graph helps us identify the influencing- and influenced technology domains.

The network graph indicates that 11 technology domains directly influence the food domain. Eight of the eleven influencing domains originate from food (8, 9, 20, 23, 28, 31, 35 and 39) whilst three domains (15, 16 and 17) originate from pharma. The

domains impacting the food domain (10) that originate from pharma account for 138 patents, while the domains originating from food account for 57 patents.

The central positioning of Food (10) in the network graph shows that this technology domain can be considered as the core MN domain. Additionally, technological development from the pharmaceutical domain, especially medicinal preparations containing: inorganic active ingredients, organic active ingredients and materials or reaction products thereof with undetermined constitution, influence the core MN domain.

Figure 7. Grouping of the technology pairs in the MN industry. Network graph of bidirectional and unidirectional impact within the MN industry (1984-2013)



3.4 DISCUSSION & IMPLICATIONS

This study proves that the MN industry is a result of a bona fide food-pharma convergence. Additionally, the results indicate that the industry has surpassed the knowledge diffusion stage of convergence, and is currently in the consolidation phase of industry convergence. Nevertheless, while the medical nutrition can be classified as an industry in an advanced phase of convergence, one cannot predict

that the pharma and food industry segments will completely converge or whether the MN industry will reach a state of maturation and become an individual successful industry. This confirms previous research which revealed the MN industry to be in the relatively early development stage of the technology life cycle (42). The knowledge flows and subsequently trans-disciplinary technological convergence between the food-pharma technology domains have fine-tuned the MN industry as it is today. This study further reveals that although the MN industry's core technology domain is food, the technological development is mainly driven by pharmaceutical technologies.

Although not scientifically proven, in the past few years literature has stated that the gap between pharmacology and nutrition science has been narrowing, a development stimulated by both disciplines (76). The increase in technological convergence between food and MPOAI confirms this observation, which previously has been termed as "pharmaconutrition". Although in the past only drugs were considered pharmacologically active substances, this new treatment paradigm embraces the fact that nutrients can have profound effects on immunological, metabolic and other pathophysiological processes of diseased patients (76, 120).

Our results show that there are currently five different CPC combinations required to define MN in patent literature. This emphasizes the necessity for a specific CPC code to clearly categorize MN, which may contribute to clearly delineating MN industry boundaries. Having its own identity may lead to better consumer perception and higher market acceptance thereby stimulating MN market growth.

Considering that convergence drastically alters industry structures, companies should consider evaluating whether their activities may be affected by trends of convergence (121). By monitoring convergence trends, companies can benefit by commercializing on trans-disciplinary opportunities. The MN industry can be characterized as a convergent/converging area at the food-pharma interface and it is therefore crucial for MN companies to effectively monitor developments within as well as across industry boundaries. Both in the food- and pharmaceutical industry trends should be monitored, as our results indicate that critical knowledge is also developed in those fields (121). Especially the technological development within the pharmaceutical industry is essential since our CIA results shows that pharmaceutical technologies have the greatest impact on MN development.

The knowledge diffusion results indicate a high occurrence of patent linkage beyond the MN industrial domain implying that the first step in boundary-spanning industry convergence: knowledge diffusion, is taking place in MN development. Our empirical analysis further reveals both knowledge and technological convergence between the food-pharma technological domains, thereby showing the first three phases of convergence of the linear model of convergence in the MN industry.

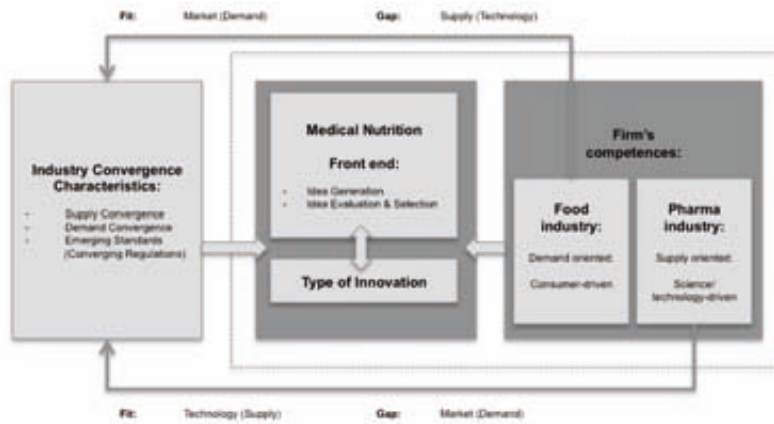
Nevertheless, it is often argued that factors other than technology are involved in the process of industry convergence. Weaver (2007) and Karvonen & Kassi (2013) believe that technology and industry convergence are often intrinsically linked, yet these two concepts are causally and conceptually distinct (90, 122). Examples of those factors include: regulation, quality standards, business model innovation,

changing customer requirements and industry channel structure. The process of food-pharma convergence is nurtured by the trend of regulatory convergence with respect to costly clinical research increasingly required for MN. These factors can be divided into supply (science, technology) and demand (consumer needs) factors.

The absence of competencies in either supply or demand understanding may lead to considerable problems at the front end of innovation (idea generation, evaluation and selection) (86). Our results indicate that the front end of MN innovation is affected by convergence (Figure 8). Especially as the process of innovation requires the combination of new knowledge and competencies owned by different industries domains (86). Perhaps this is one of the reasons that the MN industry may currently be facing an innovation cliff (3, 42, 54). We would argue that in the MN industry, front-end innovation challenges are related to the converging industries. For example; the food industry counterparts of the trans-disciplinary venture might experience challenges on the technological/supply aspect of the convergence (e.g. clinical trials (endpoints, quality standards, pharmacokinetics and pharmacodynamics (76)) whereas the pharmaceutical participant may find the consumer/demand experience (e.g. taste, texture, tolerance, smell) a particular bottleneck (Figure 8). Successful convergence would therefore require awareness on matching skills, experience and resources that would complement the, otherwise lacking, absorptive capacity (86). Innovation managers must be aware of competence gaps on the supply and/or demand side. One way to bridge this gap is to identify external partners, already at the idea generation phase, with the additional competences to account for the missing absorptive capacity (86). Such innovation strategies by means of acquisition and consolidation are already occurring in the MN industry and may contribute to progressing to the final stage of convergence: maturation (3).

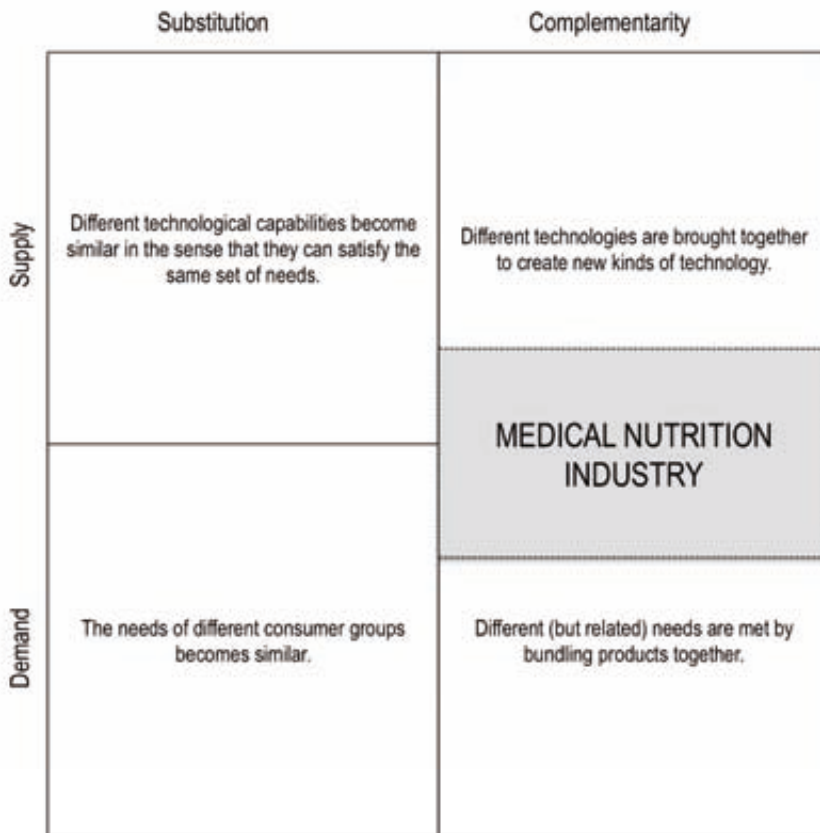
We argue that the result of food-pharma convergence into the MN industry is both supply (technology) and demand (consumer) driven. For example, technology has made it possible to reduce the volume of high-protein oral nutritional supplements (ONS) while simultaneously, due to a higher awareness of MN effectiveness, the demand for low-volume high-protein ONS is rising. Due to convergence of the supply (pharma) and demand (food) sides, a new MN value chain emerges. Value chain reconfiguration as a result of industry convergence may lead to the elimination of entire value chain steps or activities while other, value-added value chain activities may be introduced (122, 123).

Figure 8. Front end of innovation activities in converging industries.
Adapted from (86)



In addition to diagnosing the MN industry to be in stage three of the industry convergence life cycle, the process of convergence in itself comes in two varieties; substitutive and complementary. Such a classification allows for characterization of the convergent industry. In the case of substitutive convergence, innovation leads to a phasing out of the two formerly discrete operating industries. Consequently; the added value of the complementary products combined is higher when compared to the individual components, thereby resulting in technological substitution from a consumer perspective ($1+1=1$). Complementary convergence is the process whereby previously unrelated products are bundled together to form a new combined and integrated class of product with added value for end-users ($1+1=3$) (122, 123). In this case, the convergence between technologies results from technology fusion or by bundling exemplify complementarities (124). The MN industry belongs to the second category in the view that MN replaces neither conventional foods nor pharmaceutical products (Figure 9).

Figure 9. Categorization of MN industry convergence, adapted from (124)



Ultimately, additional research is required to understand the full impact of the MN industry within the context of the individual food and pharmaceutical industries. While this study focused on the use of patents to identify the stages of industry convergence, future research could focus on complementary data and methods for mapping the convergence process. One option may be to look at clinical research data by assessing to what extent these studies meet pharma industry standards. The MN industry offers a unique dataset for studying industry convergence and experimenting with tools on how this is best accomplished.

CHAPTER 4

BARRIERS TO INNOVATION IN THE MEDICAL NUTRITION INDUSTRY: A QUANTITATIVE KEY OPINION LEADER ANALYSIS

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ABSTRACT

Innovation is a necessity for survival in dynamic and complex industries such as the medical nutrition industry. To remain competitive, medical nutrition companies must embrace innovation activities that improve productivity. Nevertheless, innovation is a difficult undertaking and companies must first overcome numerous barriers inhibiting innovation. Studying these barriers provides insight into the dynamics of innovation, which simultaneously is a first step in the process of overcoming them. This study investigates the exogenous barriers that inhibit medical nutrition innovation.

Primary data was collected by qualitative interviews from 17 medical nutrition key opinion leaders (KOLs) through and quantitative data by means of a questionnaire from 77 KOLs. Medical nutrition innovation barriers were identified and ranked according to importance.

This study shows that barriers impact all steps of the medical nutrition value chain. Nine main innovation barriers emerged from the research. The most significant barriers are associated with financial aspects and clinical research, whereas the least significant are associated with product barriers. Medical nutrition companies must realize that investment in innovation is and remains crucial within this industry.

4.1. INTRODUCTION

The health industry is acknowledging that most low-hanging fruits have been picked in the pharmaceutical sector and that the industry provides fewer successes than it did in the past (7, 8). During the last decades of the 20th century the potential of nutrition for the prevention or treatment of diseases or risk factors for disease was rediscovered (7, 12). Therefore, product development in the health and life sciences is experiencing a shift from the development of specific-target pharmaceutical products to multi-target nutritional therapy products. The European medical nutrition (EU MN) market is a fast-growing nutrition market, driven by new knowledge on MN effectiveness. MN consists of targeted nutritional compositions for intervention in disease progression and symptom alleviation. We found that the EU MN is currently in the growth phase of the technological life cycle (10). This phase is characterized by the highest rate of technological developments yielding the most innovations when compared to the other phases (10, 79). An industry's capacity to innovate is considered the primary driver for economic development, which in turn is seen as a predictor of future growth. Nevertheless, innovation is a difficult and non-trivial undertaking. Innovation is a necessity for survival in dynamic and complex industries (125) such as the MN industry, yet not all innovations contribute to commercial success. To remain competitive, MN companies must embrace innovation activities that improve productivity and fulfill the patients' unmet needs. Only a small number of MN companies manage to leverage their knowledge and maximize their innovation capability (126). However, innovation corresponds with high (financial) risks and uncertainties. This creates a catch-22 situation, whereby innovation is necessary in order to stimulate industry growth. This shows us that there is an obvious need to systematically assess what inhibits the flow of innovation from existing players and prevents new players from entering the market.

Earlier research on the topic of industry innovation predominantly focused on success factors stimulating innovation, often disregarding obstacles (126, 127). An opposite approach is the *barriers approach to innovation* (128, 129). The aim of the barriers approach is initially to explore the nature, origin, and importance of the barriers, in order to identify their impact on the value chain. Studying barriers to innovation provides insight into the dynamics of innovation, which simultaneously is a first step in the process of overcoming them (128). Better understanding of barriers to innovation can assist companies to foster the development of an environment that supports innovation (130, 131). Companies can identify the right approach for innovation by analyzing the innovation barriers, and adapting their business strategies accordingly.

Even though innovation is considered the key driver in advancing the MN industry through the technological life cycle, a surprisingly limited amount of research is dedicated to the topic of innovation barriers. Our research aims to identify the main barriers, as experienced by key opinion leaders (KOLs) in the MN innovation process. The current study focuses specifically on the relation between innovation barriers and the underlying causes. KOLs were interviewed on the topic of innovation barriers, and were asked to rank them in terms of importance. This study provides novel insights into the topic of innovation barriers in the MN industry.

Innovation & the value chain

Innovation has always been at the heart of technological progress but more than ever it has become a fundamental strategy of companies. The effect of globalization on business activities forces companies to constantly adapt and develop new products and technologies resulting in intense competition. The race ends for those who do not innovate (132). Definitions of innovation vary widely, yet in a broad sense, can be defined as: “*the process of turning opportunity into new ideas and of putting these into widely used practice*”(125). This paper focuses on technological innovation which concerns translational application of innovative knowledge in new processes and products (127).

Technological innovation is the result of a company’s process or product idea successfully passing through the value chain (133). The medical nutrition value chain can be broken down into six sequential steps: (1) Translational science; (2) Product development; (3) Clinical research; (4) Product notification (5) Reimbursement granting and (6) Product marketing. By managing the value chain, companies drive ideas from the concept phase to the end of the product lifecycle (134). This approach requires the translation of nutrition science through food and ingredient technology to generate innovative impactful products of high quality, stability, safety and value for consumers (135).

The barriers approach to innovation

Innovation is a complex phenomenon and thus needs a multilevel model of analysis. A barrier to innovation is any factor that negatively influences the innovation process. Barriers are also known as obstacles, constraints and inhibitors that prevent an innovation from commercial exploitation. Although subtle differences exist between these terms, they are used as synonyms here.

Barriers to innovation are grouped relative to their relationship with the company, resulting in the dichotomous categories; endogenous to the firm and those exogenous to the firm (130, 131). Endogenous barriers may arise for example due to organizational routines, lack of technical expertise, resource related or human nature related e.g. risk-adverse top managers (128, 130). Exogenous barriers may include financial barriers e.g. reluctance of investors, governmental barriers e.g. policies and regulations and collaboration barriers e.g. differences in objectives between players (128, 130, 136). Barriers can further be classified into general/relative barriers. General barriers are barriers affecting all types of companies, while relative barriers selectively affect companies in specific sectors (128).

The focus of the present research lies on the relative exogenous barriers, since this results in a cross-industry perspective. It is believed that barriers may act on one or more points of the value chain. Consequently, by aligning the barriers along the value chain; a barrier can have a different effect during the various stages (130).

4.2. METHODOLOGY

The methodology of this research is build-up into three individual data collection moments. First by determining and visualizing the innovation barriers and their underlying causes by means of qualitative root cause analysis (137, 138). Next, the innovation barriers are quantitatively ranked by the KOLs in the questionnaire by means of priority ranking. Finally, the first two steps are integrated to generate a top-down view of what is inhibiting innovation in the medical nutrition industry (Table 1).

Participants

Thirty faculty members of the European Society for Clinical Nutrition (ESPEN) (practicing MD, dieticians, nurses, researchers, academics, and consultants) were selected to participate in the semi-structured interviews. Selection was based on their experience in the field of MN.

Exploratory Interviews

The selected participants were first contacted and informed of the nature of the study and invited to take part. A structured format was used for the interview schedule where each participant was taken through a standardized set of questions asked in a similar way¹. By means of theme coding, the barriers were first categorized into general innovation barriers and subsequently into several barrier categories (139). The results from the interviews were used as input for the subsequent innovation barrier prioritization process questionnaire.

Questionnaire

The aim of the survey was to prioritize the main inhibiting MN innovation barriers as identified during the interviews. 220 questionnaire participants were selected from the ESPEN faculty members. Selection was based on active KOL members with extensive MN knowledge. The anonymous online questionnaire was created and distributed through the online web survey program SurveyMonkey. KOLs that did not respond to the initial survey received a follow up letter 1.5 week later to increase response rates.

Study design

A Root Cause Analysis (RCA), also known as causal tree analysis or argumentation tree analysis is used for visualizing associations between arguments (137, 138, 140). This method provides a structured and process-focused framework with which to approach the underlying causes of events, in this case of the MN innovation barriers. Understanding the cause of such a barrier is the key for companies to develop effective strategies to overcome these challenges. Semi-structured qualitative interviews serve as a data collection tool for the purpose of the RCA (139). In this research RCA is applied top-down to identify the main barriers of innovation in the MN industry.

¹ Interview format available upon request

² It should be noted that since conventional patents are usually classified and published within

The prioritization process was based on previously published prioritization methods (141, 142) and adapted to fit MN, the goal and subject of our research. The results from the RCA and the prioritization process are combined to create a top-down view of the innovation barriers, their relative importance and the underlying causes. These results are combined to create an RCA tree visualizing all three aspects.

Table 1. Study design

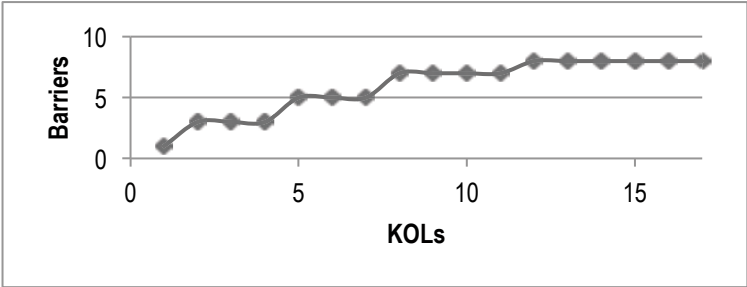
Step 1: Root cause analysis (137, 138, 140)	
1.1	<i>Data collection:</i> establishment of the barriers and causes through semi-structured interviews.
1.2	<i>Data analysis:</i> an iterative process categorizing and visualizing the barriers with its underlying causes: <ul style="list-style-type: none"> a. The identified barriers are classified into main categories by means of data labeling; b. The barriers and causes are visualized in a causal tree showing the interrelations of the causes of the innovation barriers.
Step 2: Innovation barrier prioritization (141, 142)	
2.1	<i>Data collection:</i> a survey is sent to 220 KOLs in which the previously main identified innovation barriers are stated. The KOLs were asked to prioritize the 3 most important innovation barriers ranging 1-3 (1 being highest priority, presents a weight of 3).
2.2	<i>Data analysis:</i> Each score was multiplied by the weight for the respective criterion. The sum of these weighted scores reflects the total weighted score of the innovation barrier. The total weighted scores were finally re-scaled to a range from 1-100 in order to facilitate final interpretation.
$WR_{IB} = \frac{\sum ((n_{R1} * 3) + (n_{R2} * 2) + (n_{R3} * 1)) * 100}{\sum ((n_{R1} * 3) + (n_{R2} * 2) + (n_{R3} * 1))_{HRB}}$ <div> <div>WR = Weighted ranking</div> <div>n = number of times</div> <div>IB = Innovation barrier</div> <div>R_{1/2/3} = rank_{1/2/3}</div> <div>HRB = Highest rated barrier</div> </div>	
Step 3: Result Integration (139)	
3.1	The results of the main innovation barrier prioritization are integrated and subsequently visualized in an RCA tree.
3.2	The point of impact in the value chain of each innovation barrier is identified and visualized.

4.3. RESULTS

Saturation of innovation barriers mentioned by the KOLs during the qualitative interviews was reached after 12 interviews (fig. 1). Seventy-seven KOLs completed the online questionnaire. The demographic characteristics of the respondents were as follows: 7.8% was aged between 25-40yrs, 45.5% between 40-55yrs and 46.8%

≥55yrs. The majority of participants fulfilled a position as practicing MD (40.7%), followed by academics (31.6%) and consultants (10.5%).

Figure 1. Saturation of innovation barriers mentioned during KOL interviews



Eight main barriers were identified and ranked from analysis of the exploratory interviews. Table 2 shows the weighted rankings of the importance of exogenous factors negatively influencing the adoption of innovation. Only one barrier (clinical trial research) has a weighted ranking above 50 indicating the severe importance of this barrier. The second and third barriers are directly related to financial barriers. The main barriers were classified and ranked according to importance into the following categories: financial barriers (119); clinical trial barriers (100); knowledge barriers (76); collaboration barriers (35); and product barriers (11). Each category is described below with its respective underlying causes.

Table 2. Ranking of importance of medical nutrition innovation barriers

Rank	Innovation Barrier	Weighted ranking	Barrier category
1	Difficulty to carry out randomized controlled clinical trials	100	Clinical research
2	Difficult to obtain reimbursement	44	Financial
3	Low return on investment	42	Financial
4	Lack of awareness among governments concerning MN	38	Knowledge
5	Lack of awareness among medical staff concerning MN	38	Knowledge
6	Collaboration barrier between industry and academia	35	Collaborati on
7	Lack of funds from state / government	33	Financial
8	Consumer acceptance of product characteristics	11	Product

4.3.1. Descriptive results

Financial

Financial barriers may also vary during the different phases of the business cycle of the economy due to the differentiated availability of resources and the investment climate (128). The current economic downfall (2008-2012) has proven an underlying cause of MN financial barriers. The lack of financial resources and difficulty in obtaining national reimbursement and ROI are all related to the current economy. The economy also negatively contributed to the decline in governmental grants.

Second; medical nutrition reimbursement. Globally, healthcare costs are growing and healthcare systems are being reformed (31). One of the results is the decline in reimbursement of medical products, including MN products. The decrease of reimbursed MN products which in turn will lead to a stifling of innovation as companies are hesitant to develop unreimbursed products (29, 31). In addition to that, despite the unified EU directive concerning MN, reimbursement policies differ among EU countries. Although clinical evidence concerning MN effectiveness is generally required, precise country-specific reimbursement guidelines are lacking. This further complicates the process of acquiring reimbursement for companies developing MN.

Third; return on investment (ROI). Similar to other industries (143), difficulties in predicting a monetary return on investments, especially in radical innovation poses a barrier in the MN industry. Especially with the threat of decline in MN reimbursement, forecasting a MN product's ROI is considered a significant financial barrier.

Clinical research

The development of MN is relatively young (10), regulatory frameworks or guidelines have not been well established for all stages of medical nutrition development (144). The execution of clinical trials has proven to be the most significant constraining factor in the development of medical nutrition. This situation arises due to several underlying factors, including: high clinical research costs; difficulty to blind the studies; size of the patient groups/power of the study and; regulatory interpretations of MN clinical studies at EU level. The difficulty to blind studies results from limitations specific to nutrition support. For example; highly malnourished patients, seriously in need of nutritional support, cannot be randomized to a no-feeding group and are therefore excluded from participation in clinical research (145).

Knowledge

The European Nutrition for Health Alliance (ENHA) was established in 2005 to raise awareness concerning the relevance and urgency of malnutrition. Their mission was to ensure that the issue of malnutrition was included in policy discussions about nutrition and that appropriate actions are being taken by policymakers and stakeholders at the EU and member state levels (146). Nonetheless, awareness

concerning MN effectiveness among both governments and medical professionals is at present still perceived as an innovation barrier. Especially since the issue of malnutrition is of high societal importance with significant economic consequences, its under-recognition, under-detection and under-management is alarming (146). This issue ought to be prioritized, especially with the knowledge that malnutrition costs EUR 12 billion/year in the UK alone (146).

Collaboration

Typically, academia and industry collaboration is initiated during the early stages of the MN value chain, translational science and clinical research. Despite the benefits that result from collaboration, it is well-known that companies and academia lack a systematic approach for capturing the full potential of such relationships (147, 148). According to the MN KOLs, collaboration between academia and industry is inhibiting MN innovation. This barrier may be due to the differences in objectives between academia and industry. Exaggerated; academia mainly focuses on scientific research whereas the industry focus lies primarily on economic benefit created by scientific research.

Product

Each firm may independently encounter various endogenous product barriers, due to for example technological difficulties. Since our focus lies on the exogenous barriers to innovation, endogenous barriers are not taken into account. Nevertheless, product barriers also arise at the exogenous level. In MN, consumer acceptance is perceived as such a product barrier.

4.3.2. Data integration

Integrating the results from the RCA with the ranking, results in a causal tree (fig. 2). This tree visualizes which main barriers are impacting innovation and which causes underlie these barriers. Since barriers usually mutually reinforce their impact, the identification of the root causes of the innovation barriers may assist in their elimination or reduction. The causal tree, from left to right, starts with the innovation barrier categories, followed by the main innovation barriers and ends with the underlying causes.

Figure 2. Integration of RCA and importance ranking of medical nutrition innovation barriers

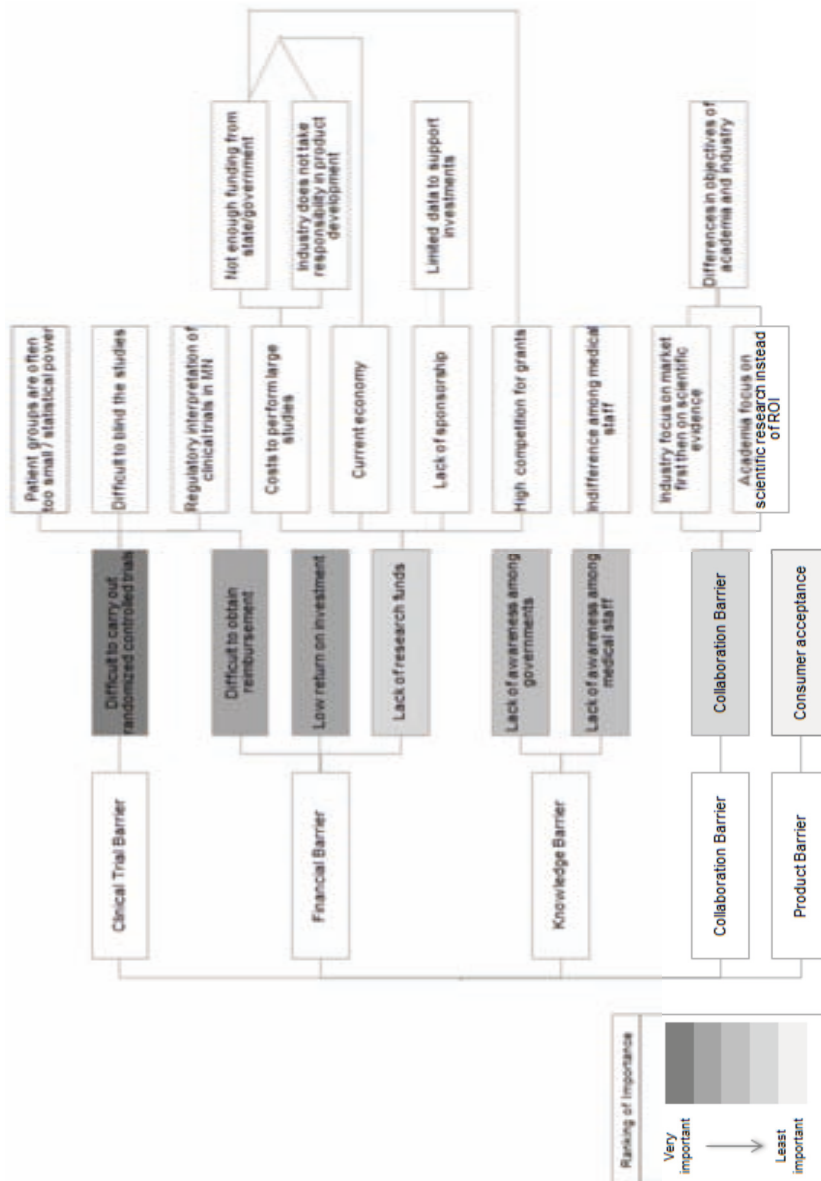


Figure 3. depicts the point of impact of the innovation barriers on the medical nutrition value chain. This gives an indication on the complexity of the impact of the barriers to the innovation process, the actors involved, and the barrier interaction. Barriers may act one or more stages of the value chain, and their impact may be different at their various points of action (128). Of particular interest is the role of barriers during the initial stages of the value chain, since inability of an actor to overcome them leads to a passive attitude and avoidance of innovation (128). Numerical, most barriers have an impact at the final marketing stage of the MN value chain. Financial and collaboration barriers exist on three out of six stages of the value chain (translational science, product development and clinical research).

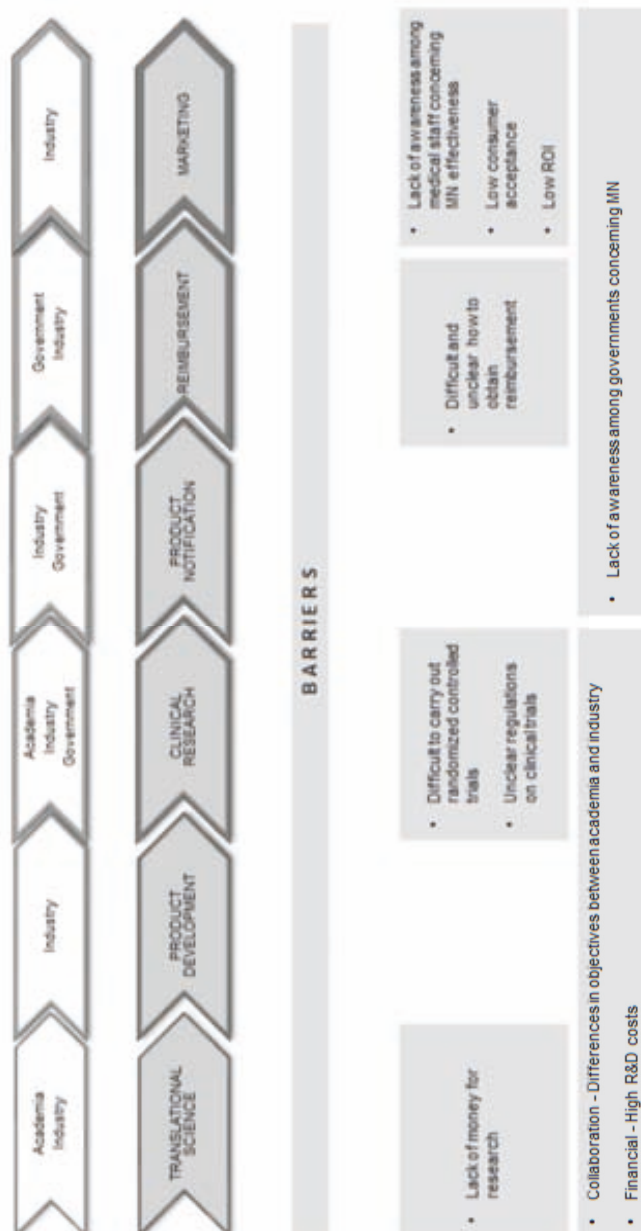


Figure 3. Point of impact of medical nutrition innovation barriers along the value chain

4.4. DISCUSSION

Our analysis reveals that nine exogenous innovation barriers have the potential to interrupt all steps of the MN value chain (fig 3.). These barriers are grouped into five categories (ranked according to importance): financial; clinical research; knowledge, collaboration and; product related. Industry success and survival is dependent on the degree companies incorporate innovation into their organizational strategy. MN companies that successfully embrace innovation in their strategy increase their chances for company growth and commercial survival. The first step is to acknowledge the presence of barriers hindering innovation, followed by understanding how to overcome them in order to effectively implement innovation practices. Since barriers may be industry-specific, it is important to identify innovation barriers specific to the MN industry. In this paper we set out to explore the factors that inhibit innovation in the medical nutrition value chain.

During this study we found that the likelihood of translational application of innovative knowledge very much depends on a company's capability of overcoming innovation barriers. Academia and industry struggle in collaborating during the early stages of the value chain and a lack of financial resources further complicates this. Often, challenging and costly clinical research needs to be performed to evaluate effectiveness and safety. The ROI of MN products is highly dependent on the possibility of obtaining reimbursement for that particular product. This consequently depends on the regulatory standards of that particular nation. Deploying public affairs for better regulatory guidelines at both clinical research and reimbursement level remains challenging considering the un-standardized regulatory practices in the EU-region alone. Additionally, a low awareness on the issue of malnutrition and MN effectiveness still exists at state/governmental level, limiting reimbursement opportunities. Response of both consumers and health care professionals are of particular importance at the marketing level. Low awareness here inhibits the adoption of innovation.

The present RCA suggests that clinical trial and financial barriers are interrelated. We can assume that by solving the root causes of these two barriers, both may be solved. The fact that financial barriers are the highest rated barrier is consistent with literature (149, 150). However, barriers in carrying out clinical research are MN industry specific. MN innovation is predominantly constrained by difficulties encountered in practical aspects of clinical research e.g. double blinding and the size of patient populations versus the statistical power of the study.

Literature has widely acknowledged that creating a tight network of collaboration between industry and academia is an unavoidable part of any innovation strategy (151, 152). Although efforts are being made to stimulate collaboration between academia and the MN industry (144, 153) this factor remains to be an important barrier inhibiting innovation. Much of the tension between industry and academia arises from the conflicting desire of academia to perform perfect research, and the desire of industry to quickly bring new reliable products to the market (148). One

solution is for both industry and academia to remain focused on the needs of the consumer as the target for both research and sales.

Consumers and healthcare professionals are commonly rightfully skeptical of information coming from industry, a source that stands mainly to make a profit (148). This reinforces the importance of collaboration with- and the role for academia in providing independent scientific advice and education to healthcare professionals and consumers. Consequently, this will lead to a higher awareness among healthcare professionals and consumers concerning MN effectiveness.

Although exogenous barriers cannot be easily influenced at the short-term (128), the company can adjust their organizational strategy in such a way so as to overcome them. If companies are able to adapt their organizational strategies in such a way, they transform these barriers into positive opportunities and develop a unique competitive advantage. Organizational strategies to overcome exogenous MN innovation barriers could involve:

- Adopting (orphan drug) pharmaceutical-oriented clinical research with clear end-points and cost-effectiveness methodologies to set a golden medical nutrition clinical research standard thereby also facilitating the reimbursement procedure;
- Higher involvement of academic research institutions to facilitate collaboration and reduce investment;
- Initiating education programs and/or conferences to increase awareness among medical staff and government.

Since this study only focused on exogenous innovation barriers from a top-down viewpoint, future research should further investigate which endogenous barriers are experienced by MN companies. In combination with results from this study this will provide a complete overview of all barriers.

As a final note, transparent regulatory legislation at EU level would most likely benefit MN innovation. Even though this is challenging to accomplish on the short-term, the aim of regulatory bodies should be to protect the consumers without discouraging innovation. Especially legislation concerning clinical research and reimbursement are essential and will most likely eradicate numerous MN innovation barriers currently experienced within the industry. However, new regulations will most likely also create significant new barriers. By establishing MN clinical guidelines, all MN products have to comply to the same set of (compositional) guidelines, even though the products target patients with very specific and deviating nutritional needs. This may force industry to deliver the cheapest possible product complying with guidelines instead of a radical innovation. Apart from non-technical factors such as market and economic forces, food sciences and nutritional technologies are also considered primary drivers of the food industry. Challenging external environments offer opportunity but also require firms to become more innovative to succeed. MN companies must therefore realize that investment in innovation is and remains crucial.

Our results provide insights for existing but also starting MN companies attempting to innovate. Understanding these MN innovation barriers can aid the innovation process and development of firm strategies and government policies that contribute to economic growth, job creation and increased wealth. Especially in an industry with such high social values, innovation benefits everyone: from economic value for industry and government to social value to patients.

CHAPTER 5

PATENTING IN THE EUROPEAN MEDICAL NUTRITION INDUSTRY: TRENDS, OPPORTUNITIES AND STRATEGIES

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ABSTRACT

Medical nutrition products are specific nutritional compositions for intervention in disease progression and symptom alleviation. This industry finds itself on the interface between the food and pharmaceutical industry and even though it represents one of the fastest growing segments within the health and life sciences, it is still a relatively unknown industry. At present, insights concerning industry development and patenting in the European medical nutrition industry are limited. This research presents a systematic patent portfolio analysis of the industrial patenting trends and patenting strategy categorization of the 5 leading companies.

Focusing on EU patent applications, we calculated company specific patent-, product- and market shares and average forward- and backward- citations. These indicators were combined to illustrate the European medical nutrition industry trends and company specific patent- and innovation- strategies. We found 222 European medical nutrition patent applications between 1990 up to 2010 with company specific patent shares ranging from 1-58%.

The analysis of the industry trends shows that the industry currently resides in the growth phase and is estimated to reach the stage of maturation within two years with approximately 400 patents. Predominantly neurological diseases, cancer and diabetes show opportunity for future MN innovations while gastrointestinal and infection related diseases may have already reached a market saturation stage. Only three distinct patent strategies can be distinguished within this industry: the Prospector; the Analyzer; and the Reactor.

5.1. INTRODUCTION

Knowledge is the key ingredient in every innovation-driven industry. Knowledge and innovation are clearly imperative for creating a sustainable competitive advantage (154). At the start of the invention process, novelty and creativity lead to a product innovation (155, 156). It is crucial for companies to protect new assets in order to remain competitive and valuable in the competitive market environment.

There are various legal intellectual property instruments aimed at excluding the competition for a specified period of time. Such measures are perceived as rewarding for the inventor for developing new knowledge, while additionally providing the opportunity to commercially exploit it. By strategically combining various Intellectual Property (IP) methods, optimal protection of the innovation can be achieved (157).

In the health and life science industry, patents are considered valuable instruments for protecting innovations. Although a costly endeavor, patenting is considered essential because of a twenty-year exclusivity period (158, 159). During this time, the applicant may recover the high investments incurred during research and development through premium product pricing or receiving royalties. The (financial) benefits of patenting are optimally exploited before expiration, after which the market value of the innovation decreases. As a result, companies adopt numerous other strategies for extending the protection life-time of an innovation. Nevertheless, the decision to patent remains complex (160).

The European (EU) Medical Nutrition (MN) industry is relatively new within the historical scope of the health and life sciences and represents one of the fastest growing segments within this sector. This industry finds itself on the interface between the food and pharmaceutical industry with its own Foods for Special Medical Purposes (FSMPs) regulations (161). MN products are prescribed food compositions that consist of targeted nutritional compositions for intervention in disease progression and symptom alleviation. The EU MN industry is led by 5 companies: Abbott Nutrition, B Braun, Danone (Nutricia), Fresenius Kabi and Nestle. This industry is perceived as an industry in an early development stage. In the case of the MN industry, its growth is most likely attributable to an increase in societal awareness on the functional health benefits of nutrition.

Thus, the growth is driven by an expanding body of knowledge which demonstrates the benefits of nutritional intervention on improving and supporting an individual's health status (58). Since the EU MN industry is a relatively new industry, academic insights into the industry development and innovation protection strategies are lacking. This paper presents MN industry trends, innovation opportunities and patent strategies thereby aiding both industry as well as academia in their search for new research and business opportunities. By completing a patent analysis at an industry and company level for the EU MN industry, we aim to:

1. At industry level: analyze and compare patents applied for by the main competitive MN companies, thereby providing an industry patent landscape. We look at the stage of maturity the industry finds itself in within the technological

life cycle and at disease areas that offer possible product innovation opportunities.

2. At company level: evaluate company specific patent indicators with which to categorize the MN companies' patenting strategies.

Background information

As an industry emerges, IP protection mechanisms are yet undefined. However, companies may have different motives to patent and therefore may employ diverse patenting strategies (160). The decision to apply for a patent can be influenced by the degree of technology or knowledge innovation, ranging from incremental, to radical. Incremental inventions consist of minor improvements or adjustments to existing inventions or technologies. Radical inventions exhibit key characteristics that are inherently different from existing inventions or technologies. The latter type is considered to form a crucial basis from which subsequent incremental developments may evolve (162, 163).

Patent applications describe in detail the date and nature of the invention, inventor, the applicant, and are categorized according to a complex system of international patent codes (IPCs). Data is readily available, organized in discrete categories and can be disaggregated to specific technological areas recognized through the IPCs (110). This research is based on patent applications; whether or not a patent is truly granted is a process that will take several years.

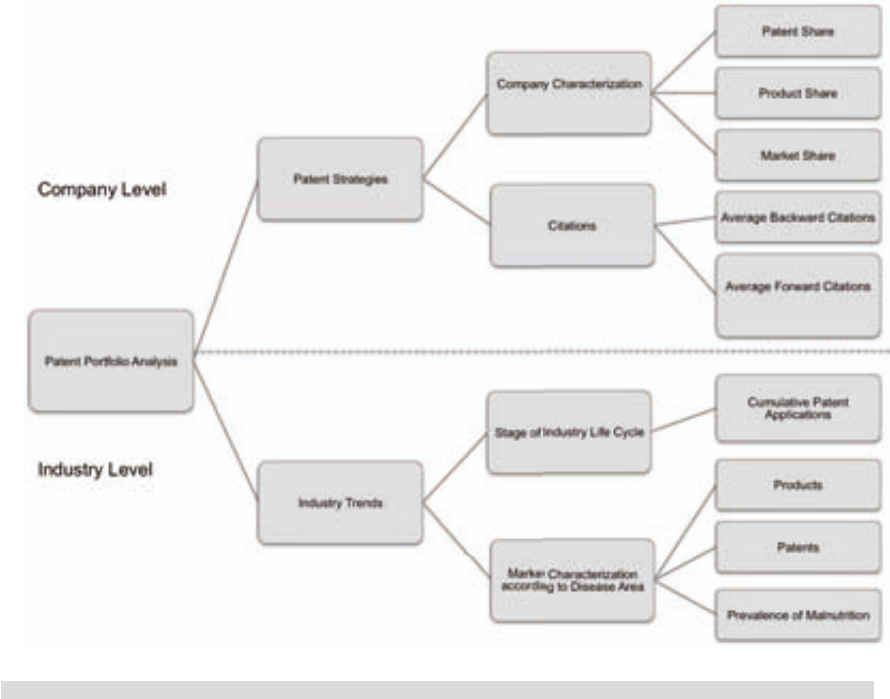
Moreover, patents can be analyzed based on citations. Citations of the patent are allocated by the examiner in the patent application file, and indicate the history of related inventions. These patent citations are often used in patent analyses. Two types of citations exist: backward and forward citations. The former refers to the number of previous patents as an indicator of related preceding knowledge on which the new patent is based. The average number of backward citations in a patent has proven to be related to how radical or incremental an invention is. For example, patents with lower numbers of backward citations are considered to refer to radical inventions. Forward citations indicate the frequency of a newer patent application citing the original patent application. It serves as an indicator for the economic value of the patent and the technological importance of the invention (98, 102, 164). In the European Patent Office (EPO) system, the patent applicant may include citations to prior patents, but ultimately it is the patent office examiner who determines which citations are included in a patent. Therefore, the patent citations are considered to be unbiased and trustworthy patent indicators (165).

To perform this study, different patent indicators and company specific characteristics such as market- and product share, are combined. By using this information in a patent portfolio analysis, one can identify industrial developmental trends and patent strategies on industry level as well as at the company level (166-169). This study combines different types of publicly available information to look at the EU MN industrial trends and the companies' patenting strategies through a patent portfolio analysis.

5.2. MATERIALS AND METHODS

The method of this patent portfolio analysis is based on methods by Chen, Ernst and Tseng (79, 98, 169) . The patent portfolio analysis (Fig. 1) is based on the five leading companies according to market shares of the EU MN industry: Abbott Nutrition, B Braun, Danone (Nutricia), Fresenius Kabi and Nestle. The analysis is divided into two parts; starting off with analyzing the industry-level development trends. The industry is evaluated based on the timeline of patent applications and the disease areas the patent targets. Subsequently, patent strategies at company-level are defined. Data on company characterization (patent-, product-, and market share) and company-level citations (forward- and backward-citations) is collected in order to systematically categorize the company strategies.

Figure 1. Research framework of the patent portfolio analysis in the European MN industry: 1. Company-Level Patent Strategies 2. Industry-Level Trends.



Patent Search

Data on patent indicators was retrieved from the Derwent Innovations Index, pertaining to the European published patent applications (EP) between 1995 and 2010². Furthermore, two different search fields were combined: assignee (patent applicant) and international patent code (IPC). The former search field refers to the five selected companies. Correct IPCs were obtained from the classification database at the Espacenet portal³: A23L001⁴ in combination with A61K031/035/045⁵. Only compositional patents, publishing nutritional compositions of MN: tube feeding (TF) and oral nutritional supplement (ONS) were selected, as based on the definition provided by the ESPEN Guidelines on MN (28). We did not filter between pending, granted and rejected patents.

Industry-level Data

The first step in revealing the industry-level developmental trends in the MN industry was to create a patent application timeline. According to Ernst, technological change within an industry follows a certain pattern with different development stages (79). Logically, four stages within the technological life cycle are identified, those being: Emerging, Growth, Maturity and Saturation (Fig 2). For the MN industry we created such a timeline of cumulative patent applications between 1995 and 2010.

To complete the characterization, the marketed products, patent application and prevalence of malnutrition were segregated into 9 different disease areas: cancer, gastrointestinal, infection, neurological, respiratory, dementia, heart and coronary, genitourinary and renal, and diabetes (28).

Recent large-scale multi-center surveys consistently show that malnutrition risk is common across many disease areas in hospitals. These studies indicate the prevalence of malnutrition among patients with a wide variety of diseases (55, 58, 170). The division of these disease areas is also applied to the EU MN industry products and patent applications. These marketed European MN products were extracted from the MN company websites. Different flavors were not taken into account as separate products.

Company-level Data

To compare the patent indicators to specific company characteristics: patent shares, product shares and market shares were calculated (Table 1). The product shares were calculated with data from company websites on product information. Market shares are determined based on revenue information from the companies' annual reports

² It should be noted that since conventional patents are usually classified and published within eighteen months after filing, the patent record set covering 1990 - present might not be complete.

³ http://v3.espacenet.com/eclasrch?locale=nl_NL&classification=ecla

⁴ A23L001: foods or foodstuffs; the preparation or treatment.

⁵ A61K031/035/045: pharmaceuticals.

and were later confirmed by the companies. Market shares are solely based on the companies' revenue figures of MN products in Europe in 2009. By plotting the different company characteristics in a 3-dimensional graph, the MN companies were classified based on three dimensions: patent share, product share and market share. The dependent variable in the determination of the companies' patenting strategies was patent share, and the independent variables were the average backward citations and average forward citations, while the control variables were the product share and market share. By combining the patent indicators, company characteristics, we were able to define the MN companies' patent strategies.

This study took all European filed patent applications into account that met the search criteria, even though not all patent applications end up as an actual granted patent. As this fell beyond the scope of the research objective, we did not analyze this criterion.

Table 1. Calculation methods of patent indicators, industry characteristics and company characteristics			
Indicators	Source	Description	Calculation
Patent Indicators			
Patent Share	Published patent application document	The percentage of all patents in the EN industry attributable to a company	$\text{Patent Share} = \frac{\sum \text{total nr of patents in the market}}{\sum \text{nr of patents owned by the company}} \times 100$
Average Backward Citations	Published patent application document	Average number of patents containing prior knowledge. Indicates whether an invention is radical or incremental.	$\text{Average Backward Citations} = \frac{\sum \text{nr of backward citations in all patents}}{\sum \text{nr of patents owned by the company}} \times 100$
Average Forward Citations	Published patent application document	Average number of times the patent application has been cited. Indicates whether an invention is relevant and valuable.	$\text{Average Forward Citations} = \frac{\sum \text{nr of forward citations in all patents}}{\sum \text{nr of patents owned by the company}} \times 100$
Industry Characteristics			
Industry Life Cycle	Published patent application document	The annual growth of patent applications between 1995-2009	
Products	Company brochures, company websites	All EN products in the European market according to disease areas	
Prevalence of Malnutrition	MNI malnutrition	The prevalence of different disease areas in European hospitals	
Company Characteristics			
Product Share	Company brochures, company websites	The percentage of all products in the EN industry attributable to a company	$\text{Product Share} = \frac{\sum \text{nr of products owned by the company}}{\sum \text{total nr of products in the market}} \times 100$
Market Share	Annual reports	The percentage of total sales in the EN industry attributable to a company	$\text{Market Share} = \frac{\sum \text{annual revenue of the company}}{\sum \text{annual revenue in the EU EN industry}} \times 100$

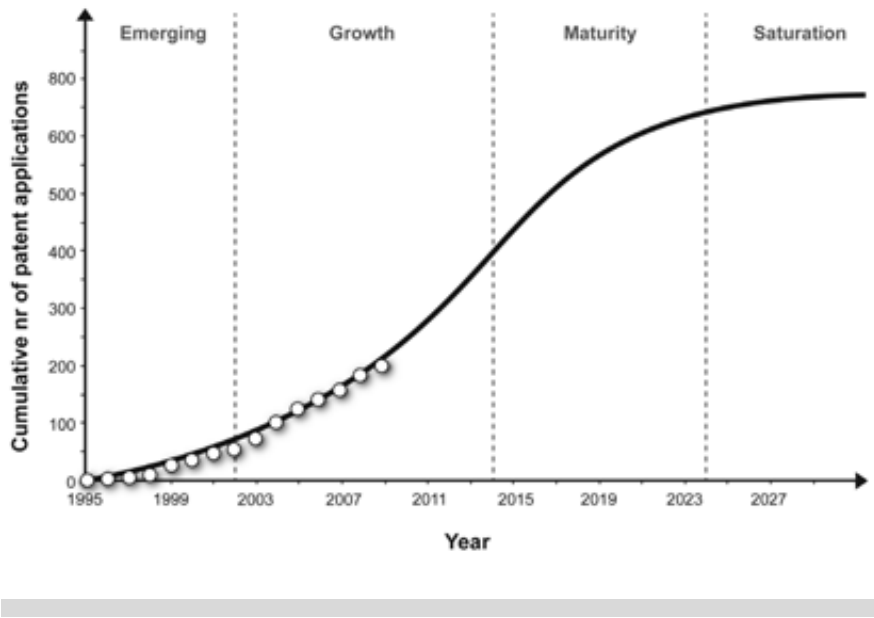
5.3.RESULTS

The patent search revealed 222 eligible patent applications.

5.3.1. Industry Level Development Trends

We assumed that the MN industry, just like any other industry (79), follows a certain technological development pattern. Figure 2 illustrates this development of cumulative patent applications and confirms that the MN industry does indeed follow the standard development pattern and currently resides in the growth phase.

Figure 2. Cumulative industry life cycle development (adapted from: Ernst 1997). White circles indicate the technological development of the EU EN industry between 1995 and 2009

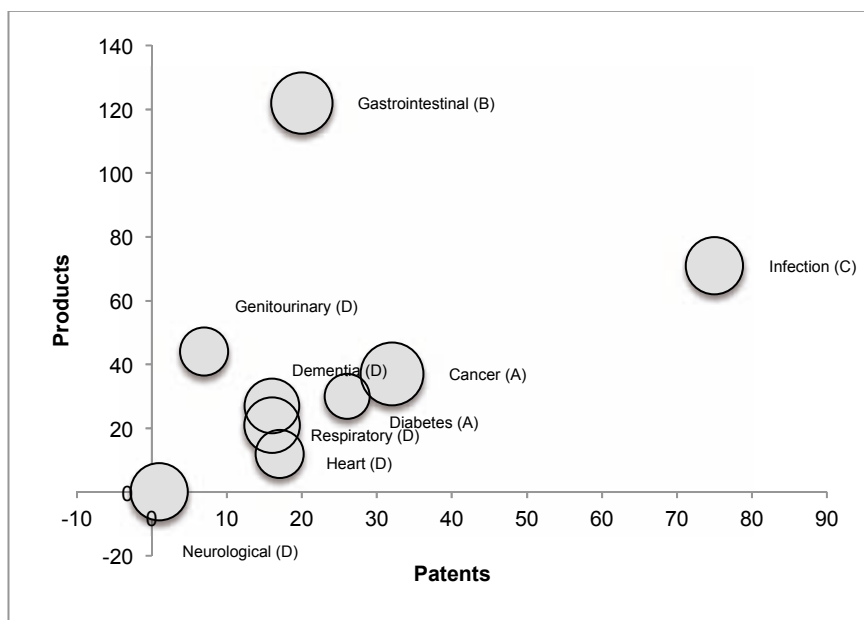


Number of patents, products and the prevalence of malnutrition were calculated across 9 different disease areas. We classified the disease areas into 4 groups (A-D) according to prevalence of malnutrition, number of patents and number of products. These 4 groups characterize EU MN industry niches that reside in different stages of innovation development (Table 2, Fig 3).

Table 2. Disease group classification

Group	Malnutrition	Patents	Products
A	High	Intermediate	Intermediate
B	High	Intermediate	High
C	Intermediate	High	High
D	Low/Intermediate	Low	Intermediate

Figure 3. Unmet needs and innovation opportunities in the EU MN industry – Patent vs Product vs Prevalence of Malnutrition – the bubble size indicates the prevalence of malnutrition according to disease area in hospitals (MNI, 2010)



Group A – “Opportunity Niche”

This market niche can be defined as a niche with a high unmet medical need due to a high prevalence of malnutrition, and an intermediate number of patents and products. Therefore the disease area “cancer” may offer future innovation opportunities for MN companies developing MN products.

Group B – “Low Hanging Fruits”

With a very high prevalence of malnutrition among patients in this disease area and many products for these patients, this market niche seems quite saturated. Additionally, an intermediate number of patented inventions can be observed possibly indicating that MN compositions in this niche are either difficult to be patented or unnecessary since the compositions are not unique. This is an easy-to-access niche where patenting is not necessary and with a high patient need. However, competition is also fierce in this niche.

Group C – “Future Defense”

This seems to be a relatively saturated market niche with a high number of patients suffering from malnutrition but also with a high number of patented inventions and a high number of marketed products.

Group D – “Latent Opportunity Segment”

Although the prevalence of malnutrition and thus medical need of most disease areas, except neurological diseases, in this group is relatively low compared to the other disease areas, the number of patents and products are correspondingly low. This results in an opportunity niche which offers MN companies some innovation opportunity. Especially for new Small and Medium Sized Enterprises (SMEs) these disease areas may be of opportunity interest since there are few patents and marketed products and thus a low level of competition with the big nutritional companies.

Overall these results show that there are many niches which yield innovative capacity in the emerging EU MN industry both to the larger nutritional companies as well as to the new SMEs.

5.3.2. Company Level Patent Strategies

The number of patent applications differs substantially between the 5 leading companies, ranging from a patent share of 1-58% (Table 3).

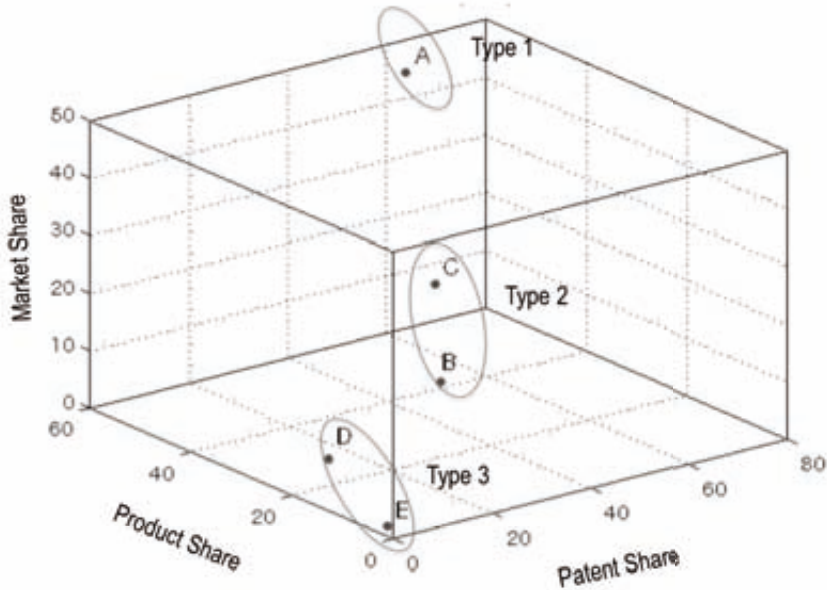
Table 3. Company specific descriptive patent analysis results

	Type 1 Company A	Type 2 Company B	Type 2 Company C	Type 3 Company D	Type 3 Company E
Patent Indicators					
Patent Share (%)	58	22	17	2	1
Average Backward Citations (Radical < Incremental)	16	31	27	13	11
Average Forward Citations (Low value < High value)	5	20	12	5	11
Company Characteristics					
Product Share (%)	59	13	10	15	3
Market Share (%)	45	17	37	8	1

Even though empirical evidence suggests that 66-87% of firms' inventions are patented (171) this has not been observed in our data set describing the MN industry. Our results show that patent strategies for the five leading companies differ extremely (Table 3).

When evaluating the company-level patent strategies, the data reveals three distinct company behaviors. Figure 2 depicts the company classification by means of a 3-dimensional graph based on three dimensions: patent share, product share and market share. The X-axis of the classification in this study shows the patent share, the Y-axis the product share and the Z-axis the market share. The characteristics of company Type 1 include: high patent share, high product share and a high market share, describing only company A. Type 2 company characteristics display an intermediate patent share, intermediate product share and an intermediate market share, including companies B and C. The characteristics of Type 3 companies are: a very low patent share, a low product share and a low market share, describing companies D and E.

Figure 4. Company classification according to their patent-, product-, and market shares. Three types of companies can be distinguished: Type 1, Type 2 and Type3.



To further characterize the companies, average backward citations and average forward citations are taken into consideration and the 5 companies are plotted in Figure 5.

- The X-axis of the patent strategy classification displays the patent shares of the EUMN companies.
- The Y-axis in this figure is the average backward citations of each company's patents. The company specific average backward citations are an indication of how radical a company's inventions are. The lower the number of average backward citations, the more radical the inventions are considered to be.
- The Z-axis is the market share of the companies, indicating the market share the company holds in the EU MN industry.

The cube graph is divided into 8 spaces in Figure 3. The 5 EU MN companies fall within only 3 quadrants and are divided into category 1, 2 and 3. In Figure 5, identical company clusters are exhibited as in Figure 4, thus displaying three different patent strategies across the same clusters. The average forward citations are

not displayed in the figure but are also taken into consideration. The different clusters are described and further elaborated on.

Type 1

This cluster is characterized by the highest patent, product and market shares indicating a dominant position in the EU MN industry (Fig 5c). Furthermore, company A has relatively low average backward citation counts, meaning its inventions are radical, and low average forward citation counts, indicating low values of its inventions. There are two explanations for these observations. First; the company patents all of its radical inventions. Since the citation results indicate that many of its inventions appear to be radical but may turn out to be of an overall low value. Overall, radical inventions are of high risk and therefore may turn out to be of low value thus explaining this pattern. Second, the company could be applying an “offensive blocking” patent strategy. This entails the building of a wall of patents surrounding the few crucial core patents, keeping the competition at a distance (157). Since some patented MN compositions may be difficult to protect from competition, this may be applied by Type 1 company within the MN industry.

Type 2

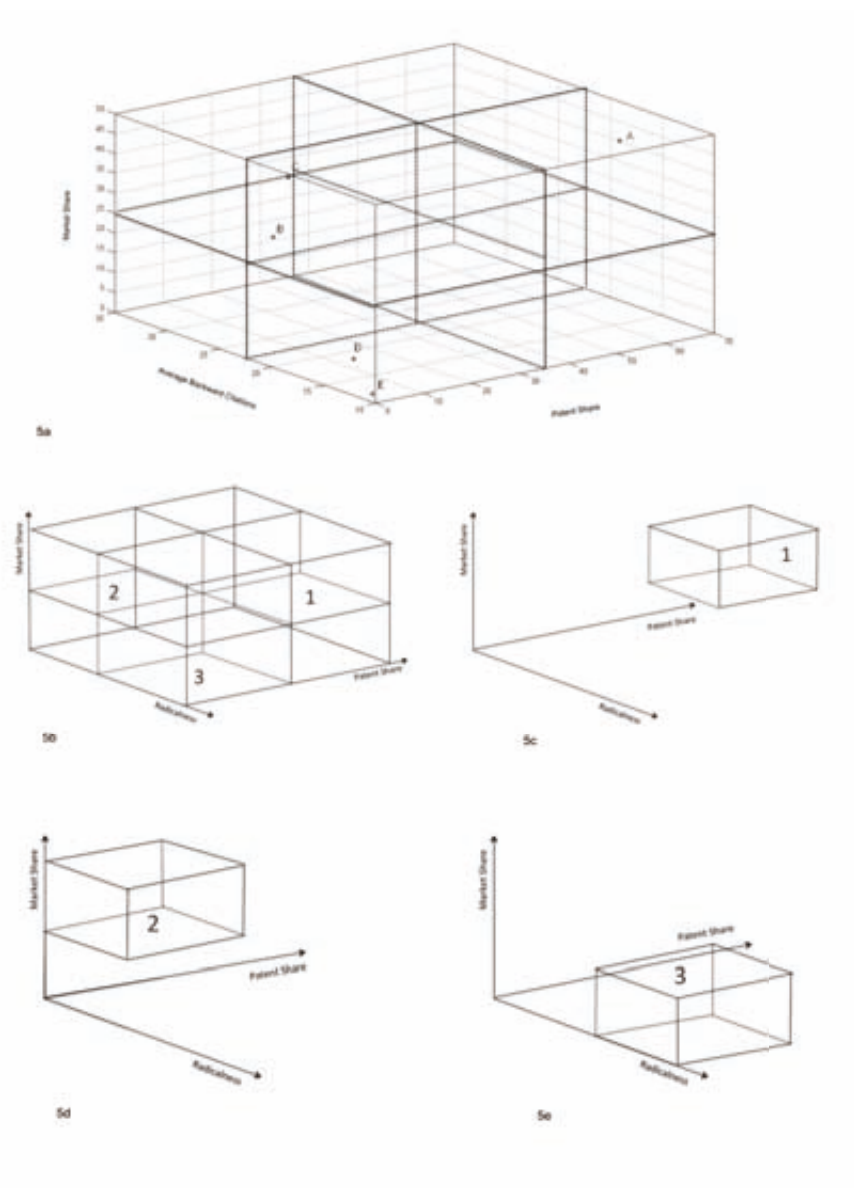
The Type 2 EU MN companies (Fig 5d) are characterized by intermediate patent-, product- and market shares indicating a stable position within the industry. The inventions patented by these companies are typically incremental with high value as observed in companies B and C in Table 2. This is an indication that in the EU MN industry, incremental inventions can be of high value and therefore also worth protecting and commercializing. Reasoning behind this strategy is most probably a “defensive blockade” to prevent the competition from imitating the invention (157).

Type 3

The final cluster of companies, Type 3 (Fig 5e), exhibit low patent, product and market shares in the MN industry. Their citation patterns indicate their patents to be radical but of low value. Although this citation pattern is similar to the Type 1 citation pattern, the Type 3 companies have very different company classification indicators and therefore a different explanation exists for their citation pattern. It is assumed the combination of company characteristics with citations data indicate these radical patents may be used as a marketing tool.

While using the EPO database we encountered one inherent problem. This has to do with the number of forward citations received by a patent. Older patents have a higher chance of receiving forward citations, simply because the period over which the citations are counted is longer compared to younger patents (162).

Figure 5. Patent strategy classification according to patent share, average backward citations and market share. Figure 5a shows where the 5 largest EU EN companies (A,B,C,D and E) are plotted in the cube graph. Three distinct patent strategy clusters can be identified. Figure 5c: Group 1. Figure 5d: Group 2. Figure 5e: Group 3.



5.4. DISCUSSION & CONCLUSIONS

Conclusions

The company specific patenting strategies show that while some EUMN companies use patenting for its original function to protect the company's inventions, others patent to block competition or even deploy this IP method as a marketing tool. These observed patenting differences might be explained by the original roots of the EUMN companies. Some EU MN companies originate from the food industry while others originate from the pharmaceutical industry. The patenting trends in these two industries differ tremendously and therefore most probably influence the patent strategy choice within the EUMN industry. The growth rate of MN patents is the same as for other industrial life cycles and will lead to maturity in 2-3 years.

The results of the industry development trends suggest that the MN industry shows a growth rate in the quantity and type of patent applications, implicating sufficient innovation opportunities. Based on our patent analysis, the MN industry is best described as being in start-up growth phase. The industry is forecasted to reach the stage of maturation by 2014 with approximately 400 patents (Fig 2). Nevertheless, while certain disease areas show growth opportunity for future MN innovations (e.g. cancer, diabetes and neurological diseases), others may have already reached a stage of market saturation (e.g. gastrointestinal and infection related diseases).

Discussion

Even though patenting is seen as an important tool in the technological strategies, in the EU MN industry patenting has proven to be of variable importance to the five key players. The dataset reveals incoherent patenting behavior across industry-level, whereby certain companies seem to simply patent all their inventions while others only patent their (rare) radical inventions. Previous research confirms this irregular patenting behavior in other life sciences industries where it was observed that patenting was proven to be an ineffective intellectual property protection strategy (172, 173). Therefore, if a company is willing to forgo patenting for mere freedom to operate, other IP methods may also be effective.

The high frequency of incremental inventions in the MN industry appears to be a similar trend as what has been demonstrated in the pharmaceutical industry where on average more than half (51%) of all FDA approved drugs are incremental innovations (174). Although beyond the scope of this research, we expect this to be similar in the MN industry with more introductions of incremental than of radical innovations. Another similarity between these two industries is the high value of incremental inventions within the MN industry just as in the pharmaceutical industry (174). The low value of many radical MN inventions, a result of this research, may be explained because radical inventions are often high risk and only a few will result in a marketed product and yield a profit while the rest fails.

At company-level, the three patenting behaviors conform to the business strategy typology framework as published by Miles et al. (1978) (175). This analysis

framework can be applied to organizations as an integrated and dynamic whole. This framework essentially defines four strategic types of organizations: Defenders, Analyzers, Prospectors and Reactors. Each type has its own unique strategy. Three of the typologies fit our observations of the EU MN companies: the Prospector; the Analyzer; and the Reactor.

TYPE 1 – The Prospector

MN companies classified under type 1 are best describes as prospector companies. The Prospector's leading capability is that of finding and exploiting new product and market opportunities. This type of company's priority lies in maintaining a reputation as an innovator in product development. Company type 1 clearly exhibits a very low average number of backward citations as an indicator of radical innovativeness. For the prospector, maintaining a reputation as an innovator in product and market development may be as important as high profitability. Due to the inevitable "failure rate" associated with radical innovations, it may be difficult to attain high profitability on all the innovative products [29]. This may be the explanation of the low value of patents in Company Type 1; as a result of the high attrition rates, such patents are regarded as less valuable to competitors

As a result, the prospector can resort to an offensive patent strategy. By building a wall of patents around the core-innovation, the prospector intends to fully benefit from market exclusivity. Especially in the MN industry it may be difficult to protect a proprietary MN composition and it may therefore be advisable to build such a protective wall of similar patents around the main valuable patent to prevent imitation from competitors.

TYPE 2 – The Analyzer

Type 2 MN companies display the characteristics of "The Analyzer". An analyzer company moves toward new products or new markets but only after viability has been demonstrated. This may be accomplished through imitation or incremental innovation – only the most successful product innovations developed by other companies are adopted. At the same time, the majority of the Analyzer's revenue is generated by a fairly stable set of products and customer groups. This type of organization must learn how to achieve and protect an equilibrium between conflicting demands for technological flexibility and for technological stability (Miles et al. 1978) [29].

Results show that incremental inventions in the MN industry are generally of higher value than the radical inventions. This proves that patenting incremental inventions with this company-level strategy may result in a high return on investment (ROI).

TYPE 3 – The Reactor

The final type of organization exhibits a pattern which usually consists of responding inappropriately to environment change and uncertainty. As a consequence companies within this group exist in a state of almost continuous instability. This type of strategy usually arises when one of the other three strategies is improperly applied. A reason for developing such a strategy may be that management does not fully shape

the organization's structure and processes to fit a chosen strategy. Another reason may be the tendency of a company's management to maintain the organization's current strategy-structure relationship despite overwhelming changes in environmental conditions. Unless a company operates in a monopolistic industry, it cannot continue to behave as a Reactor indefinitely. Since the EU MN industry can be defined as an oligopolistic market and not a monopolistic market, this inclines that the type 3 companies will have to alter their strategy to a more stable strategy to stay profitable.

For this type of company it also appears that they apply the strategy of using its patents as a marketing tool, a novel approach applied in several industries. It entails that companies use their patents to promote their novel and radical inventions to set the product apart from other products in the market (176). In the MN industry case, this marketing technique will be targeted at the medical professionals prescribing the MN to the patients. A patent may provide the customer with the confirmation of the effectiveness of the MN product especially if this product is based on a radical and therefore relatively unknown invention. In the case of the MN industry, companies may use the term "proprietary composition" or the patent number to convince medical professionals to prescribe their products to patients.

This research is based on "composition of matter" patents. A suggestion for future research is to also take into account the "technological" patents. This is because "technology" patents are often applicable in different industries and therefore not specific for the MN industry. Additionally, there is no standardized IPC code for MN. Since the MN industry is a fast-growing industry it would therefore be advisable to the European Patent Office to create such a code.

Overall, this study illustrates the EU MN industry can be characterized as an inventive and fast developing market dominated by 5 large nutritional companies with 3 different patent strategies. With such optimistic future prospects, understanding of the most applicable methods for protecting IP would aid both the academic as well as the industrial sector. This paper presents the first systematic analysis of industry trends and patenting activities in the EU MN industry in order to provide both academia as well as industry with an overview of this emerging inventive market.

CHAPTER 6

A DECISION FRAMEWORK TO EVALUATE INTELLECTUAL PROPERTY STRATEGIES IN THE MEDICAL NUTRITION MARKET

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ABSTRACT

In the medical nutrition (MN) market, insights into the motives driving intellectual property (IP) protection strategies remain unclear. This emerging market has expressed the pressing need for clarity on the subject of applicable IP methods. The aim of this study is therefore to evaluate the role of patents and alternative IP instruments for the protection of innovations in the MN market, and to construct an IP decision framework facilitating IP selection. Data collection consists of a literature study on the topic of IP strategies, combined with a supplementary questionnaire sent out to MN companies.

Although there are many different strategic motives to apply for a patent in the MN market, the classic protective motives prove to be most important. While our findings acknowledge that patenting is of paramount importance to this industry, different scenarios call for combining the various IP methods for the optimal protection of the MN innovation. One must therefore always carefully consider additional IP rights. Our IP decision framework provides both MN companies and academic R&D departments with a tool to assess the best applicable IP strategy for the protection of MN inventions.

6.1. INTRODUCTION

To protect an invention, one must consider employing different types of available intellectual property (IP) methods. The type of IP that has received the most attention and has been subjected to vigorous study is the patent. A patent protects new and useful inventions and provides the applicant with a granted 20-year period of exclusivity in return for complete disclosure of the invention (160, 177-181).

In the health and life sciences sector, patents are considered essential instruments for protecting innovations. A relatively new and emerging industry within this sector is concerned with medical nutrition (MN) (182). MN deals with the prevention and treatment of malnutrition related disorders that arise due to either inadequate or improper diet, or underlying diseases whereby the body is unable to handle certain essential nutrients (7). MN counteracts this nutrient imbalance either through tube feeding or through the administration of oral nutritional supplements. MN products are perceived as “borderline-products” on the interface of the food- and the pharmaceutical- industry but with their own Foods for Special Medical Purposes (FSMPs) guidelines (7).

Within the European MN industry, patenting has proven to be important. Previous research has demonstrated that MN companies adopt different patenting strategies with knowledge concerning the driving forces and motives to patent in the MN market still lacking (182). There is also an explicit need expressed by the MN market for clarity in their search for suitable IP methods in this industry [interviews with KOLs].

The present paper adds to the existing body of knowledge on patenting and other IP methods by investigating IP strategies and motives to patent specific to the MN market. Through questionnaire analysis, the factors that are considered to be important in the decision to patent in the MN market are revealed. This knowledge is then combined with results from a literature study to construct an IP decision framework supporting MN companies but also R&D departments in their IP strategy decision processes. The framework is meant to serve as a helpful tool, which can assist MN companies and R&D departments in shifting from unclear IP situations to clear cut decisions regarding the strategy of choice. The objective of the study is to provide smaller and larger MN companies and R&D departments with a decision framework to assess the best applicable IP strategy to protect their market position. This framework assists both industry and R&D departments involved in MN R&D by protecting their inventions and evaluating project-licensing possibilities.

Background information

Intellectual Property Rights

Internationally recognized IP rights for protecting inventions include: trade secrets, copyrights, brands/trademarks, and patents (Table 1) (157). Despite their commonalities, each IP has its own rules and standards which differ between countries, based on the international standards published in the TRIPS agreement (183). Trade secrets are regarded as valuable information that is kept secret within a company because it provides an economic advantage over other companies. Obviously, the length of a trade secret’s lifespan is equal to the duration to which the

information is kept hidden from the competition, but the costs of keeping the secret can be very high (184).

Table 1. Summary of the different available IP methods and the use thereof (157, 185)

IP Method	Protection	Subject of protection	Scope of rights	Duration	Costs
Trade secret	Information that has commercial value to protect secrecy	Product formulas, chemical compounds, blueprints, dimensions, tolerances, customer lists, suppliers, financial information	Prevents disclosure or acquisition by dishonest means, or use of the secret information without permission	As long as information remains secret	None
Trademark	Identifying signs and symbols	Words, personal names, letters, numerals, figurative, elements, and combinations of colors, symbols or other devices used to distinguish goods or services	Excludes others from using the mark	Generally 10 years from registration, renewable indefinitely for additional 10 year terms	Low
Copyright	Original expressions of authorship	Works of authorship, including writings, books, papers, photographs, music, art, recording, software	Prevents others from reproducing or distributing copies; preparing derivative works; performing or displaying the work publicly; and transmitting sound recordings	At least 50 years from publication in US	None
Patent	Useful, new and non-obvious processes and products	Machines, articles of manufacture, and composition of matter, chemical compound, processes	Excludes others from making, using, selling, offering to sell, or importing the patented invention, as defined in claims issued in a particular country	20 years from filing of the patent application.	High

Copyright (©) protects work of authorship. These innovations are generally expressed in a tangible medium and can remain in the copyright domain for at least 50 years from publication. Trademarks (™) give the right to identify goods or services using that trademark and to exclude others from using it. A trademark lasts 10 years from registration and can be renewed for an additional 10 years (157). Lastly, a patent gives the inventor the right to exclude others from producing, using, selling, offering to sell, or importing the invention without permission and has a statutory duration of 20 years (157, 186). Within industrial patent strategies, an increasing event is the patent (application) lapse. The lapse of a patent right occurs when an official deadline has been missed (187, 188). When a patent (application) has lapsed, other companies are no longer able to apply for a similar patent since prior art has been created. Thus, a company may strategically apply the patent lapse to prevent competition from patenting the same invention.

Patents are not always effective and a number of studies have shown cases where patenting is ineffective (172, 173, 179). Therefore, if a company is willing to forgo patenting for mere freedom to operate, using copyright as defensive publishing is more attractive. More specifically, defensive publishing is the publication of an invention with the purpose of creating prior art. Thereby, preventing patents being granted for this specific invention (189).

Patent motives

The initial purpose of a patent is to provide companies with the exclusive right to commercialize a patented invention. However, in addition to their initial purpose to protect, patents can be employed in various other ways of which some are considered as strategic motives (160, 190, 191) (Table 2). These strategic motives are more important with respect to patenting-products than for -processes. Patent strategies can be categorized into two main types; offensive- and defensive blockage. Companies patent offensively to prevent other companies from using their inventions in the same, similar or related fields of application. As a result walls of patents can be built around the invention, not intended to be used, only to protect the actual invention also known as a patent thicket (160). Defensive blocking is patenting an invention to prevent other companies from patenting their inventions and suing it for infringement. Even if the company doesn't need the patent on this invention to receive a return for profit (191). In addition to these two motives, studies have demonstrated that additional strategic motives exist, including: to reward R&D personnel, generation of licensing income, to exchange potential (in,-out,- cross-licensing), international market extension, improve company value and image, and to prevent infringement lawsuits (173, 178). Over recent years, the patent has developed another important economic potential that is to use it as a marketing tool. Nowadays patents are being deployed as convincing devices for communicating a unique product innovation, setting it apart from other products in the market. Patents as a marketing tool are first and foremost used in patent product advertising, where patent numbers or claims such as "proprietary product" are used in a product advertisement (192).

A recent questionnaire by Blind et al. (160) analyzed the motives to patent and grouped the various motives in different clusters: 1. Protective motives: protection from imitation and safeguarding markets, 2. Blocking motives: blocking competitors defensively and offensively, 3. Reputation motives: improvement of technological image and increase in company value, 4. Exchange motives improved access to the capital market, exchange potential and licensing income and 5. Incentive motive: motivation of staff and internal performance indicator. More research on motives to patent has been conducted by the PatVal EU project on European inventors (193). This study shows that smaller companies more often license their patents to third parties, when compared to larger companies.

Motives not to patent

Some inventors regard their inventions as not patentable and there are several reasons that may lead companies to forgo patent protection. These motives are: Patent provides weak protection for that specific case; Product does not meet patent requirements; High costs of acquiring and enforcing a patent and fear of disclosing valuable trade secrets (181). Currently it remains unclear what the value of patenting holds for the MN market.

IP decision framework

In 2002, Daizadeh et al. propose a user-friendly approach for assessing the best overall legal and business strategy to protect a company's invention (194). This IP decision framework is tailored to companies operating within the biotechnology industry. Biotechnology also falls within the scope of the health and life sciences sector, but possesses other characteristics to those of the MN industry. An example is that the development of a product in the biotechnology industry usually revolves around a single-compound with a specific target whilst MN products are multi-target nutritional therapy products. Other differences are the lower profit margins in the MN industry and the mandatory clinical trials in biotechnology but not in MN product development. These differences all influence a lower applicability of Daizadeh's IP decision framework in the MN industry. In addition, Daizadeh et al. only take three possible IP methods into account: patent, trade secret and defensive publication. This framework excludes the possibility to utilize a trademark and patent lapse as an IP method. Therefore this IP decision framework can be used as a foundation for a MN specific IP decision framework and additional information gathered through extensive questionnaires will complete the framework.

6.2. MATERIALS AND METHODS

6.2.1. Questionnaire

Administration of the questionnaire

In this descriptive quantitative research, data was collected through an email questionnaire. Respondents were selected based on their employment position within the MN companies based in the EU and US. Ultimately, questionnaires were sent out industry wide to 14 relevant professionals working in a research and development,

intellectual property or management position. The questionnaire was created and distributed through the online web questionnaire program, SurveyMonkey. Follow-up emails and phone calls were used to increase response rates.

Questionnaire Design⁶

Taken that a firm's patent strategy is sensitive information, therefore data was collected through an anonymous online questionnaire. The questionnaire consisted of both open and closed questions. The questionnaire was built up of three parts. First, general questions concerning the use of IP methods within the MN industry were asked (3.1), then the motives to patent were examined (3.2&3.3), followed by questions concerning important factors in the decision to patent (3.4). The respondents were asked to provide information regarding their employing company's patenting strategies: the company's motives to patent (or not) and the relative importance of different IP methods. In the research by Blind et al. (160), the motives to patent were divided into various groups: protecting motives, blocking motives, reputation motives, exchange motives and incentive motives. 11 different motives to patent and 7 motives not to patent were introduced to the respondent in the questionnaire. For these questions, respondents were asked to rank the importance of these motives on a 5-point Likert scale (not relevant, to very important). A few questions required yes/no answers or percentages. For the majority of the questions, the respondents were asked to explain their answers in more detail. Table 3 summarizes the types of questions that were included in the questionnaire.

Analysis

By means of weighted ranking, the importance of the IP methods, motives to patent and motives not to patent are calculated (141). Each score was multiplied by the weight for the respective criterion (Very important = 5, Important, Not relevant = 1). The sum of these weighted scores divided by the number of respondents reflects the average weighted score. Since there are only a limited number of active MN companies, statistical analysis could not be performed to seek out any differences between SMEs and large MN companies. The results of this questionnaire therefore are a valid representation of the current MN market and are meant to provide an overview of the current situation.

IP decision framework

A MN industry specific IP decision framework was created by combining the questionnaire results and the existing general IP decision framework created by Daizadeh et al. (194). This MN industry specific IP strategy recommendation framework was developed with a 7-step approach. The most important factors according to the different MN companies derived from the questionnaire involved in their decisions to patent were included in the IP decision framework.

⁶ Sample questionnaire available upon request

6.3. RESULTS

The questionnaire generated a response rate of 71%. The final dataset consists of 10 MN companies, with 3 large companies and 7 small and medium enterprises (SMEs). The participating companies combined are responsible for the greatest share of the development and production of MN in Europe and the United States.

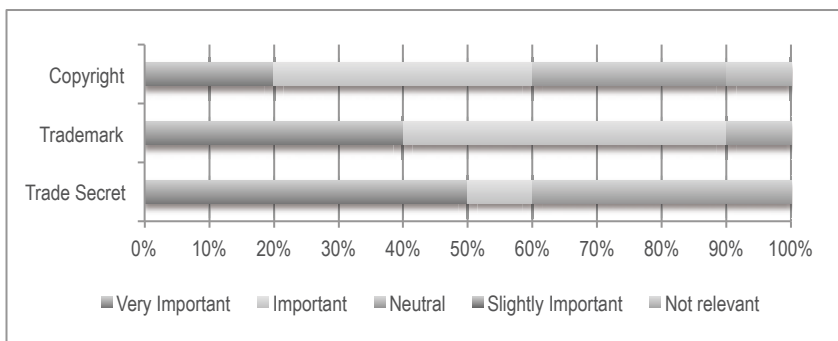
6.3.1. IP Rights

Results from the questionnaire indicate that 70% of all respondents believe patenting to be a necessary IP measure to protect a MN invention. In addition, 80% of the respondents have observed a dramatic increase in the importance of patenting in the MN industry in the past 10 years. This is confirmed by previous research demonstrating an increase in the number of patent applications in the EU MN industry (182). The respondents explain this increase in importance with a number of reasons. The main reason mentioned concerns the advances in knowledge that nutrients may even support the treatment of diseases in addition to only improving a patient's nutritional status. This enables the MN developer to file a patent for a nutritional composition in combination with a disease application. One of the respondents mentioned the following:

"The combination of specific nutrients with a disease application allow for IP filing and this is needed to protect products coming out the complex, time consuming and very costly R&D".

In addition to the importance of patenting for the MN companies, other IP rights are also considered to be of great value. By means of weighted ranking, the importance of each IP method is calculated. Each score was multiplied by the weight for the respective criterion. The sum of these weighted scores reflects the total weighted score of the IP method. In consecutive order: Trademark (average sum of ranks: 4,3), Trade secret (4,1) and Copyright (3,6) were ranked from most important to least important (Fig. 1). By means of a trademark, a product can be visually differentiated from the competitor to the consumer and is assessed as most important by the respondents. Trade secrets are employed by companies when a process or composition is difficult to be reverse engineered by the competition and thus can be kept a secret within the company. This is also perceived as an important IP method in the MN market. Copyright is perceived as the least relevant IP method in the MN market with only 20% of the respondents ranking it as very important.

Figure 1. The importance of applicable IP rights in the MN industry (5-point Likert scale: Very important – Not relevant)

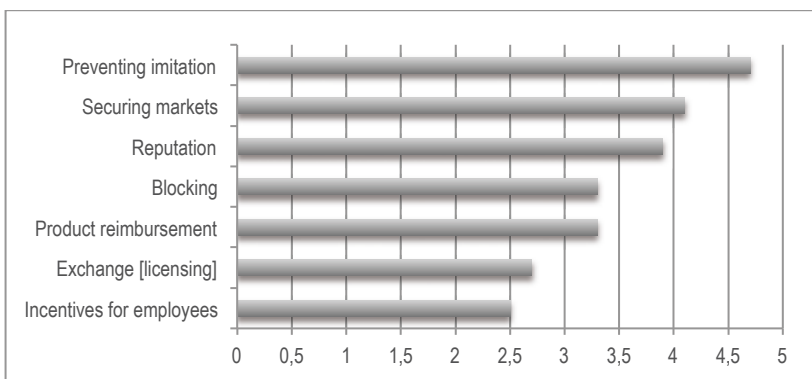


6.3.2. *Motives to patent*

7 different groups of motives to patent were introduced to the respondents and were asked to rate the importance of each motive for their company.

The two motives that are considered to be most important according to the MN companies are the prevention of imitation (Fig. 2) and the securing of international markets. These are both protective motives. Besides this intentional motivation of patent protection, further motives emerged to be of great importance; reputation and the blocking of competition were ranked as third and fourth most important. Motives considered to be less important in the decision to patent are: Granting for product reimbursement; Exchange motives and Incentives for employees.

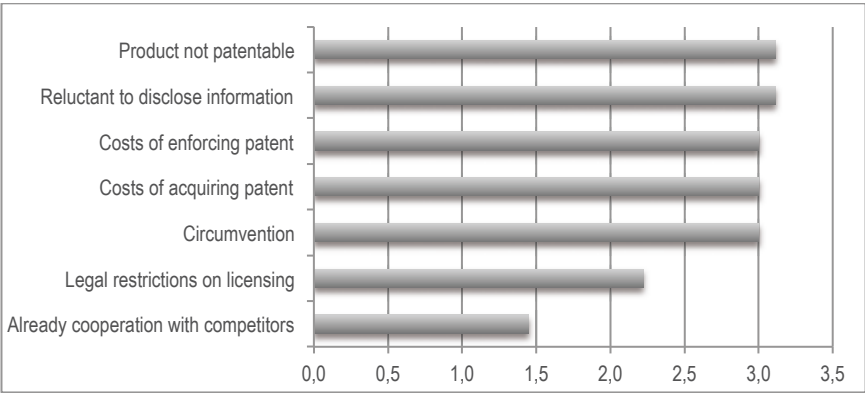
Figure 2. Ranking of importance of motives to patent in the medical nutrition market. X-axis depicts the average weighted score per motive.



6.3.3. *Motives not to patent*

There are also reasons to decide to forgo patenting and the MN companies were asked about their preference among a number of motives not to patent. The two most important reasons to forgo patenting for MN companies are that a product is not patentable and secondly that companies are reluctant to disclose information required for patenting (Fig. 3). These motives are closely followed by the motive that competitors could easily invent around a patent, the costs of enforcing and acquiring a patent. Motives considered to be less important in the decision to patent are: did not want to become subject to legal restrictions on licensing and already cooperation with competitors. Interesting to notice, mainly for SMEs the costs of acquiring and enforcing a patent is important compared to the large companies.

Figure 3. Ranking of importance of motives not to patent in the medical nutrition market. X-axis depicts the average weighted score per motive



6.3.4. *Factors involved in IP decision*

Several factors (A-D) resulted from the questionnaire to be important in the MN companies’ decision to patent and are discussed separately. These factors are integrated in the MN specific IP decision framework described in the final results section (3.5). The following factors are discussed due to data significance or surprising findings: A. clinical trials; B. return on investment (ROI); C. radical versus incremental inventions and D. patent type.

A. Clinical Trials

Since clinical trials are resource intensive, a company may choose to protect an invention with a higher investment by means of a patent (195). 80% of the MN companies agreed that clinical trials are important in their decision process whether

to patent a MN invention. The reasons were related to validation and efficacy of the product.

B. Return on investment

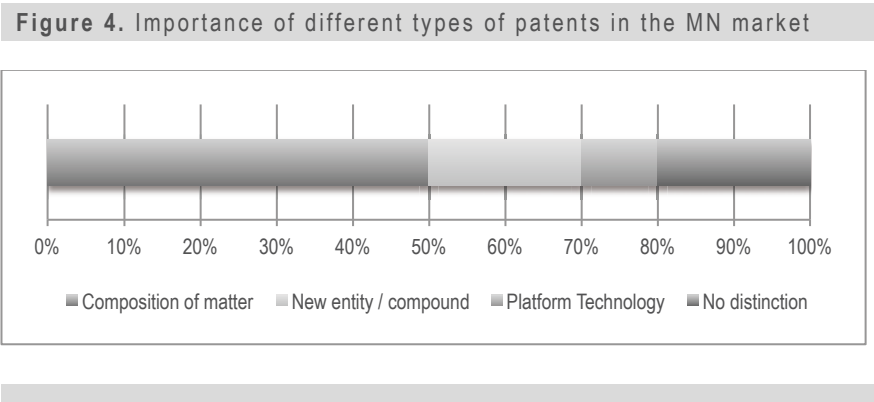
Innovations in the health and life sciences are lengthy and costly with almost 60% of patent life expired before market introduction. Therefore, knowledge of R&D and patent costs, and the expected revenue of the invention are important for analyzing the return on investment (ROI), a performance measure used to evaluate the efficiency of an investment (195). Resulting from the questionnaire, according to 80% of the MN companies, ROI is regarded as an important factor in the decision whether to patent or not.

C. Radical versus Incremental invention

Radical innovations are crucial in the development of a market but barely provide benefits if competitors are able to copy it with little or no extra cost. Radical innovation may be easier to protect from imitation than incremental innovation for the same reasons as a stand-alone innovation might be easier to protect than complex and interdependent innovation (196). In our study, 90% of the respondents more often patent radical inventions which are novel, unique creations and which have an influence on future technology compared to incremental inventions, which are current inventions that are renewed, adjusted, modified and/or improved.

D. Type of patent

Generally, three different types of health and life science patents exist: *Composition of Matter*; *New Chemical Entity (NCE)* and *Platform Technology*. The MN companies were asked to choose between these three patent choices or whether no distinction was made. Composition of matter patents relate to the nutritional composition of a product and include mixtures of ingredients (Fig. 4). 50% of the MN respondents selected composition of matter to be the most important factor involved in the decision to patent. A considerably lower number of respondents (10%) preferred to patent a platform technology, a generic technology that can be used in several applications.



6.3.5. IP Decision Framework

By combining the results of the questionnaire sent to the MN companies, with Daizadeh's IP decision framework, and rational argumentation, we designed the following MN IP decision framework (Fig. 5) (194). Choosing an IP method to protect MN inventions requires the consideration of multiple variables. The decision whether to apply for a patent, a trade secret, trade mark, defensive publication or patent lapse depends on various factors. These various factors have to be taken into account by the MN companies in their decision to patent, since a wrong choice can have a significant impact on a company's market position. The factors that have been proven to be important in the companies' decision to patent as a result from the questionnaire (3.4) are integrated in this MN specific IP decision framework. The framework consists of a 7-step approach (Fig. 5) based on Daizadeh (197).

Step 1: Radical Invention. The first step that has to be taken into account is whether an invention is considered to be radical. Since radical inventions are rare and involve high development costs and have the possibility to change the industry a particular type of IP protection is necessary (196).

Step 2: Easily Circumvented. In this step the companies ask the question whether or not a competitor can easily apply for a similar patent thereby circumventing the other patent in the process. Respondents stated that in the MN market granted claims are often very narrow and therefore circumvention can be quite easy. In addition, Allowed claims normally require specific formulations or disease states, it is easy for competitors to commercialize products without licensing patents. To avoid being circumvented, a thicket of similar patents can be built around a patented invention to block competition.

Step 3: IP amenable to reverse engineering. The third step to be taken in the decision framework concerns the simplicity of reverse engineering the invention. If an invention product cannot be easily reverse engineered it may be valuable to forgo patenting and to choose a trade secret. However, if an MN product can be easily reversed then a defensive publication or a patent application followed by a patent lapse is advisable.

Step 4: Costly clinical trials or high development costs. For the development of an MN product, clinical trials are important for validation and to prove efficacy. The development of an MN product may be very costly and the associated costs have to be taken into account when choosing a proper IP method.

Step 5: expected return on investment. An important step in this framework is the expected return on investment. The return on investment concerns the amount of money invested in the development of the product against the expected revenue of the product. If the market revenues are low in comparison to the development costs, it is advisable to protect the product by a trade secret or defensive publication since the costs of a patent may be too high in comparison. When an invention cannot be protected by a trade secret than defensive publication is advisable. The advantage of defensive publication is that patents cannot be granted on this specific invention by competitors described in the publication. A respondent argued that especially in the MN industry the profit margins for products are slim, and thus with a low ROI and therefore not worth patenting in some cases. In these cases, a defensive publication may be the solution.

Step 6: Complicated platform technology. A complicated platform technology is a technology that can be used in several applications. It is the fundamental science behind a lot of products within the MN market and is therefore very important to patent. In addition, companies can also choose to opt for a trade secret, especially when it is difficult for competitors to unravel a platform technology.

Step 7: Unique composition of matter. The composition of matter relates to chemical compositions and may include mixtures of ingredients. For MN products it is difficult to get a patent on a composition of matter, since MN products are often composed of naturally derived food substances and not a new chemical entity such as in the pharmaceutical industry. However, respondents stated that composition of matter provides the broadest protection and that it is most easily defended. Therefore, with a unique composition of matter a company is also advised to patent and/or to apply for a product trademark.

Intellectual Property
Decision Model

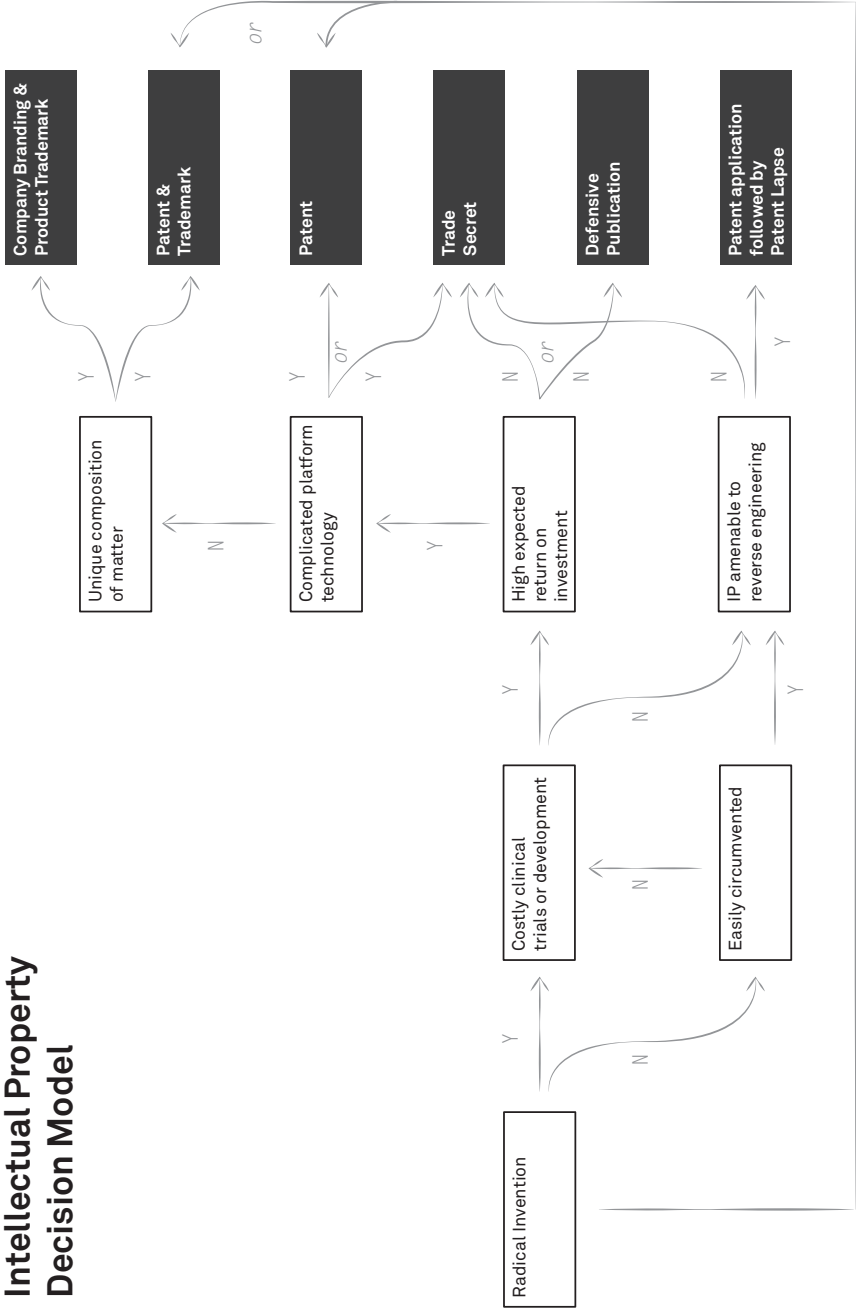


Figure 5. IP decision framework

6.4. DISCUSSION & CONCLUSIONS

In today's R&D driven world, it is the IP portfolio that makes or breaks a company's commercial success. In the newly emerging MN market, there is a pressing need for assessing the suitability of IP protection strategies. This paper not only provides insights into the relevance of various IP methods for MN companies, but also offers a method for assessing a suitable IP strategy. Our IP decision framework facilitates clear-cut decisions regarding the strategy of protecting IP. Furthermore, IP methods should be applied in a proactive way in the MN industry to protect MN innovations and in doing so maintain a competitive niche. As our findings acknowledge; applying different IP methods is perceived by the questionnaire respondents as essential to protect a MN innovation.

Although patents are considered valuable instruments for protecting innovations in the health and life science industry, there are also many reasons to forgo patenting. The most important motive not to patent in the MN market is that certain MN products are simply unpatentable. This argument supports the choice by some MN companies to apply alternative IP protection strategies, such as trademark, trade secret and/or copyright. Especially trademarks are considered to be an indispensable IP method due to their ability to visually differentiate a company's product from a competitor directly to the customer. Trade secrets also proved to be considered by questionnaire respondents as important in the MN market, however there are limitations. Trade secrets as a form of IP can only be applied if reverse engineering by competitors is considered close to impossible. It is therefore recommended that companies operating in the MN industry should always look beyond the boundary of the patent and carefully assess if any other relevant IP methods are applicable.

Additionally, SMEs indicate that the cost for both filing and enforcing a patent, are important motives to consider alternative IP methods. Previous literature confirms this perceived cost-sensitivity of SME firms (179). The most logical explanation for this phenomenon is that SMEs have a lower budget available for the development of a product in comparison to large multinationals. However, SMEs should be aware that the presence of patents in the IP portfolio increases company value, which is favorable for both attracting investors and increasing the likelihood for acquisition or alliance with other/larger companies (169).

When it comes to patenting, previous research has indicated that patenting behavior differs between companies within the MN industry (182). Even though there are many different strategic motives to apply for a patent in the MN market, the protective motive of preventing imitation proves to be most important. This confirms that the original rationale behind the patent system continues to fulfill its purpose within the MN market (198). This motive is closely followed by the motives for securing foreign markets and enhancing company reputation. Especially in the health and life sciences, a sector that revolves around high-tech state-of-the-art technologies, a company's technological reputation is valuable. In other words; a company's technological reputation can distinguish it from competition.

The type of patent that has proven to be particularly relevant in the MN market is the *composition of matter* patent. Although the pharmaceutical and MN products are

both developed for patients with specific disease conditions, the products differ on many levels. The main difference revolves around the way the product is built-up; a pharmaceutical product is usually based on a new single-compound entity while a MN product usually describes a combination of existing nutrients. Since most patented inventions in the pharmaceutical industry are *single-compound entities* (199), we expected most MN patents to concern the nutritional compositions. This holds true for the MN market, where 50% of the MN companies stated to file for *composition of matter* patents, in which the nutritional composition of a MN product is patented. The disadvantage of this type of patent is that it does not always offer very broad protection.. This may explain why one of the most important motives not to patent is that companies are reluctant to publically disclose information about the invention. By providing this information, the fear exists that competitors may be able to incrementally adjust the originally patented invention, thereby circumventing the patent.

Additional factors that are specifically associated with the patenting behavior of MN companies include; reimbursement granting, the use of a patent as a marketing tool, involvement of clinical trials, ROI, and invention radicalness. Since these factors proved to be important within this market, they were integrated in the IP decision framework. Reimbursement granting is perceived as a factor influencing the patent decision process, most likely due to regulatory demands.. Certain national competent authorities require a MN invention to be patented before it is eligible for reimbursement and market entry [interviews KOLs]. Patents may also be deployed as a marketing tool (192) by labeling MN products as a “proprietary product” or “patent pending” in product brochures, for example. In the view that MN products are directed towards healthcare professionals, who understand the significance of patents, such labels prove to be valuable in advertising campaigns. However, healthcare professionals should be aware that in some cases MN companies may already advertise with a “proprietary product” with only a pending patent application.

In comparison to the pharmaceutical and biotechnology industry where clinical trials are mandatory, the R&D process of a MN product does not have to include clinical trials unless you want to assign a certain claim to your product or its effectiveness. Therefore the execution of clinical trials also affects the decision to patent since clinical trials are associated with higher development costs. If a MN company decides to perform clinical trials to determine the effectiveness of a MN product with the corresponding costs, they may do wise to also invest in the filing of a patent. This offers a temporary monopoly in order to ensure the protection and profitability of the high-investment invention from competition especially if the invention has a high expected ROI. ROI is therefore also an additional decision factor in the MN specific IP decision framework. The final characteristic that influences the patent decision process is the radicalness of the invention. Even though the chance of successfully developing a radical invention is distinctly lower than an incremental invention, the ROI of radical innovations are generally significantly higher (200). Since radical innovations are novel, unique creations that can influence future development, a company will set itself apart from competition and will be especially driven to protect such an innovation.

There are a few limitations to this study. First, a relatively small sample of MN companies participated in this study. However, since there are a limited number of MN companies, these represent a large share of the industry. In addition, it is a young and developing market and therefore representative for the MN industry. A drawback of the questionnaire analysis method is that it suffers from inter-respondent variation. For example, a response of 'very important' for one respondent could be equal to a response of 'important' for another respondent (172).

The above discussion shows that many complex factors determine the decision about whether or not to protect a particular MN invention and selecting the appropriate IP strategy. The data summarizes the most important factors affecting the decision of a MN company or academic institution seeking IP protection. In the IP decision framework, some of the factors affecting the decision in choosing the appropriate IP strategy are standard variables while others are specific to the MN market. Although the decision framework can be used as a general roadmap evaluating the appropriate protection; it cannot answer all in-depth business questions. Nevertheless, the decision on the type of protection is dependent on the nature of the innovation and the economics of commercialization. Each invention requires a careful assessment of whether the total benefits, either economic and/or intangible/societal, exceed the total cost of the protection.

By using this MN decision framework, one can consider the different options available, whether to use the acquired knowledge themselves or to transfer the knowledge or invention (e.g. by means of out-licensing). Such an assessment is highly complex and unique for every invention.

With this research we have made an attempt to simplify the complexity of the IP strategy decision by means of a MN specific IP decision framework. The framework serves as a tool to assist both industry and academic R&D departments in making clear-cut decisions on the most applicable IP method. The proposed IP decision framework can benefit further from additional research, by assessing its value in the practical setting.

CHAPTER 7

PATIENT NEEDS AND RESEARCH PRIORITIES IN THE ENTERAL NUTRITION MARKET – A QUANTITATIVE PRIORITIZATION ANALYSIS

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ABSTRACT

A quantitative systematic identification and prioritization of unmet needs and research opportunities in relation to enteral nutrition was conducted by means of a tailor-made health research prioritization process.

The research objectives were reached by conducting qualitative interviews followed by quantitative questionnaires targeting enteral nutrition key opinion leaders (KOLs). (1) Define disease areas that deserve more research attention; (2) Rank importance of product characteristics of tube feeding (TF) and oral nutritional supplements (ONS); (3) Assess involvement of KOLs in enteral nutrition R&D process. KOLs ranked three product characteristics and three disease areas that deserve additional research attention. From these, overall priority scores were calculated by multiplying ranks for both product characteristics and disease areas.

17 qualitative interviews were conducted and 77 questionnaires (response rate 35%) were completed and returned. (1) Disease areas in ONS and TF with highest priorities are: ONS: *general malnutrition & geriatrics*, TF: *intensive care*. (2) TF product characteristics with highest priorities are: composition and clinical evidence from a KOL perspective; tolerance and ease of use from a patient perspective. ONS product characteristics with highest priorities are: composition, clinical evidence and taste from a KOL perspective; taste from a patient perspective. We find a high discrepancy between product characteristic prioritization from a KOL and patient perspective. (3) Although 62% of all KOLs give advice to enteral nutrition companies on patient needs, they under-influence the setting of research priorities by enteral nutrition companies.

This study provides a systematic approach to achieve research prioritization in enteral nutrition. In addition to providing new directions for enteral nutrition research and development, this study highlights the relevance of involving KOLs in the identification of research priorities as they have the ability to provide a balanced view of the unmet patient needs.

7.1. INTRODUCTION

The health and life science industry, which is an important driver of the health care sector, revolves around addressing unmet medical needs. A medical need is defined as the fundamentals required to sustain a healthy individual (201). To achieve optimal health services, policies and strategies from a public health perspective but also from a health care industry perspective, it is necessary to identify and prioritize medical needs, thereby functioning as the basis for research priorities. Unfortunately, there is limited knowledge of patient needs and priorities. As a result, there is often a mismatch between research driven by the interests of scientists, funders and powerful interest groups and the health needs of the population.

The enteral nutrition (EN) market targets patients that require nutritional support to prevent or treat malnutrition or alleviate and manage symptoms of specific medical conditions. Through advancements in the fundamental knowledge of human bodily functions, a wide range of EN products are now available for several (previously unmet) medical needs/conditions. These products are prescribed by medical professionals for the nutritional support of patients in the dietary management of diseases. With 33 million people at risk of malnutrition throughout Europe, the development of specific and targeted EN products is crucial (153). Although awareness concerning the importance and effectiveness of EN is growing (33), there are still numerous unmet medical needs that need to be addressed, at the interface between pharma and food, by the EN industry.

Unmet medical needs can be fulfilled through 'market pull' strategy, where the unmet medical need functions as the innovation opportunity input. The first step is to assess these unmet medical needs by means of a so-called needs assessment. This allows for the accurate evaluation of health related patient needs and may eventually function as innovation opportunity input for the EN industry (202, 203). The assessment of patient needs leads to the understanding of patient experiences and addresses which needs should be prioritized to improve the quality of care (204, 205). The identification of patient needs is an essential success factor in the complex process of product development and innovation (206-208). Products are more likely to be successful when built around customer needs as opposed to only addressing technological opportunities (206). Need assessment can be performed by means of health research prioritization (HRP) and may provide directions for future resource allocation and strategic planning at institutional, regional, national as well as international level (209).

Although, during the past decades, an unprecedented number of innovations have had great clinical impact on the prevalence and treatment of disease-related malnutrition, an overview of unmet patient needs with priorities is lacking within the EN market. Considering the widespread prevalence and adverse consequences of malnutrition and the effectiveness of EN, such an overview would contribute to both fulfilling the unmet patient needs as well as the exploitation of commercial innovation opportunities (34). Therefore, the aim of this research was to assess unmet patient needs and research priorities in the EN market by means of quantitative questionnaires targeting EN key opinion leaders (KOLs).

Health Research Prioritization

HRP processes assist researchers, policymakers and industry in effectively targeting research that is needed most (210). In addition, HRP stimulates to evaluate health research and to identify its strengths, weaknesses, gaps and opportunities (211). Setting successful research priorities is complex, because choosing between priorities creates ethical equipoise (212). Nevertheless, the efficacy of setting prioritization has previously been demonstrated by various research groups (211, 213, 214). The aim of prioritization is to develop a relative ranking list rather than to define an absolute cut-off beyond which diseases are not considered important (215).

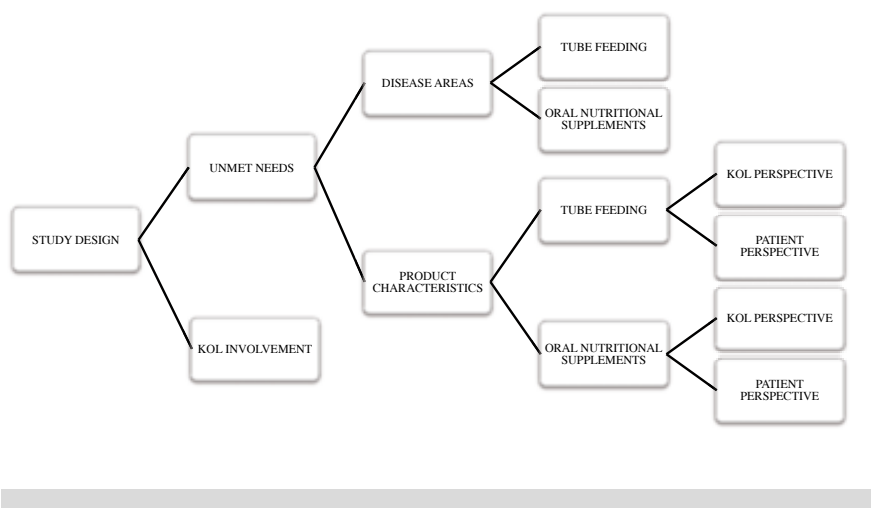
Several extensively tested and comprehensive approaches to HRP are available to guide researchers in setting their research priorities (210, 216). Nevertheless, it has proven impossible to set a golden standard/best practice in HRP since the context of priority setting varies per case (210). Therefore, researchers develop their own unique research prioritization method based on an existing HRP method but adapted to their subject and research goal. A tailored prioritization was developed for this research to rank patient needs in the EN market in order to uncover research priority insights and innovation opportunities. EN patient needs exist at different levels. Our focus lies on assessing which disease areas require research attention but also which product characteristics require improvement. The research methodology was predominantly based on a prioritization research described by Balabanova et al. who developed a prioritization method to establish strategic priorities for the German national public health institute concerning infectious pathogens (209). Their research solely focused on the prioritization of infectious diseases in Germany. In our research, this method was extended by prioritizing both EN related disease areas but also the EN product characteristics. The aim of the research described here was to identify and prioritize unmet patient needs (disease areas and product characteristics) and research opportunities in the EN market by means of quantitative questionnaires targeting EN KOLs. This research also aimed to evaluate the opinions of the KOLs on their current involvement in EN research and research prioritization efforts. The objectives of this research are as follows:

1. To determine the unmet needs and research priorities in the EN market by means of health research prioritization:
 - 1.1 To assess the disease areas that require more research attention in the EN market;
 - 1.2 To assess which product characteristics have the highest priority in EN development.
2. To evaluate the degree of involvement of KOLs in the EN R&D process from a KOL perspective.

7.2.METHODOLOGY

The prioritization process was based on previously used prioritization methods (209, 210) and adapted to assess EN unmet patient needs and research priorities. The multi-staged prioritization process started with the compilation of a list of disease areas and product characteristics of EN by means of qualitative exploratory interviews. This was followed by the development of evaluation criteria, weighting of the criteria and ranking of the disease areas and product characteristics by means of an online questionnaire (209). This research also aimed to evaluate the opinions of the KOLs on their current involvement in EN research and research prioritization efforts.

Figure 1. Research framework



7.2.1. Study subject

Since patients do not have direct experience with more than a subset of innovations and generally only one disease area, KOLs were approached. Two-hundred-twenty KOLs with extensive EN knowledge (practicing MD, dieticians, nurses, researchers, professors, lecturers, and consultants) of the European Society for Clinical Nutrition (ESPEN) faculty were invited to participate in an email-survey. The aim of the survey was to investigate patient needs in the EN market. The anonymous online survey was created and distributed through the online web survey program SurveyMonkey. KOLs that did not respond to the initial survey received a follow up reminder e-mail 1.5 weeks later to increase response rates.

7.2.2. Exploratory interviews

A set of questions was pretested by means of 17 exploratory pilot interviews with KOLs, in order to validate the survey tool as well as the possible answers to the

questions. By means of saturation curves all possible answers were ensured. Saturation was reached after 17 interviews. This procedure was intended to increase content validity of the survey.

7.2.3. Survey design & analysis

The survey consisted mainly of closed questions with a few open questions for gathering in-depth insights. The demographic information of the respondents was collected and included: title, profession, age, country of residence and department. Thirty-four questions were divided into two sections: unmet needs (disease areas & product characteristics; and current KOL involvement in research prioritization (Figure 1). Both tube feeding (TF) as well as oral nutritional supplements (ONS) were taken into account in this study. A copy of the survey is available on request.

7.2.4. Unmet need prioritization – Disease areas

The KOLs were asked to answer 10 closed questions on the topic of unmet needs for TF and ONS. In the section concerning disease areas, respondents were presented 13 disease areas and were asked to rank the 3 disease areas according to their assessment of whether these disease areas require or deserve to be investigated more thoroughly (1 being highest priority). The ranking is multiplied by the weight of the respective criterion, e.g. 1 being the highest ranking, receives a weight of 3. The higher the sum of these weighted scores reflects the higher unmet need prioritization. The total weighted scores were finally re-scaled to a range from 1-100 in order to facilitate final interpretation (209). Two cut-off points were applied to assign the re-scaled weighted scores into three priority groups: 0-33 – low priority; 34-66 – medium priority; 67-100 – high priority (209).

7.2.5. Unmet need prioritization – Product characteristics

In the category concerning product characteristic priorities the respondents were presented with 11 product characteristics and were asked to rank the 3 most important product characteristics ranging 1-3 (1 being highest priority). The KOLs were asked to rank the importance and improvement priority of the product characteristics. In addition, they were asked to rank the product characteristics from their perspective as well as from the patients' perspective. This was done to measure a possible discrepancy in the ranking of the unmet product needs between the KOL and patient perspective. To ensure ranking validity in our research, a single response group prioritized the product characteristics both from a patient and KOL perspective. The rank 1 reflects the highest, and 3 the lowest level of importance of a criterion. The ranking methodology is identical to the one applied to the disease area prioritization (section 2.3.1).

In the applied methodology, we followed the principles of good practice in health research priority setting (209, 210). We reached a proper level of objectivity and transparency by integrating the following components: (1) Involvement of a broad range of external experts with the extensive knowledge in the area of EN, (2) the compilation of a list of disease areas, product characteristics and content characteristics of EN by means of qualitative exploratory interviews, (3) weighting of the criteria and ranking of the disease areas and product characteristics.

7.2.6. KOL involvement

Twelve questions were asked to assess current KOL involvement in patient need prioritization. It was assessed what percentage of KOLs are involved in the different stages of R&D by means of 4 closed dichotomous questions. Their opinion on the degree of their involvement was measured by means of a 5-item Likert scale (not at all, a little, a moderate amount, very much, an extreme amount). Each item on the Likert scale was appointed a value; the mean of these values represents the degree of KOL involvement. KOLs were asked to assess their involvement both in the R&D process of products in academic setting as well as their involvement in R&D process in industry setting.

To assess the difference in KOL involvement in industry setting and academia setting, the Wilcoxon signed rank test of non-parametric data was applied. This test is used to compare matched samples, repeated measurements on a single sample, or in this case, two related samples to assess whether their population mean ranks differ. A *P*-value <0.05 was considered to be statistically significant. Statistical analyses were performed using a statistical package program (SPSS, Version 20.0).

7.2.7. Statistical analysis between groups

Total results were analyzed and differences between respondent groups according to demographic characteristics were analyzed. The respondents were grouped according to two demographic characteristics: age (25-55; and 55 and up); and geographic regions (Northern Europe; Southern Europe; Eastern Europe; and Outside Europe). To assess differences between groups in unmet need prioritization, the Mann-Whitney U Test and Kruskal-Wallis analysis were applied (Table 1) In the KOL involvement section, the demographic groups were compared by means of the Chi-squared test for the dichotomous questions and the T-test for the Likert scale questions (Table 1). A *P*-value <0.05 was considered to be statistically significant. Statistical analyses were performed using the statistical program SPSS, Version 20.0.

Table 1. Statistical analysis between groups

Survey section	Age groups		Geographic characteristics
<u>Unmet needs:</u>			
<div><div>- Disease area ranking</div><div>- Product characteristic ranking</div></div>	Mann-Whitney U Test (two samples)		Kruskal-Wallis one-way analysis of variance by ranks (more than two samples)
<u>KOL involvement:</u>			
<div><div>- Dichotomous questions</div><div>- Likert questions</div></div>	scale	Chi-squared test T-test	Chi-squared test T-test

7.3. RESULTS

7.3.1. Demographic characteristics of the sample

A response rate of 35% was reached, seven cases failed to complete the questionnaires, leaving 77 respondents with valid data received from 27 different countries. The demographic characteristics of the respondents were as follows: 53% between 25-55yrs and 47% ≥55yrs. The majority of participants fulfilled a position as practicing MD (41%), followed by Professor (32%) and Consultant (11%).

7.3.2. Disease area priorities

The 13 disease areas identified in prior exploratory interviews were presented to the participants. The respondents were asked to rank the three disease areas according to their assessment of these disease areas requiring or deserving to be investigated more thoroughly. The disease areas that received the highest research priority in ONS are (1) General malnutrition and (2) Geriatrics followed by (3) Non-surgical oncology and (4) Surgery & transplantation as medium priorities. The disease area ranked as most important in TF is (1) Intensive care, followed by (2) General malnutrition and (3) Surgery & transplantation as medium priorities. Figure 2 presents the ranking of the diseases according to their weighted total score into three priority groups for ONS and TF.

Figure 2. Disease area ranking according to weighted scores for ONS and TF. Three priority groups: Low: 0-33; Medium: 34-66; High: 67-100

	ORAL NUTRITIONAL SUPPLEMENTS		TUBE FEEDING	
	DISEASE AREA	RELATIVE RANKING	DISEASE AREA	RELATIVE RANKING
100	General malnutrition	100	Intensive care	100
	Geriatrics	93.2		
66	Non-surgical oncology	54.7	General malnutrition	62.8
	Surgery & transplantation	34.2	Surgery & transplantation	61.2
33	Gastroenterology	30.8	Gastroenterology	33.3
	Intensive care	15.4	Non-surgical oncology	27.9
	Renal failure	15.4	Geriatrics	27.1
	Pulmonary	12.8	Pulmonary	14.7
	Cardiology	10.3	Cognitive	10.9
	Hepatology	10.3	Cardiology	9.3
	Cognitive	7.7	Metabolic	4.7
	Metabolic	6.8	Hepatology	3.9
	Infectious diseases	3.4	Infectious diseases	1.6
0			Renal failure	0.8

7.3.3. Product characteristic priorities in ONS and TF

From a KOL perspective, the following TF product characteristics were ranked as most important: (1) Composition and (2) Clinical evidence, followed by (3) Tolerance. The TF product characteristics that need to be improved from a KOL perspective are: (1) Composition; (2) Clinical evidence; followed by (3) Tolerance; and (4) Price. The product characteristics, which from a patient perspective, were ranked as most important in TF, are: (1) Tolerance and (2) Ease of use, followed by (3) Price. Similarly, the TF product characteristics that need to be improved from a patient perspective are: (1) Tolerance; (2) Ease of use; followed by (3) Price. Table 2 shows the TF product characteristic ranking results both from a KOL as well as patient perspective.

Table 2. TF product characteristic weighted ranking from a KOL and patient perspective

TUBE FEEDING				
	KOL PERSPECTIVE		PATIENT PERSPECTIVE	
	Important	To be improved	Important	To be improved
Composition	100	100	18,1	30
Clinical evidence	69,5	96,6	16	31,7
Tolerance	56,3	62,2	100	100
Caloric density	24,5	25,2	3,5	9,2
Ease of use	18,5	22,7	69,4	72,5
Price	18,5	42,9	42,4	60,8
Volume	9,3	11,8	24,3	22,5
Taste	4,6	13,4	16,7	20
Viscosity	4	7,6	4,9	6,7
Shelf life	0,7	3,4	8,3	6,7
Smell	0	2,5	17,4	25

The product characteristic that is considered to be most important according to the KOLs in ONS is (1) Composition, followed by (2) Clinical evidence, (3) Taste, (4) Tolerance and (5) Price. The Dproduct characteristics that need to be improved according to the KOLs in ONS are (1) Clinical evidence and (2) Taste. From a patient perspective, the product characteristics that were ranked as most important in ONS were (1) Taste, followed by (2) Price and (3) Tolerance. Table 3 shows the TF product characteristic ranking results both from a KOL as well as patient perspective.

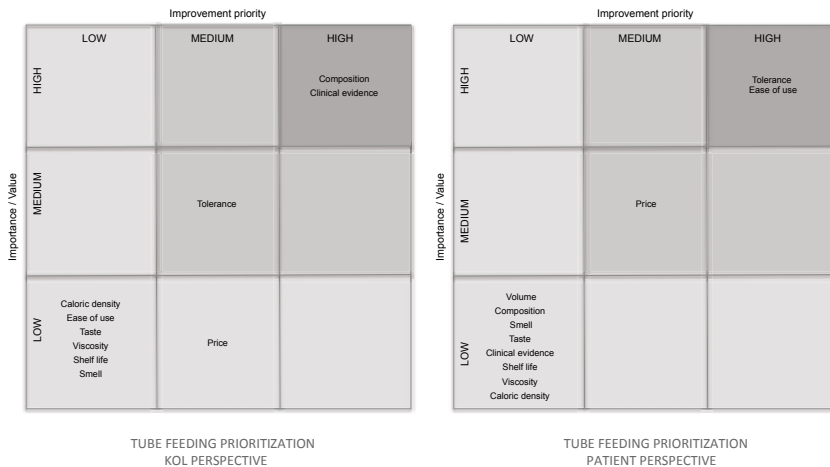
Table 3. ONS product characteristic weighted ranking from a KOL and patient perspective

	ORAL NUTRITIONAL SUPPLEMENTS			
	KOL PERSPECTIVE		PATIENT PERSPECTIVE	
	Important	To be improved	Important	To be improved
Composition	100	61,9	6,8	7
Clinical evidence	65,9	100	2,5	12
Tolerance	43,7	48,6	43,2	41,1
Caloric density	27	13,3	4,3	3,8
Ease of use	11,9	21,9	28,4	19,6
Price	34,9	59	47,5	46,2
Volume	14,3	15,2	19,8	14,6
Taste	57,1	92,4	100	100
Viscosity	1,6	0	2,5	4,4
Shelf life	0	4,8	1,9	3,8
Smell	10,3	22,9	28,4	39,9

7.3.4. Tube feeding priority matrices

The TF product characteristic results were combined and visualized in the product characteristic priority matrices (Figure 3). The left matrix gives a representation of the TF prioritization from a KOL perspective, while the right matrix represents the patient perspective as ranked by the KOLs. The x-axis of the chart depicts the need for product characteristic improvement and the y-axis the importance of the specific product characteristic. The product characteristics situated in the upper right quadrant are those assigned to the *high* priority group (dark grey shading). The three surrounding quadrants represent the *medium* priority group (medium grey shading). The remaining five quadrants represent the *low* priority group (light grey shading).

Figure 3. TF product characteristic priority matrix – Left: KOL perspective; Right: Patient perspective



KOL perspective

The TF priority matrix indicates *composition* and *clinical evidence* to be most important to be improved from a KOL perspective. *Tolerance* is assigned to the medium priority group. The majority of the product characteristics is assigned to the low TF priority group. Those being: *price*; *caloric density*; *ease of use*; *taste*; *viscosity*; *shelf life*; and *smell*.

Patient perspective

From a patient perspective, the product characteristics assigned to the high priority group are *tolerance* and *ease of use*. *Price* is assigned to the medium priority group. Again, most product characteristics are assigned to the low TF priority group, in this case from a patient perspective. Those being: *volume*; *composition*; *smell*; *taste*; *clinical evidence*; *shelf life*; *viscosity*; and *viscosity*.

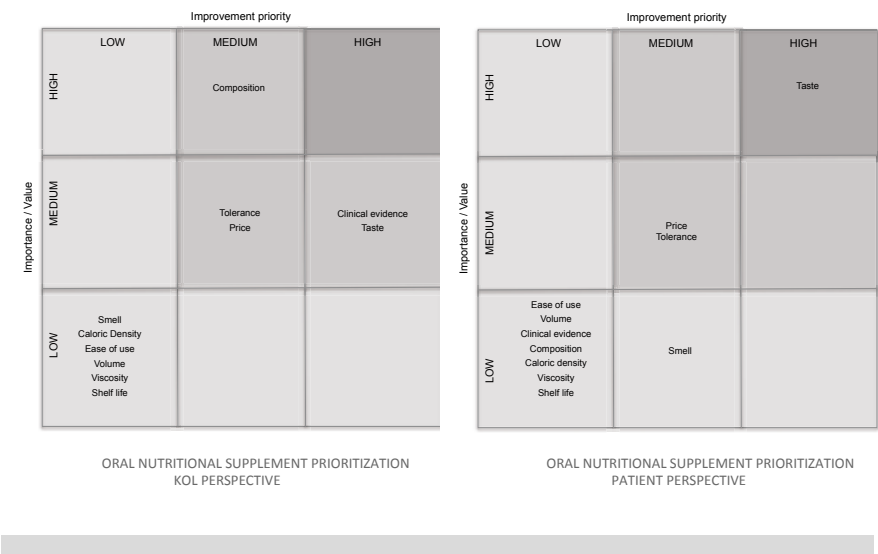
KOL perspective versus Patient perspective

When focusing on the medium- and high-quadrants within the priority matrix, the results show that none of the TF product characteristics are ranked equivalently from the patient as well as from the KOL perspective. These results indicate a clear discrepancy between the prioritization of product characteristic from a KOL and patient perspective.

7.3.5. Oral nutritional supplement priority matrices

Identical to the TF results, the ONS results were combined and visualized in the product characteristic improvement priority matrices (Figure 4). The left matrix gives a representation of the ONS prioritization from a KOL perspective, while the right matrix represents the patient perspective as ranked by the KOLs. The x-axis of the chart depicts the need for product characteristic improvement and the y-axis the importance of the specific product characteristic. The product characteristics situated in the upper right quadrant are those assigned to the *high* priority group (dark grey shading). The three surrounding quadrants represent the *medium* priority group (medium grey shading). The remaining five quadrants represent the *low* priority group (light grey shading).

Figure 4. ONS product characteristic priority matrix – Left: KOL perspective; Right: Patient perspective



KOL perspective

Notable, none of the ONS product characteristics are assigned to the high priority group from a KOL perspective. The product characteristics allocated to the medium priority group are: *composition*; *tolerance*; *price*; *clinical evidence*; and *taste*. The majority of the disease areas is assigned to the low priority group. Those being: *smell*; *caloric density*; *ease of use*; *volume*; *viscosity*; and *shelf life*.

Patient perspective

The ONS priority matrix depicts *Taste* to be most important to be improved from a patient perspective. The product characteristics with a medium improvement priority are *price* and *tolerance*. Again, the majority of the disease areas is assigned to the low priority group. Those being: *smell*; *ease of use*; *volume*; *clinical evidence*; *composition*; *caloric density*; *viscosity* and *shelf life*.

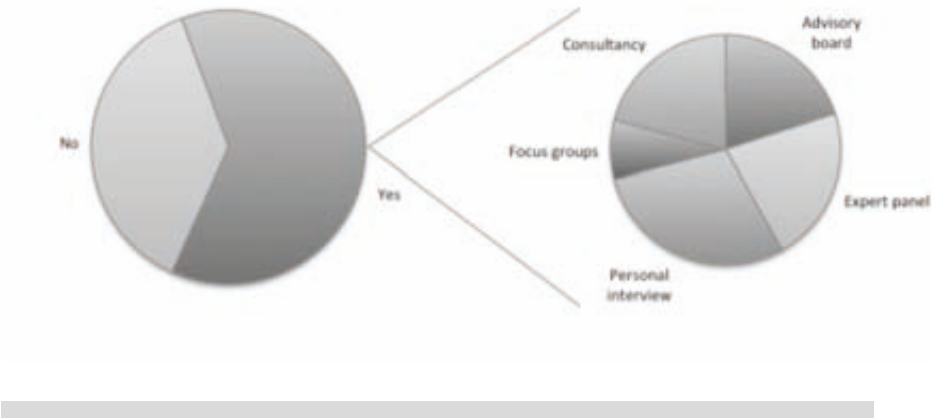
KOL perspective versus Patient perspective

When focusing on the medium- and high-quadrants within the priority matrix, the results show that only two - price and tolerance - for ONS are ranked equivalently from the patient as well as from the KOL perspective. These results indicate a clear discrepancy between the prioritization of product characteristic from a KOL and patient perspective.

7.3.6. KOL involvement in the EN R&D process

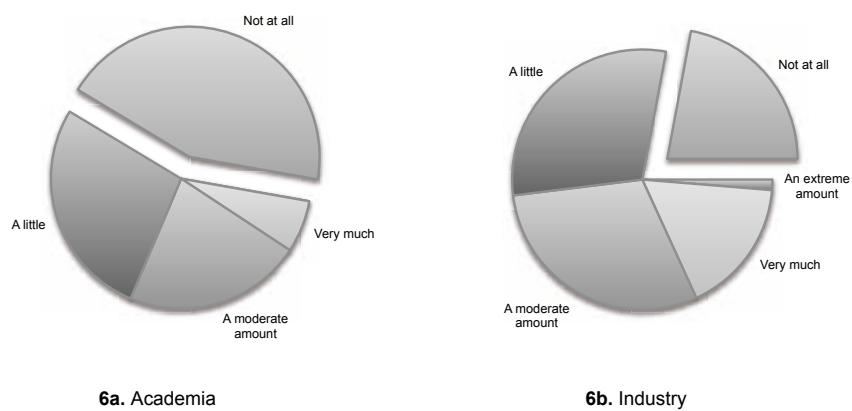
Results from the questionnaire indicate that unmet needs in EN are widely researched by 91% of the respondents. Unmet patient needs were investigated in most cases by direct contact with the patients (78%), followed by participating in research programs (61%) and questionnaires (40%). The majority of the respondents (62%) advise EN companies concerning patient needs, with personal interviews being the preferred route of communication between the KOLs and industry (Figure 5).

Figure 5. Majority (62%) of the KOLs advise EN companies on the topic of EN patient needs. Most KOLs give advice through personal interviews (65%), expert panels (49%), consults (47%) and advisory boards (45%).



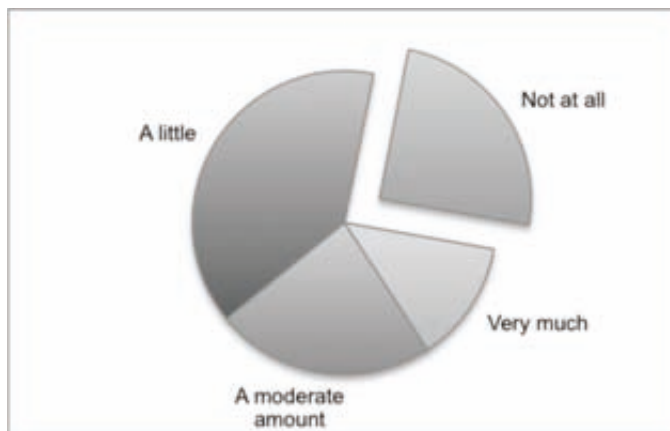
The KOLs indicated to be involved “*little*” or “*a moderate amount*” in the academic R&D process of EN products with a total mean score of 2.45 (SD=1.06), and a range of 4.0 and a median of 2.0 (Figure 6). KOLs indicated to be even less involved in the EN R&D process in industry setting, total mean score: 1.9 (SD=0.96), with a range of 3.0 and a median of 2.0. The p-value for difference between involvement in the academic and industry R&D process based on Wilcoxon signed-rank test was significant ($p<0.0001$). This indicates that KOLs indicated to be involved to a greater extent in the academic R&D process compared to the industry R&D process of EN products.

Figure 6. Comparison between the involvement of KOLs (n=77) in the industry and academic R&D process of EN products. Score (%) of involvement posed on the x-axis.(5-point Likert scale: 5: An extreme amount, 4: Very much, 3: A moderate amount, 2: A little, 1: Not at all). ($p<0.0001$). Academic: total mean score: 2.45 (SD=1.06), with a range of 4.0 and a median of 2.0. Industry: total mean score: 1.9 (SD=0.96), with a range of 3.0 and a median of 2.0



Research relating to EN is done by most of the participating KOLs (n=52, 68%). Moreover, this research is in most cases (n=30, 58%) in collaboration with or research sponsored by EN companies. Influencing the research priorities set by EN companies by KOLs can only be done to a small extent, according to the respondents (fig 7).

Figure 7. Extent of influence by KOLs setting of research priorities by EN companies. (Likert scale: 5: An extreme amount, 4: Very much, 3: A moderate amount, 2: A little, 1: Not at all). Total mean score: 2.25 (SD=0.98), with a range of 3.0 and a median of 2.0.



Although 62% of all KOLs give advice to EN companies on the topic of patient needs, they also experience their involvement with the industry R&D process is considerably less than in the academic R&D process ($p<0.0001$) (fig. 6). In addition, they feel they are only to a small extent able to influence the setting of research priorities by EN companies.

Statistical analysis between groups

No significant differences ($p<0.05$) were observed between the demographic groups in the disease area and product characteristic prioritization. Likewise, no significant differences ($p<0.05$) were observed between the demographic groups in the assessment of KOL involvement.

7.4. DISCUSSION

This study provides a systematic approach to achieve research prioritization in EN. With disease related malnutrition as a major public health burden, EN has proven to be a cost-effective therapy. Faced with a decline in resources available for the development and reimbursement of EN products (31, 55, 217), this research proves EN to be of substantial societal value and therefore development should continue to be stimulated. Since the unmet patient need rather than commercial interest must guide the EN product development process, this strategic prioritization overview of disease areas and product characteristics could balance academic and industry viewpoints. In addition to providing new research directions for EN development, this research shows the perceived differences in KOL involvement between academia and industry. Although we have observed several efforts to stimulate communication (e.g. ESPEN and MNI) and the interaction between academia and the EN industry (151), communication has proven to remain a critical barrier inhibiting EN innovation (54).

Unmet needs – Disease areas

The results from this research show that factors other than the prevalence of malnutrition may and should affect the prioritization of the disease areas in EN. The disease areas in ONS and TF with the highest priorities according to the KOLs (ONS: *general malnutrition & geriatrics*, TF: *intensive care*) are in line with strategic goals set by interest groups such as ESPEN, the Medical Nutrition International Industry (MNI) and the European Nutrition for Health Alliance (ENHA) (153). The positioning of surgery and transplantation (ONS & TF), non-surgical oncology (ONS) and general malnutrition (TF) in the medium priority group showed that these disease areas should also be given more EN research attention. The low priority group contains both disease areas with a low prevalence (e.g. renal failure, hepatology and pulmonary) as well as a high prevalence (e.g. infectious diseases, gastroenterology) of malnutrition. This shows that the importance of a disease area may be defined by multiple factors rather than by its prevalence alone. The allocation of metabolic diseases to the low priority group is noteworthy since most metabolic patients are completely dependant on the use of EN. It was therefore expected that the allocation of this disease area would be in a higher prioritization group. This is probably a result of a relatively low prevalence of patients with metabolic disorders in comparison to other disease areas.

Unmet needs- product characteristics

From a KOL perspective, clinical evidence is perceived as one of the priorities in both ONS as well as TF. Since EN is primarily prescribed by medical professionals, the need for clear and concise clinical evidence is evident. Nonetheless, obtaining clinical evidence for EN products remains a challenge due to several reasons (54). Literature shows that in most instances EN is an adjunct therapy and the effects may be confounded with the primary therapy; there is often a lack of specific biomarkers; it is difficult to design adequate control groups, “placebo nutrition” is neither technically feasible nor ethically acceptable; and patient stratification occurs according to the degree of the patient’s primary disease rather than their nutritional imbalance (218).

Since patients are often prescribed EN when they are unable to tolerate conventional foods, logically, tolerance of EN products is considered a priority, especially from the patient perspective. Numerous studies have demonstrated shortcomings of TF; the intolerance to this type of feeding may result in symptoms such as diarrhoea or delayed gastric emptying (219, 220). Nonetheless, this product characteristic is also ranked relatively high in ONS. Therefore, we propose that additional research attention should be paid to the improvement of the tolerance of TF and ONS.

In addition to the importance of tolerance, it is well known that the sensory perception of ONS products is often experienced by the patients as distasteful. Patients may dislike the flavour, texture or smell (221). Moreover, due to disease or treatments, malnourished patients often suffer from reduced or altered taste, resulting in a decline in food intake (221, 222). It is therefore not surprising that KOLs have indicated that from a patient perspective, the taste of ONS has the highest priority. Especially since taste significantly affects ONS patient compliance which ultimately influences the effectiveness of the nutritional treatment.

The ranking of taste in TF is particularly unusual. We expected this product characteristic to receive no ranking prioritization since TF does not pass through the patient's oral cavity. Surprisingly, a KOL clarified that in specific countries, TF compositions may be administered as an ONS. The reason being that certain ONS and TF products have similar compositions, but that TF has significantly lower costs.

The overall product characteristic prioritization shows that non-economic factors such as composition, taste and tolerance are valued highest. Nevertheless, costs are also considered important both from a KOL as well as a patient perspective. EN products are generally reimbursed within Europe, dependant on country-specific regulations (31, 32). However, the healthcare regulation landscape is affected by the economic downfall and EN reimbursement possibilities are continuously diminishing, whereby there is an increase pressure on the out-of-pocket expenses for the patient. Especially in the case of ONS, product reimbursement is likely to decline, forcing patients to pay out-of-pocket.

KOL versus patient perspective

In the EN industry, the primary goal of technological innovation is to address unmet medical needs. One would assume that during this process of addressing unmet patient needs in EN, patients or patient groups/representatives are approached in order to express their needs. However, our results indicate that within the relatively small and growing EN industry, there is a clear discrepancy in the ranking of the unmet product needs between the KOL and patient perspective. To ensure ranking validity in our research, a single response group prioritized the product characteristics both from a patient and KOL perspective. When focusing on the medium- and high-quadrants within the priority matrix, the results show that only two out of eight - price and tolerance - for ONS are ranked equivalently from the patient as well as from the KOL perspective. This observation leads to a second question; which of the two opinions is most valuable in influencing the EN industry R&D decisions? Since the opinion of the KOLs is overall more knowledgeable on

both the perspectives and based on a set of arguments, we would rationally assume their input to be more influential when it comes to setting research priorities. On the other hand, the opinion of patients remains important, yet they lack the extensive knowledge to create a balanced set of research priorities. This emphasizes why the perspective of KOLs is more influential in the prioritization process of EN R&D.

A second observation is the discrepancy between patient and KOL perspective regarding TF and ONS. It appears that the prioritization of ONS product characteristics from both perspectives is more alike than that for TF. Although ONS and TF are both perceived as EN, they seem to be two distinct markets. In China this difference is emphasized at regulatory level, where ONS is perceived as nutrition whilst TF as a pharmaceutical product. This difference is at present less defined in Europe. The reason for the differences between TF and ONS can be explained by the fact that the use of TF is often the physician's responsibility while the use and choice of ONS is often the patient's responsibility. We therefore argue that in the case of ONS, the patient perspective may be more important than for TF.

KOL involvement

Innovation in the EN industry can be stimulated from both a pull/demand side, i.e. customer needs, and the push/supply perspective, i.e. progress in science/technology. Given the fact that our results indicate that KOLs are only marginally involved in influencing EN research priorities, the EN market seems to function as a science/technology-push market. We propose that although a science/technology-push innovation system may seem profitable for EN companies, the identification of patient needs has proven to be an essential success factor in the complex process of product innovation (207, 208). Products are more likely to be successful when built around customer needs as opposed to only technological opportunities. At present, there appears to be a push and pull innovation system imbalance in the EN market. By redressing this imbalance, the EN market can move towards a more pull-oriented market thereby revolving more around the unmet patient needs and realizing a societal benefit.

Considerations

The methodology of this research is partly based on a previously executed ranking exercise among communicable diseases in Germany (209). We adopted the same cut-off points as in Balabanova et al. in our ranking methodology of disease areas and product characteristics. This resulted in the allocation of a high number of disease areas and product characteristics to the low priority groups. We therefore propose that in future studies, priority group cut-off points should be considered and if needed, re-calculated.

Although, the ranking of health-related criteria is likely to correlate with societal values and reflect socio-economic, cultural and health system structures in a country (209), no differences (statistically tested) in ranking were observed between the different demographic profiles. Our results show that, irrespective of their age and geographic location, the KOLs represented in this research are fairly concordant in assessing EN priorities. Moreover, where in general a 35% response rate in online

surveying is considered relatively high, we only approached actively involved ESPEN faculty members and thus a higher response rate was expected. This, satisfactory, response rate may be attributable to the number of questions (n=34) in the survey, which may have been considered as too many by a number of KOLs. Nevertheless, we do not expect that this might have led to sampling bias since we observed a wide distribution of demographic characteristics among our KOL sample such as age, geographic location and area of expertise. Based on our saturation curve and statistical analyses of the demographic profiles, we therefore consider our KOL sample to be a representative group of EN KOLs.

Future research

This prioritization tool or its components can be applied across different disciplines in the health and life sciences to give balanced guidance on unmet needs that require additional research attention. Additionally, future prioritization analyses may focus on the prioritization of distinct disease areas within the EN market since the importance of EN product characteristics may differ between disease areas. Another recommendation for future research is to involve patients and allow them to only rank the sensory perception of the EN products (smell/taste/intolerance) (in the case of altered sensory perception i.e. chemotherapy) or let KOLs experience (taste/smell) the EN products and prioritize the sensory product characteristics.

In conclusion, to ensure the fulfillment of the unmet patient needs both at the level of disease areas and product characteristics, it is the joined responsibility for industry and academia/KOLs to create a network of collaboration and communication. This will be beneficial both from a societal as well as from a commercial perspective. This research provides the first systematic prioritization of unmet patient needs in the EN market and may function as a stepping-stone for future repeated EN unmet needs measurements.

CHAPTER 8

FUTURE INDUSTRY DEVELOPMENT

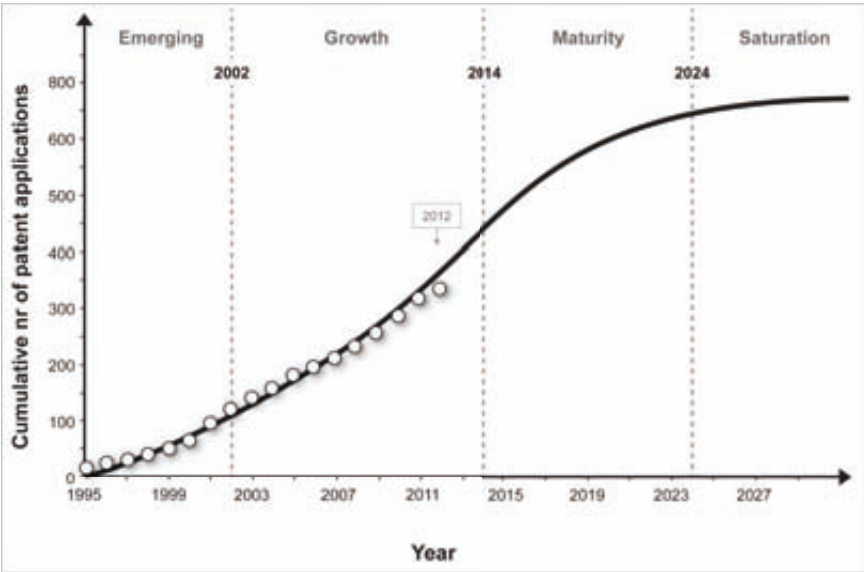
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8.1.CURRENT MEDICAL NUTRITION INDUSTRY DEVELOPMENT

As an industry emerges its innovation activities correspondingly develop. It is therefore crucial for companies within emerging industries to manage innovation using appropriate strategies and business models. There is an extensive body of business oriented literature demonstrating that effective management of innovation works best when matched with the distinct stages of industry development (223). Examining these patterns is a crucial prerequisite for adopting the appropriate innovation strategies and business models for improving product development and enhancing value creating activities (223).

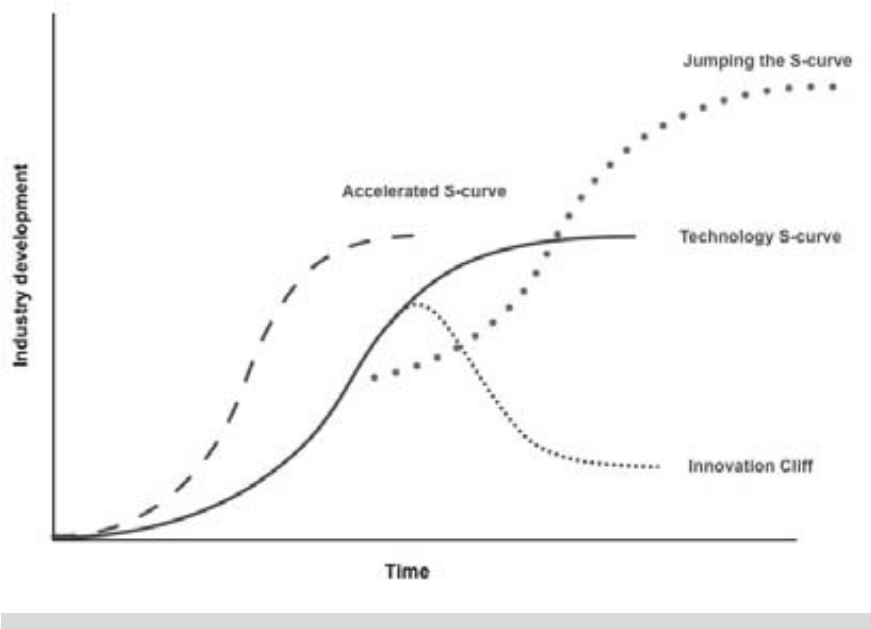
Figure 1. Medical nutrition industry development 1995-2012. Updated from Weenen et al. 2013b.



First, we identify the current stage of development in which the industry is in. In short, industry development is represented by an S-curve, delineating four key stages; emerging, growth, maturity and saturation (79, 224). The main method for evaluating the industry development phase is by analysing the state-of-the-art via patent applications. These are a primary measure reflecting an industries' technological development, which in turn illustrates on the industry's development phase. We visualized a cumulative patent application timeline for the development of medical nutrition from 1995 to 2009 (10). Here we update, including 2012 (Fig. 2.). Since 2002, a steep increase in cumulative patenting activity is observed, which is considered to indicate that the technological development of the industry is currently in the growth stage.

Nevertheless, it is of importance to forecast the industry development curve, in order to infer future performance (Fig. 3). From a macro-perspective, four different future scenarios may exist for medical nutrition industry development, namely; classic S-curve, steep S-curve, innovation cliff and jumping the S-curve. Here we will argue the possibility of each of the four scenarios, based on literature review and interviews with key opinion leaders in the field of medical nutrition (225).

Figure 2. Medical nutrition industry development scenarios. Black line: Classic S-curved technology life cycle (10). Red line: Steep S-curved technology life cycle. Blue line: Innovation cliff. Green line: Jumping the S-curve. Adapted from: (79, 226-229)



8.2.FUTURE INDUSTRY DEVELOPMENT

1. Classic S-curved technology life cycle

The classic technology development S-curve was introduced in economics by Mansfield (1961) in a publication concerning the diffusion of new technologies. The S-curve has since been widely used in management and economic theory (227). The classical S-curve starts off with the emerging stage, which is characterized by a relatively low technological growth, followed by; the growth stage, in which the technological progress rises steeply, the maturity phase, where the growth slows and when it has reached saturation, reveals a plateau. During the saturation stage, the technology approaches its underlying natural limitation.

Based on the development stage an industry finds itself in, strategic R&D decisions can be made (79). The classic S curve of technology development is worth keeping in mind when considering the current status of the medical nutrition industry and where this industry may be headed. At present, the medical nutrition industry finds itself in the growth phase of the technology life cycle. Based on our data; if the industry performance continues to follow the classic curve, saturation could be reached by mid 2024.

2. Accelerated S-curved technology life cycle

For a very successful and fast-growing industry, the angle of the upward inflection in the emerging and growth phases may be less than 120° (229). The curve follows a similar pattern to the classical S-curve, and eventually levels off at a sustainable high level. One aspect that contributes to the steepness of the curve during the emerging and growth phases is the length of the product development timelines: the shorter this timeline, the steeper the curve. The product development timelines for medical nutrition are significantly shorter when compared to pharmaceutical new product development, yet longer when compared to other fast-moving consumer goods (e.g. conventional foods). Therefore we predict that the emerging and growth curve for medical nutritional products will fall in between the two other industry categories. Based on this knowledge, it is assumed to be highly unlikely that the medical nutrition industry performance will follow the steep S-curve.

3. The innovation cliff

An industry is, more often than not, perceived as durable and stable, capable of surviving many decades. Nevertheless; industries are fragile and prone to collapsing (43). This is represented by the green curve in Fig 3, which illustrates the so-called 'innovation cliff' scenario.

During this scenario a technology initially follows the performance characteristics of the classic S-curve in the emerging and growth phases and all seems well. However, the curve is suddenly truncated (229) while the industry plunges off the metaphorical innovation cliff, and ceases to exist any longer. Many different factors can lead to the sudden demise of a technology. Two key factors contributing to this phenomenon include innovation barriers and/or reduced innovation adoption. Surprisingly; the majority of interviewed medical nutrition key opinion leaders predict that the medical nutrition industry is heading towards an innovation cliff within the coming 2-3 years. Based on theoretical models adopted from literature and results from our previous research (225) we propose two different explanations as to why the medical nutrition industry



might be headed towards this innovation cliff: 1- technology/innovation development and 2- technology adoption.

Abernathy – Utterback technology development life cycle

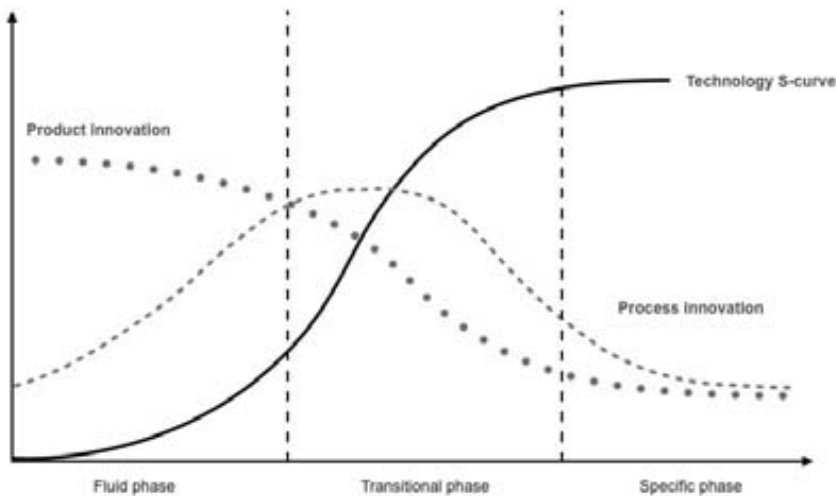
The technology development life cycle explores the roles of the manufacturing companies, as they respond to the forecasted unmet needs within the market. It describes a scissor-curve technology life cycle describing the evolutionary phases of technology development. Abernathy and Utterback's technology life cycle (Fig. 4.) consists of three phases: fluid, transitional and mature (230). The fluid phase is characterized by extreme diversities in new product designs. It is in this phase where competitors attempt to meet the various needs of the emerging customer, resulting in a high throughput of innovative product designs in order to grab the attention of the first-mover consumers.

The fluid phase then gives way to a transitional phase, where product innovation decreases and process innovation is on the rise. During this phase a dominant design typically emerges, which has been accepted either by the market or selected as such by the regulatory authorities. Some technologies eventually transition to the mature phase, where product and process innovation lose momentum and the primary focus of the company is mainly set on reducing the manufacturing cost.

When including the classical S-curve describing the industry life-cycle to the Abernathy-Utterback model, the mid-emerging phase of the industry life-cycle is manifested slightly before the crossing of product and process innovation in the fluid phase. This implies that not all of the customers' needs have been fulfilled and the dominant design has not yet been adopted.

This description typifies the current EU medical nutrition industry situation, which is supported by previous research into innovation barriers within the medical nutrition industry (225). As a result, the main obstacles include the regulatory ambiguity at both the clinical research as well as at the reimbursement level. Clinical research is perceived by the surveyed KOLs as the main innovation barrier, and it is intricately linked to other financial barriers. This includes the consideration of the chances for being granted reimbursement, which would ultimately stimulate the decision to perform clinical studies. This lack of clarity and standardization may prevent the adoption of a dominant design. Therefore a slippery slope is assumed, linking the clinical research barrier with the absence of establishing a dominant design, which in turn reduces the capacity for process innovation. All in all, this scenario would result in medical nutrition industry heading towards the innovation cliff.

Figure 4. Abernathy-Utterback technology development life cycle - adapted from (230, 231)



The chasm of technology adoption

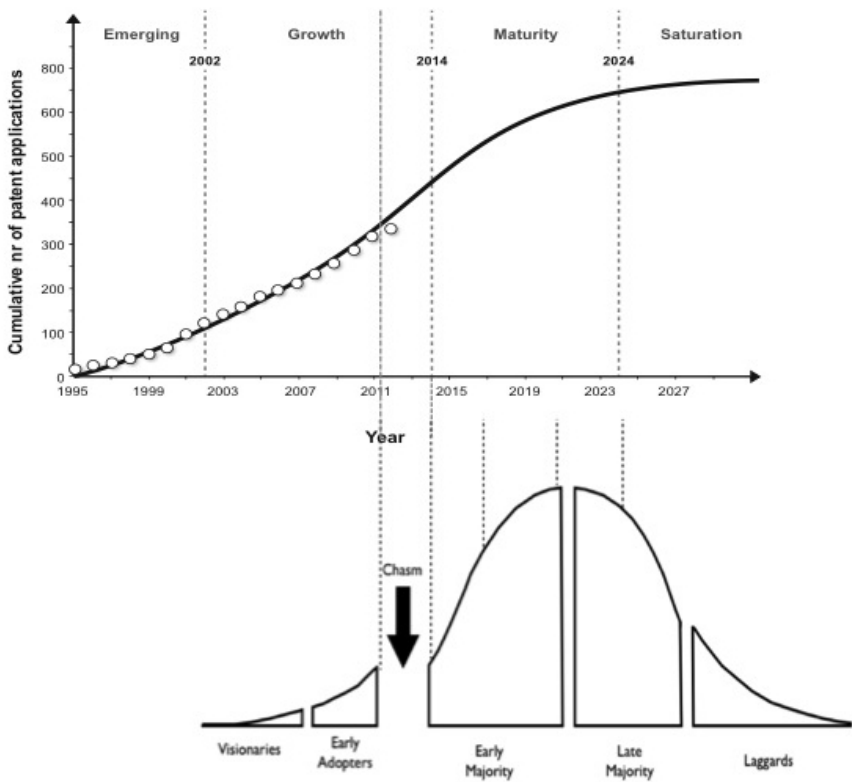
The technology adoption life cycle is a model developed to understand the acceptance of innovation by the consumer market over time. Geoffrey Moore discovered that companies often fail to make the transition from the growth phase to maturity in the technology adoption life cycle (Fig. 5.) (232). This gap is known as *the chasm*, during which product sales drop (232). Crossing this chasm is often nearly impossible but progressing beyond it is considered crucial for the ability of an innovative industry to reach the stage of maturity and saturation.

In the medical nutrition industry, innovation adoption is influenced by both healthcare professionals as well as by the patient. Generally, healthcare professionals prescribe medical nutrition and assess which type/nutrient content of medical nutrition is best. However, medical nutrition product characteristics such as taste, smell and tolerance are assessed by the patient. In the view that the medical nutrition industry is a relatively young industry (10), innovation adoption is still at an early stage. The early adopters, in this case mainly the nutrition-oriented healthcare professionals have realized the potential of medical nutrition. Nevertheless, the awareness of available products is low (225) which may cause the medical nutrition industry to fall victim to the chasm.

The challenge of crossing the chasm in this case is to raise awareness among all healthcare professionals concerning nutritional interventions through medical nutrition. Subsequently, if awareness among the medical professionals is heightened,

they will be able to educate their patients which in turn will stimulate innovation adoption.

Figure 5. The medical nutrition chasm of technology adoption adapted from Moore (1991)



Based on sections 3a and 3b, the synergistic effects of technological development and market adoption pose a serious risk for the medical nutrition industry to face the innovation cliff. It is therefore, in any scenario, of utmost importance to address innovation barriers and increase general awareness on effectiveness of medical nutrition in order to prevent this negative scenario from happening in reality.

4. Jumping the S-curve

As dark and gloomy as the previous scenario might seem, this scenario provides a more optimistic future for the medical nutrition industry. Generally, once the growth phase has been surpassed, the natural evolution of the industry is to reach the stage of saturation, where technological growth reaches homeostasis. Successful industries are those with companies that manage to jump the classical S-curve halfway through its growth phase to the next technology S-curve. Such a feat can only be accomplished when companies understand the dynamics of the S-curve, which implies the anticipation of market decline. One way of jumping the S-curve and taking advantage of this knowledge, is to radically innovate their way to a new S-curve (233).

Generally there are two types of innovations; incremental and radical. Incremental innovations consist of minor improvements or adjustments to existing inventions or technologies. Radical inventions exhibit key characteristics that are inherently different from existing inventions or technologies. The latter type is considered to form a crucial basis from which subsequent incremental development may evolve (163, 234). Most organizations are familiar with leveraging core products through incremental innovation. This approach is perceived as less risky. It assures positive revenue growth as opposed to the discontinuous and radical approach of breakthrough innovation. In prior research, we demonstrated that even though radical innovation is crucial for industry and company performance, only a few medical nutrition companies innovate radically (10).

For an industry to jump the S-curve, companies are to strategically innovate towards the next S-Curve and jump at the optimal moment. Generally, the optimal time to start building the next S-curve is during the growth phase of the technology life cycle. Whilst in the technological growth phase, companies are still able to maximize their returns while starting to invest in a new radical technology (226, 233). One way for the medical nutrition companies to jump the S-curve is by identifying new opportunities, such as unmet needs. This can be in the form of addressing unmet patient needs, related to product characteristics, but also by responding to unmet medical needs

As a rule of thumb; if one company successfully jumps the S-curve through radical innovation, the (incremental) others may follow. The radical innovator, will always benefit from first-mover advantages, and has a chance of establishing a dominant technology design. Furthermore, radical technology innovation is a strategy to overcome the innovation barriers as described in Weenen et al. (225).

CHAPTER 9

MAIN CONCLUSIONS, IMPLICATIONS & FUTURE RESEARCH

9.2 published as:

Weenen TC, Pronker ES, Fernald KDS, Commandeur H, Claassen E, (In press 2013) Pharma-Nutrition – an Overview: Bridging a pharma-like innovation gap in medical nutrition.

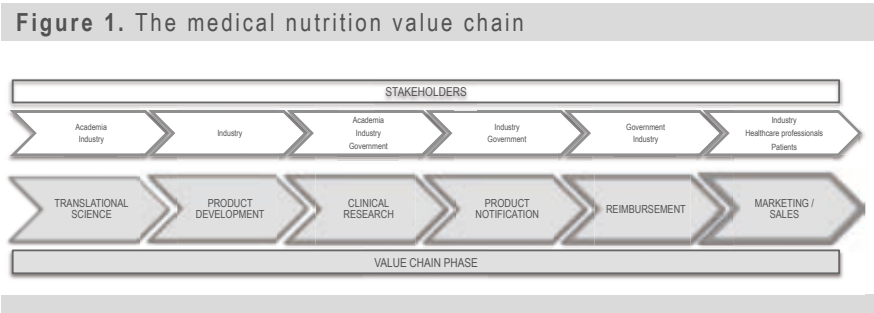
9.1.MAIN CONCLUSIONS

To meet the aims of this research, the approach to studying the origin and development of medical nutrition is multidisciplinary, encompassing scientific, industrial, technical, economic and regulatory disciplines. This research evaluates both past and present trends from the various disciplines, from which future scenarios are forecasted.

This dissertation describes the innovation dynamics within the European medical nutrition industry. We show that although the relatively new and emerging medical nutrition industry offers innovation potential, a lack of medical nutrition innovation may result in a gloomy future for the medical nutrition industry. We also aimed to increase theoretical understanding and empirical knowledge by analyzing the medical nutrition innovation system and the functioning thereof. To conclude, based on the research we propose different possible future scenarios for the medical nutrition market.

Delineating the medical nutrition boundaries and the European medical nutrition innovation system

Medical nutrition innovation is understood as the whole process from the invention, protection and production of a novel nutritional composition, and finally to the innovation adoption: from prescription by healthcare professionals to patient acceptance. These medical nutrition innovations are developed along the value chain from basic research to innovation diffusion and adoption within the market (Figure 1). Although the value chain represents all steps from invention to innovation, it does not take into account the complex network and feedback loops of stakeholder interaction. Understanding innovation dynamics and stakeholder interaction within an industry is best understood when applying the innovation system approach. This approach takes into account that innovation takes place within the context of a wider system where interaction between actors at different societal levels are needed in order to turn an idea into a successful innovation (40). It incorporates all actors and activities in value creation and diffusion that are necessary for innovation to take place, leading to economic development.



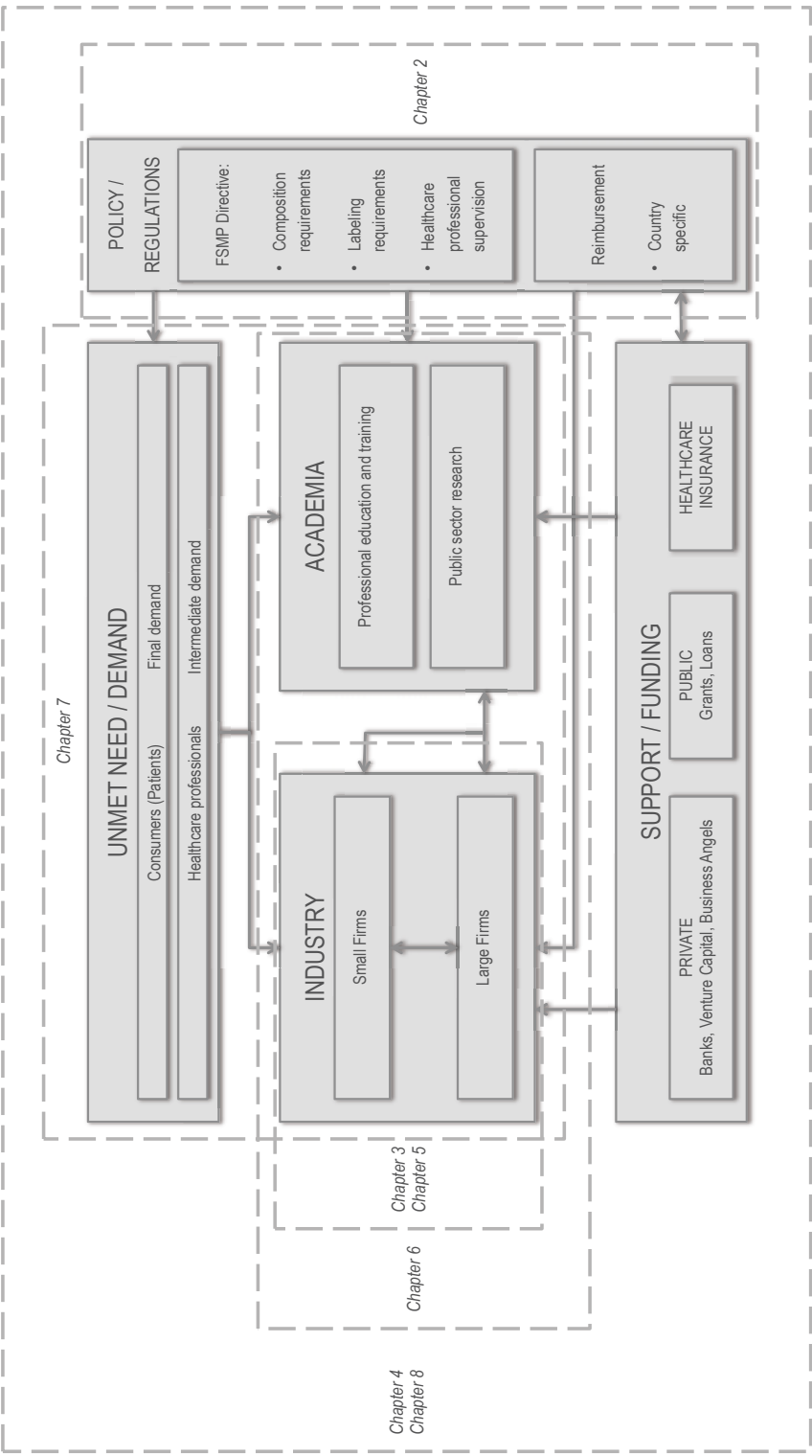


Figure 2. Present European medical nutrition innovation system (adapted from (1, 2). Arrow directions indicate the direction of influence between stakeholders.(3)

is essential. As it turns out, medical nutrition boundaries are not clearly defined. *Chapter 1.1* describes the positioning of the medical nutrition industry at the food-pharma industry. Since the concept of medical nutrition lacks universal coherence *Chapter 2* set out to define the medical nutrition product category according to different features. The way an innovation system is structured and how it functions is dependent on the market and industry's development phase (*Chapters 2 and 5*). *Chapter 5*, reveals by means of a cumulative patent application timeline that the medical nutrition is currently in the early growth phase of industry life-cycle. Patent analysis in *Chapter 3* confirms that the medical nutrition market is still in the growth phase, being the epitome of food and pharma industry domain convergence. *Chapter 3* further reveals that although the medical nutrition industry's core technology domain is food, technological development is mainly driven by pharmaceutical / pharmacological technologies.

In terms of the present medical nutrition innovation system, figure 2 provides an overview of the networks within which the medical nutrition stakeholders are embedded, and their subsequent inter-relationships. As shown, the main components of the framework are: Demand/Unmet need, Industry, Academia, Support/Funding and Policy/Regulations. Each chapter of this dissertation explores the dynamics of stakeholder innovation activities in the medical nutrition innovation system.

Chapter 2 can be seen as an introduction to the topic of defining medical nutrition, and touching upon the very complex nature of the regulatory system. It briefly explains the *Foods for Special Medical Purposes Directive*, which sets out the European medical nutrition requirements intended as guidance for medical nutrition companies. Having explored the regulations and policy arena within which medical nutrition is found, it is the one all encompassing stakeholder that influences all others in the medical nutrition innovation system.

Chapter 3 describes how technological development from different industry domains has caused industry convergence, resulting in the development of the medical nutrition industry. Quantitative patent industry domain analyses show that although medical nutrition is more "food" than "pharma", technological development is mainly driven by pharmacological concepts. We therefore propose that it is important for medical nutrition companies to effectively monitor technological developments within as well as across the boundaries of the medical nutrition innovation system.

Chapter 4 identifies the conditions that negatively impact the entire medical nutrition innovation system, as experienced by 77 key opinion leaders representing the medical nutrition industry. This research shows that although barriers impact all steps of the medical nutrition value chain, the most significant medical nutrition barriers are associated with financial aspects and clinical research, whereas the least significant are considered the product barriers. The chapter provides strategic recommendations to overcome barriers at the regulatory, demand, industry and academia levels. Moreover, *Chapter 4* emphasizes how nutrition companies must realize that investment in innovation is and remains crucial for both economic and societal benefits. At the combined academia, industry, and policy level, adopting (orphan drug) clinical research with clear end-points and cost-effectiveness

methodologies may aid the reimbursement procedure and facilitate innovation adoption by healthcare professionals. Increasing awareness of medical nutrition effectiveness among medical staff and government may be achieved by initiating education programs and/or organizing conferences. Lastly, higher involvement of academic research institutions in the commercial medical nutrition innovation process can lead to higher patient acceptance and possible R&D investment reduction. Such involvement improvement would enhance the performance of the medical nutrition innovation system at industry; academia and unmet patient need levels.

An important aspect of the innovation system both for industry and academia is the ability to protect valuable ideas. In the view that medical nutrition is a technological endeavor, it is necessary to research the most effective asset protection strategies. *Chapter 5* endeavors to uncover the patenting strategies of the key players of the medical nutrition industry thereby proving that patenting behavior differs between the different companies. Between the five dominant European medical nutrition companies, the patent strategies range from few patent applications to excessive patent activity. *Chapter 6* complements *Chapter 5* by offering insights into applicable intellectual property strategies that can increase the protection of medical nutrition inventions. *Chapter 6* adds to the existing body of knowledge on the importance of patenting and other intellectual property rights, by investigating strategies and motives for optimal protection of medical nutrition inventions. The intellectual property decision framework provides industry as well as academia with a decision framework to assess the best applicable intellectual property strategy. This strategy is usually dependent on the characteristics of the invention as well as the development process of the invention. Interaction between researchers working in private firms and those working in publicly financed institutions such as universities is seen as particularly important because it may provide unique competitive advantages for industry players and economical benefits for the public research domain (235). Properly aligned intellectual property strategies at academia level may stimulate technology-transfer opportunities from universities/research institutions to private firms, contributing to a more efficient and better-functioning medical nutrition innovation system.

Fulfilling the unmet patient needs and increasing patient acceptance is the fundamental desired outcome of the medical nutrition innovation system. *Chapter 7* offers an overview of unmet patient needs relating to disease areas and product characteristics, uncovered by means of quantitative questionnaires targeting medical nutrition key opinion leaders. Mapping the unmet needs translates directly into research and innovation opportunities for both academia and industry. Innovation in any industry can be stimulated from both a pull/demand side, i.e. patient needs, and the push/supply perspective, i.e. progress in science/technology. This chapter demonstrates that medical nutrition key opinion leaders are marginally involved in influencing medical nutrition research priorities. It is therefore assumed that at present, innovation in the medical nutrition market functions mainly as a result of science/technology-push market. We propose that although a science/technology-push innovation system may seem profitable for medical nutrition companies, the identification of patient needs has proven to be an essential success factor in the complex process of product innovation. Products are more likely to be successful

when built around customer needs as opposed to only technological opportunities (206). At present, there appears to be an innovation system imbalance in the medical nutrition market, whereby push factors are dominant and the pull factors almost non-existent. By readdressing this imbalance, the medical nutrition market can move towards a more pull-oriented market thereby revolving more around the unmet patient needs, realizing a societal benefit and increasing innovation adoption.

The dynamics of the medical nutrition innovation system induces the realization that social well-being and economic growth are dependent on the participation and performance of all stakeholders in the innovation system. Since innovation systems co-evolve with the process of technological change, it is important to continue monitoring medical nutrition industry development. *Chapter 8* explores four potential future scenarios for the medical nutrition industry: the classic S-curved technology life cycle; the accelerated S-curved technology life cycle; the innovation cliff and jumping the S-curve. We conclude this dissertation by exploring the implications of these scenarios for the medical nutrition innovation system.

9.2. IMPLICATIONS – BRIDGING THE MEDICAL NUTRITION INNOVATION CLIFF

The health and life sciences are moving towards pharmanutrition oriented product development such as medical nutrition. Faced by innovation declines, pharma and nutrition industries are converging in order to fill the gap. On the one end the conventional food industries are converging with more health-oriented industries, while on the other hand the pharmaceutical industry is moving into the (pharma)nutrition space. It is estimated that in approximately 20 years, 50% of the pharmanutrition industry will be pharma owned (236). Enabled by a growing body of evidence, technology development and plenty of unmet needs to fulfill, the medical nutrition industry offers ample future potential. The industry development forecast analysis shows four possible future scenarios. These scenarios include both successful as well as more unfavorable possible outcomes. Currently the newly emerging medical nutrition industry is within the growth-phase of the industry life-cycle yet all signs currently point in the pessimistic direction that the medical nutrition industry is heading towards an innovation cliff. In view of this diagnostic observation, the industry has the chance to pre-emptively jump the cliff by starting a new S-curve. The optimal time to start building the next S-curve is during the growth phase of the technological life cycle. Although the medical nutrition industry is currently encountering rapid growth in the growth phase of the technological life cycle, it is time to start thinking ahead. To prevent the dreaded industry saturation plateau, or even worse, the innovation cliff that may lie ahead, companies must realize that incremental innovation alone is insufficient. The solution for future success lies in the radical innovations. These radical innovations allow for jumping the S-curve, gain competitive advantage and start building the medical nutrition industry's future.

An illustrative case-in-point of a more mature industry which has been facing innovation decline since the early 1990s, is the pharmaceutical industry. In its early history, the productivity of the pharmaceutical industry and market approval of

innovative therapies was relatively easy, which is explained by some critics due to the selection of low-hanging-fruits (237). Currently, the pharmaceutical pipeline is drying up as patents on blockbuster products are expiring and the realization is setting in that incremental innovation is insufficient for sustaining business models (36, 238, 239). The perception of this innovation deficit has motivated large firms to exploit various other strategic options for capturing radical innovations. Since the early 1990s the pharmaceutical industry has been going through significant strategic consolidation of large pharma firms as well as the acquisition of small biotech (Appendix A). Solving this innovation deficit required that firms successfully combined or coordinated merger and acquisition (M&A) activities, strategic alliances, and licensing deals alongside conventional in-house R&D (240-242).

Learning from the pharmaceutical industry, staying ahead of the medical nutrition innovation cliff requires radical innovation. Although the adoption of a clear generic competitive corporate strategy such as described by Porter (154) is essential, we focus on the implementation of internal development versus acquisition strategies. We propose two development strategies for the medical nutrition industry to achieve this and jump to the next S-curve: first by incorporating radical innovation strategies into their own corporate DNA (organic growth) and second through capturing radical innovation by acquiring smaller innovative medical nutrition start-ups (inorganic growth). The first can only be accomplished if companies adopt systematic processes for initiating, supporting, and rewarding radical innovation in-house activities (243, 244). The challenge in this organic growth strategy lies in the fact that it is easier for existing companies to innovate incrementally since this only requires the leveraging of existing knowledge and resources. On the contrary, new entrants will have a considerable advantage in radical innovation since they do not have to change their knowledge background. Furthermore, large companies, such as the medical nutrition market leaders, may have a difficult time implementing radical innovation because they operate under a “managerial mindset/constraint”.

The second strategy of inorganic growth through radical innovation acquisition only offers potential if medical nutrition start-ups continue to emerge and invest in the development of radical innovation. Entrepreneurial start-ups are a valuable source of knowledge necessary to develop radical innovation (245). Research has shown that active acquisition industries encourage radical innovation, particularly at the SME level (246).

The medical nutrition industry, at present in the growth stage of the industry life-cycle, may be considered as especially attractive to start-ups. When demand is growing in an industry, firms can achieve initial success without the intense competitive threat that firms face in mature and overregulated markets. In other words, there is more than sufficient market opportunity available for multiple entrants to achieve commercial successes (133).

Since development and production costs are relatively high in the medical nutrition industry, it is highly unlikely that medical nutrition start-ups will develop into fully integrated nutrition companies [FINCOs]. Most likely, medical nutrition market leaders will view these small innovative firms as prey as opposed to competitors, and will incorporate them into their companies. Even if the SMEs are the source of new

ideas, commercialization and wide product diffusion will usually happen only after acquisition by the incumbent. Generally, being acquired is an attractive exit strategy for small firms.

In a similar profile as the pharmaceutical industry but 15 years later, M&A activity within the medical nutrition industry has increased since 2004 (Figure 3.). A total of 11 mergers and acquisitions and 3 joint ventures/ partnerships have occurred within this industry. In particular since 2010, acquisition has become more frequent. More start-ups may be realizing the potential of the medical nutrition industry in the last few years and are entering the playing field. In addition, large medical nutrition companies may already encounter difficulties in developing radical innovations and are shifting from organic to inorganic growth through acquisition.

However, companies cannot solely rely on insourcing innovation since this is often only a quick-fix. Additionally, if entry barriers prove to be unscalable for medical nutrition start-ups, the flow of innovation will come at a halt and the acquisition opportunities for large medical nutrition companies will decline accordingly. The optimal innovation strategy is therefore a balanced integration of both organic and inorganic growth. Such a strategy will enable medical nutrition companies to jump the S-curve themselves when acquisition opportunity is low and stock up on radically innovative start-ups when it is an active acquisition industry.

Here, we primarily focused on the process of radical innovation since this is considered the most challenging type of innovation. And although radical innovation has proven crucial, the importance of organizational ambidexterity must not be neglected. Organizational ambidexterity can be described as a company's ability to align the development of both radical as well as incremental innovations (247). This holds particularly true for the medical nutrition market where incremental innovations have been proven valuable (*Chapter 6*). Incremental innovation can be achieved by enhancing and prolonging medical nutrition product life cycles (248). Examples for incremental medical nutrition innovation may include: more convenient packaging, taste improvement or increasing the tolerance of existing products. Therefore, to succeed in the medical nutrition industry, a company requires competences in both exploratory (radical) as well as exploitative (incremental) activities.

Figure 3. Medical nutrition industry M&A

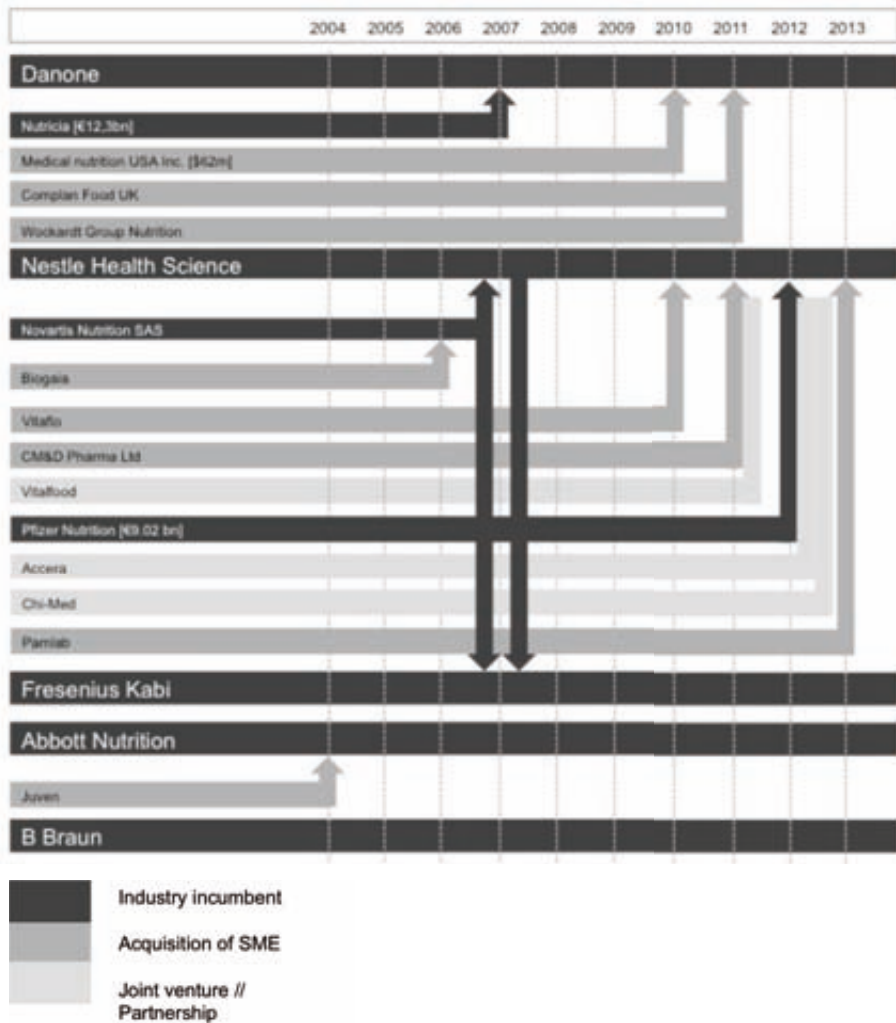
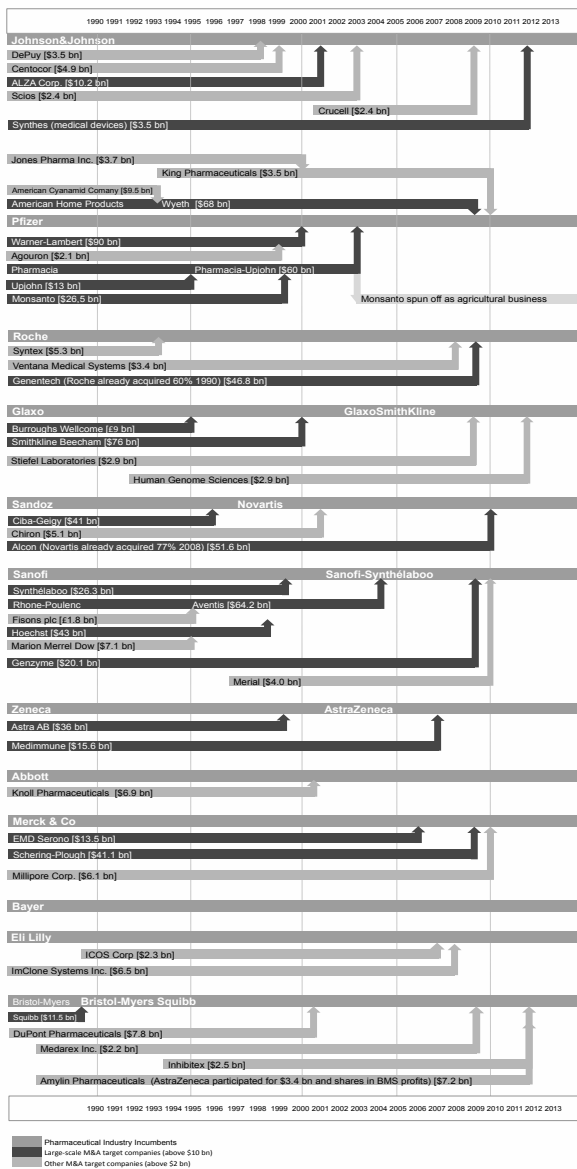


Figure 4. Pharmaceutical M&A from 1990-2013.



9.3. SUGGESTIONS FOR FUTURE RESEARCH

Although most aspects of the medical nutrition innovation system are thoroughly described in this dissertation, the funding aspect of the medical nutrition innovation system is only briefly explored in *Chapter 3*. Presently, medical nutrition start-ups are unlikely to start investing in innovation if governments are unwilling to support them financially. *Vise versa*, governments are not aware where financial support is necessary if the awareness concerning the public health benefit of medical nutrition is low, which is needed to legitimate policy support. Especially since one of the most important barriers according to medical nutrition key opinion leaders is related to the financial aspects of the medical nutrition innovation system further research into this aspect deems useful.

The research in this dissertation focused on the European medical nutrition industry. As highlighted in *Chapter 2*, regulations, terms and definitions of medical nutrition differ tremendously between geographic regions. This implies that the medical nutrition innovation systems between these regions will also vary. A proposed research topic would be to improve the understanding of the idiosyncratic properties of particular geographic regions of the medical nutrition innovation systems (249). Such insights can contribute to the alignment of different innovation strategies for companies to operate in different geographic areas.

Regulatory framework conditions have been identified as important factors influencing the performance of innovation systems (250). The regulatory landscape of the European medical nutrition market is currently changing which will most likely affect the dynamics of the entire European medical nutrition innovation system. Medical nutrition regulatory changes may be ambivalent; the primary goal to protect patients may also result in a higher (economic) burden for companies to fulfill specific regulations, thereby reducing innovation. Nevertheless, overall, policymakers are trying to limit the negative impacts of regulation on the innovative activities of industry, and have started to look more systematically for options to create ambidextrous regulations thereby protecting the consumer environment as well as promoting innovations (250). In the view of the changing medical nutrition regulatory landscape, regulatory impact assessments provide a critical area for further analysis.

Finally, further research into the causes of heterogeneity in business performance within the medical nutrition industry would be interesting (251). Although value-adding medical nutrition innovation strategies are proposed in this dissertation from a macro-level perspective, insights into managerial dynamic capabilities and mental maps of top managers at firm level would further complement this. The medical nutrition industry is defined as an oligopoly, where medical nutrition innovation is concentrated within five multinational companies. Comparison of these companies' specific dominant logic, the mental maps developed by the top managers through innovation experience, presents possibilities for future research.

While the findings in this thesis are specific to the present medical nutrition industry, we argue that the growing importance of this industry in the future deserves further academic attention.

SAMENVATTING

Dankzij het vervagen van grenzen ontstaat convergentie tussen voorheen gescheiden industrieën en komen nieuwe industrieën tot stand. Ditzelfde geschiedt ook in de health & life science sector: de kloof tussen farma en voeding wordt steeds kleiner. Door combinatie en integratie van farmaceutische- en voedings-technologieën worden radicale innovaties gerealiseerd op de voedings-farma interface. Reden voor deze convergentie is onder andere het groeiende wetenschappelijke bewijs voor de rol van voeding in de preventie en/of behandeling van ziekten. Daarnaast verschuift de zorgvraag als gevolg van onder andere de vergrijzing naar meer chronische en ouderdomsziekten, wat vraagt om combinaties van therapieën, voeding en medicijnen. De medische voedingsmarkt biedt vandaag de dag belangrijke innovatie kansen van aanzienlijk maatschappelijk belang. Een van de industrieën die is ontstaan ten gevolge van voedings-farma convergentie is de medische voedingsindustrie. Medische voeding is specifiek samengestelde voeding die gebruikt wordt in de dieetbehandeling van verschillende ziektebeelden en ziekte gerelateerde ondervoeding. Medische voedingsproducten worden binnen Europa door medische specialisten zoals artsen en diëtisten voorgeschreven en zijn alleen in apotheken verkrijgbaar. Veelal worden de resultaten van klinische studies ingezet om deze medische specialisten te overtuigen van de effectiviteit van deze producten. Wettelijk zijn klinische studies niet verplicht tenzij het medische voedingsproduct een nieuw, nog niet onderzocht ingrediënt bevat. In dat geval moet de veiligheid van dat ingrediënt worden bewezen.

De doelstelling van dit proefschrift is om een wetenschappelijke bijdrage te leveren aan het ontstaan en de ontwikkeling van de Europese medische voedingsmarkt. Het functioneren van deze markt is afhankelijk van de dynamiek van het gehele medische voedings-innovatiesysteem. Een dergelijk systeem beschrijft alle stappen van de medische voedingswaardeketen en alle betrokken partijen in een complex netwerk.

De hoofdstukken in dit proefschrift tonen aan dat door een toename in wetenschappelijk bewijs, technologische ontwikkeling en on vervulde patiëntbehoeften, de medische voedingsmarkt uitgebreide kansen biedt voor de toekomst. Om een mogelijke toekomstige innovatiekloof de voorkomen is het noodzakelijk voor medische voedingsbedrijven om tijdig te realiseren dat zowel incrementele als radicale innovatie cruciaal is. Ook al bieden convergentie industrieën zoals de medische voedingsindustrie verhoogde radicale innovatie kansen, ze zijn niet zonder risico's voor (startende) bedrijven. Om deze risico's aanzienlijk te verkleinen kan de kennisbasis van bedrijven verbreed worden door middel van samenwerkingsverbanden met verschillende academische en commerciële partners en/of kennis acquisitie om zo de benodigde kennis te integreren en radicale innovaties succesvol in de markt te kunnen zetten.

SUMMARY

As the boundaries between many once-distinct industries are blurring and consequently combine, this process gives rise to new industries. This also holds true for the health and life science sector. In the past few years the gap between pharma and nutrition science is closing. One reason is the increasing scientific evidence regarding the potential of nutrition and the role in the prevention or treatment of diseases and/or risk factors for disease. Furthermore, there is a transition in healthcare demand towards more chronic and age related diseases due to factors such as obsolescence. The medical nutrition industry, found in the pharmanutrition domain, offers ample innovation opportunities of high societal importance. Medical nutrition products are specially formulated nutritional compositions for the dietary management of patients with diseases, disorders or medical conditions that cause distinct nutritional requirements and are prescribed under healthcare professional supervision. Although clinical research is not mandatory, it is often executed to convince healthcare professionals on the product's effectiveness.

Since we are dealing with a relatively new industry, academic insights into medical nutrition innovation are lacking. Motivated by the multi-leveled societal importance of medical nutrition, this PhD dissertation aims to advance the understanding of the innovation dynamics of the European medical nutrition industry. It starts off by delineating the boundaries of medical nutrition; followed by an analysis of the medical nutrition innovation system and concludes by proposing possible medical nutrition industry future scenarios.

The nine chapters in this dissertation show that the medical nutrition industry offers extensive future opportunities due to an increase in scientific evidence, technological development and unmet patient needs. To prevent a possible innovation cliff, medical nutrition companies must realize that both incremental and radical innovation is crucial. Even though convergent industries such as the medical nutrition industry offer innovation opportunities, they are not without risk. Expanding a company's knowledge base by means of industry-academia collaborations and/or by means of inorganic growth (innovation acquisition) can significantly reduce these risks

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From March 1st 2013, she will start as a Healthcare Consultant at Philips Healthcare Transformation Services.

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ON THE ORIGIN AND DEVELOPMENT OF THE MEDICAL NUTRITION INDUSTRY

Product development in the health and life sciences is shifting from the development of target-specific pharmaceutical products to multi-target therapies, including medical nutrition. Medical nutrition consists of nutritional compositions, prescribed by medical professionals for the nutritional support in the dietary management of diseases. The European medical nutrition industry is rapidly maturing, driven by new knowledge on medical nutrition effectiveness and increasing public awareness on its importance. Nevertheless, there are still numerous unmet medical needs that can only be addressed through innovation by the medical nutrition industry.

This dissertation describes the innovation dynamics within the European medical nutrition industry, through exploring the origin and development of this industry and all stakeholders involved. The research is multidisciplinary, encompassing scientific, industrial, technological, economic and regulatory disciplines. Although the relatively new and emerging medical nutrition industry offers innovation potential, the results show that a lack of medical nutrition innovation may result in a gloomy future for the medical nutrition industry.

The dynamics of the medical nutrition innovation system induces the realization that social well-being and economic growth is not only dependent on the innovation activity of both the food and pharma industries but requires input from key opinion leaders in academia; patients; regulatory and funding bodies.

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