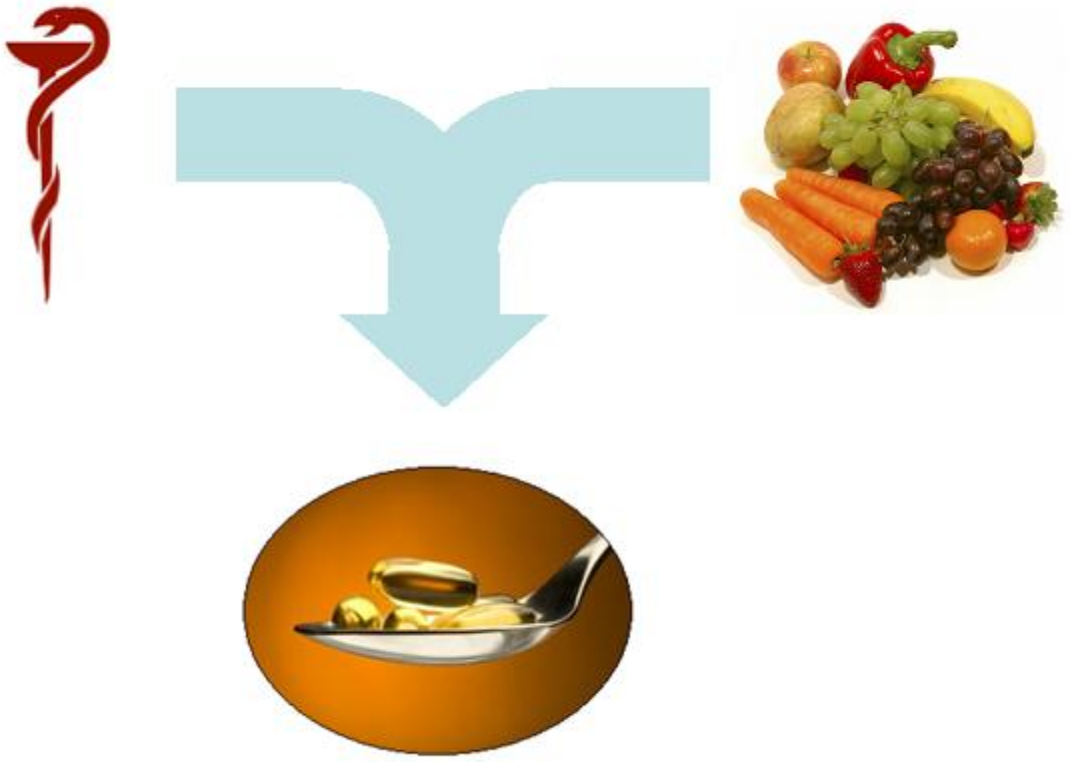
The emerging European nutraceuticals innovation system

A functional comparison with the United States nutraceuticals innovation system



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"*Let food be thy medicine, and medicine be thy food*"
Hippocrates (460–370 BC)

Summary

Last decades the role of dietary active components in human nutrition has become an important focus of research and has increased the awareness of consumers about diet and proper nutrition. A new product category that has emerged from it is ´nutraceuticals´. A nutraceutical is "*a food or a part of a food with demonstrated safety and health benefits that go beyond the basic dietary needs and is presented in a nonfood matrix or nonconventional food format*". The last twenty years the global nutraceuticals market has shown impressive growth rates and the global nutraceuticals industry is nowadays a multi-billion dollar industry. However the European market is lagging behind in this growth: where the global and United States (US) market grew over 10 fold over the period 1999 – 2006, the European market only grew 5 fold. Possible explanations that have been put forward for this restricted growth are problems with consumer acceptance of nutraceuticals in Europe and the European regulatory framework. These are both aspects of the European nutraceuticals innovation system (IS). Accordingly, this study applies a technology specific innovation system (TIS) approach to study the lagging behind in size and growth of the European nutraceuticals market compared to the US and global nutraceuticals market.

The main research question of this study was: "*What are the strengths and weaknesses of the emerging nutraceuticals innovation system in the European Union compared to the emerging nutraceuticals innovation system in the United States over the period 1990 – 2011?"*. The structures of the current European and US nutraceuticals IS have been described by mapping the actors groups, institutions and networks involved in each IS. Also, dynamic analyses have been performed according to the TIS approach. This TIS approach takes seven emergent properties (system functions) of a TIS into account, including regulatory aspects and consumer acceptance, which is measured looking at consumer skepticism. The TIS approach allows mapping these functions over time by building a historical event database of activities relating to the TIS. To complement this data, various interviews have been conducted. The more the seven system functions are fulfilled, the better the performance of the TIS is expected to be, and the higher the chances for a successful development, diffusion, and implementation of nutraceutical technology.

The results showed that from 1990 the main weakness of the European nutraceuticals IS was the lack of European regulations regarding the use of health claims and thereby the lack of fulfillment of F4. This resulted in the lack of the formation of one European market (F5) which caused F1: entrepreneurial activity to lag behind. From 2000 the ongoing uncertainty about the future of the European nutraceuticals market (F4) influenced investments in the nutraceutical industry and F6: resource mobilization was lagging behind as well, which also negatively influenced entrepreneurial activity (F1). In the US the opposite happens; in 1994 the Dietary Supplements Health and Education Act (DSHEA) came into force which permitted the use of health claims on nutraceuticals in the US. Accordingly F4 was fulfilled. As a result a market for nutraceuticals was created (F5) which stimulated entrepreneurial activities (F1).

Another weakness of the European IS, and also the US nutraceuticals IS, was the lack of scientific substantiation (F2) of many nutraceutical products, which encouraged consumer skepticism. In Europe this was the result of the lack of a European Union inspection agency that could effectively ban scientifically unsubstantiated products off the market. In the US this was the result of the DSHEA, under which little scientific substantiation was required for the use of health claims on nutraceuticals.

In 2006 Regulation (EC) 1924/2006 on the use of health claims changed the European nutraceuticals market significantly. At first this new regulation created uncertainty in the industry, but when the

impact of this new regulation became clear uncertainty decreased and entrepreneurial activities (F1) rose again. This regulation positively influenced F2: knowledge development and F5: market formation by assuring a high level of scientific substantiation and creating one European market for nutraceuticals. The high level of scientific substantiation reduced consumer skepticism regarding nutraceuticals and positively influenced F7: creation of legitimacy / counteract resistance to change. Therefore the new Regulation (EC) 1924/2006 can be regarded as the main strength of the European nutraceuticals IS: it has opened the door to a scientifically grounded nutraceuticals market with nutraceutical products that truly benefit consumers. However for this new regulation to be successful it is necessary for the European Union to establish an inspection agency that can effectively ban scientifically unsubstantiated nutraceutical products of the market. Furthermore the individual European countries should have public relations agencies that provide consumers with complete and unbiased information about nutraceuticals and their potential health benefits. This can decrease consumer skepticism and increase consumer acceptance of nutraceuticals in Europe.

List of abbreviations and definitions

Abbreviations

ACE	Angiotensin-Converting-Enzyme
ANA	American Nutraceutical Association
CRN	Council for Responsible Nutrition
DSHEA	Dietary Supplement Health and Education Act
EFSA	European Food Safety Authority
EHPM	European federation of associations of Health Product Manufacturers
ENA	European Nutraceutical Association
ERNA	European Responsible Nutrition Alliance
FDA	Food and Drug Administration (United States)
FIM	Foundation for Innovation in Medicine
IADSA	International Alliance of Dietary/Food Supplement Associations
IS	Innovation System
PCB	Polychlorinated Biphenyl
NIS	National Innovation System
NPN	Natuur- & gezondheids Producten Nederland
NREA	Nutraceutical Research & Education Act
PASSCLAIM	Process for the Assessment of Scientific Support for Claims on Foods
PAHs	Polycyclic aromatic hydrocarbons
SIS	Sectoral Innovation System
TIS	Technological Innovation System

Definitions

Actor	Actors can be individuals but are more often organizations such as firms, governmental organizations, non-governmental organizations, venture capitalists, universities, research institutes, etc. (Markard and Truffer, 2008; Edquist, 2005).
Borderline products	In the 1990s, nutraceuticals, and other new products arriving on the market accompanied by health claims for which no regulatory framework was established, were being referred to by the British government as borderline products.
Dietary supplement	A dietary supplement is a product taken by mouth that contains a "dietary ingredient" intended to supplement the diet (FDA.gov, 2012). In the United States, nutraceuticals belong to the category dietary supplements.
Food supplement	Concentrated sources of nutrients or other substances with a nutritional or physiological effect whose purpose is to supplement the normal diet" (EU, 2012). In the European Union, nutraceuticals belong to the category food supplements.

Infomercial	Infomercials are direct response informational television programs in which information about a product is given and consumers have the possibility to directly buy the product.
Innovation system	The network of institutions in the public and private sectors, whose activities and interactions initiate, import, modify, and diffuse new technologies (Freeman, 1987).
Institution	Institutions are the rules (regulations, legislations social, cultural and technical norms, shared expectations etc.) that make up the rules of the game (Markard and Truffer, 2008; Edquist, 2005).
Network	Networks link the actors and facilitate the transfer of tacit and explicit knowledge, and other resources (Jacobsson and Johnson, 2000).
Nutraceutical	A nutraceutical is a food or a part of a food for oral administration with demonstrated safety and health benefits beyond the basic nutritional functions to supplement diet, presented in a nonfood matrix or nonconventional food formats, in such a quantity that exceeds those that could be obtained from normal foods and with such frequency as required to realize such properties, and is labeled as a 'nutraceutical'.
Precautionary principle	The precautionary principle states that in case of absence of scientific consensus whether an action or a policy might harm the public or environment, the burden of proof that the action is *not harmful* falls on those taking the action.
Structure/function claims	Structure/function claims describe the role of a nutrient or dietary ingredient intended to affect the structure or function of the body.
Technological innovation system	A technological innovation system is a set of networks of actors and institutions that jointly interact in a specific technological field and contribute to the generation, diffusion and utilization of variants of a new technology and/or a new product (Markard and Truffer, 2008 p611).

Contents

1. Introduction

1.1 Problem definition

Last decades the role of dietary active components in human nutrition has become an important focus of research and has increased the awareness of consumers about diet and proper nutrition. An important product category that has emerged from this focus on dietary active components in human nutrition is ´nutraceuticals´. The term nutraceuticals was first introduced by DeFelice in 1989 and in 1994 DeFelice defined nutraceuticals as "any substance that may be considered a food or part of a food and provides medical or health benefits, including the prevention and treatment of disease" (DeFelice, 1994, p1). Since DeFelice has introduced the term nutraceuticals many different definitions have followed. A recent study of Palthur *et al.* (2010, p25) has reviewed 25 different definitions, took their central concepts, and has suggested one working definition:

> "A nutraceutical is a food or a part of a food for oral administration with demonstrated safety and health benefits beyond the basic nutritional functions to supplement diet, presented in a nonfood matrix or nonconventional food formats, in such a quantity that exceeds those that could be obtained from normal foods and with such frequency as required to realize such properties, and is labeled as a 'nutraceutical'."

Coinciding with the emergence of nutraceuticals consumer demands have change considerably towards food products that contribute directly to their health, with correspondingly high expectations of consumers and the food industry as a result (Tewfik and Tewfik, 2008; Hsieh and Ofori, 2007; Menrad, 2003; Mollet and Rowland, 2002). In the last twenty years the emerging nutraceuticals technology has created a global market with impressive growth rates estimated between 15% and 20% annually (Verbeke, 2005; Hilliam, 2000), with Japan, the United States (US), and the European Union (EU) as major markets (global market share 39%, 31%, and 28% respectively, Nutraingredients-usa.com, 2010). The global nutraceuticals market was estimated to be worth over US $80 billion in 2008 and is estimated to be US $176,6 billion in 2013 (Ahmad *et al.,* 2011; EU, 2008). Other estimations of the global market size of nutraceuticals range from US $70 billion to US $250 billion annually, depending on the definitions of nutraceuticals used (Yeung *et al*., 2007). Despite the global nutraceuticals market is expected to keep growing strongly (Ahmad *et al.*, 2011; Nutraingredients-usa.com, 2010; Ridinger, 2007), the European nutraceuticals market is lagging behind in this growth (Nutraingredients-usa.com, 2010; Basu *et al.*, 2007; Bech-Larsen and Scholderer, 2007). Where the *global market* for nutraceuticals grew more than tenfold from US $5.7 billion to US $75.5 billion over the period 1999 – 2006, the *European market* for nutraceuticals grew less than fivefold from US $1.8 billion to US $8 billion over the same period (Basu *et al*., 2007). Extrapolating this data to the *US market* shows an estimated growth of the US nutraceuticals market from US $2 billion to US $20 billion over the period 1999 – 2006. So the diffusion of nutraceuticals in Europe is still low with market shares of less than 1% of the total foods and drinks market (Siró *et al*. 2008). An assessment by the European nutraceuticals industry even predicts a decrease of the size European nutraceuticals market in Euros of 25% the coming two years due to the strict European regulations on health claims (European Health Claims Alliance, 2010). The US market on the contrary is the largest and most rapidly expanding nutraceuticals market in the world with an annual growth rate of over 7% (nutritionaloutlook.com, 2011, Basu *et al*., 2007). In the US about two-thirds of the population takes at least one type of nutraceutical health product (Ahmad *et al.*, 2011).

The lagging behind in size and growth of the European nutraceuticals market has been studied before by focusing on the influence of EU regulations on the European nutraceuticals market. These studies found that firms that attempt enter the European nutraceuticals market encounter several problems due to the lack of harmonized regulations that might hamper market access and/or their innovation process (Gilsenan, 2011; Bech-Larsen and Scholderer, 2007; Yeung *et al.*, 2007; Coppens *et al.*, 2006; Kwak and Jukes, 2001). Other studies have focused on consumer acceptance as a possible explanation of the lagging behind in size and growth of the European nutraceuticals market (Granato *et al*., 2010; Lähteenmäki *et al*., 2010; Ares and Gámbaro, 2007; Verbeke, 2005; Menrad, 2003; Urala and Lähteenmäki, 2003; Weststrate *et al.*, 2002, among others). These studies linked the acceptance of a specific functional ingredient of a nutraceutical to the consumers' knowledge of the health effects of the specific functional ingredients. Thus, functional ingredients that are on the market for a longer period of time (e.g. vitamins, fiber, minerals like calcium, iron) achieve considerably higher rates of consumer acceptance than ingredients which are used for a short period of time (e.g. flavonoid, carotinoids, Omega-3 fatty acids) (Verbeke *et al*., 2009; Menrad, 2003).

Besides these studies highlighting specific problems of the European nutraceuticals industry, the inadequate regulatory regime and the ambiguity regarding consumer acceptance also demonstrate the emerging character of the European nutraceuticals industry; where existing technologies generally have a set of institutions and regulations to support them (Hekkert *et al*., 2007), no regulations have yet been established to support the emerging nutraceuticals technology. Also, in order to develop well, a new technology has to become part of an incumbent regime, or it even has to overthrow it (Hekkert *et al*., 2007). Therefore emerging technologies often encounter the resistance to change from the incumbent regime. The lack of consumer acceptance illustrates such resistance to change.

This emerging character is supported by the relative short time nutraceutical products have been on the European market: the first nutraceutical products have only entered the European market in the mid 90s (Menrad, 2003). Thus, previous studies have found specific problems (e.g. the regulatory system, acceptance problems) and have made progress on the understanding of the lagging behind in size and growth of the European nutraceuticals market. However, these problems have been studied in isolation while they are part of a so-called emerging European nutraceuticals technology specific innovation system. By taking the entire nutraceuticals innovation system into account, this study creates a more comprehensive understanding of the development of the European nutraceuticals Innovation System (IS) and its strengths and weaknesses.

1.2 Aim

The aim of this research is comparing the emerging European nutraceuticals innovation system with the emerging US nutraceuticals innovation system to better understand the strengths and weaknesses of the European nutraceuticals innovation system, as the US is the largest and most rapidly expanding nutraceuticals market. This is done by mapping the development of the emerging European and US nutraceuticals IS over time using the Technological Innovation System (TIS) approach (Hekkert *et al*., 2007). Furthermore policy recommendations are given to overcome the weaknesses of the European nutraceuticals IS.

1.3 Delineation

The European nutraceuticals market lags behind in size and growth compared to the US nutraceuticals market. Since important aspects regarding this problem such as consumer acceptance

and regulations are characteristics of the European nutraceuticals IS, this study focuses on the European nutraceuticals IS and compares it with the US nutraceuticals IS.
The term nutraceutical was coined in 1989, and in 1992 DeFelice noted that at that moment there were no corporate structures that were capitalizing the new nutraceuticals market in the US (DeFelice, 1992). In Europe, the first nutraceutical products have been launched in the mid 90s (Menrad, 2003). Furthermore the term nutraceuticals first appears in the scientific database ´Scopus´ in 1991 (Journal of Pharmacy Technology, 1991). Therefore the chosen timeframe of over which the TIS analyses are performed is 1990 – 2011.

1.4 Research questions

The following research questions are used to study the strengths and weaknesses of the European nutraceuticals IS and give policy recommendations to overcome the weaknesses of the European nutraceuticals IS.

Research question 1:
What are the strengths and weaknesses of the emerging nutraceuticals innovation system in the European Union compared to the emerging nutraceuticals innovation system in the United States over the period 1990 – 2011?

Research question 2:
What recommendations can be given to policy makers in the European Union to overcome the weaknesses of the emerging European nutraceuticals innovation system?

1.5 Scientific relevance

The main part of this study focuses on comparing the European and the US nutraceuticals IS with each other in order to determine the strengths and weaknesses of the European nutraceuticals IS. While these studies have made progress on the understanding of the low diffusion of nutraceuticals in the EU on particular aspects (e.g. the regulatory system, acceptance problems), none of these studies have taken an innovation systemic approach to study these problems. By mapping the development of the emerging European nutraceuticals IS over time, this study creates a more comprehensive understanding of the performance of the nutraceuticals TIS and its strengths and weaknesses. More importantly, by applying the TIS approach this study contributes to innovation theory by introducing the TIS approach in the life-sciences field. The life-sciences field is a specific field with different characteristics compared to the energy sector, in which the TIS approach has become an accepted tool for studying an emerging TIS (Van Alphen *et al*., 2009; Suurs, 2009; Negro and Hekkert, 2008; Negro *et al*., 2008; Hekkert *et al*., 2007; Negro *et al*., 2007). Life-science industries such as the nutraceuticals industry are often characterized by long development times, rigid patenting laws, strict regulations and ethical issues. By taking this into account when applying the TIS approach an example is set for future studies to apply the TIS approach in the life-sciences field.

1.6 Societal relevance

In its health strategy the European Union is committed to promoting healthy lifestyles by stimulating healthy food choices (EU, 2011). By comparing the European nutraceuticals IS with the emerging US nutraceuticals IS lessons can be learned that help to design recommendations to EU policy makers to overcome the weaknesses of the European nutraceuticals innovation system. A better performing European nutraceuticals IS can increase the health benefits of nutraceuticals to the European citizens, for example by a higher diffusion of nutraceuticals in the EU or higher quality products.

Also, a better performing European nutraceuticals IS contributes to the competitiveness of European nutraceutical firms. This will have a positive influence on economic activity within the EU and will promote competitiveness of European nutraceutical firms on the global market.

1.7 Outline

Chapter 2 discusses the theoretical foundation of the study. The methodology is discussed in chapter 3. It represents the research design and the operationalization of the conceptual model. Next the data collection, data analysis, and the validity and reliability of the study are discussed. Chapter 4 discusses the results of the analysis of the European nutraceuticals innovation system. Chapter 5 gives the results of the analysis of the US nutraceuticals innovation system. After these results have been discussed the European and US nutraceuticals innovation systems are compared with each other in chapter 6. Chapter 7: Conclusions gives the answers to the research questions and in chapter 8: Discussion gives a critical review of the study.

2. Theory

This study starts with analyses of the European and US nutraceuticals innovation systems. These analyses are performed by applying a technology specific innovation system (TIS) approach. This approach originated from innovation systems (IS) theory, which is discussed first. But before theory is discussed, a general introduction in nutraceuticals is given to get a better understanding of what nutraceuticals actually are.

2.1 Nutraceuticals – an introduction

The increased knowledge on the relationship between nutrients and health has resulted in several new products categories, such as Nutraceuticals. The word nutraceutical is a portmanteau of the words nutrient and pharmaceutical, and the product category represents a unique intersection of the pharmaceutical and food industries. The term was introduced in 1989 by Dr. DeFelice (DeFelice, 1994) and since then many different definitions have followed (Palthur *et al.,* 2010). Due to their overlap with foods and pharmaceuticals, nutraceuticals operate in a grey area. This is reflected in EU and US regulations since both regions have no official definition of a nutraceutical. Especially in Europe nutraceuticals have led to regulatory difficulties as authorities did not know whether to label nutraceuticals as food or as pharmaceuticals (Menrad, 2003). Nowadays in the EU nutraceuticals fall within the product category 'food supplements' which are defined as "concentrated sources of nutrients or other substances with a nutritional or physiological effect whose purpose is to supplement the normal diet" (EU, 2012). In the US nutraceuticals fall within the product category dietary supplements, which are defined as "a product taken by mouth that contains a "dietary ingredient" intended to supplement the diet" (FDA.gov, 2012).

The definition of a nutraceutical used in this study in short: 'A nutraceutical is a food or a part of a food with demonstrated safety and health benefits that go beyond the basic dietary needs and is presented in a nonfood matrix or nonconventional food format.' (for complete definition see introduction). This definition clearly differentiates nutraceuticals from functional foods, another product category that has emerged from the increased knowledge on the relationship between nutrients and health. Where functional foods are considered products in a conventional food format with added substances to promote a healthy state in an individual, a nutraceutical needs to be presented in a nonfood matrix or nonconventional food formats (Palthur *et al.,* 2010). The relationship between food, functional food, nutraceuticals, and pharmaceuticals is represented in Figure 2.1 (Dharti *et al*., 2010).

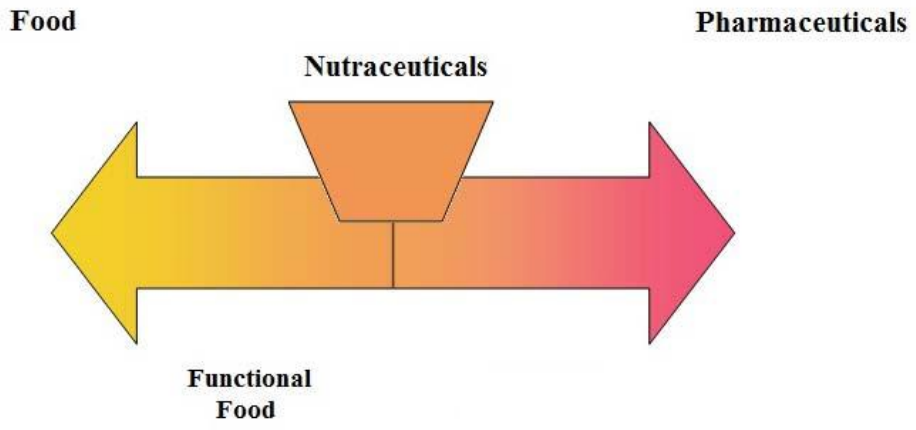

Figure 2.1 Relationship between food, functional food, nutraceuticals, and pharmaceuticals (Dharti *et al*., 2010, p34)

Since the early 1990s, the world has witnessed the explosive growth of a multi-million dollar nutraceutical industry with a global growth from $5.7 billion to $75.5 billion over the period 1999 – 2006 (Verbeke, 2005). In the dynamic and evolving nutraceutical industry opportunities emerge from various scientific disciplines, including genomics, proteomics, and metabolomics (Dureja *et al*., 2003). The opportunities emerging from the new developments in these disciplines provide an interesting growth market for companies from the food and pharmaceutical industry (Dureja *et al*., 2003).

Many nutraceuticals are being used as alternatives for both nutrition and medicine and seem attractive because they do not require an appointment with a health care provider and are easily available without a prescription (Dharti et al., 2010; Hilliam, 2000). Some examples of nutraceutical products are fish oil capsules containing omega-3 fatty acids for their benefits against heart disease, and antioxidant capsules and probiotic capsules to support the immune system. By providing such nutrients, nutraceuticals can provide essential substances needed for a healthy diet, and can supplement the diet with important nutrients in case of disease or the prevention of disease, thus adding to a healthier life (Dharti *et al*., 2010). However, since they are not regulated as pharmaceuticals and often do not undergo substantial scientific evaluation, their health benefits are often questioned (Dharti *et al*., 2010; Espín *et al*., 2007).

Thus because of their position between food and pharmaceuticals, nutraceuticals have witnessed regulatory difficulties and the EU and the US both have no definition for nutraceuticals. Also, despite the explosive market growth, the health benefits of nutraceuticals are often questioned, and nutraceuticals encounter problems regarding consumer acceptance (Granato *et al*., 2010; Lähteenmäki *et al*., 2010, among others). These issues are properties of the emerging nutraceuticals innovation system. Accordingly, the theory of innovation systems is discussed in the next section.

2.2 Innovation Systems

The process through which technological innovations emerge are complex and characterized by complicated feedback mechanisms and mutual interactions involving science, technology, learning, production, policy, and demand (Edquist, 1997; Lundvall *et al*., 2002; Negro, 2007). Because of this complexity, firms interact with other organizations in order to gain, develop, and exchange various kinds of knowledge, information, and other resources (Negro, 2007). Thus, innovation is not an isolated process but an interplay of actors in a certain context. This context is labeled as an Innovation System (IS).

Freeman (1987) was the first to introduce the concept of innovation systems, which he defined as "the network of institutions in the public and private sectors, whose activities and interactions initiate, import, modify, and diffuse new technologies". Later IS have been defined on different levels of aggregation such as National Innovation Systems (NIS) (Lundvall, 1992), Sectoral Innovation Systems (SIS) (Breschi and Malerba, 1997), and Technological Innovation Systems (TIS) (Nelson and Nelson, 2002). Thus, the NIS focuses on the national level, the SIS on the sectoral level, whereas the TIS uses a technology as a starting point and is not necessary limited to national boundaries or one particular industrial branch.

A model of a NIS is represented in Figure 2.2 (Kuhlmann and Arnold, 2001). The NIS represents a structural model of an IS and is used in this study to describe the current state of the European and US nutraceuticals innovation system. Figure 2.2 shows several blocks that build up the innovation system. The *demand side* is where demand for a product, technology, or innovation emerges. The *framework conditions* of an IS contains the financial environment, taxation and incentives (subsidies),

propensity to innovation and entrepreneurship, and mobility (Kuhlmann and Arnold, 2001). These make up the framework in which the actors within the IS have to operate. The *political system* consists of the national and regional governments, the governance, and the research and technological development policies. These have a profound influence on the framework conditions. The political system also affects the *education and research side* since many of these institutes are controlled by the government, such as universities and national research institutes. Furthermore, the political system affects the *infrastructure* of the IS through research and technological development policies that create intellectual property rights (IPR), standards and norms, and institutes that support innovation. The *infrastructures* in its turn support the education and research side and the industrial system in the development of technology and innovation. The *industrial system* consists of the firms that operate within the IS and links with the Education and Research side, sometimes supported by *intermediary organizations*.

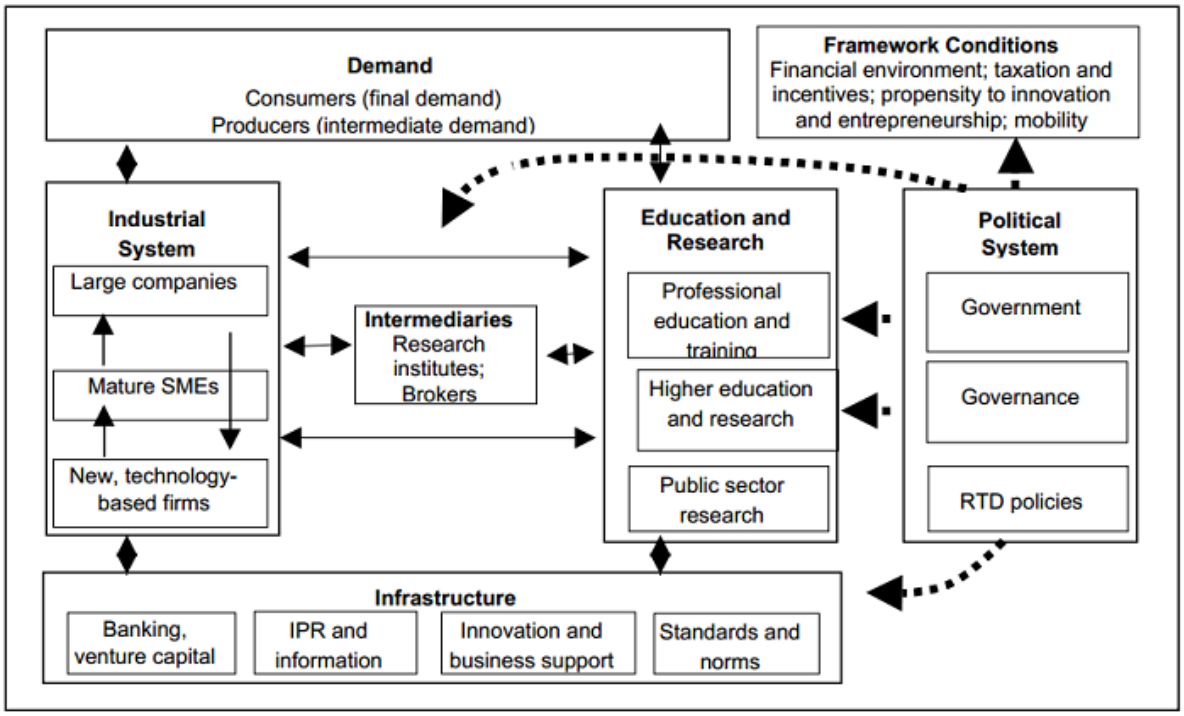

Figure 2.2 A national innovation system model (Kuhlmann and Arnold, 2001)

2.3 Technological Innovation Systems

The theory on Technological Innovation Systems (TIS) is rooted in evolutionary economic theorizing on socio-technical change and is part of the broader family of IS approaches such as NIS and SIS, as described above (Markard and Worch, 2009). Since TIS theory uses a technology as a starting point, a TIS can be national, regional, and international. Figure 2.3 shows the potential overlap of a technological innovation system with national innovation systems and sectoral innovation systems (Negro, 2007).

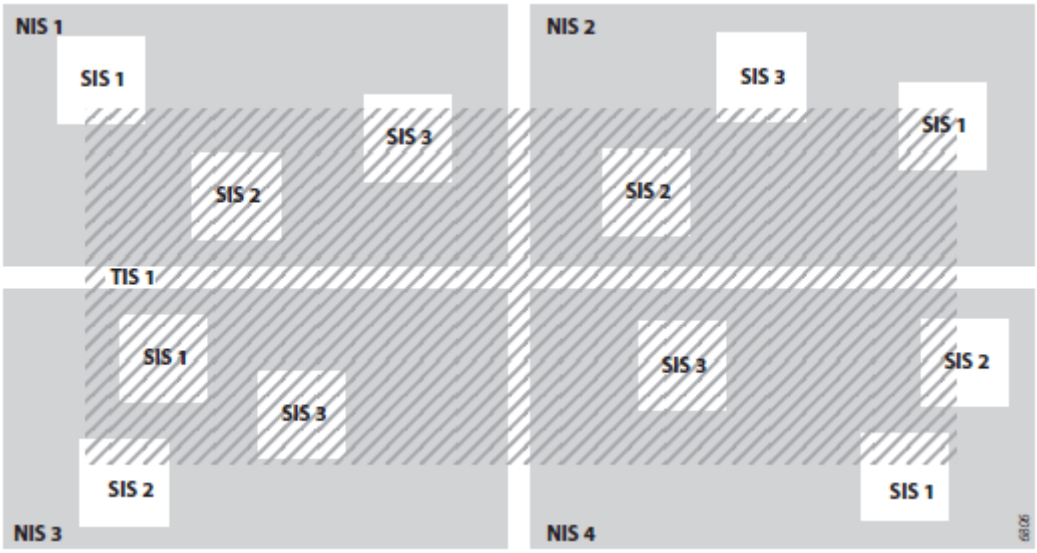

Figure 2.3 Potential overlap of technological innovation system within national and sectoral innovation systems (Negro, 2007, p27)

To study the nutraceuticals innovation system, the following definition of a technological innovation system is adopted from Markard and Truffer (2008, p611):

> "A technological innovation system is a set of networks of actors and institutions that jointly interact in a specific technological field and contribute to the generation, diffusion and utilization of variants of a new technology and/or a new product."

Actors can be individuals but are more often organizations such as firms, governmental organizations, non-governmental organizations, venture capitalists, universities, research institutes, etc. (Markard and Truffer, 2008; Edquist, 2005).
Networks link the actors and facilitate the transfer of tacit and explicit knowledge, and other resources (Jacobsson and Johnson, 2000).
Institutions are the rules (regulations, legislations social, cultural and technical norms, shared expectations etc.) that make up the rules of the game (Markard and Truffer, 2008; Edquist, 2005).

Therefore institutions are said to be passive and actors active; institutions evolve and change as a result of the effects of actors and the activities of actors (Markard and Worch, 2009).
A structural analysis according Figure 2.2 creates the first insight in the relevant actors, networks, and institutions of the European and US nutraceuticals IS. However, insight in the present structure of the nutraceuticals IS is not sufficient to understand the process of change and determine the TIS' strengths and weaknesses. To understand such process the dynamics of the IS need to be taken into account. The dynamics are understood as the interaction between the activities that influence the goal of the innovation system, where the goal is to contribute to the development and diffusion of innovations (Hekkert and Negro, 2009; Hekkert *et al*., 2007). Because in a TIS the number of actors, networks, and institutions is generally much smaller than in a NIS, complexity is reduced which makes a dynamic analysis possible (Hekkert *et al*., 2007). The activities that contribute to the goal of the innovation system (both positive and negative), are called 'functions of innovation systems'.

2.4 Functions of Innovation Systems

In order to understand the dynamics of a TIS, the activities that take place within the system are mapped, since the process of change is the result of many interrelated activities (Hekkert *et al*., 2007). For this goal the TIS approach has been developed; it enables to study the dynamics and the emergence of a new technology over time and enables to identify general patterns responsible for the course of the emergence of a new technology, including success and failure of the innovation system (Markard and Worch, 2009; Negro and Hekkert, 2008; Hekkert et al., 2007; Negro et al., 2007). The strength of the TIS approach lies in the focus on the system level as the core unit of analysis (Suurs and Hekkert, 2009; Hekkert *et al*., 2007). Since a TIS is not restricted by geographical and sectoral dimensions, the advantages of using the system level (meso-level) and a specific technology as a starting point are that it "cuts through both the geographical and the sectoral dimensions" (Hekkert *et al*., 2007, p416). Furthermore the TIS approach differentiates from other innovation system approaches by analyzing an emerging TIS rather than a mature TIS (Negro, 2007).
The TIS approach uses the central concept of System Functions of which seven are discerned. These System Functions are emergent properties of the interplay between actors and institutions (Hekkert *et al*., 2007; Negro *et al*., 2007). The more the seven System Functions are fulfilled, the better the performance of the TIS is expected to be, and the higher the chances for successful development, diffusion, and implementation of the new technology (Negro *et al*., 2008). Ultimately, TIS performance is measured by the market size of nutraceuticals. The seven System Functions are described below.

Function 1: entrepreneurial activities

Entrepreneurial activities are essential for an IS because without entrepreneurs there would be no innovation and the innovation system would simply not exist (Negro, 2007). These are activities in which the potential of new knowledge, networks and markets is converted into actions which will generate new business opportunities (Hekkert *et al.*, 2007). These activities are most commonly performed by new entrants or already existing firms that diversify their business strategy to take advantage of new developments in knowledge, networks, and markets (Hekkert *et al.*, 2007). Uncertainty is inherent with entrepreneurial activities and many forms of learning take place. According to their essential role in innovation and the IS, entrepreneurial activities are the most important indicator for the performance of an IS. When entrepreneurial activities lag behind, causes may be found in the other six functions (Hekkert *et al.*, 2007).

Function 2: knowledge development

The development of knowledge is essential for any innovation process. Therefore R&D and knowledge development are essential within the innovation system (Hekkert *et al.*, 2007). R&D activities are often performed by researchers but other actors can also be responsible for knowledge development (Suurs, 2009).

Function 3: knowledge diffusion

The role of networks is the exchange of information (Suurs, 2009). Adequate knowledge diffusion helps policy decisions to be consistent with the latest technological insights and R&D agendas to be affected by changing norms and values (Hekkert *et al.*, 2007).

Function 4: guidance of the search

Guidance of the search is an important activity and represents the process of selection. It can be seen as the activities that positively affect the visibility and the clarity of the specific needs among technology users (Hekkert and Negro, 2009). Guidance of the search involves numerous actors, such as governments, technology users, and technology producers, in which the technology itself is a variable instead of a constant (Hekkert *et al.*, 2007).

Function 5: market formation

New technologies often struggle to compete with existing technologies because the new technology is still in the development phase and not yet well adapted to existing standards and the functions it has to perform. Therefore diffusion will be slow (Hekkert *et al.*, 2007). A protected space for new technologies can overcome this, and can be created by temporary niche markets, favorable tax regimes or minimal consumption quotes, and activities in the sphere of public policies (Hekkert and Negro, 2007).

Function 6: resources mobilization

The input of resources, both financial and human capital, is necessary for all activities within the innovation system and for a specific technology. For a specific technology, the input of resources is necessary to create knowledge (Hekkert *et al.*, 2007).

Function 7: creation of legitimacy / counteract resistance to change

For a technology to develop well, it is necessary to fit into existing regimes or to replace existing regimes. Because of opposition from existing regimes, replacement of existing regimes can be catalyzed by advocacy coalitions (Hekkert *et al.,* 2007).

It can be stated that Functions 2 to 7 support Function 1: entrepreneurial activity; Functions 2 to 7 create the right climate for entrepreneurial activities to flourish (Negro, 2007). However the combination of all System Functions leads to system performance, and thus the fulfillment of all System Functions is essential for system performance.

To summarize, a structural analysis of the nutraceuticals IS according the NIS model and a dynamic analysis of the nutraceuticals IS according the TIS approach for both Europe and the US is made. The structural analysis enables an overview of the current state of the nutraceuticals IS and the dynamic analysis enables to study the dynamics and the emergence of the nutraceuticals IS. By comparing the results of the analyses of the European and the US nutraceuticals IS, it is possible to determine the strengths and weaknesses of the European nutraceuticals IS.

3. Methodology

This chapter will discuss the methods used to determine the strengths and weaknesses of the European nutraceuticals innovation system (IS) and to answer the two research questions. First the research design is discussed. It gives a general outline of the performed research methods. Next the operationalization of the System Functions is given. After the operationalization, the data collection methods are discussed, and next the data analysis is discussed. Lastly the validity and reliability of the used methods is discussed.

3.1 Research design

To answer the two research questions, first a structural and then a functional analysis of the European and the US nutraceuticals IS is carried out. The structural analysis gives a static description of the European and the US nutraceuticals IS according Figure 2.2 (p. 12). The TIS approach gives a dynamic description of the European and US nutraceuticals IS by performing a functional analysis by mapping the System Functions over time using a database of events (Hekkert *et al*., 2007). Also, semi-structured interviews are conducted to gain in depth information in the European nutraceuticals IS and to verify results of the historical event database analysis. By applying the TIS approach on the case of the European nutraceuticals IS the regulatory and acceptance problems regarding nutraceuticals in Europe are studied not in isolation but in relation to the entire TIS.

This study is an explorative research that uses a comparative case study to answer the research questions. Studying more than one case helps to establish relationships within the IS and creates more insight into the strength and weaknesses of the European nutraceuticals IS. For this comparison a qualitative research design is used; the TIS approach (Hekkert *et al*., 2007).

The analyses are meso-level analyses where the European and US nutraceuticals IS are the unit of analysis. The cases of the European and US nutraceuticals IS are being compared with each other. Although the US nutraceuticals IS is analyzed as well, the majority of the research is focused on the European nutraceuticals IS; the aim is to better understand the strengths and weaknesses of the European nutraceuticals IS. The case of the US nutraceuticals IS has been chosen as comparison with the European nutraceuticals IS because both are the most important world markets, next to Japan (Nutraingredients-usa.com, 2010). Because data on the US nutraceuticals IS is more accessible, using the US as comparative case gives an advantage over Japan. Also the US market is the largest and most rapidly expanding market of the world, in contrast to the European nutraceuticals market which lags behind in size and growth compared to the US and world nutraceuticals market (nutritionaloutlook.com, 2011, Basu *et al*., 2007).

3.2 Operationalization

The main part of this study consists of the analyses of the European and the US nutraceuticals IS according the TIS approach. Each of the System Functions is operationalized in various indicators based on the work of Hekkert *et al.* (2007) and Negro *et al.* (2008). Each of these indicators is represented by an event category. An indicator can either have a positive (+1) or negative (-1) contribution to the fulfillment of the System Function. Every single event from the event database is assigned to one event category and will get a +1 or -1 score. The scores are not weighted because their influence on the innovation system is unknown beforehand. The scores of all indicators within a System Function combined lead to an end score per year for each System Function. The results of the operationalization of the System Functions are given in Table 2.

Function 1: entrepreneurial activities

The essence of entrepreneurial activities is to convert knowledge into business. Indicators to measure entrepreneurial activities are the number of new entrants, the number of diversification activities of incumbent actors (Hekkert *et al.*, 2007). Accordingly the number of nutraceutical development projects started by new entrant and the number of projects started by incumbent actors are counted. Additionally the number of projects terminated regarding the development of nutraceuticals is counted.

Function 2: knowledge development

Knowledge development is essential for any innovation process (Hekkert and Negro, 2009). Accompanying activities include investments in R&D projects, the number of patents on nutraceuticals, and scientific research papers written on the subject of nutraceuticals (Suurs, 2009). Investments in R&D on nutraceuticals are assigned to Function 6: resources mobilization since initially this is the investment of a resource; no knowledge has been developed yet. The measurement of this System Function is therefore limited to the number of patents regarding to nutraceuticals and the number of scientific research papers published on the subject of nutraceuticals.

Function 3: knowledge diffusion

The role of this System Function is the exchange of information. The exchange of information occurs when actors in the nutraceuticals IS interact with each other. But not all interactions between the actors can be measured and not all of the interactions are relevant. The most relevant interactions between actors are meetings of professionals such as workshops, conferences or annual meetings, and coalitions between actors within the TIS (Suurs, 2009). Furthermore knowledge spillover occurs when mergers and acquisitions take place. Accordingly mergers and acquisitions are included as well.

Function 4: guidance of the search

Guidance of the search provides clarity about consumer needs and technological possibilities (Hekkert and Negro, 2009). Expectations expressed in scientific literature and newspapers are used as an indicator to map the state of the debate and measure the positive and negative expectations. Also expressed positive expectations and expressed negative expectations towards regulations are used as an indicator of Function 4.

Function 5: market formation

Market formation is about creating a protected space for the emerging technology in which it can develop (Hekkert and Negro, 2009). Niche markets provide such a protected space and are used as an indicator of market formation. An important factor to influence the creation of a market for nutraceuticals is market approval or ban of nutraceuticals by governments and the approval or ban of health claims by governments. Accordingly market approval and ban of nutraceuticals will be used as an indicator, and the approval or restriction on health claims on nutraceutical products will be used as an indicator of Function 5.

Function 6: resources mobilization

Resources are an essential input for all activities within the IS (Hekkert and Negro, 2009). Indicators for the fulfillment of Function 6 are (R&D) investments and subsidy programs in nutraceutical technology by governments, companies, and other organizations. Firms also collect money by the

issue of shares. Accordingly this is used as an indicator as well. Also an indicator is the expression of a lack of financial support by actors in the nutraceuticals IS.

Function 7: creation of legitimacy / counteract resistance to change

New technologies often encounter resistance from existing technologies or lobbying groups. Therefore legitimacy for the technology needs to be created. Indicators to measure the resistance and the creation of legitimacy are lobbying activities in favor of, and against nutraceuticals, and expressed positive and expressed negative sentiment towards nutraceuticals. Furthermore, since previous studies found that the European nutraceuticals industry encountered acceptance problems of consumers (Granato *et al*., 2010; Lähteenmäki *et al*., 2010; Ares and Gámbaro, 2007; Verbeke, 2005), this study includes consumer skepticism as an indicator of Function 7. Expressed negative sentiment towards nutraceuticals will not take positive or negative expectations towards regulations into account since this is an indicator of Function 4: guidance of the search.

Performance of nutraceuticals innovation system

The development of the performance of the nutraceuticals innovation system is measured according the market size of nutraceuticals in Euros or US $ per year. The size of the nutraceuticals market reflects the extent to which consumers adopt and use nutraceutical technology. Accordingly size of the nutraceuticals market reflects the performance of the nutraceuticals IS.

Table 3.1: Operationalization of the system functions (based on Negro *et al.,* 2008)

Function	Activity	Sign
Function 1: Entrepreneurial activities	Nutraceutical projects started by new entrants	+1
	Nutraceutical projects started by existing firms	+1
	Nutraceutical projects /firm stopped, not completed	-1
Function 2: Knowledge development	Patents for nutraceuticals	+1
	Scientific research articles	+1
Function 3: Knowledge diffusion	Workshops, Conferences, meetings	+1
	Mergers	+1
	Coalitions, network formation	+1
Function 4: Guidance of the search	Sources raising positive expectations about nutraceuticals	+1
	Positive expectations towards regulations	+1
	Sources raising negative expectations about nutraceuticals	-1
	Negative expectations towards regulations	-1
Function 5: Market formation	Creation of niche markets for nutraceuticals	+1
	Market approval	+1
	Lack of niche incentives	-1
	Restriction on claims/ban on nutraceuticals	-1
Function 6: Resources mobilization	(R&D) investments by companies	+1
	(R&D) investments by governments	+1
	(R&D) subsidies by organizations	+1
	Firm collects money by the issue of shares	+1
	Expressed lack of financial support	-1
Function 7: Creation of legitimacy / counteract resistance to change	Lobbying actions in favor of nutraceuticals	+1
	Positive sentiment towards nutraceuticals	+1
	Lobbying actions against nutraceuticals	-1
	Negative sentiment towards nutraceutical industry	-1
	Consumer skepticism	-1
Performance of the innovation system	Market size in Euros of nutraceuticals per year	€

3.3 Data collection

For the structural and TIS analysis of the European and the US nutraceuticals IS are two corresponding historical event databases were built. This method was developed Poole *et al.* (2000) and Van de Ven *et al.* (2000), and was refined by Negro *et al.* (2008) to be applied on a technological system level. The aim was to retrieve as many historical events relating to each nutraceuticals IS as possible. The retrieved events are listed chronologically in the database and receive a corresponding event number. Each event is listed with a reference to the original document and a description of the event. The events in the database can then be assigned to an event category within one of the System Functions in order to analyze the development of the nutraceuticals IS over time.

Before performing the structural and TIS analyses one exploratory interview was conducted with a manager/scientist with over 10 years of experience in the European nutraceuticals industry. This interview helped to create first insights in the European nutraceuticals industry, added to the understanding of the problems in the European nutraceuticals industry and helped to refine the operationalization.

Data for the historical event databases was collected by searching the LexisNexis database over the period 1990 – 2011 for events related to the nutraceutical sector. For the European nutraceuticals IS the search term used was 'nutraceutical', the geographical location was set on the European Union. The same procedure was followed for collecting data on the US nutraceuticals IS. The search term used was 'nutraceutical' and the geographical location was set on the United States. This resulted in over 7.000 articles for the European nutraceuticals historical event database and over 10.000 articles that needed to be analyzed for the US nutraceuticals historical event database. Due to time constraints it was needed to narrow down the amount of data to be analyzed. To keep the amount of data manageable but reduce the chance to miss out on important events the sources searched were limited to 'European news'. The results were then narrowed down by selecting nutraceuticals under the header 'markets'. For the US the sources searched were limited to 'US news'. Also for the US the results were narrowed down by selecting nutraceuticals under the header 'markets'. This yielded 4855 newspaper articles and press releases relating to the European nutraceuticals IS and 3799 newspaper articles and press releases relating to the US nutraceuticals IS. Thus, a more manageable amount of a total of about 9000 articles was retrieved for the European and US nutraceuticals IS together. All data retrieved was then going to be screened for events that were going to be assigned to an event category within one of the System Functions and to be added to the historical event database. The effect of narrowing down the results to the nutraceuticals market was that the domain of the study was narrowed down nutraceuticals market as well.

The scores for the event categories 'patents' and 'scientific research articles' within Function 2: knowledge development, have been obtained differently. For Europe the score for 'patents' have been obtained by searching the Scopus database for patents registered at the European Patent Office (EPO) over the period 1990 – 2011 containing the word 'nutraceutical'. For each year the number of patents published at the EPO has been counted and a score per year for the number of patents has been given. This score has been included in the historical event database. The same has been done to obtain the score for patents in the US nutraceuticals IS, only then the patents published at the US patent office were counted.

The score for 'scientific research articles' has been obtained by searching the Scopus database for articles containing the word 'nutraceutical' over the period 1990 – 2011. These results have been refined by selecting either the European countries or by selecting 'US' under the header 'Country'.

For each year the number of scientific research papers available at the Scopus database has been counted which gave a score per year for the number of scientific research papers published. This score has been included in the historical event database.
The performance of the European nutraceuticals IS and the US nutraceuticals IS has been measured according the market size of nutraceuticals per year (€ or US $). Little data on both the European and the US nutraceuticals market size was publicly available. This data has been retrieved from press releases that reported data from Datamonitor and Euromonitor, and from scientific research papers that mentioned data on the market size of nutraceuticals in Europe and the US. Datamonitor and Euromonitor are independent research institutes and do not publish results; their data is only available on payment.

Furthermore, semi-structured interviews were conducted with experts in the field. Semi-structured interviews have the advantage that they can evoke answers that are unanticipated by the researcher and rich and explanatory in nature (FHI260.org, 2012). The interviews were conducted because these play an important role in gaining in-depth information from the actors and in verifying the results of the analysis of the European nutraceuticals IS. The interviews created insights in the perspectives of the different actor groups and unravel their underlying assumptions and motives regarding to nutraceutical technology. Furthermore, by discussing the results of the structural and dynamic analyses the interviews allowed to verify whether the interpretations of the data and the interpretations of the dynamics between the System Functions were sound. Altogether the interviews allowed to triangulate the date and played an important role in the understanding of the development of the European nutraceuticals IS.
The experts have been selected in such a way that, according to the structural representation of the innovation system (Figure 2.2), the demand, industrial system, education and research, intermediaries, and political system are all represented in the interviews. A total of 19 interview invitations had been sent to actors within the European nutraceuticals IS. 10 invitations had been sent to actors in the industrial system, 4 to actors from education and research, 3 to actors from the government, 1 to an intermediary organization, and 1 to an actor on the demand side. 8 European actors responded and were willing to be interviewed. To verify the results of the US nutraceuticals IS analysis a total of 15 interview invitations had been sent to actors in the US nutraceuticals IS. Unfortunately none of these US actors was willing to be interviewed. Table 3.2 shows the role of the interviewed experts in the European nutraceuticals IS. On request the interview data has been anonymized.
The interviews have been conducted face to face and have been recorded. The subjects that have been discussed during the interviews are: the role and responsibility of the interviewee in the nutraceuticals IS, the structural description of the nutraceuticals IS (its actors, relations, missing blocks), and each System Function. During the discussion of each System Function ambiguities from the dynamic analysis were discussed as well as important properties of the System Function. For example, for Function 1 the business climate was discussed and for Function 4 the relevant regulations and their impact on the industry were discussed. At the end of the interview the interviewee was asked for his opinion on the strong points and the weak points of the innovation system, and the future opportunities of the industry. The complete list of interview questions can be found in Appendix A.

Table 3.2: Interviews European nutraceuticals IS

Interview number	Date interview	Role within the European nutraceuticals IS
IV 1	22-11-2011	Secretary at Dutch Nutraceutical Association
IV 2	25-1-2012	General director at food and nutrition innovation support program
IV 3	26-1-2012	President at pro-biotic food supplement manufacturer Board president at food and nutrition innovation support program Board member at Dutch industry organization for nature and health products
IV 4	30-1-2012	Director at Dutch industry organization for nature and health products
IV 5	6-2-2012	Scientist food safety at Dutch inspection agency
IV 6	15-3-2012	Manager science and quality, specialist food safety, nutrition and health at the Netherlands Nutrition Center
IV 7	23-2-2012	Professor food science in the Netherlands
IV 8	21-3-2012	Professor/director at Utrecht University + Danone-research

3.4 Data analysis

The following analysis has been performed on the European and US historical event database separately. All the gathered data from the LexisNexis database has been scanned for events. Every event found has been assigned to one event category of the operationalization of the System Function and has been given a +1 (positive) or a −1 (negative) score, according to the positive or negative contribution of the event category to the IS. The single events were not weighted since the importance of an event was not known beforehand. Several events, such as endorsement practices, were difficult to assign to one of the event categories because of ambiguity; there was overlap with more than one event category. After assigning all events to one of the event categories, the ambiguous events were reviewed and assigned to the most appropriate System Function. In case of endorsement practices this was Function 7: creation of legitimacy / counteract resistance to change. The assigning of the events to the event categories resulted in an end score for every event category. All scores of the event categories within a System Function together resulted in a final score for each System Function per year. For each of the seven System Functions a graph has been plotted in that showed how the fulfillment of the System Function developed over time. The results on performance of the IS system for EU and the US respectively were given in a table instead of in a graph.

Next the interviews were conducted and analyzed by writing down the entire interview using the recording. The interview was then sent to the interviewee to determine whether the answers had been interpreted correctly and to correct possible errors.

After the interviews were conducted the results could be written. First the results of the structural analyses of the nutraceuticals IS were writing by using the interview data and the data of the historical event database. This gave an overview of the current state of the nutraceuticals IS.

Second, a narrative was created of the development of the nutraceuticals IS over the period 1990 – 2011. The interview data and the descriptions of the events in the historical event database enabled to create a detailed reconstruction of the development of the nutraceuticals IS from 1990 – 2011. Additionally to give a graphical representation of how the nutraceuticals IS had developed over the period 1990 – 2011, a graphical timeline of the most important events in the development of the nutraceuticals IS was created.

Third, the scores of the fulfillment of each System Function per year, the interview data, and the descriptions of the events in the historical event database enabled to create a detailed description of the fulfillment of each of the System Functions.
And lastly, to compare the European nutraceuticals IS and the US nutraceuticals IS, the results of the structural analysis, the narrative, and the fulfillment of the System Functions have been used. These results have created insights in what the important events in each TIS were that have shaped the TIS. These insights made it possible to compare the development of both TIS and identify the strengths and weaknesses of each TIS.

3.5 Validity and reliability

In order to ensure research quality it is important to meet certain requirements from a methodological point of view. Four criteria are commonly used to assess the quality of field research: construct validity, internal validity, external validity, and reliability.

Construct validity refers to the quality of the operational measures of the concepts being studied (Yin 2003). Two ways of increasing construct validity are using multiple source of evidence (source triangulation), and adopting different angles from which to look at the phenomenon at hand (investigator triangulation) (Yin, 2003; Eisenhardt, 1989). First, an exploratory interview helped to refine the operationalization, which increases the construct validity. Second, by using multiple sources of evidence such as press releases and expert interviews, the data has been triangulated, which also increases the construct validity. And last, by analyzing the results of the structural analysis, the narrative, and the fulfillment of the System Functions, different angles on the data are created, which also increases the construct validity.

Internal validity refers to whether causal relationships can be established between variables and results (Yin, 2009). The internal validity in case studies is often problematic but can be increased by a clear research framework, pattern matching techniques, and rival explanations (theory triangulation) (Yin, 2003; Eisenhardt, 1989). Conducting an exploratory interview increases the internal validity by facilitating the designing of the research and refining the operationalization. Also validating the data by conducting expert interviews increases the internal validity. Furthermore, by mapping events over time, the fulfillment of each System Function over time can be verified over time. Since events between the different System functions are related to each other in time, event sequences can be observed and thereby the interactions between System Function (Suurs, 2009)

External validity or generalizability refers to the domain to which the results of this study can be generalized (Yin, 2009). Because this research uses a case study design and applies to a specific technological innovation system, the external validity is difficult to establish (Yin, 2009). By comparing the cases of the European and US nutraceuticals IS with each other the generalizability is increased.
Reliability refers to demonstrating that the operations of a study can be repeated with the same results (Yin, 2009). Transparency through good documentation and clarification of research procedures and replication through a case study database ensure sufficient reliability (Eisenhardt 1989). By carefully documenting the process of data collection and data analysis this study is assured of a high level of reliability. Additionally, all data has been saved and the interviews have been recorded in order for other researchers to be able to view the data.

4. Results European nutraceuticals innovation system

This chapter provides the results of the analysis of the European nutraceuticals innovation system (IS) over the period 1990 – 2011. A total of 555 events were found and 8 interviews have been conducted. The results start with a structural analysis of the current European nutraceuticals IS according the innovation system framework of Kuhlman and Arnold (2001). Second a narrative is given showing the development of the European nutraceuticals IS. Third the fulfillment of each System Function is discussed separately. The references of the narrative of the European nutraceuticals IS and the references of the fulfillment of the System Functions of the European nutraceuticals IS can be found in Appendix B. This is done because adding the vast amount of references of the European nutraceuticals IS analysis amongst the general references would strongly decrease the searchability of all the references of the research. The historical event database can be found in an enclosed CD-ROM in Appendix E.

4.1 European nutraceuticals innovation system

Figure 4.1 (based on Kuhlmann and Arnold, 2001) gives a graphical representation of the European nutraceuticals innovation system. The several blocks within the picture describe the components of the European nutraceuticals IS. It needs to be noted that it is a simplified model that does not take the differences between the national nutraceutical innovation systems of the European Union member states into account. In the past the European nutraceuticals IS was fragmented consisting of different national nutraceuticals IS with their own political system, market, and demand. With the introduction of Regulation (EC) 1924/2006 on nutrition and health claims made on foods this significantly changed and one European market for nutraceuticals was created (IV4, Eur-lex.europa.eu (2), 2012).

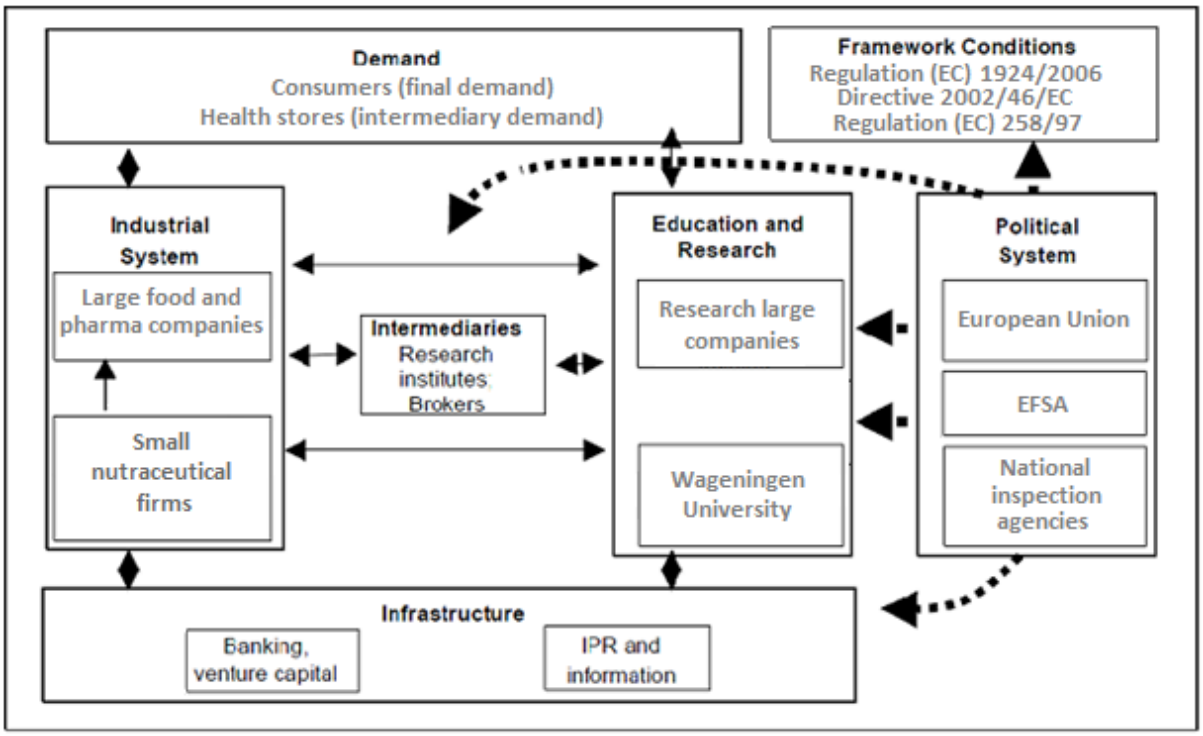

Figure 4.1 A structural framework of the European nutraceutical innovation system model (based on Kuhlmann and Arnold, 2001)

In the current European nutraceuticals IS the main actors in the *industrial system* are small firms that only produce nutraceutical products. The largest product categories are fish oil supplements and probiotics (European Health Claims Alliance, 2010). Besides the generally small life-science firms, larger firms originating from pharmaceutical and food industries are getting more involved in the nutraceuticals industry. Pharmaceutical companies are being attracted to the nutraceutical sector by the shorter development times and lower product development costs, and having expertise in organizing clinical trials to scientifically substantiate health claims. Food companies are being attracted to the nutraceuticals sector by having expertise in developing and marketing high quality food products (Menrad, 2000; Menrad, 2003). Some large players in the field are Nestlé, Danone, and Novartis.

On the *demand side* the main actors are end users. Another actor group on the demand side is health stores that buy nutraceuticals from producers and sell these products under their private label.

On the *education and research side* the main actors are Universities such as Wageningen University (WU) in the Netherlands. WU has a large influence on the knowledge on the relation between nutrition and health. Research departments of large companies also conduct research on nutraceuticals and the relation between nutrition and health in order to develop nutraceutical products. Smaller companies conduct little research because of the high costs involved.

The main actors in the *political system* in the past have been national governments. Nowadays however the EU has become increasingly important by building the institutions through regulations that influence the framework conditions and infrastructure. On the European level The European Food Safety Authority (EFSA) assesses whether and how national authorities comply with the regulations set by the European Commission, and intervenes when necessary. National inspection agencies monitor the national markets.

The *framework conditions* are largely set on European level. In European law nutraceuticals are labeled as food supplements. The most important regulations on European level that control nutraceuticals are Directive 2002/46/EC, which establishes harmonized rules for the labeling of food supplements and introduces specific rules on vitamins and minerals in food supplements (Eur-lex.europa.eu, 2012), Regulation (EC) 1924/2006 on nutrition and health claims made on foods (Eur-lex.europa.eu (2), 2012) and Regulation (EC) 258/97 on novel foods (Ec.europa.eu, 2012).

4.2 Narrative European nutraceuticals innovation system 1990 – 2011

The first proposal for a Directive on claims on food and food supplements circulated in the European Union in 1980 (Nutraceuticals International, 1-8-2002). Because agreement could not be reached the proposal was dropped and food and food supplements (including nutraceuticals) became subject to national regulations. In 1992, after several revisions, the proposal was resurrected but again it was dropped because the European Commission (EC) could not agree on its content (Nutraceuticals International, 1-8-2002). In 1993 Sweden was one of the first countries with regulations to control nutraceuticals (Nutraceuticals International, 1-7-1993).

In 1995 the first studies and patents regarding nutraceuticals showed up. The first research publication related to the role of omega-3 and omega-6 fatty acids in proper nervous system and visual functions, and the possible use of omega-3 and omega-6 fatty acids in nutraceuticals. A year later in 1996 the first entrepreneurial activities regarding nutraceuticals started to occur such as the German Sandoz Nutrition GmbH installing a new plant for nutraceutical purposes (Nutraceuticals International, 1-7-1996), and US company Nutrition For Life International Inc extending its operations to the UK (Nutraceuticals International, 1-9-1996). Also the first conferences and meetings were held

in 1996, such as a seminar organized by a consultancy and advisory grouping within the French drug industry called Industrie Sante (English: Health Industry). Besides scientific progress, the regulatory challenges for the nutraceuticals industry were also being discussed (Nutraceuticals International, 1-8-1996).

In 1996 the discussion of these regulatory challenges was the first sign that the nutraceuticals industry was going to encounter difficulties regarding to regulations. Because there was no European regulatory framework for nutraceuticals, nutraceuticals were subject to national regulations. Even in national regulations within EU countries there was no definition of a nutraceutical, and countries were very reluctant in providing a marketplace for nutraceuticals. To illustrate, according to Nutraceuticals International (1-8-1996), the German health authorities appeared to have launched a virtual assault on dietary supplements and nutraceuticals. German health authorities accused manufacturers of dietary supplements and nutraceuticals of bringing pharmacologically-active products onto the market as dietary supplements and nutraceuticals to avoid a costly approval process. Another example of this reluctance is when in 1996 the UK Department of Health's Advisory Committee on Borderline Substances recommended the removal from National Health Service prescribing of more than 200 unlicensed vitamins, minerals and supplements, as well as other products (Nutraceuticals International, 1-12-1996).

Besides national governments being reluctant towards nutraceuticals, the general public was also suspicious towards nutraceuticals. Consumers were especially skeptical about health claims on nutraceuticals as appears from several studies: one study performed in 1997 by the UK National Consumer Council People found that health claims were often confusing and misleading and thus meaningless to most people (Nutraceuticals International, 26-2-1997). Additionally, a UK Advertising Standards Authority research report from August 1997 found that 35% of advertisements for vitamins, dietary supplements, and nutraceuticals were considered unacceptable and had broken the British Codes of Advertising and Sales Promotion.

Also in 1997 the first European regulation was designed which was going to have an impact on the nutraceuticals industry: Regulation (EC) 258/97 on novel food and novel food ingredients. According to Regulation (EC) 258/97, foods and food ingredients that had not been on the European market in the EU before 15 May 1997 are considered novel foods and novel food ingredients (Ec.europa.eu, 1997). To market a novel food or novel food ingredient, companies must apply to an EU country authority for authorization, presenting a scientific information and safety assessment report. Since the nutraceuticals industry sometimes works with new substances this was the first EU regulation with which the industry had to comply.

Regulations to control nutraceuticals were differing widely throughout the EU, which had a blocking effect on the marketing of nutraceuticals in Europe. During the period 1996 – 2000 all over the EU it was being acknowledged that current legislation was not equipped to deal with nutraceuticals. For example: in 1996 Paul Britten criticized the legislative framework in the UK, which he called outdated because it was never designed to deal with nutraceutical products (Nutraceuticals International, 1-1-1997). Also, in 1996 Green Party European Parliamentarian Paul Lannoye of Belgium sent a report to the European Parliament in which he highlighted the bureaucratic and legal obstacles which confront the European nutraceuticals industry (Nutraceuticals International, 1-1-1997).

The borderline products[1], as nutraceuticals and functional foods were called by the British government, were a source of frustration for both companies and the regulatory authorities because there was no regulatory framework for these products. Each EU member state was applying either national food or pharmaceutical regulations. As a result national regulations in the different EU countries were completely different from each other (Nutraceuticals International, 1-7-1996). Conferences and meetings were organized on a regularly basis (mainly in the UK) to discuss these regulatory challenges (Nutraceuticals International, 12-9-1996; 1-1-1997; 1-10-1997).

In a response to these problems several European nutraceutical and nutritional industry associations start lobbying in 1998 for the harmonization of European regulations (Nutraceuticals International, 1-7-1998). At the end of 1998 lobbying activities were getting more widespread with Lord Donoughue, a UK government's spokesman in the upper chamber of parliament, pleading for harmonization of regulations on nutraceuticals on a European level (Nutraceuticals International, 1-12-1998). Also, the Proprietary Association of Great Britain[2] established a working party to oversee its new public relations program related to vitamins, minerals and supplements (Nutraceuticals International, 1-11-1998).

Despite the lack of harmonization of regulations there was confidence in a growing nutraceuticals market in Europe in 1998, endorsed by large investments in nutraceuticals by Danone and Nestlé (Nutraceuticals International, 1-5-1998). Following Danone and Nestlé, Novartis and Numico also directed their strategy towards nutraceuticals (Extel Examiner, 27-8-1998; 27-8-1998). By the year 2000 there was still an ongoing uncertainty about European regulations, a lack of harmonization of European regulations, and investments in the European nutraceutical industry were declining. Most large companies that had entered the European nutraceuticals market at the end of the 1990s were exiting the industry again after 2003 because they could not obtain significant market shares.

In 2002 new EU regulations were designed that influenced the marketing of nutraceuticals. Directive 2002/46/EC relating to food supplements established harmonized rules for the labeling of food supplements and introduced specific rules on vitamins and minerals in food supplements. Also in 2002 the European Commission published a draft proposal for a regulation on nutrition, functional, and health claims made on foods (Nutraceuticals International, 1-8-2002). The European nutraceuticals industry was optimistic and was expecting improvements in the complex regulatory systems by which it was controlled. The proposed European directive on food supplements was expected to result in a market with adequate freedom for the industry to operate in (Nutraceuticals International, 1-12-2001). However, when the new Food Supplement Directive proposal was published it forbade non-specific claims, which proved to be most efficient in marketing (Bech-Larsen and Scholderer, 2007). After consultation with EU member states, consumer groups, and the food industry, the European Commission withdrew the draft for further revision.

After several revisions the Food Supplements Directive 2002/46/EC came fully into effect on August 1, 2005. The Directive however was only half finished with important aspects such as the upper limits for vitamins and minerals in food supplements being significantly delayed. As a result of the gaps in the legislation many of the individual member states of the EU were reverting back to their original legislation (Nutraceuticals International, 1-12-2004).

[1] Nutraceuticals and other new products arriving on the market accompanied by health claims for which no regulatory framework was established were being referred to by the British government as borderline products.

[2] Proprietary Association of Great Britain is the UK trade association for manufacturers of over-the-counter medicines and food supplements

In 2006 new regulations on nutrition and health claims made on foods were introduced. Regulation (EC) 1924/2006 was initially embraced by the nutraceuticals industry. Finally there were uniform regulations throughout the EU which would aid the marketing of nutraceuticals on a European level. As a result firms start to invest in nutraceutical projects again. However this positive sentiment did not last for long. Soon the industry became aware that the criteria of scientific substantiation would be similar to those set out in 2003 by PASSCLAIM (Process for assessment of scientific support for claims on foods), a European Commission Concerted Action Project (Nutraceuticals International, 1-10-2006). PASSCLAIM had established guidance on the criteria that should be used when assessing the scientific credibility of a proposed claim. These criteria were very stringent and cover the number of subjects in the study, subject compliance, the validity of relevant bio-markers, the duration of the study and a number of other parameters (Nutraceuticals International, 1-10-2006). The required level of scientific substantiation for the approval of health claims was similar to the requirements pharmaceutical products needed to meet (IV1). Peter Berry Ottaway[3], an important nutraceuticals industry insider, foresaw the industry would encounter many problems to meet the criteria set out by PASSCLAIM and emphasized that 2007 would be a challenging year for the nutraceuticals industry (Nutraceuticals International, 20-10-2006). Because mainly small firms are active in the European nutraceutical industry (IV3,4,6), very few nutraceutical firms have access to the funds needed to pay for clinical studies. Additionally, demonstrating the relationship between a nutraceutical product (which often consists of many active components) and human health (there is no objective reference of what health is) is very difficult (IV1,2).

Coinciding with these negative expectations the entrepreneurial activities, market approval for new nutraceutical products, and the number of patents filed at the European Patent Office strongly declined in 2007.

After three years of less activity within the European nutraceuticals industry the number of patents regarding nutraceuticals filed at the EPO strongly increased in 2009, and the year thereafter the number of new nutraceutical product launches also started to increase again. These new nutraceutical products entering the European market were mostly products containing omega-3 fish oils. Despite this increase in entrepreneurial activity in the European nutraceuticals industry, the uncertainty concerning regulations persisted and the number of approved new health claims on nutraceutical products was still limited (Ec.europa.eu, 2011). In 2010 The Guardian (10-6-2010) reported that 80% of the health claims applied for under Regulation (EC) 1924/2006 was rejected by the European Commission and that the regulation was killing the nutraceuticals industry and the job losses were already being felt.

At the moment there is a list of 19 approved health claims and a bill has been designed in which about 200 new health claims are approved under Regulation (EC) 1924/2006 (IV7). The EFSA had received over 44.000 applications on health claims, and had reduced these to 2800 health claims that have been evaluated (IV5, IV6). Of the 2800 health claims about 200 health claims have been approved by the EFSA, which means that about 95% of the evaluated health claims have been rejected (IV7). These EFSA approved health claims still need to be approved by the European Parliament. The European Parliament is expected to vote on the bill in which the health claims are formulated mid 2012 (IV4,6,7). The European food supplement industry is heavily concerned about these developments and is expecting the market size in Europe for non-vitamin and non-mineral

[3] Peter Berry Ottaway is a food scientist and technologist with considerable experience in food law. As a consultant Peter Berry Ottaway specializes in the scientific, technological and legal aspects of dietetic foods, functional foods, food supplements and micronutrients.

containing food supplements, to which also nutraceuticals belong, to decrease with 25% from 2010 till 2013 (European Health Claims Alliance, 2010).

It can be concluded that European nutraceutical innovations have suffered from the uncertainty about regulations and the lack of one uniform market, both associated with lack of harmonized regulations in the EU. A timeline of the most important events that have influenced the development of the European nutraceuticals IS is represented in Figure 4.2.

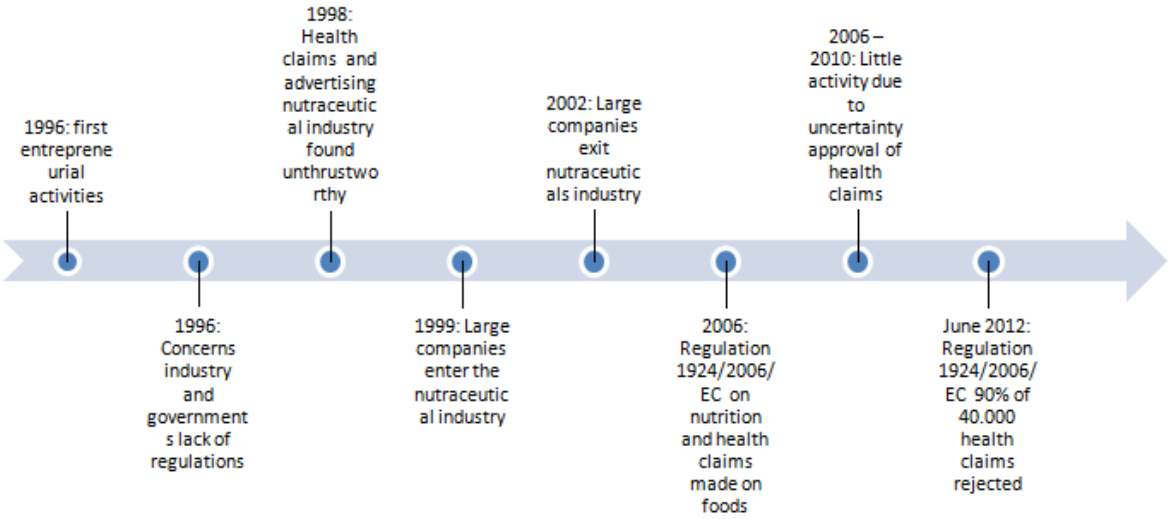

Figure 4.2 Timeline of important events in the European nutraceuticals IS

4.3 Results European nutraceuticals innovation system analysis per System Function

The following part discusses the results of the fulfillment of each System Function of the European nutraceuticals IS separately.

4.3.1 Function 1: entrepreneurial activities

The first nutraceutical related entrepreneurial activities in the Europe started to occur in 1996 with the German Sandoz Nutrition GmbH installing a new plant for nutraceutical purposes (Nutraceuticals International, 1-7-1996). The next couple of years till the end of 1999 several other small nutraceutical manufacturers entered the European nutraceuticals market. In 1999 the first large companies such as Novartis and Numico entered the European nutraceuticals market. They pursued an acquisition strategy in which small nutraceutical and food supplement companies were acquired in order to get a stake of the growing European nutraceuticals market.

After these large companies had entered the European nutraceuticals market a period of little entrepreneurial activity followed. No entrepreneurial activities were observed in the European nutraceuticals IS between 2000 and the end of 2002. This is graphically represented in Figure 4.3.

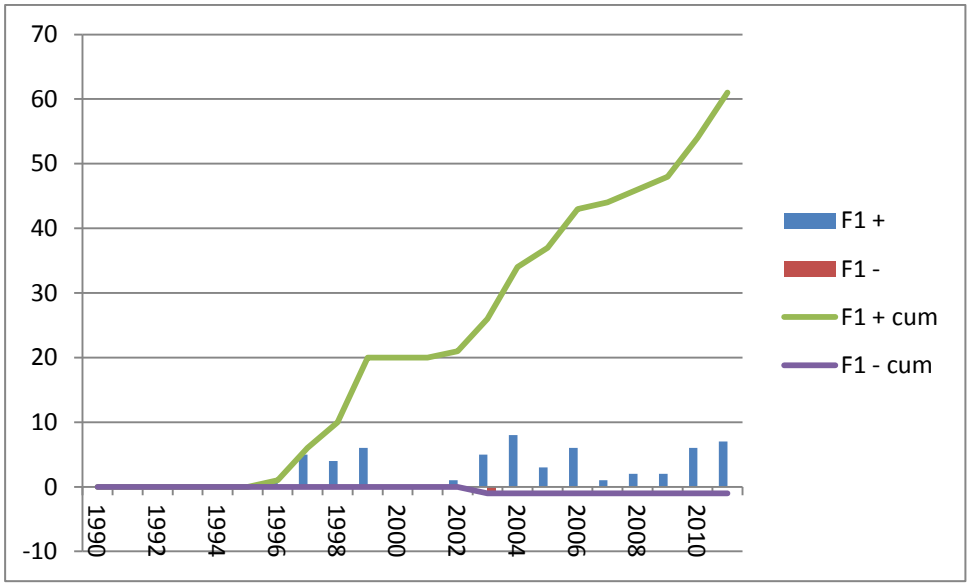

Figure 4.3 Score development Function 1: Entrepreneurial activities EU 1990-2011

At the end of 2002 entrepreneurial activities started to rise again. During the following years until 2006 a gradual rise of entrepreneurial activity was observed. These entrepreneurial activities generally came from small firms with different geographical backgrounds. Some were US or Canadian based firms starting entrepreneurial activities in Europe, but most were UK or Scandinavian based firms. For example, the Danish Nordic Phytopharma Group introduced Immulina, a natural immune-stimulatory nutraceutical, and the US nutraceutical firm Natrol expanded its operations to the UK (Nutraceuticals International, 1-5-2006; 1-6-2006). At the same time the large companies were struggling to obtain significant market shares. As a result most large companies exit the European nutraceuticals market for consumer products after 2003. Some large companies such as DSM and BASF however remained active in the nutraceuticals industry as a supplier of raw materials. A problem encountered by these large companies was their unfamiliarity with the patenting strategies in the nutraceuticals industry (IV3). Large companies (mainly pharmaceutical or nutritional based companies) were used at patenting their inventions, as this is common in their core business. In the

nutraceuticals industry however, patenting is far less common and small and medium sized companies (SME's) in the nutraceuticals industry relied to a large extent on trade secrets (IV3).
After new regulations on nutritional and health claims made on foods had been formulated in 2006 (EC 1924/2006) a strong decline in entrepreneurial activities and the number of patents granted at the European Patent Office (EPO) was observed. This was anticipated by Peter Berry Ottaway who noted in October 2006 that the industry would encounter many problems because of the new regulations (Nutraceuticals International, 20-10-2006). Ottaway realized Regulation (EC) 1924/2006 was going to have a profound impact on the marketing of nutraceuticals, functional foods, and supplements, and the use of health claims would require significant investments by suppliers of nutraceuticals (Nutraceuticals International, 10-2006).
In 2010 the entrepreneurial activities started to rise again, with several new products being launched on the UK market. Nowadays the business environment of the European nutraceuticals industry is considered difficult (IV3,4). Firms have difficulties bringing innovative products on the market, which is characterized by a high level of 'me-too' products (IV3,5). Also, more and more firms pursue a business model similar to the pharmaceutical industry, in which one illness is treated by one substance (IV2,8). However, the strength of nutraceuticals should be fighting illness with a natural product that contains several active ingredients instead of just one (IV2,8). Also the industry has been focusing on making products with higher concentrations. Because many nutraceutical products come from natural resources, this poses a risk of active ingredients losing their natural context and becoming ineffective (IV3). Thus, entrepreneurial activities in the European nutraceuticals industry are imitating business models of the pharmaceutical industry instead of focusing on the core strengths of the nutraceuticals industry (IV3).
At the moment still mainly SME's operate in the European nutraceutical industry (IV4,5,7). Large companies had tried to enter the European nutraceuticals industry but encountered problems regarding patenting and scientific substantiation of health claims. Where small companies generally undertake less research, large companies have higher reputations at stake and therefore give more importance to the value scientific substantiation of their products.
However a growing number of large food and pharmaceutical firms is investing in the area between food and pharma and see opportunities in products such as nutraceuticals (IV8). These firms are aware that illness often is caused by a combination of factors and that food related products can address multiple targets (IV8). Industry entrepreneurs have especially high expectations of the increased acceptance and use of nutraceuticals in (preventive) healthcare and personalized nutrition (IV2,3,4,8). Nowadays medical practitioners are still unfamiliar with personalized medicine. However, due to the rising healthcare costs and the decreasing number of new products brought to the market by pharmaceutical companies, personalized nutrition an nutraceuticals provide new opportunities since these are relative unexploited areas in healthcare, (IV2,3,4,8).
Developments in personalized nutrition are expected to be driven by improved methods of fast and accurately screening individuals on their dietary needs/shortcomings (IV2,3). This will allow providing patients with a tailored nutraceutical product. Critics expect products to become too expensive. Supporters, however, think that people are willing to pay a premium price since products serve their individual needs.

4.3.2 Function 2: knowledge development

The first research publications in Europe mentioning the term nutraceuticals showed up mid 1990. One of these studies discussed the possible use of omega-3 and omega-6 fatty acids in

nutraceuticals, which could benefit proper nervous system and visual functions. Two other publications related to the angiotensin-converting-enzyme (ACE) inhibiting properties of α-lactalbumin and β-lactoglobulin. ACE is related to the regulation of blood pressure, and ACE-inhibitors are used to treat high blood pressure. Even though these were the first research publications mentioning the term nutraceuticals, studies relating to active ingredients were already in progress before mid 1990. Researchers were only starting to use the term nutraceutical mid 1990 (IV2,3,4,7). Especially research on the relationship between health and certain plants, such as the blood cholesterol lowering properties of plant sterol esters, was subject of several studies before the 1990s.

It took until 1999 for a real onset in research publications and patents applications using the term nutraceutical to occur. From 2001 till 2005 the number of patents per year outnumbered the number of studies per year (see: Figure 4.4). Despite very little investments in nutraceutical research projects were observed during this period, there is a relative high amount of patents. About a quarter of the patents issued during this period are property of large companies such as DSM, BASF, and Novartis. These companies were focused on patenting their inventions, whereas SME's in the European nutraceuticals industry relied to a large extent on trade secrets (IV3). When some of these companies exit the European nutraceuticals industry after 2003 because they could not obtain significant market shares, the number of new patents started to decline. However the number of research publications on nutraceuticals in scientific journals tripled (see: Figure 4.4).

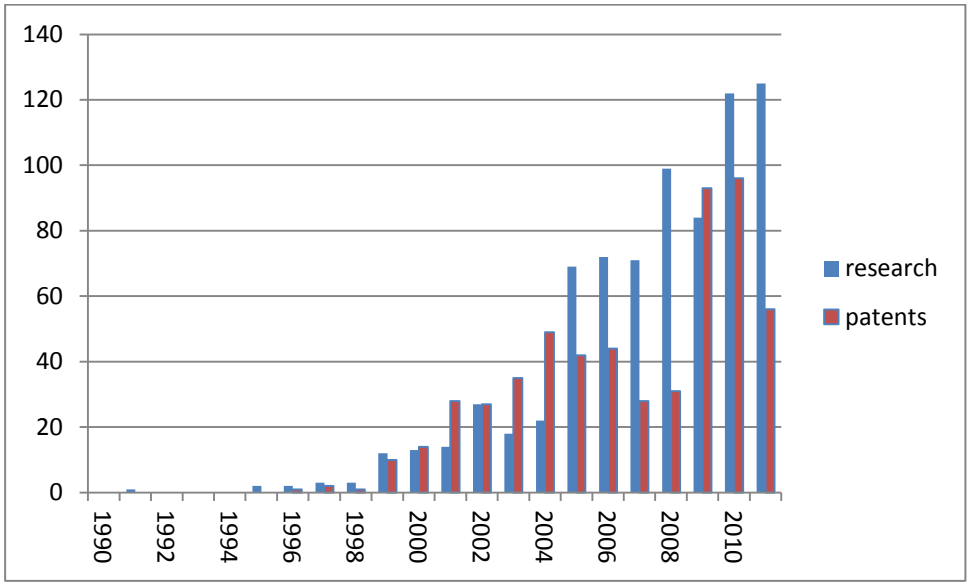

Figure 4.4 Score development Function 2: Knowledge development EU 1990-2011

The increase in research publications on nutraceuticals after 2004 in scientific journals might be related to the increasing popularity of the term nutraceuticals among scientists (IV2). After 2008 something remarkable happens; the number of granted patents tripled to 93 new patents registered at the EPO in 2009, the reason for this is left unexplained.

Nowadays the European nutraceuticals industry relies on existing knowledge regarding the influence of compounds in food on human health, and little investments are being made in the development of new knowledge (IV4,5,7). This results in a homogenous marketplace with little differentiation between the products. Also the industry follows a paradigm where one illness can be cured with one active ingredient that acts on one target (IV2). In this respect a shift in focus where a variety of active

ingredients leads to a desired effect will create more opportunities to innovate. This development should correspond with improved methods accurately screening individuals on their dietary needs/shortcomings and can lead to personalized nutrition (IV2,3).
Despite the significant amount of patents, industry experts state that patents play a minor role in the nutraceuticals industry and are expected remain so in the future. Because many products in the nutraceutical industry are naturally based (plants, bacteria) it is difficult to obtain a patent on a nutraceutical (IV2,3,6). Relationships between the active substances and human health are being discussed for longer periods of time, therefore putting such an active substance in a pill is not sufficient enough to obtain a patent (IV3). Furthermore, a patent requires revealing the invention, including the production process. The exclusivity obtained by the patent often does not compensate the revealing of the invention (IV3).

4.3.3 Function 3: knowledge diffusion

The first observed activity in the European nutraceuticals IS within Function 3: knowledge diffusion was in 1996. A seminar was organized by the French drug industry in which the roles of the different players involved in the development and regulation of health food products was discussed (Nutraceuticals International, 1-5-1996). All over Europe, but mostly in the UK, conferences and meetings were organized like "Functional food, nutraceutical or pharmaceutical; technical developments and the regulatory challenge" (Nutraceuticals International, 12-9-1996). Many of these meetings focused on the opportunities and the regulatory issues regarding nutraceuticals (Nutraceuticals International, 13-3-1997; 17-5-1999).
The first network was formed in 1975: 'The European Federation of Associations of Health Product Manufacturers' (EHMP). The EHPM represents health products manufacturers in Europe, including manufacturers of herbal preparations, functional foods, nutraceuticals, and food supplements. The EHPM has national member associations throughout the EU. Some of the most active members within the EHPM are the French, English and Dutch member associations (IV4). In 1998 the European Responsible Nutritional Alliance (ERNA) was founded to represent major food supplement manufacturers and suppliers such as BASF, Bayer, DSM, and Herbalife (Nutraceuticals International, 1-7-1998). The International Alliance of Dietary/Food Supplement Associations (IADSA) was also established in 1998 to face up to the increasing globalization of markets and global regulatory challenges in the vitamins and supplements sector (Nutraceuticals International, 20-3-1998).
In 1999 the first alliances between companies were observed in the European nutraceuticals IS. UK drug wholesaler AAH Pharmaceuticals has joined forces with Roche to study trends in the UK vitamins, minerals and supplements sector (Nutraceuticals International, 1-2-1999), and the French based company Thallia Pharmaceuticals entered into a research agreement with the UK based Rowett Research Institute for the development of nutraceutical products (Nutraceuticals International, 1-4-1999).
Also in 1999 the Dutch Koninklijke Numico NV started its acquisition strategy with the acquisitions of the German nutraceutical companies Viva GMBH and Pharma Burger GMBH & Co, and the acquisition of the UK based company Larkhall Natural Health (AFX news, 7-1-1999; Extel Examiner, 15-1-1999). Thus, Numico illustrated that large companies have tried to obtain a stake in the European nutraceuticals market. Numico CEO Hans van der Wielen set the company's target in increasing nutraceuticals and health food sales to 1 billion Dutch guilders by the end of 2003 from the 261 million Dutch guilders in 1999, mainly through acquisitions (Extel Examiner, 12-3-1999). This strategy failed however and in 2003 Royal Numico was almost bankrupt and finally admitted defeat

in its battle to carve out a successful and significant niche in the vitamins and supplements sector by selling off its nutraceutical units (Nutraceuticals International, 1-11-2003). In 2007 Numico went back to its core business (baby food), performing well again and was acquired by the French Groupe Danone (sync.nl, 2007).
Another large player in the field of nutraceuticals was Merck KGaA which in 1996 acquired the British company Seven Seas (Nutraceuticals international, 1-6-1996). In 2000 Merck KGaA officially stated that it was firmly committed to its activities in the nutraceuticals arena, and was expecting revenues from this business to double by the end of 2002 (Nutraceuticals International, 1-10-2000). Currently Merck S.A. C.V., a subsidiary of Merck KGaA is still active in the nutraceuticals industry (Fero industries, 1-7-2011).
In the meantime many conferences and meetings were being held and a steady amount of event was observed every year within Function 3 (see Figure 4.5).

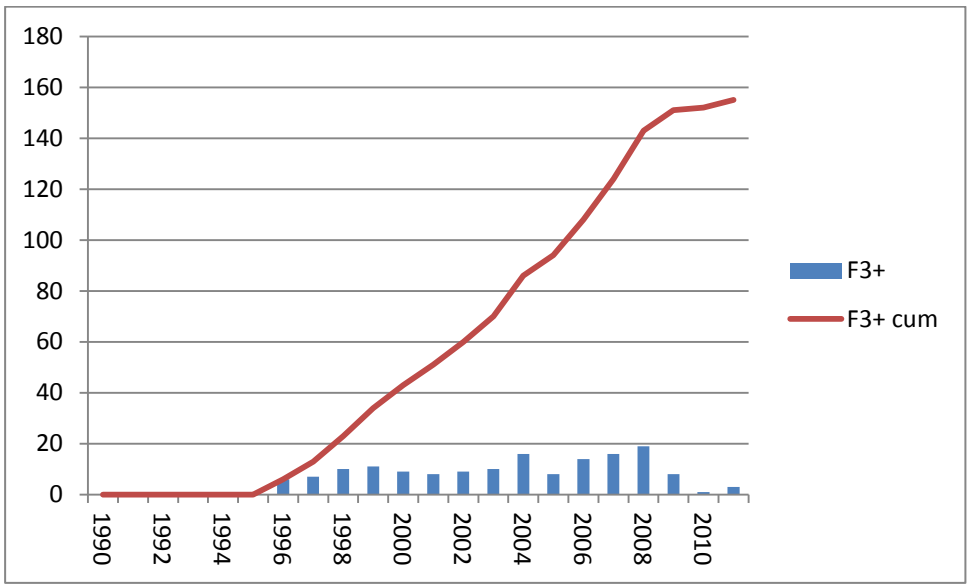

Figure 4.5 Score development Function 3: Knowledge diffusion EU 1990-2011

Most of these conferences focused on the consequences of the European regulations on nutraceuticals and food supplements, and how the European nutraceuticals market would look like in the future (Nutraceuticals International, 26-5-2004; 1-2-2004; 19-11-2003). Not only the industry was holding conferences and meetings on European regulations on nutraceuticals and food supplements, also national and European governmental institutions had difficulties with the unclear regulations and were holding conferences on the topic (Nutraceuticals International, 1-12-2006; 21-10-2005; 1-5-2004). Therefore, in an attempt for clarity and transparency, the European Commission had issued a "questions and answers" statement on the proposed European Union Nutrition and Health Claims Regulation in 2007 (Nutraceuticals International, 1-7-2007). Later that year, in response to all uncertainties regarding European regulations, the EFSA had published a guidance on how to request approval of health claims under Regulation (EC) 1924/2006 (Nutraceuticals International, 1-8-2007). While mergers, acquisitions, and network formation were still taking place from 2006 to 2009, the ambiguity and concerns regarding the European regulatory framework remained (IV3,4). At the end of 2008 regulators, scientists, and industry representatives came together in Prague to discuss the food supplement industry's top four regulatory concerns (Nutraceuticals International, 1-11-2008). These concerns were the setting of maximum levels for

vitamins and minerals, the approval of health claims, the future of botanical ingredients in food supplements, and the recently adopted regulation on free movement of goods (EU Regulation No 764/2008).
These industry's concerns were being confirmed when in July 2009 80% of submitted claims had been rejected by the EFSA (Nutraceutical Business & Technology, 2009). The industry assumed that 95% of all submitted health claims will be rejected after all applications have been reviewed by the EFSA (European Health Claims Alliance, 2010).
Besides the EHPM, ERNA and IADSA another international industry organization is the European Nutraceutical Association (ENA). As a partner of the American Nutraceutical Association (ANA) the ENA is a relatively new organization founded in 2005 that provides a scientific platform for nutraceuticals. From the industry, concerns are expressed about the gap between scientific institutes and the nutraceutical industry. There is a lack of conferences where universities and industry meet and knowledge development is not in line with market needs. More effort should be devoted to open collaborations between universities and the industry in which needs and knowledge are being freely exchanged (IV3).

4.3.4 Function 4: guidance of the search

Especially regulatory issues, and to a lesser degree scandals such as the questioning of efficacy and the contamination of fish oil supplements with dioxin have played an important role in the development of the European nutraceuticals IS (IV1). Regulatory issues have caused a lot of uncertainty about how the industry would develop and what was allowed, especially regarding to health claims made on nutraceuticals (IV1,3,4).
In 1993 the first Act on natural remedies, which included nutraceuticals, came into force in Sweden (Nutraceuticals International, 1-7-1993). Then in 1996 the first concerns relating to regulations were expressed by Paul Britten of the UK Medicines Control Agency Borderline Section. Paul Britten said legislation was outdated and nutraceutical products were technically outside the law. The borderline products were a source of frustration both for companies and the regulatory authorities because there was no clarity about regulations and regulations between different countries were often in conflict with one other (Nutraceuticals International, 1-7-1996). Each member state was free to apply national legislation. As a result a product could be considered a food or a pharmaceutical depending on which country the product was being sold (Nutraceuticals International, 1-7-1996). Many negative comments were placed against regulatory issues throughout EU countries from 1996 till 2000. For example, Peter Berry Ottaway called for a definition of the term 'food supplement', which didn't exist in 1998 (Nutraceuticals International, 1-6-1998). Also, a joint venture between the UK's consumer organizations, enforcement authorities (including the Medicines Control Agency), and industry bodies, named the Joint Health Claims Initiative, was calling the regulations regarding health claims both incomplete and inflexible (Nutraceuticals International (2), 1-6-1998).
However during the same period many positive expectations about a growing nutraceuticals industry in Europe were expressed as well: Jean-Christian Kipp, general director of management consultancy firm Arthur D Little in France, expected the attitudes of Europeans towards nutraceuticals were about to change (Nutraceuticals International, 1-8-1999). Also Euromonitor, a world leader in strategy research for consumer markets, was expecting a strong growth of the nutraceuticals market fostered by a wider acceptance of self-medication and increasing health awareness (Nutraceuticals International, 1-2-1999).

Nevertheless, the diversity of regulations between countries made it very difficult for companies to internationally market their products (IV3,4). For instance, in The Netherlands there was a very liberal policy, probably the most liberal in Europe, in which products could be accompanied with health claims as long as they were not misleading (IV5). The burden of proof lied with the government. German law on the other hand was much stricter on nutraceuticals and more liberal on pharmaceuticals. As a result products that would be considered food supplements[4] in the Netherlands could be considered pharmaceutical products in Germany (IV3,4). Even within the different Bundesländer in Germany different regulations were applied (IV5). Even though since January 1993 controls on the movement of goods within the internal market of the EU had been abolished, nutraceuticals could not freely be transported across countries within the EU (Europa.eu, 2012).

In 1996 it was being acknowledged that current legislation was not equipped to deal with nutraceuticals. The European Commission had been attempting to introduce legislation on health claims made on food products for over 20 years, with the first proposal for a directive being circulated in 1980 (Nutraceuticals International, 1-8-2002). Since agreement could not be reached on how stringent and far-reaching legislation should be, the proposal was dropped and was resurrected in 1992. Again agreement could not be reached and the proposal was officially dropped again in 1995 with no prospect on developments in the near future. In 1997 Regulation EC 258/97 on novel food and novel food ingredients came into effect in Europe. The Commission considered foods and food ingredients that had not been used for human consumption to a significant degree in the EU before 15 May 1997 novel foods and novel food ingredients (Ec.europa.eu, 2012). To market a novel food or ingredient, companies must apply to an EU country authority for authorization, presenting the scientific information and safety assessment report. Five years later in June 2002, the Commission published a draft proposal for a regulation on nutrition, functional, and health claims made on foods (Nutraceuticals International, 1-8-2002). This was the first time a proposal spoke about health claims and it was the antecedent of regulations on health claims that would be established in 2006 The Directive 2002/46/EC relating to food supplements established harmonized rules for the labeling of food supplements and introduced specific rules on vitamins and minerals in food supplements. The aim was to harmonize the legislation and to ensure that these products were safe and appropriately labeled so that consumers could make informed choices. The European nutraceuticals industry was optimistically, expecting improvements in the complex regulatory systems by which it was controlled (IV1,4). The proposed European Directive on food supplements was expected to result in a market with adequate freedom for the industry to operate (Nutraceuticals International, 1-12-2001). However, the new Directive forbade non-specific claims, which proved to be most efficient in marketing. After consultation with member states, consumer groups and the food industry, the EC withdrew the draft for further revision. The food supplements Directive, which was adopted by the European Parliament in mid-2002, came fully into effect after several revisions on August 1, 2005. However important aspects such as the upper limits for vitamins and minerals were still absent in the new directive (Nutraceuticals International, 1-12-2004). The gaps in the legislation had led to many of the individual member states of the EU reverting to their original legislation (Nutraceuticals International, 1-12-2004).

Despite these difficulties regarding regulations, also a rise in positive expectations about a growing European nutraceuticals market was observed during this period. For example, the British newspaper

[4] official definition of nutraceutical products in The Netherlands and the EU

The Independent was calling the European nutraceuticals market a booming market, and Britons were one of the largest consumers of nutraceuticals in Europe (The Independent, 2005). Figure 4.6 shows this rise in positive events within Function 4 after 2004

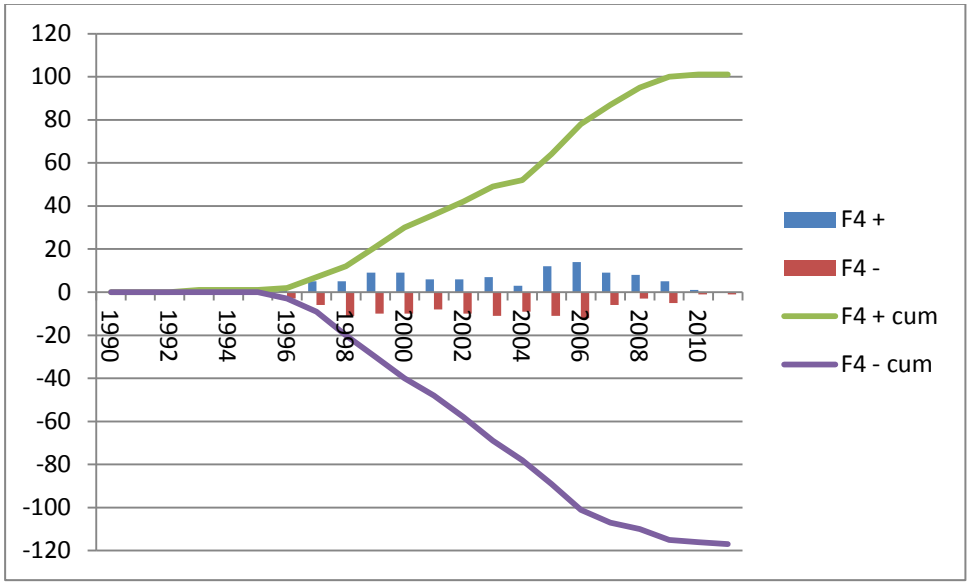

Figure 4.6 Score development Function 4: Guidance of the search EU 1990-2011

When in 2006 Regulation (EC) 1924/2006 on nutrition and health claims made on foods was finally adopted, concerns were being raised by companies because the conditions of the use of health claims were very strict. Regulation (EC) 1924/2006 was based on the precautionary principle. The precautionary principle states that in case of absence of scientific consensus whether an action or a policy might harm the public or environment, the burden of proof that the action is *not harmful* falls on those taking the action. In this case; claims would only be added to the permitted list after a full review of the scientific evidence by the European Food Safety Authority (EFSA). Accordingly it was expected that Regulation (EC) 1924/2006 would have a profound impact on the marketing of nutraceuticals, functional foods, and food supplements since many substances might not pass this evaluation. It would require a significant investments in clinical trials by suppliers of nutraceuticals in order to stay on the market because the current level of scientific evidence supporting the claims used by the industry was expected not to be strong enough (Nutraceuticals International, October 2006). As a consequence a number of health claims needed to be drastically modified or removed (Nutraceuticals International, October 2006).

The procedure in selecting whether a claim was going to be approved was as follows. Health claims could be submitted at national government bodies. Each EU member state then had to submit a list of claims submitted health claims in their country with scientific evidence to support the claim at the EFSA. Submissions by the industry, NGO's or trade bodies directly at the EFSA were not permitted. The national lists had to be submitted no later than January 31, 2008, which were then sent to the EFSA. The EFSA evaluated the claims on three criteria. First the structure of the active ingredient needed to be characterized. Second holistic claims in terms of general wellbeing were not allowed, and third the claim needed a sufficient amount of scientific substantiation (IV6). The EFSA was required to inform the European Commission of those claims that could be accepted before January 31, 2010. The total of 44.000 health claims that had been submitted at the EFSA was downgraded by the EFSA to 2.800 health claims which were going to be evaluated (IV7,6). Many complaints were

raised by the nutraceuticals industry on the application process (IV6). Neither the European Commission nor the EFSA had created a set of guidelines for the application procedure. As a result it was unclear to the nutraceutical industry how to apply for the approval of a health claim which caused confusion and resentment towards the European Commission (IV6).

The EFSA had a hard job on evaluating the submitted health claims and the evaluation deadline of 31-1-2010 was not met (The Guardian (London), 10-6-2010). On 10-6-2010 The Guardian (London) reported that 80% of 40.000 submitted health claims were rejected by the EFSA and that Regulation (EC) 1924/2006 was killing the nutraceuticals industry and job losses were already being felt. According to an assessment by the nutraceutical and food supplement industries in 2010, 95% of health claims for 'other substances' (non vitamin and mineral containing) food supplements was going to be rejected (European Health Claims Alliance, 2010).

However, some companies in the nutraceuticals industry such as Winclove have said to initially embrace Regulation (EC) 1924/2006 because it could abolish junk products from the market and increase the trustworthiness of the nutraceuticals industry (IV3,4). Nevertheless the *implementation* of Regulation (EC) 1924/2006 has been criticized by the industry, such as Winclove and the Natuur- & gezondheids Producten Nederland[5] (NPN). The implementation of Regulation (EC) 1924/2006 was too rigorous and left little freedom for the nutraceuticals industry to operate: when a claim was not fully scientifically proven, the claim could not be used in communications to consumers (including marketing and labeling of products), even when safety was proven and health benefits were likely (IV3). Suggestions by the industry have been made at the European Union to eliminate the worst junk products from the market and then slowly increase the level of scientific substantiation needed for the use of a health claim (IV2,4). This would allow nutraceutical manufacturers in time to increasingly support the claims made on their products with scientific evidence. Also suggested was the introduction of a grading system in which products were allowed to use health claims that are very likely but not fully scientifically proven in combination with an indication to the degree of uncertainty (IV2,4). This would create an incentive to develop new products since they can be marketed in an earlier stage. From here on manufacturers could then invest their money to fully proof the efficacy of their product (IV,4). The European Commission however has not implemented such a system because it means that customers might be misled by a health claim since in essence it has not been scientifically proven (IV5). Also the question remained whether companies would invest in additional research to support their health claims once they were on the market (IV5). Where the nutraceuticals industry is pressing for a more liberal regulatory regime, scientists and government employees are stressing the importance of inspection (IV7,8). At the moment there is no European inspection agency that monitors the European market on the use of scientifically unsubstantiated health claims, and that can effectively ban products off the market that make scientifically unsubstantiated claims. These scientifically unsubstantiated products make it very difficult for companies that do invest in expensive clinical research to bring products on the market for a competitive price (IV8). In this way innovation in products that are proven to be effective is hampered and the industry is bringing few quality products to the market (IV8).

Despite these negative opinions of the industry towards the implementation of Regulation (EC) 1924/2006, Simon Pettman, director of international food and nutrition policy consultancy organization EAS, said that international regulators are closely monitoring developments regarding regulations in the European Union, as authorities in many countries increasingly look for models on

[5] Dutch industry organization for health products such as food supplements and herbal preparations

which to base their legislation (Nutraceuticals International, 1-6-2008). Whether Regulation (EC) 1924/2006 really is going to have a severe impact on the nutraceutical industry, nutraceuticals innovation, and the size of the nutraceuticals market will become clearer in the years to come.

Besides these regulatory issues slowing down the development of a nutraceuticals market, numerous of events, especially relating to fish oil supplements and probiotics, have raised positive expectations about a growing market. For example, the southern Welsh producer of fish oil products VeryWise Nutrition was growing rapidly and doubled its workforce in two years. The first positive signals about fish oil came from a meeting of a group of obstetricians who highlighted the benefits of fish oil in reducing high blood pressure during pregnancies (The Herald (Glasgow), 23-5-1994). For probiotics the first positive signals came in 2005 from reports in UK newspapers about a study published in the journal Clinical Nutrition which mentioned that the use of probiotic supplements could reduce the severity of common cold symptoms (Western Mail, 13-9-2005).

However, also negative expectations have been commonly expressed. In this regard the case of fish oil supplements and its questioning whether these supplements were beneficial to human health are characteristic to controversies in the nutraceuticals industry: after positive expectations were being raised about the health benefits of fish oil supplements, these positive expectations were tampered when fish oil supplements came widespread in the news from February to April 2006 because of dioxin contamination. (Nutraceuticals International, 1-5-2006; Chemist & Druggist, 22-4-2006). Elevated levels of dioxins in fish-oil supplements were discovered in first the UK, and afterwards in rest of Europe (Nutraceuticals International, 1-5-2006). This episode caused reputational damage for some companies such as Boots, a leading drugstore in the UK, which had to remove its home brand fish oil products from the market (Nutraceuticals International, 1-5-2006; Chemist & Druggist, 22-4-2006). Nevertheless, this negative publicity did not stick with the public for long (IV5,6). In 2006 a study was started in which fish oil supplements were given to school children to improve their behavior and concentration in the classroom. (Western Mail, 12-6-2006). Also, in 2007 NICE, the UK National Institute for Health and Clinical Excellence recommends doctors to prescribe fish oil supplements to patients who have had a heart attack as part of preventive measures (Pulse, 24-5-2007). The study of fish oil supplements with children and the doctors prescribing fish oil supplements suggests that the trust in the safety of fish oil supplement had recovered in Europe. While in 2010 trust in the safety of fish oil supplement seemed to have recovered and newspapers were talking again about the benefits of fish oil (Daily Mail (London), 13-7-2010), other sources still questioned the efficacy of fish oils in the period 2009 – 2011. For example, to contrary belief fish oil supplements were said to have no benefit to heart patients receiving optimal medical care according to Dr. Jochen Senges of the Heart Centre in Ludwigshafen and the University of Heidelberg in Germany (Business Recorder, 4-5-2009). Also, for patients undergoing cancer treatment fish oil could be harmful according to a study by the University Medical Centre Utrecht (Press Association Mediapoint, 12-9-2011,).

As with fish oil supplements, other scandals did not stay with the public for a long time. For example, the contamination of nutraceuticals with the carcinogenic substances called Polycyclic aromatic hydrocarbons (PAHs) in the Netherlands was hardly picked up by the media and thus did little damage to the industry (IV5). Also the controversy regarding to the efficacy of fish oil supplements as described above, can also be seen with other products such as probiotics, of which a study at Utrecht University found that adverse effects may occur in patients suffering from acute infection in the pancreas (The Statesman, 2008). Often there is no scientific consensus about the efficacy of nutraceuticals (IV5). This is the reason why of the 2800 evaluated health claims only about 200 have

been approved (IV6,7). All of the health claims relating to botanicals and probiotics have been rejected because of insufficient characterization of the active substance or bacteria (IV6,7). There are two ways in how the number of approved health claims can increase in the future. First the bill which lists the approved health claims still needs to be approved by the European Parliament. The voting on this bill is expected to take place somewhere mid 2012. If the European Parliament does not approve the list then a more liberal regime with more approved health claims could be the result (IV6). The other way how the number of approved health claims could increase, is when the industry is able to accurately characterize probiotic bacteria stems and the active substances in botanicals (IV6).

Concluding, many regulatory issues have occurred and also several scandals have occurred. These both have had a profound impact on the fulfillment of Function 4: guidance of the search in the European nutraceuticals IS. Also, more negative than positive events have been observed within Function 4. However since the number of both positive and negative observed events has decreased the over past 5 years (see Figure 4.6 above), it seems that ambiguity about how the future European nutraceuticals market would look like has decreased. Regulation (EC) 1924/2006 has eventually created clear set of rules which the industry has to obey.

4.3.5 Function 5: market formation

Until 1996 no events were observed that created a uniform European market for nutraceuticals. In 1996 a niche market was created for nutraceuticals when European Union's Internal Market Council installed a special procedure which allowed temporary two-year marketing authorizations to be issued for foodstuffs coming from research intended for dietary purposes (Nutraceuticals International, 1-7-1996). It took until 2002 for the next market formation events to take place. These events in 2002 all related to regulations that created a market for nutraceuticals, such as a request of the European Commission to lift a ban on distance selling[6] of food supplements in Austria (Nutraceuticals International, 1-8-2002). Also, after hard lobbying by the EHPM and the ERNA, a proposal to update the EU's body of pharmaceutical legislation which would classify many products within the scope of Directive 2002/46/EC as medicinal was rejected (Nutraceuticals International, 1-11-2002).

It was the lack of uniform European regulations on nutraceuticals that has had the most influence on the formation of a market for nutraceuticals (IV3,4,5). Before 2002 every European country had its own regulations. As a result there were many national markets in Europe that were very different from each other. For example, the Dutch and the UK market were relatively liberal, whereas the German market was very conservative. Due to these regulatory differences between EU countries, it was very difficult to market nutraceutical products on a European level.

Directive 2002/46/EC relating to food supplements was the first effort to harmonize rules for the labeling of food supplements and introduced specific rules on vitamins and minerals in food supplements at the European level. After 2004 the effect of the harmonization becomes visible with more products getting market access, such as Metafolin[7] by Merck (Nutraceuticals World, 1-5-2006). The first effects of harmonization are also visible in Figure 4.7 which represents the fulfillment of Function 5.

[6] Distance selling is when consumers purchase goods or services through distance communication such as the internet or mail.

[7] Metafolin contains a natural form of folate and plays a key role in central metabolic pathways.

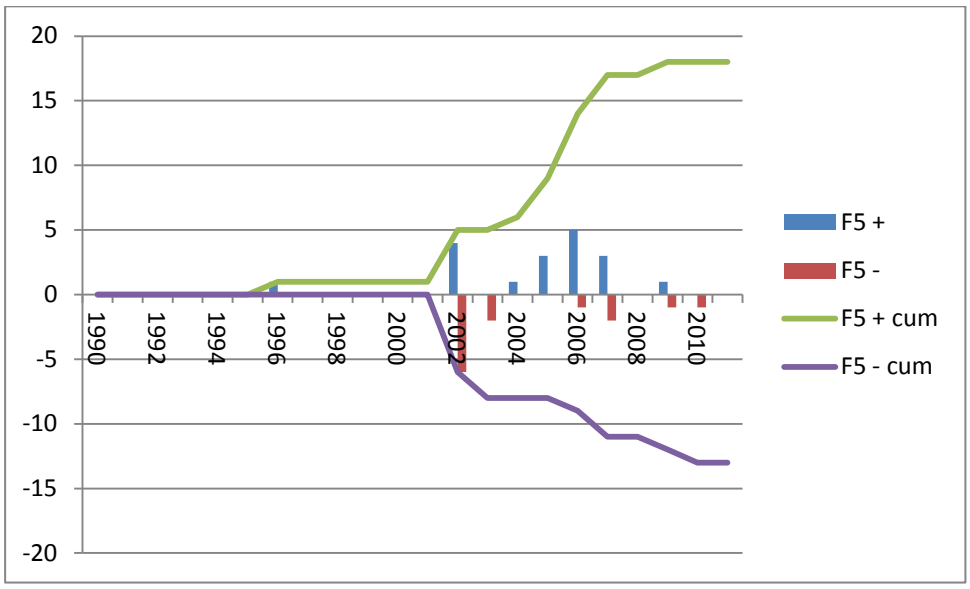

Figure 4.7 Score development Function 5: Market formation EU 1990-2011

In 2006 Regulation (EC) 1924/2006 on health claims was designed and is expected to come fully into in effect in 2012. Initially Regulation (EC) 1924/2006 caused uncertainty about the future market of nutraceuticals in Europe. Because it was unclear what health claims were going to be approved many companies were cautious with starting new projects in fear of not being able to use health claims on their newly developed products (IV2,3,4). However, on the long term Regulation (EC) 1924/2006 has a positive effect on market formation by harmonizing the different national European nutraceuticals markets. Additionally, if a European inspection agency is able to effectively ban scientifically unsubstantiated products of the market, another positive contribution to the European nutraceuticals market of Regulation (EC) 1924/2006 can be the stimulation of competition between companies (IV6,8). Because the market has long been polluted by nutraceutical products that have not been scientifically substantiated competition was disturbed competition that did try to validate their nutraceutical products and made high investments in research such as clinical trials.
At this point in time, early 2012 it only becomes clear how Regulation (EC) 1924/2006 is going to be implemented, what health claims are going to be allowed. There is still discussion on how to cope with health claims that are not being approved. Many of these are 'on hold' which means they have not rejected and the application is still in progress. At the moment there is a list of 19 approved health claims and a bill has been designed in which a list of about 200 approved health claims is included (IV7). This bill still needs to go through the European parliament for approval. This is expected to be due mid 2012 (IV4).

4.3.6 Function 6: resource mobilization

The first investments in the European nutraceuticals industry were observed in 1996. The French producer of nutraceuticals, dietary supplements, and other health-care-related products, Arkopharma, collected money by the issue of shares and described its introduction on the Paris stock exchange as a success (Nutraceuticals International, 1-5-1996). In 1998 there was confidence in a growing nutraceuticals market in Europe, endorsed by large investments in the development of nutraceutical products by big food companies such as Danone and Nestlé (Nutraceuticals International, 1-5-1998). Other big companies such as Novartis (pharmaceuticals) and Numico (medical nutrition, baby food) also saw opportunities in the European nutraceuticals market and

directed their strategy towards nutraceuticals (Extel Examiner, 27-8-1998; 12-3-1999). But between 2000 till 2004 a decline of investments was observed, which can be related to the lack of regulations and thereby the uncertainty about the future of the European nutraceuticals industry (IV4). This caused the EU market for nutraceuticals to be fragmented and risky for investors. Only two investments by governments were observed between 1990 – 2011: in 2005 the Dutch government invested € 1 million in a joint venture between the Netherlands-based Codrico BV and Thailand's PG&P Group to produce about 3,000 tons of food supplements (Nutraceuticals International, 1-11-2005a). Also in 2005 the Swedish government unveiled a five-year plan, called Food and Nutrition Program (in Finish known as ERA), to make the country a global leader in healthy nutrition, providing funding opportunities for companies involved in the development of functional foods and nutraceuticals (Nutraceuticals International, 1-11-2005b). From 2007 onwards several investments made by companies were observed such as an investment in the R&D department of the UK nutraceutical company R5 (Nottingham Evening Post, 29-3-2007), and an investment by the Swiss nutritional supplements company Exicho in the start-up of new subsidiary in Dijon (Nutraceuticals International, 1-3-2008).

With only eleven investments in nutraceutical firms and projects observed during the period 1990 – 2011, the willingness to invest in the nutraceuticals industry seems rather low (see Figure 4.8). According to the Dutch industry organization for nature and health products (Natuur- en gezondheidsproducten Nedeland, NPN) the uncertainty relating to regulations (what claims are going to be approved?) made it difficult to collect investments for nutraceutical firms (IV4). However firms themselves said they had no problem in obtaining financial or human capital (IV2,3). The willingness to invest money in nutraceutical projects is very much dependent on the nature of the particular project and it is not possible to state the willingness to invest is generally low (IV3).

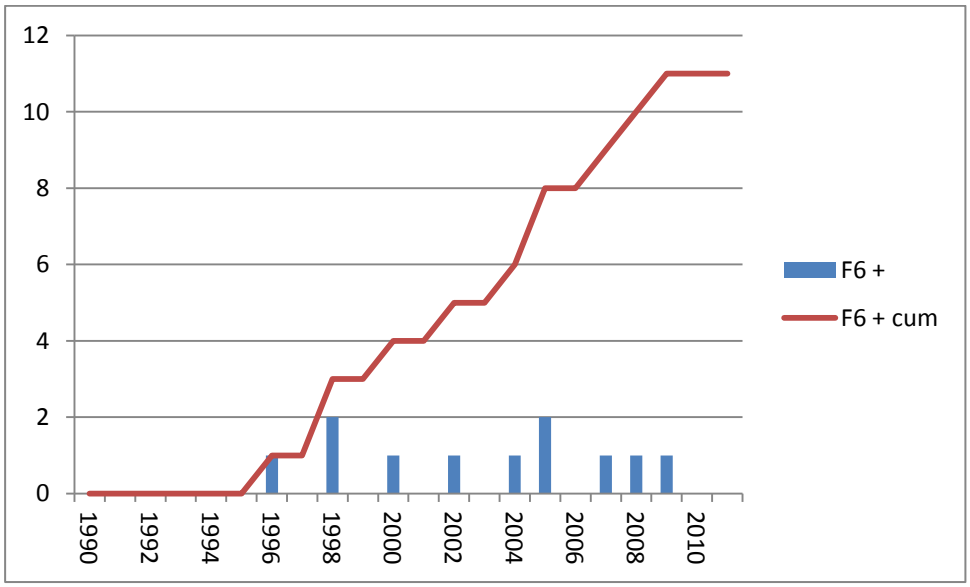

Figure 4.8 Score development Function 6: Resource mobilization EU 1990-2011

4.3.7 Function 7: creation of legitimacy / counteract resistance to change

The credibility of the European nutraceuticals industry has been an important issue in the development of the European nutraceuticals innovation system; several events have been observed that question the efficacy of nutraceuticals. The first of these events related to the negative attitude of governments regarding nutraceuticals and the European nutraceuticals industry, and were observed in 1996: the journal Nutraceuticals international (1-8-1996) stated that The German health

authorities appeared to have launched a virtual assault on dietary supplements and nutraceuticals. Also in 1996 the UK the Department of Health's Advisory Committee on Borderline Substances recommended the removal from National Health Service prescribing of more than 200 unlicensed vitamins, minerals, and supplements because these products had not demonstrated a therapeutic value or had more economic alternatives (Nutraceuticals International, 1-12-1996).

Also several studies performed on health claims and advertisement by the nutraceuticals industry were skeptical towards the nutraceutical industry: one study by the UK National Consumer Council found that health claims were often confusing and misleading and thus meaningless to most people (Nutraceuticals international, 26-2-1997). Another research report of the UK Advertising Standards Authority found that 35% of advertisements for vitamins and dietary supplements were considered unacceptable because they were potentially misleading (Nutraceuticals International, 1-9-1998). Because of the vague health claims and the distrustful advertising the nutraceuticals industry was losing credibility rapidly.

The first lobbying activities in favor of nutraceuticals started when European nutraceutical and nutritional sector associations started lobbying for uniform European regulations in 1998 (Nutraceuticals International, 1-7-1998). At the end of 1998 it seemed that lobbying activities were getting more widespread with Lord Donoughue, a UK government's spokesman in the upper chamber of parliament, pleading for harmonization of regulations on food supplements and related products in the European Union (Nutraceuticals International, 1-12-1998), and the Proprietary Association of Great Britain establishing a working party to oversee its new public relations program related to vitamins, minerals and supplements (Nutraceuticals International, 1-11-1998).

The years afterwards no lobbying activities were observed until in 2002 old problems became part of discussion again (see Figure 4.9). Health claims on nutraceuticals were found confusing (Nutraceuticals International, 1-12-2002) and in 2005 a study reported that 50% of consumers found health claims on nutraceuticals untrustworthy (M2, 23-11-2005). Instead of focusing on the trustworthiness of health claims and getting support of consumers, the nutraceutical industry focused on legislative issues such as lobbying against the upper limits of active substances set by Directive 2002/46/EC (Nutraceuticals International, 14-2-2005). No efforts undertaken by the nutraceuticals industry have been observed that try to influence consumers' perspectives on nutraceuticals and the nutraceuticals industry.

In 2008 news in the UK about two UK based nutraceutical companies, Boots and Superdrug, pronounced that these companies misled millions of people by putting less active ingredients in their products than was stated on the label (Nutraceuticals International, 1-9-2008; The Irish Times, 28-7-2008). These products concerned chondroitin and glucosamine supplements, which are both said to fight osteoarthritis. Such misleading activities by producers can be damaging for the industry as a whole. Another big problem of the European nutraceuticals industry is producers putting pharmaceutical substances in their nutraceutical products without mentioning the substance on the label (IV5,7). This is potentially very dangerous for consumers and can also be very damaging for the industry as a whole. Also a typical problem of the European nutraceuticals industry were so called 'free-riders', companies that take a substance with expected health benefits and put it in a pill without doing any research on efficacy (IV3,4,5). New sales channels such as websites, Facebook, and Ebay created opportunities for free-riders to market scientifically unsubstantiated nutraceutical products to consumers. These were difficult to trace by national inspection agencies. In this respect the new regulations on health claims can give a positive boost to the credibility of the nutraceuticals industry (IV4). It will become more difficult for these free-riders to market their product with

harmonized European regulations, and the strict monitoring of compliance with regulations. Also when consumers know a health claim has been scientifically proven and approved by the EU this can have a positive effect on the credibility of the nutraceuticals industry.

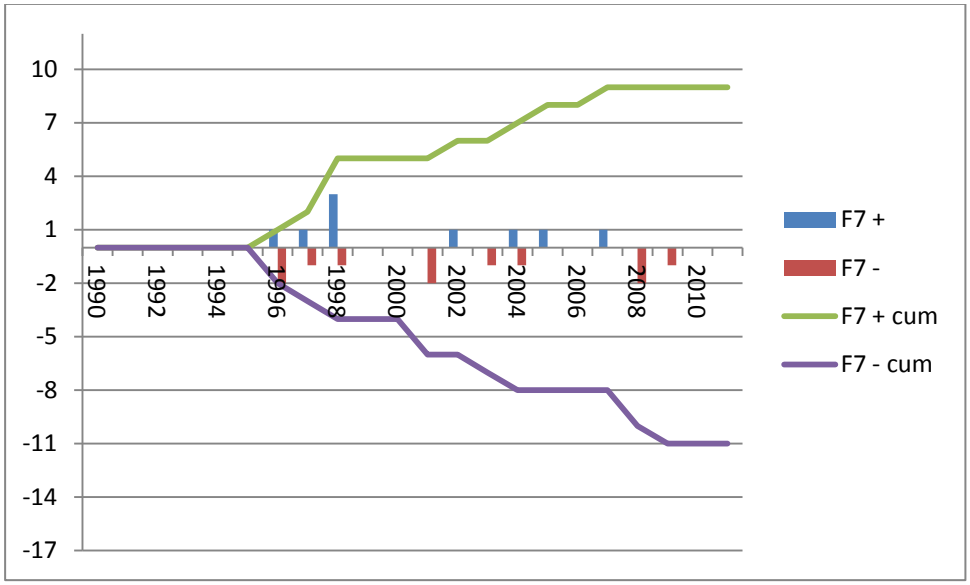

Figure 4.9 Score development Function 7: creation of legitimacy / counteract resistance to change EU 1990-2011

Concluding, studies like 'Research and Market' (M2, 23-11-2005) which were claiming that 50% of consumers find health claims on nutraceuticals untrustworthy, and incidents in the UK with Boots and Superdrug misleading consumers (Nutraceuticals International, 1-9-2008), suggest that the industry has a problem with its trustworthiness amongst European consumers. During the interviews however, industry insiders regarded no problem with the trustworthiness of the industry amongst consumers (IV3,4,6). There might be a mismatch between the image created by the media and consumer's perception of the industry. The actual perception of consumers on the European nutraceutical industry might be better than the perception that is given in the media (IV3).
Nowadays lobbying activities by the European nutraceuticals industry primarily focus on Regulation (EC) 1924/2006. The nutraceutical and food supplement industries are lobbying at the European Parliament to reject the list of approved health claims composed by the EFSA. The nutraceutical and food supplement industries would like to see less scientific substantiation for the approval of health claims to obtain a larger degree of freedom in the use of health claims (IV6,7).

Now the fulfillment of all seven System Functions of the European nutraceuticals IS has been discussed, the performance of the European nutraceuticals IS will be discussed.

4.3.8 Performance of the European nutraceuticals innovation system

Table 4.1 shows the market size of the European nutraceuticals market in the period 1990 – 2011. Data on the market size was very limited and many years are missing; only those years on which data was available are represented in Table 4.1. Because data is retrieved from different sources that are using different definitions of the nutraceuticals market, these figures cannot simply be compared with each other. It can merely be used as an indication of the development of the European nutraceuticals market over time. Since data on the size of the European nutraceuticals market of 1991 and 1995 from Euromonitor are coming from the same source, and the data of 1999 and 2006 from Basu *et al*. (2007) are coming from the same source, data of 1991 and 1995 can be compared

with each other and data of 1999 and 2005 can be compared with each other. The data from Euromonitor shows that between 1991 and 1995 the size of the European nutraceuticals market had decreased with 1 million US $. This indicates that the European nutraceuticals IS was performing badly. Data from Basu et al. shows that the European nutraceuticals market has grown four and a half times in size. This is a strong growth, however data on the European nutraceuticals market size needs to be compared with the data on the US nutraceuticals market to put the size and growth of the European nutraceuticals market into perspective.

Table 4.1: Market size European nutraceuticals industry

Year	Market size nutraceuticals in billion US $	Comment	Source
1991	0.3		Euromonitor, 1996
1995	0.29		Euromonitor, 1996
1999	1.8		Basu et al., 2007
2006	8		Basu et al., 2007

The fulfillment of several Functions of the European nutraceuticals IS were found to be lacking. Function 1 was mildly lacking, in the years 2000 – 2002 and 2007 – 2009 very few events were observed. Function 2 and Function 3 were well fulfilled with many events observed. Within Function 4 also many events were observed, however this included many negative events as well. Therefore Function 4 is considered to be not adequately fulfilled. Function 5 is also considered not adequately fulfilled: there was the lack of the formation of one uniform European market. Within Function 6 no negative events were observed. However, only eleven events were observed within Function 6. Therefore Function 6 is considered to be under fulfilled. Within Function 7 nine positive events and eleven negative events were observed. Because of the limited number of events and the relative large number of negative events Function 7 is also considered not adequately fulfilled as well.
Thus, only Function 2 and Function 3 have been adequately fulfilled. All the other Functions have shortcomings in their fulfillment. The next chapter will discuss the results of the analyses of the US nutraceuticals IS. After these results have been discussed the European and US nutraceuticals IS will be compared with each other, which will give a better understanding of the effect of the lack of fulfillment of several of the System Functions of the European nutraceuticals IS.

5. Results United States nutraceuticals innovation system

This chapter provides the results of the analysis of the US nutraceuticals innovation system (IS) over the period 1990 – 2011, in which a total of 904 events were found. Unfortunately no interview data could be collected for the US nutraceuticals IS. The results start with a structural analysis of the current US nutraceuticals IS according the innovation system framework of Kuhlman and Arnold (2001). Second a narrative is given showing the development of the US nutraceuticals IS. Third the fulfillment of each System Function will be discussed separately. The references of the narrative of the US nutraceuticals IS and the references of the fulfillment of the System Functions of the US nutraceuticals IS can be found in Appendix C. This is done because adding the vast amount of references of the US nutraceuticals IS analysis amongst the general references would strongly decrease the readability of the references of the research. The historical event database can be found in an enclosed CD-ROM in Appendix E.

5.1 United States nutraceuticals innovation system

Figure 5.1 (based on Kuhlmann and Arnold, 2001) shows a graphical representation of the structure of the US nutraceuticals innovation system. It needs to be taken into account that figure 5.1 is a simplified model of the US nutraceuticals IS that describes the most important components of the US nutraceuticals IS. The several blocks shown in the figure 5.1 are explained below.

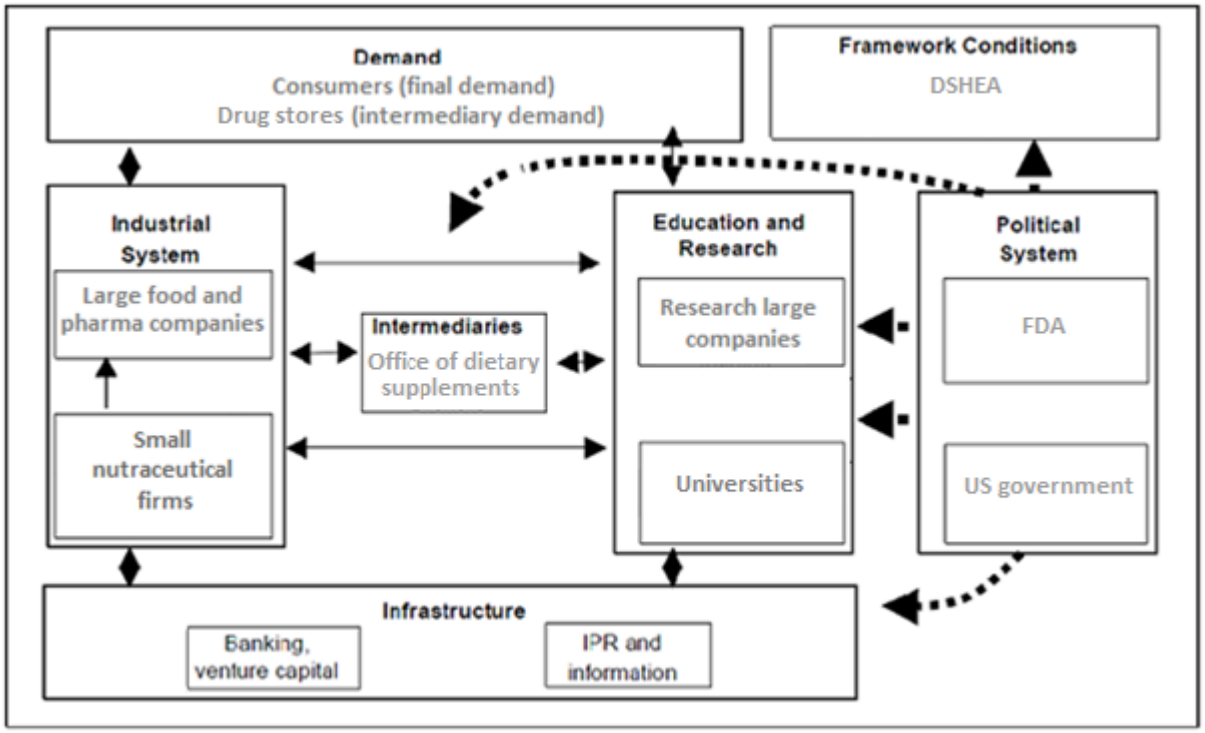

Figure 5.1 A structural framework of the US nutraceutical innovation system model (based on Kuhlmann and Arnold, 2001)

Both small and large companies are active in the *industrial system* of the US nutraceuticals IS. Some examples of large companies are Monsanto, DuPont, Johnson & Johnson, and Abbott laboratories. These companies respectively originated from the biotech, general life-science, and pharmaceutical industries. Also many small nutraceutical companies are active in the US nutraceuticals industry such as Science Based Health, Bio-Therapeutic Inc, and Michelle's Miracle. Nutraceutical companies are spread through the entire US with a higher concentration of companies in Utah (edcUTAH, 2009).

Important product categories are herbal preparations, antioxidants, and fish oil supplements (Nutraceuticalsworld.com, 2012).

The *demand side* consists of end users, which are consumers, and the intermediary demand, which are companies that buy nutraceuticals and sell these under their private label. The intermediary demand consists mainly out of drugstores such as Walgreens.

The *education and research side* consist largely out of universities and R&D divisions of nutraceutical companies. US universities conducting research on the relation between nutrition and health are City University of New York, University of North Carolina, and University of Wisconsin, amongst others (Education-portal.com, 2012). Small nutraceutical companies use this public knowledge to develop nutraceutical products and do little scientific research themselves. Large companies active in the US nutraceuticals industry, such as pharmaceutical companies, are more involved in scientific studies on nutraceuticals such as clinical trials. The reason for this is that large companies do not want to risk their reputation with scientifically unsubstantiated nutraceutical products. Furthermore large companies have the funds to carry out expensive scientific research such as clinical trials.

In the *political system* the federal US government makes the regulations. However the main actor in the political system of the US nutraceuticals IS is the US Food and Drug Administration (FDA), which is the executive department of the federal US government responsible for the regulation and supervision on nutraceuticals. The main *framework condition* is the Dietary Supplements Health and Education Act of 1994 (DSHEA). Under the DSHEA nutraceuticals are considered 'Dietary Supplements'. The DSHEA states that producers of dietary supplements cannot market a dietary supplement product as a treatment or cure for a specific disease or condition. However, manufactures of dietary supplements can make a structure/function[8] claim on a dietary supplement label if this claim is accompanied with a disclaimer stating that the claim has not been evaluated by the FDA (FDA.gov, 2012). In practice, this means for the US nutraceuticals industry there are is a great variety of health claims which they can use as long as there is a disclaimer on the label of the product (FDA.gov, 2012). The *infrastructure* mainly consists of investment companies such as Finova Mezzanine Capital and Burrill and Co, which invest in nutraceutical companies and research.

An important *intermediary* organization in the US nutraceuticals IS is the Office of Dietary Supplements (ODS). The ODS engages in the following activities: strengthen knowledge and understanding of dietary supplements by evaluating scientific information, stimulating and supporting research, disseminating research results, and educating the public to foster an enhanced quality of life and health for the U.S. population (ODS, 2012)

5.2 Narrative United States nutraceuticals innovation system 1990 – 2011

Before 1994 there were no specific laws to regulate nutraceuticals. Nutraceuticals fell under the Federal Food, Drug, and Cosmetic Act (FDA.gov, 2010). Under this law it was for nutraceuticals virtually impossible to make a medical or health claim, even if a company conducted the necessary research (PR Newswire, 1-12-1994). Despite it was difficult to use health claims on nutraceutical products, nutraceutical products such as fish oil capsules were already on the market in 1990. The problem regarding the use of health claims was discussed in a newspaper article in USA Today (14-5-1990). This article discussed the benefits of fish oil capsules by mentioning the potential positive effect of taking fish oil capsules in fighting colon inflammation. Despite the FDA agreed that there were studies that showed these benefits, the assertion of a health benefit qualified the fish oil

[8] Structure/function claims describe the role of a nutrient or dietary ingredient intended to affect the structure or function of the body.

capsules as drugs and was thus forbidden without FDA approval. Accordingly, the FDA had told about 60 manufacturers of fish oil capsules to stop making health claims (USA Today, 14-5-1990). The manufacturers could only continue selling their capsules as foods without health claims and if they could convince the FDA that the products had been used as foods in the past and were generally recognized as safe (The Associated Press, 16-7-1990).

At the end of 1991 and in 1992 several articles showed up in US newspapers that talked about the promises of nutraceuticals and the nutraceutical revolution with headlines such as “Future foods will be here sooner than we think” and “A push to label medicinal powers of some foods” (The New York Times 13-9-1992; The Atlanta Journal and Constitution, 2-1-1992; The Associated Press, 5-12-1991). Americans were becoming more health-conscious and were ever more incorporating nutraceuticals into their diets (PR Newswire, 23-4-1998).

Because of the growing demand for nutraceutical products and the problem of the use of health claims on nutraceuticals a group of top food scientists and business leaders held a meeting in January 1993 in New York to discuss the possibilities of the FDA creating a new category for nutraceuticals and allow special labeling for them (USA Today, 14-1-1993). The FDA was increasingly becoming aware of the lack of regulation for such products and the problems this was causing the nutraceuticals industry. Therefore in 1994 the Dietary Supplement Health and Education Act (DSHEA) came into force (FDA.gov, 2012). Under the DSHEA nutraceuticals were considered dietary supplements. The Act states that the dietary supplement or dietary ingredient manufacturer is responsible for ensuring that a dietary supplement or ingredient is safe before it is marketed. The FDA is responsible for taking action against an unsafe dietary supplement product after it reaches the market. Generally, manufacturers did not need to register their products with FDA nor get FDA approval before producing or selling dietary supplements. More importantly, dietary supplement or dietary ingredient manufacturers were not required to register a health claim before making a structure/function claim on a nutraceutical (FDA.gov, 2012). Because it was not required to register a health claim, the manufacturer must state in a disclaimer that FDA has not evaluated the claim (FDA.gov, 2012).

When the DSHEA came into force a wide range of opportunities regarding the use of health claims was created for nutraceutical manufacturers in the US. Accordingly, during the period 1995 – 2000 the entrepreneurial activities increased strongly. For example, the company HealthLink International alone launched 23 new nutraceutical products in 1998 (Business Wire, 12-1-1998). Also mergers, acquisitions and firms forming coalitions took place on a regularly basis. These coalitions were licensing agreements such as one of the many licensing agreements of Nutraceutix for its antioxidant Calcium D-Glucarate (Business Wire, 1-12-1999). The industry was growing strongly. Growing investments were witnessed with the largest investment observed before 2000 being an investment from Morgan Weinstein & Co. of $100 million in HealthSpan, Inc.

In line with the growing nutraceuticals market, the American Nutraceutical Association (ANA) was established in 1997. The Council for Responsible Nutrition (CRN), established in 1973, already existed but where the CRN was the leading trade association representing dietary supplement manufacturers and ingredient suppliers (including nutraceutical manufactures and suppliers), the ANA only focused on nutraceuticals.

At the end of the 90s voices were being raised that public health could be at stake because nutraceuticals might interfere with pharmaceutical products people were taking (Daily News (New York), 27-9-1999; Reuters Health Medical News, 17-9-1999). Experts were also indicating that the large degree of freedom regarding the use of health claims was hampering scientific substantiation

of nutraceutical products and was resulting in a “cowboy industry” with many misleading products on the US market (Reuters Health Medical News, 15-5-2000; The Associated Press, 26-1-1993). Accordingly, relatively few research and patents were observed and knowledge development did not onset until 2000. According to Dr. DeFelice of the Foundation for Innovation in Medicine[9] (FIM), the DSHEA did not provide incentives for nutraceutical research. For a research-oriented nutraceuticals industry, Dr. DeFelice urged US Congress to enact The Nutraceutical Research & Education Act (NREA)[10] (Reuters Health Medical News, 12-11-1998). The Act would help "...encourage quality medical and scientific research on the health benefits of food products," as Stephen H. McNamara, former FDA Associate Chief Counsel for Food, stated at the 10th Nutraceutical Conference in New York (Reuters Health Medical News, 12-11-1998). The Bill however was not accepted by the US Congress and the DSHEA is still in force, accordingly the US nutraceuticals industry still enjoys a large degree of freedom regarding the use of health claims. Only the FIM and a few physicians were ascribed a negative opinion towards the large degree of freedom regarding the use of health claims under the DSHEA, no other negative opinions towards the DSHEA were observed.

The expectations on the development of the US nutraceuticals industry were very positive: a study carried out by Research and Markets expected the US nutraceuticals industry to grow with 9% per year until 2010 (Business Wire, 4-5-2004). Furthermore, according to Tyre Lanier and Duane Larick, two food science professors at N.C. State University, nutraceuticals were the fastest growing segment of the food industry, fostered by the increased health awareness of American consumers (Business Wire, 29-8-2000; PR Newswire, 8-5-2000; News and Observer (Raleigh, NC), 5-1-2000; Capital Times (Madison, WI.), 26-4-1999). Paradoxically however, the nutraceuticals industry had registered an increase of just 5% in 1999 (Business Wire, 10-12-2001). Furthermore, according to a study by Nancy Childs, a professor at St. Joseph's University in Philadelphia, nutraceutical companies were slow to market products because of concerns about high costs and federal regulations (St. Louis Post-Dispatch (Missouri), 28-2-2000).

From 2000 onwards the amount of research and patents published regarding nutraceuticals was increasing strongly in the US. From 2002 till 2011 the functional analysis of the US nutraceuticals IS saw an average of 18 new entrepreneurial projects in the US nutraceuticals IS every year. Often these were entrepreneurial projects from existing nutraceutical companies. For example, in 2005 Martin Nutraceuticals Inc. extended its distribution channels by placing products in retail outlets, chain stores, and warehouse distribution centers (PrimeZone Media Network, 29-4-2005). Other entrepreneurial projects were projects by companies such as Science Based Health, which launched a new macular health product, MacularProtect Complete-S, which is a nutritional formulation to help protect macular and full body health. Important segments of the US nutraceuticals market were herbal preparations, antioxidants, and fish oil supplements (Nutraceuticalsworld.com, 2012).

Regularly negative stories about nutraceutical products came in the news. As a result of the publication of such stories in the mass media the nutraceuticals industry was subject of controversy in 2005 with almost 50% of consumers finding the claims on nutraceuticals and other food supplement products untrustworthy (Business Wire, 15-6-2005; 23-11-2005). Also stories came in the news questioning the efficacy and safety of fish oils. For example, the prominent cardiologist Dr.

[9] The Foundation for Innovation in Medicine (FIM), was established in 1976 by Stephen L. DeFelice, M.D. It is a nonprofit foundation whose primary purpose is to accelerate medical discovery by creating a more productive clinical research community

[10] The Nutraceutical Research & Education Act (NREA) is to amend the Federal Food, Drug, and Cosmetic Act and aims to promote clinical research on health benefits of dietary supplements and foods by establishing a new legal classification for dietary supplements and foods with health benefits.

Gruss called 99% of all fish oil supplements on the market completely worthless (Business Wire, 22-4-2009), and makers and sellers of fish oil supplements were being sued in California for not including labeling about polychlorinated biphenyl (PCB) contamination (Upi, 2-3-2010; The New York Times, 24-3-2009; St. Louis Post-Dispatch (Missouri), 23-4-2007; Palm Beach Post (Florida), 15-6-2005). PCB's are carcinogenic and are also being related to liver damage.

Over the period 2005 – 2009 the US nutraceuticals industry feared a decline in revenue and nutraceutical companies started lobbying activities. For example, industry expert William T. Shields was promoting the health benefits of enhanced Omega-3 dietary supplements (PR Newswire, 14-2-2006). Also regularly public relations activities were carried out by nutraceutical companies such as Martin Nutraceuticals Inc. which started weekly infomercial about the benefits of nutraceuticals was broadcasted on The Voice of America, an internet radio station. (Market Wire, 1-6-2006). However such infomercials[11], which were carried out frequently by Martin Nutraceuticals Inc., largely focused on individual products and were thus more associated with marketing activities. Also from 2006 onwards numerous studies that raised positive expectations about nutraceutical products appeared in the news. For example, the probiotics from Nutraceutix had shown to enhance immune function in clinical research (PR Newswire, 1-6-2006), and 5-LOXIN produced by PL Thomas in alliance with Laila Nutraceuticals had shown to reduce the symptoms of osteoarthritis (Business Wire, 1-8-2008).

No collective lobbying efforts carried out by the US nutraceuticals industry were observed that aimed to positively influence consumers' perception on nutraceuticals. Nevertheless, no more expression about the untrustworthiness of the US nutraceuticals industry was observed either after 2009. Hence it seemed the untrustworthiness of the nutraceuticals industry was of temporary nature in the period 2005 – 2009. Only a few incidents regarding nutraceutical products were observed, such as Berkeley Premium Nutraceuticals which was misleading customers with its male enhancement product Enzyte, which was found to be ineffective (Upi, 16-3-2005). Another incident regarding nutraceutical products that came widespread in the news in 2009 and 2010 was the contamination of several fish oil supplements with PCB's, which are carcinogen and could cause liver damage (Upi, 2-3-2010). These companies, CVS Pharmacy Inc., General Nutrition Corp., Now Health Group Inc., Omega Protein Inc., Pharmavite LLC, Rite Aid Corp., Solgar Inc. and TwinLab Corp., were refusing to disclose the level of contamination; a public relations campaign to promote fish oil supplements was started and the CRN released a press message saying there were no safety issues with fish oil (Business Wire, 27-4-2010). These incidents regarding fish oil supplements and Enzyte have had little influence on the US nutraceuticals industry in general: in 2011 the outlook of the US nutraceuticals industry was prosperous with a forecasted US nutraceuticals market of $207 billion in 2016 (Business Wire, 9-8-2011).

On the next page Figure 5.2 shows a timeline in which the most important event within the US nutraceuticals IS are given.

[11] Infomercials are direct response informational television programs in which information about a product is given and consumer have the possibility to directly buy the product

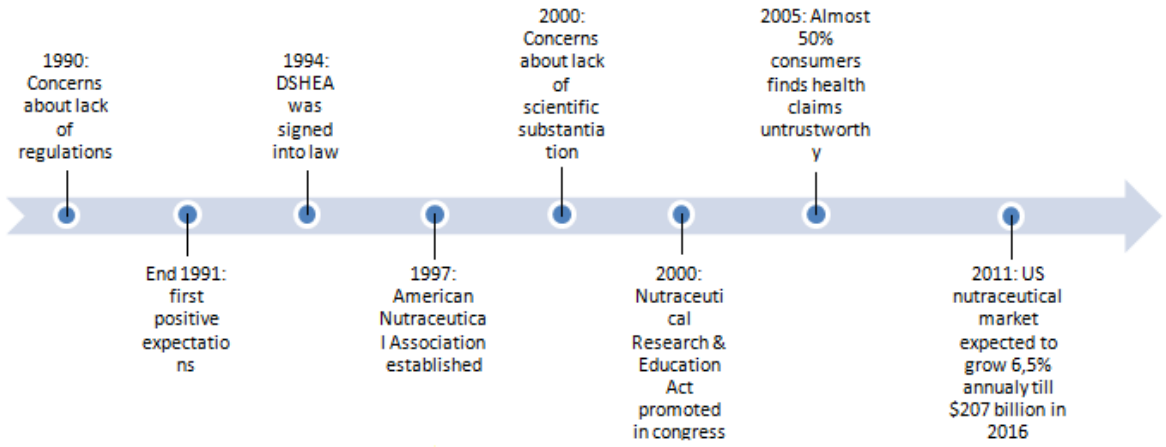

Figure 5.2 Timeline of important events in the US nutraceuticals IS

5.3 Results United States nutraceuticals innovation system analysis per System Function

The following part will discuss the results of the fulfillment of each System Function of the US nutraceuticals IS separately. In the TIS analysis of the US nutraceuticals IS over the period 1990 – 2011 a total of 904 events have been found. Unfortunately no interview data could be collected.

5.3.1 Function 1: Entrepreneurial activities

The first entrepreneurial activities observed in the US nutraceuticals innovation system were 2 nutraceutical development projects in 1995. A company called Nutraceutical started to harvest algae as a source of beta carotene for the production of nutraceuticals, and Biomune Systems announced the formation of Optim Nutrition with which it planned to enter the US nutraceuticals market (PR newswire, 1-11-1995; Salt Lake Tribune (Utah), 6-9-1995). These nutraceutical development projects came soon after the introduction of the Dietary Supplement Health and Education Act (DSHEA) at the end of 1994, which created a market for dietary supplements[12] in the US by officially defining the term dietary supplement and creating a new regulatory framework for the safety and labeling of dietary supplements (FDA.gov, 2012)

From 1995 until 1998 each year two or three new nutraceutical products entered the US nutraceuticals market. From 1998 there was a strong increase in the number of new nutraceutical products that entered the US market with seven new entrepreneurial projects that were started. These entrepreneurial projects varied from the startup of a new business unit by Photosynthetic Harvest Inc. to develop new nutraceutical products, to the launch of 23 new nutraceutical products by HealthLink International (PR Newswire, 24-6-1998; Business Wire, 12-1-1998).

Then in 1999 the number of new entrepreneurial projects in the US nutraceuticals IS strongly rose from 7 to 17 in one year. Besides chemicals and food producing companies diversifying their operations towards the nutraceuticals market, also 5 start ups of websites on which nutraceuticals were sold were observed (PR Newswire, 16-3-1999; Business Wire, 23-2-1999).

In 2000 the first company to sell fish oil nutraceuticals entered the US nutraceuticals market (PR Newswire, 1-2-2000). The fish oil market would become an important part of the US nutraceuticals market with a total of 17 fish oil nutraceutical products launched in the US over the period 1990 – 2011.

[12] A dietary supplement is the equivalent to what is called a food supplement in the European Union

From 2002 the emergence of the US nutraceuticals industry has been well in progress with an average of 18 new entrepreneurial projects observed each year. Besides the fish oil supplement market, other segments of the US nutraceuticals market in which many new nutraceutical product launches were observed were the antioxidant market, the eye health market, inflammatory market, and the weight loss market (Market Wire,28-3-2011; U.S. Newswire, 17-10-2008; PR Newswire, 14-4-2003).

As visible in Figure 5.3, at the end of the first decade of 2000 once a year a nutraceutical project was terminated in the US, and only seven nutraceutical projects in the US were observed that have been terminated over the period 1990 – 2011. A terminated project that received a lot of media attention was Berkeley Premium Nutraceuticals, which filed for bankruptcy in 2008 (The Associated Press State & Local Wire, 16-9-2008). Berkeley produced the male enhancement product Enzyte and came widespread in the news after the company's founder and CEO, Steve Warshak, and his mother, Harriet Warshak, were found guilty of conspiracy to commit mail fraud, bank fraud, and money laundering (Associated Press Online, 27-8-2008).

From 2011 onwards the future prospects of the US nutraceuticals industry, and thus entrepreneurial opportunities, are looking good with an estimated growth rate of 6.5% until the US nutraceuticals market reaches a value of $207 billion in 2016.

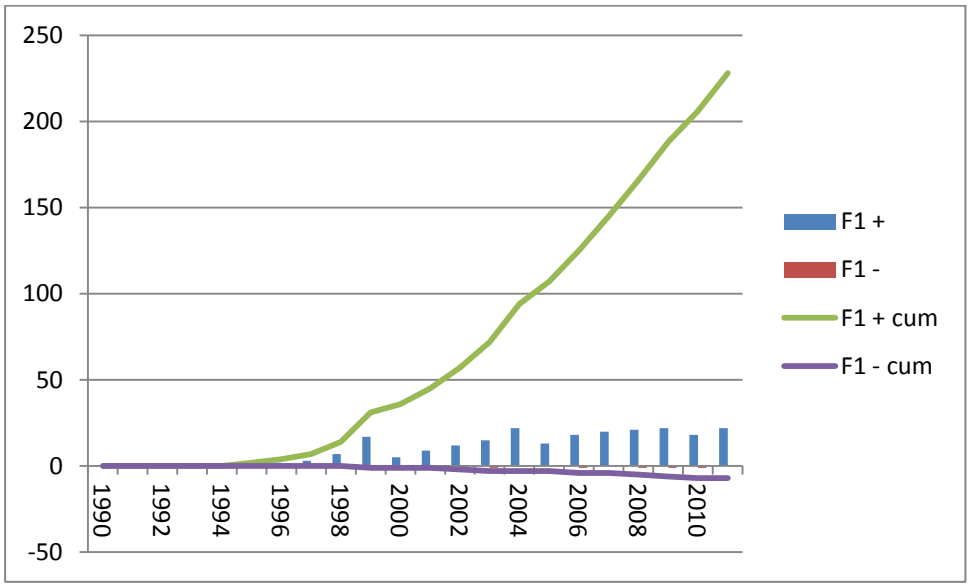

Figure 5.3 Score development Function 1: Entrepreneurial activities US 1990-2011

5.3.2 Function 2: knowledge development

The first time the term nutraceuticals was mentioned in a US scientific journal was in 1993. This article discussed the synthetic development of novel lipids which could be used for nutraceutical purposes (Blackburn and Mascioli, 1993).

It took until 1997 for the term nutraceutical to show up in a US scientific journal again. From 1997 onwards publications in US scientific journals on nutraceuticals gradually increased until a steady state of about 75 publications in US scientific journals per year was reached in 2006 (see Figure 5.3).

The number of patents mentioning nutraceuticals far exceeded the number of publications in US scientific journals mentioning nutraceuticals between 2003 and 2009 (see Figure 5.3). Over this period an average of 59 research publications per year regarding nutraceuticals was observed whereas and average of 403 patents per year was observed. The first patent mentioning the term nutraceutical was granted in 1994 and discussed the aminosugar and glycosaminoglycan

compositions in the use of a nutraceutical for the repair of connective tissue in humans (US Patent number: 5364845). The number of patents strongly increased till in 2009 555 patents were granted. In 2010 and 2011 a strong decrease in the number of patents was observed. This decrease could be explained by patents that have been issued in 2010 and 2011 had not yet been added to the database.

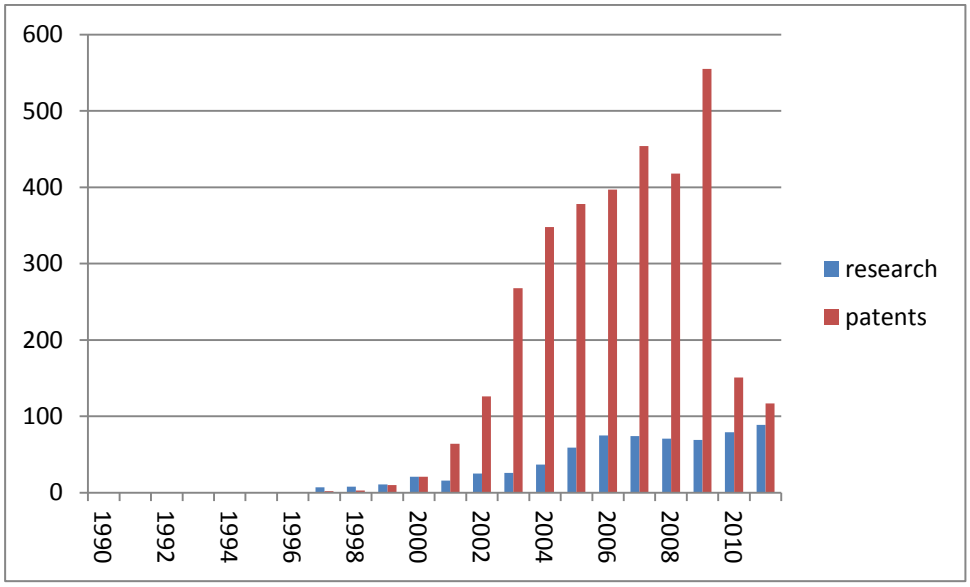

Figure 5.4 Score development Function 2: Knowledge development US 1990-2011

5.3.3 Function 3: knowledge diffusion

In 1993 the first acquisition within the US nutraceuticals industry was observed. A company called Nutraceutical purchased Solaray, which produced herbal nutraceutical products (Salt Lake Tribune (Utah), 6-9-1995). Also in 1993 the first meeting of the US nutraceuticals industry was observed. A group of top food scientists and business leaders met in New York. The group pleaded for Congress to create a new Food and Drug Administration category for nutraceuticals and allowed special labeling for them (USA Today, 14-1-1993). One and a half year after this meeting, at the end of 1994 these pleadings were heard and the Dietary Supplement Health and Education Act (DSHEA) came into effect. This new law created a range of opportunities for the US nutraceuticals industry. Before DSHEA came into effect it was rather impossible to make medical or health claims on a nutraceutical, even if a company demonstrated benefits by clinical research (PR Newswire, 1-12-1994). With the DSHEA enacted it became possible to make certain claims regarding structure, function, and deficiencies without prior FDA approval. Soon afterwards several meetings and conferences were being held in the US such as "Nutraceutical Research, Development & Marketing: Time to Move Forward?" organized by the Foundation for Innovation in Medicine (PR Newswire, 1-12-1994). This and other conferences discussed the possibilities of the use health claims under the DSHEA and explored the degree and nature of evidence required for making a claim on a nutraceutical (PR Newswire, 4-5-1995; 1-12-1994). Until 2000 conferences regarding nutraceuticals primarily focused on regulatory topics, but after 2000 new scientific developments regarding nutraceuticals became increasingly important on conferences such as the American Association of Pharmaceutical Scientists Dietary Supplements Forum, which was held in Washington D.C. in 2000 (PR Newswire, 28-6-2000). Conferences also focused on marketing related topics and showcasing new nutraceutical products such as the annual Nutracon conference (Business Wire, 17-7-2000).

The most important networks in the US nutraceuticals industry were The Council for Responsible Nutrition (CRN), established in 1973, and The American Nutraceutical Association (ANA) established in 1997. CRN is the leading trade association representing dietary supplement manufacturers and ingredient suppliers, and the ANA provides a forum which mission is to develop and provide educational materials and program on nutraceuticals and nutrition for health care professionals, consumers and sales associates from nutraceutical companies.
Most knowledge diffusion in the US nutraceuticals IS was observed around the year 2000. Between 1999 and 2001 an average of 30 events per year were observed that related to knowledge diffusion (see Figure 5.5).

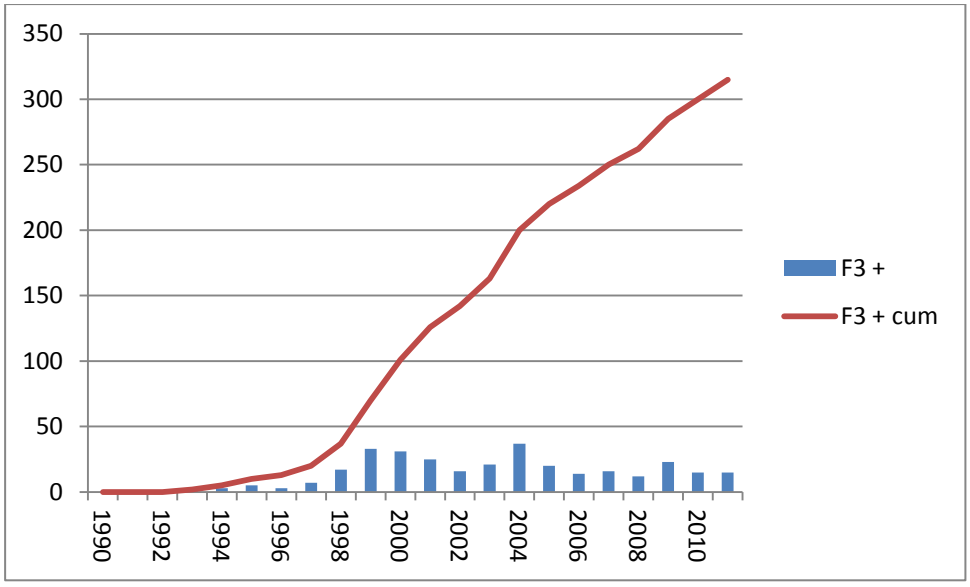

Figure 5.5 Score development Function 3: Knowledge diffusion US 1990-2011

In total 161 coalitions between companies and/or research institutes were observed in the US nutraceuticals IS in the period 1990 – 2011. Often these were licensing agreements such as the many licensing agreements of Nutraceutix for its antioxidant Calcium D-Glucarate (Business Wire, 1-12-1999), or distribution agreements such as Kaire Nutraceuticals signing 3200 new distributors in 1999 (PR Newswire, 7-10-1999), but also marketing alliances were observed such as a strategic marketing alliance between ZYTO Corp. and BioNativus for the sale of software to facilitate decision making for healthcare practitioners who use BioNativus supplements (Business Wire, 25-7-2007).
Also 104 mergers and acquisitions were observed in the US nutraceuticals IS in the period 1990 – 2011. These were mainly nutraceutical firms acquiring other nutraceutical firms such as Beneficial Holdings acquiring Beneficial Health and Beneficial Nutraceuticals (Business Wire, 15-6-2004). After 2004 the number of mergers and acquisitions and the number of coalitions observed per year declined.

5.3.4 Function 4: guidance of the search

The first positive expectations in a growing market for nutraceuticals in the US were expressed by Mr. Leveille of Nabisco Foods Group in 1992 (The San Francisco Chronicle, 15-1-1992). ''Future foods will be here sooner than we think,'' predicted Mr. Leveille at an outlook conference at the United States Department of Agriculture in 1992. ''Both the market demand and the technological know-how are well on their way to defining and delivering such a food supply.'' Mr. Leveille said. To speed up that process, the Foundation for Innovation in Medicine (FIM) had issued a 40-page white paper

called ‘The Nutraceutical Initiative: A proposal for economic and regulatory reform’. In this paper the FIM urged the FDA to provide an economic and regulatory base for a more vigorous research-grounded nutraceuticals industry (The San Francisco Chronicle, 15-1-1992). The FIM was hoping to get the FDA to grant nutraceuticals a status similar to that of orphan drugs (Foundation for innovation in medicine, 2012); it argued for a favorable tax regime and hoped that strongly suggestive data of benefits from clinical trials would be sufficient for a product to obtain market approval (Foundation for innovation in medicine, 2012). In 1994 there were still some problems relating to regulations. The absence of a well emerging nutraceutical industry was attributed to the lack of a research-driven nutraceuticals industry (Foundation for innovation in medicine, 2012).

To fill this gap in regulations and create the possibility to make health claims on nutraceuticals and other dietary supplements, new regulation was designed. In October 1994, the Dietary Supplement Health and Education Act (DSHEA) was signed into law by President Clinton (FDA.gov, 2012). This act created a regulatory framework for dietary supplements[13] and cleared the way for a nutraceuticals market in the US. Experts were expecting a growing market for nutraceutical products and expected the US nutraceuticals industry would soon be competing with the traditional food, pharmaceutical, biotechnology and health food industries (PR newswire, 4-5-1995).

The DSHEA provided opportunities for the emerging nutraceuticals industry in the US by allowing health claims on nutraceutical products. It became possible to make structure/function claims on a nutraceutical (these claims describe the role of a nutrient or dietary ingredient intended to affect the structure or function of the body). The manufacturer is responsible for ensuring the accuracy and truthfulness of these claims; they are not approved by FDA. Therefore, if a nutraceutical includes such a claim, it must state in a "disclaimer" that FDA has not evaluated this claim. The years after DSHEA came into force positive expectations were expressed by industry experts such as nutritional education consultant Nancy Hillen stating in 1996: “First among the trends in nutrition is the growth of nutraceuticals” (Charleston Gazette (West Virginia), 9-10-1996). And in 1997 Dr. DeFelice stated about nutraceuticals: “It's going to have a major impact on disease, much more than drugs” (Copley News Service, 16-11-1997). During this period scientific studies on clinical active substances and their possible use in nutraceuticals were regularly published in the press. For example one publication discussed a study that showed a selenium yeast supplement significantly reduced human cancer incidence (PR newswire, 24-12-1996). Another research publication discussed a study that found fish oil capsules could reduce flare-ups of Crohn's disease (The Associated Press, 12-6-1996).

At the end of the 1990s the first negative opinions towards regulations were expressed: public health could be at stake because nutraceuticals might interfere with the pharmaceutical products people were taking (Daily News (New York), 27-9-1999; Reuters Health Medical News, 17-9-1999). Dr. Steven H. Zeisel, of the University Of North Carolina School Of Public Health, feared possible interaction with pharmaceuticals when nutraceuticals were administered in large dosages (Reuters Health Medical News, 17-9-1999). Dr. Zeisel urged the FDA to increase inspection of nutraceuticals by creating a regulatory category for nutraceuticals that were administered in large dosages to obtain pharmacological effects (Reuters Health Medical News, 17-9-1999).

Physicians indicated that the large degree of freedom regarding the use of health claims was hampering scientific substantiation of nutraceutical products and was resulting in a “cowboy industry” with many misleading nutraceutical products on the market (The Associated Press, 26-1-1993; Reuters Health Medical News, 15-5-2000). Since the DSHEA did not provide incentives for

[13] official definition of nutraceutical products in the US

nutraceutical research, Dr. DeFelice of The Foundation for Innovation in Medicine (FIM) promoted The Nutraceutical Research & Education Act (NREA) at US Congress to increase scientific substantiation of nutraceutical products. According to another industry expert, Stephen H. McNamara, former FDA Associate Chief Counsel for Food, the NREA could increase scientific research on the health benefits of food products by giving a period of exclusive marketing rights over a health claim for the person or company that demonstrated such health benefits (Reuters Health Medical News, 12-11-1998). The Bill however was not accepted by the US Congress and nutraceutical products in the US are still regulated under the DSHEA (Reuters Health Medical News, 12-11-1998).
However this negative view regarding the large degree of freedom under the DSHEA on health claims and its effect this on scientific substantiation of nutraceutical products had only been the opinion of a small group of people, such as the Foundation for Innovation in Medicine and some physicians (Reuters Health Medical News, 12-11-1998; 15-5-2000). In 2007 the NREA was again promoted at congressman Pallone of the Energy and Commerce Subcommittee on Health. Pallone however did not reintroduce the NREA at US congress (The foundation for innovation in medicine, 10-1-2007).
Lastly, several incidents took place relating to fish oil supplements in 2007 and 2009. Contaminations with mercury had been found and for that reason physicians discouraged women to take fish oil supplements during pregnancy (The New York Times, 24-3-2009; St. Louis Post-Dispatch (Missouri), 23-4-2007). Fish oils had also been related to the functioning of certain immune cells, which could be negatively affected by fish oils. Therefore some physicians had also discouraged people with weakened immune system to take fish oil supplements (Palm Beach Post (Florida), 15-6-2005).
However the general opinion on US regulations on nutraceuticals and the growth of the US nutraceuticals market remained positive. Few events were observed within Function 4 that negatively contributed to the US nutraceuticals IS (see Figure 5.6).

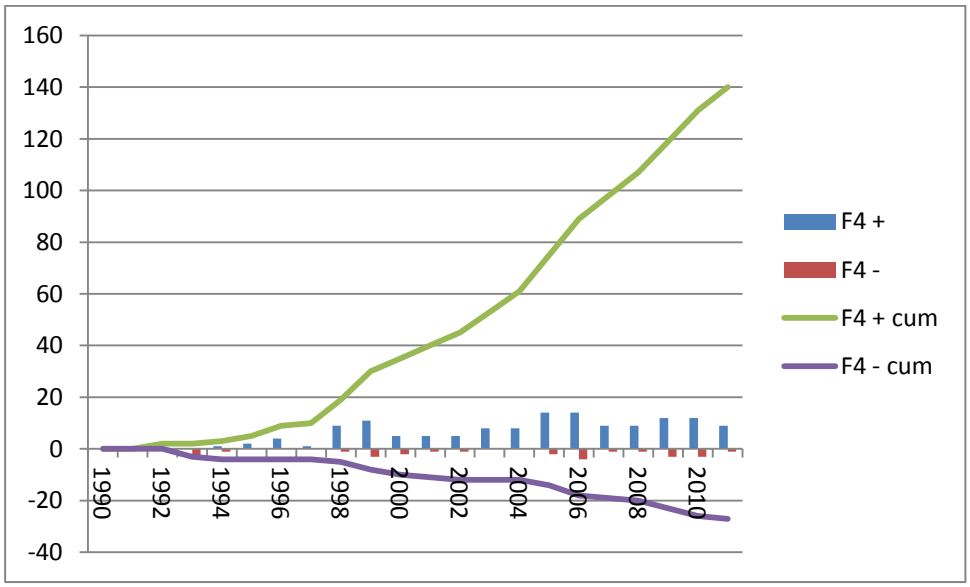

Figure 5.6 Score development Function 4: Guidance of the search US 1990-2011

5.3.5 Function 5: market formation

The first observations of FDA approving health claims were made at the end of 1999 and the beginning of 2001. The FDA approved a health claim correlating the consumption of soy protein with reducing the risks of heart disease (Business Wire, 21-10-1999), and a health claim for dairy products that links vitamin B12, as well as B6 and folic acid, to reduction in heart disease risk (Capital Times

(Madison, WI.), 29-1-2001). Very little activity was observed within Function 5, as can be seen in Figure 5.7.

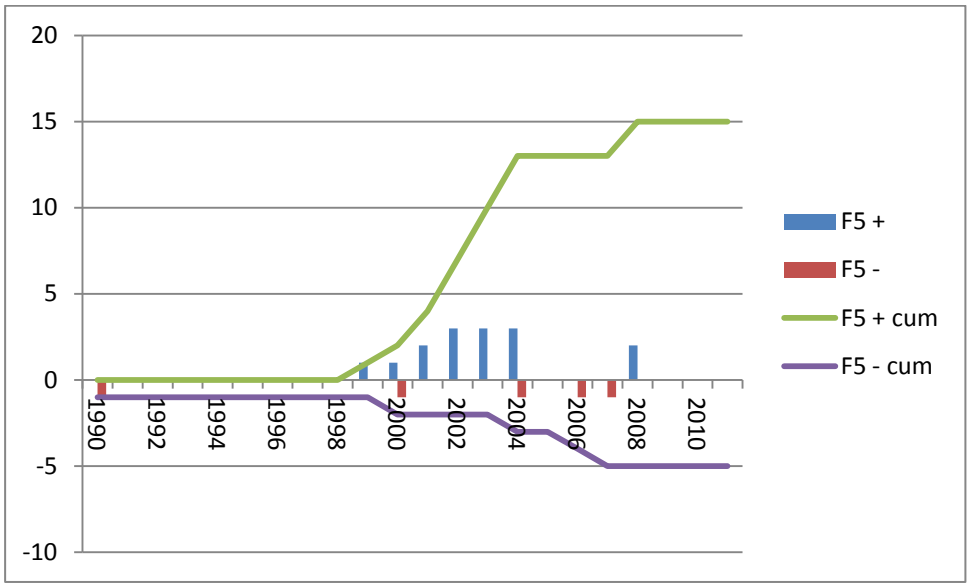

Figure 5.7 Score development Function 5: Market formation US 1990-2011

However, market formation had already started in October 1994 with the Dietary Supplement Health and Education Act (DSHEA) coming into effect. Because nutraceuticals are aimed to have a health benefit, allowing communicating this health benefit to consumers created a market for nutraceuticals. A total of 16 health claims were approved by the FDA over the period 1999 – 2008. These claims described a relationship between a food, food component, or dietary supplement ingredient, and reducing risk of a disease or health-related condition. The use of structure/function claims on a nutraceutical is allowed without prior approval, however the manufacturer is responsible for ensuring the accuracy and truthfulness of these claims; the claims are not pre-approved by FDA. Therefore, if a nutraceutical includes such a claim, it must state in a disclaimer that FDA has not evaluated this claim.

Until 2004 several approvals of health claims by the FDA were observed. In 2008 two approvals by Consumerlab[14] on the quality and manufacturing practices of fish oil supplements had been observed (Business Wire, 23-6-2008; PR Newswire, 4-8-2008). After 2008 no new health claims had been approved by the FDA. However, under the DSHEA companies could already use health claims on nutraceuticals whether the FDA has evaluated the health claim or not (FDA, 2012).

The FDA banned a few health claims that were made by nutraceutical products: in 1990 the first ban was imposed on claims on fish oil supplements of lowering cholesterol and the chance of heart attacks (The Associated Press, 16-7-1990). In 2000, after the introduction of the DSHEA, a second ban on a health claim was imposed on fish oil supplements: manufacturers were claiming omega-3 fatty acids protected against heart disease. The FDA banned these claims due to the lack of evidence and only allowed a function claim about the positive relationship between omega-3 fatty acids and cardiac wellness (Reuters Health Medical News, 2-11-2000).

In addition to these events there has been an ongoing battle on the use of ephedra[15] in weight loss nutraceuticals (The Associated Press State & Local Wire, 14-5-2007; Salt Lake Tribune (Utah), 11-1-

[14] Consumerlab is the leading provider of independent test results and information to help consumers and healthcare professionals identify the best quality health and nutrition products.

2004). Ephedra was linked to serious side effects events, such as a number of deaths (Salt Lake Tribune (Utah), 8-3-2003). Therefore the FDA placed a ban on ephedra in April 2004.
Altogether these negative events have been product specific and have not had a profound influence on market formation of nutraceuticals in general in the US. Only niche markets of the US nutraceuticals market have been affected by the bans such as the ban on ephedra supplements and the ban on health claims on fish oil supplements. In general the US nutraceutical industry enjoyed a large degree of freedom due to the freedom to use health claims under the DSHEA.

5.3.6 Function 6: resource mobilization

The first financial investments in the US nutraceuticals industry were observed in 1997. Fuisz Technologies, which is involved in the production of nutraceuticals, received a private investment of $75 million to enhance current business opportunities and to invest in general corporate purposes (PR Newswire, 23-10-1997). The following years every year an average of 4 to 5 investments in the US nutraceutical industry were observed (see Figure 5.8).

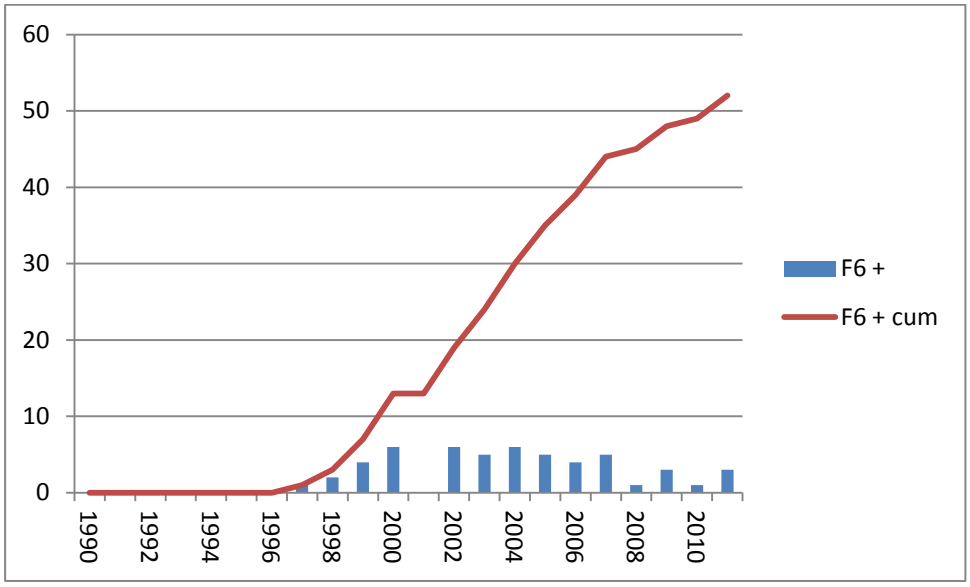

Figure 5.8 Score development Function 6: Resource mobilization US 1990-2011

The investments were research grants such as Kibow Biotech receiving $1 million for clinical research from the National Institute of Diabetes, Digestive and Kidney Diseases, (Internet Wire, 1-7-2002). Furthermore equity and debt financing was observed such as funding from Morgan Weinstein & Co. in HealthSpan, Inc. (PR newswire, 28-5-1999). These investments were mainly placed by venture capitalists. A few investments by non-profit organizations were observed too, such as the above mentioned National Institute of Diabetes, Digestive and Kidney Diseases providing US Kibow Biotech with a research grant of $1 million (Internet Wire, 1-7-2002). This research grant was to advance the development of Kibow Biotech's nutraceutical product lines that could augment kidney functions for pre-dialysis or early stage kidney failure patients (Internet Wire, 1-7-2002). Another investment by a non-profit organization was the National Alzheimer's Association funding of a three-year study at the University of Massachusetts Lowell to determine whether the SmartPill, which was developed by

[15] Ephedra supplements contain ephedrine compounds that have stimulating and thermogenic effect. These compounds stimulate the brain, increase heart rate, constrict blood vessels (increasing blood pressure), and expand bronchial tubes (making breathing easier). Their thermogenic properties cause an increase in metabolism.

researchers at the University of Massachusetts Lowell, could also delay the onset of Alzheimer's (Lowell Sun (Massachusetts), 20-10-2008).
From 2008 to 2011 however, the investments in the US nutraceuticals industry decline, which is left unexplained. In 2011 3 investments were observed. One of these was an investment in general business purposes and two were investments in research programs.

5.3.7 Function 7: creation of legitimacy / counteract resistance to change

The first lobbying activities in favor of nutraceuticals were observed in 1999. These were public relations efforts that focused on one product. For example, Nutrapharm, Inc. and healthcare agency SCIENS Worldwide Public Relations launching a national campaign in the US educating consumers and health professionals about the health benefits of Huperzine A[16] (PR newswire, 19-7-1999). Also several public relations efforts were carried out by Martin Nutraceuticals. Mainly through infomercials Martin Nutraceuticals tried to educate consumers and health professionals about Martin Nutraceuticals' products (Business Wire, 27-8-2007, 11-10-2007).
Also in 1999 the first negative opinions about nutraceutical products were expressed. An article in the New York Post (8-8-1999) stated that people should take health claims on food supplements with a grain of salt. Also several negative opinions relating to fish oil supplements were expressed. For example, Dr. Gruss, a prominent cardiologist, called 99% of all fish oil supplements on the market completely worthless (Business Wire, 22-4-2009). Also, makers and sellers of fish oil supplements were sued in California for not including labeling about PCB contamination (Upi, 2-3-2010). The only observed collective lobbying activity of the US nutraceutical industry was a response to these allegations by the Council for Responsible Nutrition (CRN). The CRN issued a statement that there were no safety issues with fish oil (States News Service, 2-3-2010).
In total a few more positive than negative events have been observed within Function 7 (Figure 5.9).

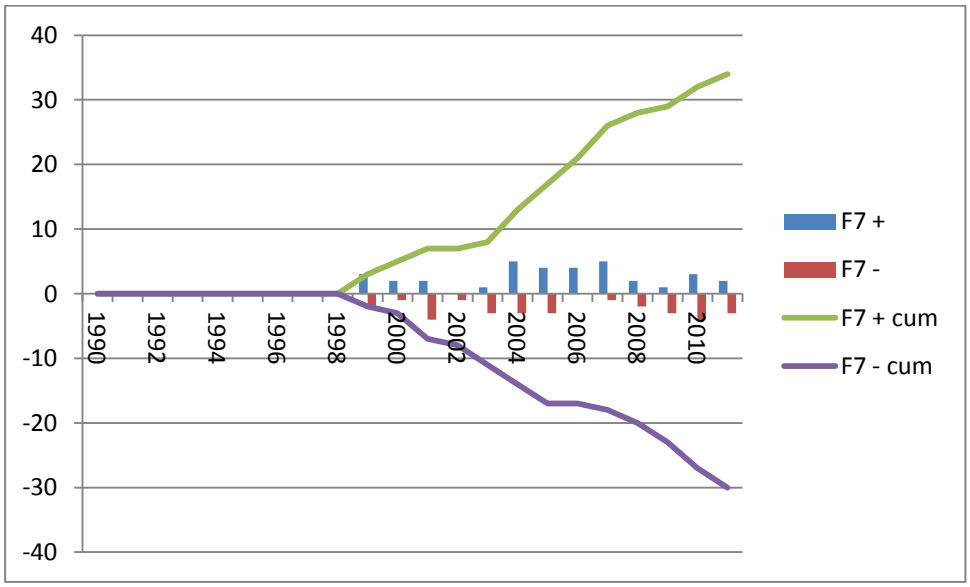

Figure 5.9 Score development Function 7: creation of legitimacy / counteract resistance to change US 1990-2011

Lastly, several lawsuits have been observed. These lawsuits have not been taken into account in the operationalization and have therefore not been included in the event count of the fulfillment of one of the system functions. However the events can still be found in the historical event database. It is

[16] Huperzine A is an acetylcholinesterase inhibititor used in the treatment of Alzheimer's disease

expected that lawsuits against producers or developers of a technology have a negatively influence on the perception of a technology by the general public, and thereby exert a negative influence on the fulfillment of Function 7.

5.3.8 Performance United States nutraceuticals innovation system

The size of the US nutraceuticals market over the period 1990 – 2011 is given in Table 5.1. Many years of data are missing, only the years of which data was available are represented in Table 5.1. Because data is retrieved from different sources which have used different definitions of the nutraceuticals market, the data cannot easily be compared with each other. It is only an indication of how the US nutraceuticals market has grown over time.

The first three figures on the market size of nutraceuticals have been based on definitions that included functional foods. It is not possible to determine how big the share of nutraceuticals is in these figures. The last three figures show an approximate market growth of the US nutraceuticals market of 5 billion US $ over the period 2006 – 2009 and an approximate market growth of 6 billion US $ from 2009 to 2010. For this last period this means an estimated market growth of over 20% in one year. However this is just an indication.

Table 5.1: Market size US nutraceuticals industry

Year	Market size nutraceuticals in billion US $	Comment	Source
1997	15.4	Functional foods and nutraceuticals	Nutrition Business Journal
1998	4.5	Functional foods and nutraceuticals	Frost & Sullivan
1999	15.8	Functional foods and nutraceuticals	Kalorama Information
2006	21.3		Datamonitor
2009	26.9		Nutrition Business Journal
2010	33		Reportlinker

Concluding, most System Functions of the US nutraceuticals IS have been well fulfilled over the period 1990 – 2011. Many entrepreneurial activities have been observed, thus fulfilling Function 1. Also many published studies on nutraceuticals and patents on nutraceuticals have been observed within Function 2. Knowledge diffusion showed many mergers and acquisitions, and many collaborations between companies and/or research institutes. Thereby Function 3 is fulfilled as well. Function 4 showed a far greater extend of events positively contributing to the US nutraceuticals IS than events negatively contributing to the IS, accordingly Function 4 is well fulfilled. Function 5 showed little activities and might seem not adequately fulfilled. However since in 1994 the DSHEA created a market for nutraceuticals in the US little activity was needed within Function 5. Therefore Function 5 is said to been fulfilled as well. Function 6 shows a fair amount of events. Moreover, no expression of the lack of resources within the US nutraceuticals IS has been observed, therefore the fulfillment of Function 6 has been satisfactory. Function 7 shows approximately an equal amount of positive as negative events. This means there was still a fair amount of resistance against nutraceuticals. Function 7 is therefore said to be not adequately fulfilled.

Thus the results of the functional analyses of the European and US nutraceuticals IS have been very different. The next chapter will analyze and discuss these differences in detail.

6. Case comparison EU and US nutraceuticals innovation system

Over the past twenty years the global market for nutraceuticals has shown impressive growth rates estimated between 15% and 20% annually (Hilliam, 2000; Verbeke, 2005). Over the period 1999 – 2006 the *global market* for nutraceuticals grew more than tenfold from $5.7 billion to $75.5 billion, whereas the *European market* for nutraceuticals only grew less than fivefold from $1.8 billion to $8 billion (Basu et al., 2007). The *US market* is the largest and most rapidly expanding nutraceuticals market with an expected annual growth rate of 7% from 2012 till 2015. These figures raise the question why Europe is lagging behind in this growth. Previous studies have explained the lagging behind in size and growth of the European nutraceuticals industry by the lack of harmonized European regulations and the lack consumer acceptance regarding nutraceuticals in Europe. This research does not study these problems in isolation but uses and innovation systemic approach to create a better understanding of the strengths and weaknesses of the European nutraceuticals IS. This chapter focuses on the following research question: *What are the strengths and weaknesses of the emerging nutraceuticals innovation system in the European Union compared to the emerging nutraceuticals innovation system in the United States over the period 1990 – 2011?*

This chapter compares the development of the European nutraceuticals IS with the US nutraceuticals IS over the period 1990 – 2011. The fulfillment of the seven System Functions according the performed TIS analyses will be discussed over three periods: 1990 – 1999, 2000 – 2005, 2006 – present. The reason to discern these periods is to increase clarity by highlighting the various properties of these periods in terms of the fulfillment of the System Functions in both innovation systems. The symbols F1 – F7 refer to the seven System Functions. A (-) sign before F1 – F7 denotes a negative contribution to the IS.

The references of the case comparison between EU and US nutraceuticals Innovation System can be found in Appendix D.

6.1 1990 – 1999: The early onset and the lack of regulations regarding nutraceuticals

The first period, 1990 – 1999, was characterized by the lack of a regulatory system (-F4) for nutraceuticals in both Europe and the US. In July 1993 the Act on natural remedies came into force in Sweden (F4) (Nutraceuticals International, 1-7-1993). This Act also controlled nutraceuticals and Sweden was thereby the first country in the EU to enact legislation on nutraceuticals. During the same period the lack of regulations in the US triggered calls for US legislation on nutraceuticals (-F4) (PR Newswire, 1-12-1994). In the US, nutraceuticals were controlled by the Federal Food, Drug, and Cosmetic Act (F4) (FDA.gov, 2010). Likewise, the EU nutraceuticals were controlled by individual member states' medicine and food law. This meant that in both the US and the EU it was nearly impossible for manufacturers of nutraceuticals to put nutraceutical products with health claims on the market since this entailed they would be classified as a pharmaceutical.

This gap in legislation was soon acknowledged by the US Food and Drug Administration (FDA). Little controversy existed on nutraceuticals in the US according the little events within F7: creation of legitimacy / counteract resistance to change. Quickly after recognition of the problem of the lack of regulations on nutraceuticals, the Dietary Supplement Health and Education Act (DSHEA) came into force in the US in 1994 (F4). This fulfillment of F4 was the most important enabling factor for the development of a market for nutraceuticals (F5) and the fulfillment of entrepreneurial activities (F1) in the US. Under the DSHEA manufacturers of nutraceuticals enjoyed a large degree of freedom regarding the use of health claims. In the US the manufacturer of a nutraceutical is responsible for the accuracy of a health claim. In practical terms this means little scientific substantiation is needed

to use a health claim on a nutraceutical. Because of this large degree of freedom regarding the use of health claims a market was created for nutraceuticals in the US (F5) and the entrepreneurial activities (F1) grew fast with 17 observed entrepreneurial activities in 1999. In 1998 the sales of the US nutraceutical industry were estimated to be US $4.5 billion (PR Newswire, 1-3-1999).

Where in the USA the FDA saw the problem of the lack of regulations for nutraceuticals and took action, in Europe during the period 1990 – 1999 the nutraceutical industry was still regulated on national level (-F4). Consequently market formation on a European level did not take place (-F5) and the European market for nutraceuticals was fragmented and existed of individual member states' markets. As a result in some markets where liberal regulations regarding health claims on nutraceuticals were enforced such as the Dutch and UK, a market for nutraceuticals was created (F5) and entrepreneurial activities (F1) took place. While in other markets, such as the German market, very strict regulations regarding the use of health claims (-F4) kept market formation (-F5) and entrepreneurial activities low (-F1). Also, more controversy existed in Europe regarding nutraceuticals according the higher incidence of both positive and negative events within F7: creation of legitimacy / counteract resistance to change. In 1999 the sales of the emerging nutraceuticals industry in Europe was estimated to be US $1.8 billion (Basu *et al.*, 2007).

Thus during this first period, 1990 – 1999, the signing into law of the DSHEA in the US led to the fulfillment of F4: guidance of the search. As a result this enabled the fulfillment of F5: market formation and F1: entrepreneurial activities. In Europe the absence of regulations on a European level caused the lack of fulfillment of F4: guidance of the search. As a result F5: market formation and F1: entrepreneurial activities were lagging behind too. Only in a few countries such as the UK and The Netherlands entrepreneurial activities were taking place because of liberal regulations regarding the use of health claims on nutraceuticals. Table 4.1 gives an overview the key characteristics of the seven System Functions over the period 1990 – 1999 in Europe and the US.

Table 4.1: Key characteristics of the System Functions within the European and US nutraceuticals innovation system 1990 – 1999

System functions	Europe	US
F1: entrepreneurial activities	• Entrepreneurial activities limited to countries with liberal regulations	• Entrepreneurial activities grow strongly after DSHEA is signed into law
F2: knowledge development	• Limited research and patents mentioning the term nutraceuticals	• Limited research and patents mentioning the term nutraceuticals
F3: knowledge diffusion	• Establishment of trade organizations ERNA and IADSA • First mergers and acquisitions in 1999 • Conferences on lack of regulations	• Establishment of trade organization ANA, • first mergers and acquisitions in 1993,
F4: guidance of the search	• Lack of European regulations, nutraceuticals are controlled on national level	• Dietary Supplement Health and Education Act (DSHEA) is signed into law
F5: market formation	• Lack of one European market	• Market for nutraceuticals is created after DSHEA is signed into law
F6: resources mobilization	• Limited and incidental investments in nutraceutical technology	• Gradual rise in investments in nutraceutical technology from

		1997
F7: creation of legitimacy / counteract resistance to change	• Mildly controversy about nutraceuticals	• Little controversy about nutraceuticals

6.2 2000 – 2005: Optimism is taken over by uncertainty

The entrance of the first large companies such as Novartis, Numico, and Danone on the European nutraceuticals market in 1999 marked the transition to a new period for the European nutraceuticals IS. These large companies were engaging in entrepreneurial activities (F1) driven by confidence in a growing European market for nutraceutical products. These positive expectations (F4) were fueled by the growing awareness of consumers about the relationship between diet and health, and the expectations of the formation of a regulatory framework for nutraceuticals in Europe.

Meanwhile in the US the liberal regulatory framework regarding the use of health claims (F4) made it easier for nutraceutical companies to market their products, which was visible in the growing number of entrepreneurial activities (F1). From 2002 and onwards an average of 18 new entrepreneurial projects (F1) was observed every year. This gradual increase of the total number of entrepreneurial nutraceutical projects in the US suggested that the emergence of the US nutraceuticals industry was well in progress and the US nutraceuticals industry was a healthy industry with sufficient opportunities for entrepreneurs to start a business (F1, F5).

Where in the US expectations on the nutraceuticals industry were mainly positive (F4), in Europe the optimism that was initially visible in F4: guidance of the search, turned into uncertainty because the large companies that had entered the European nutraceuticals industry could not obtain significant market shares. One of the reasons they could not obtain significant market shares was that the large companies were unfamiliar with the patenting strategies in the nutraceuticals industry. Between 2000 and 2002 no new entrepreneurial activities (-F1) were observed in Europe and in 2002 there was a growing negative sentiment towards the European regulations (-F4): industry expert Peter Berry Ottaway amongst others was complaining about the time it took to create harmonized European regulations for the European nutraceuticals industry. The lack of entrepreneurial activity (-F4) in Europe coincides with a strong decrease in investments in nutraceutical projects (-F6) between 2000 and 2004. Furthermore individual member states in the EU were banning several health claims (-F5) that were making on nutraceutical products. Accordingly the large companies in Europe that engaged in nutraceutical technology experienced problems in bringing new product to the market (-F1): they tried to develop nutraceutical products that were validated with scientific research such as clinical trials but could not get health claims approved at the European Food Safety Authority (EFSA). The large companies were unable to obtain significant market shares of the European nutraceuticals market exited the European nutraceuticals industry around 2003 (-F1). Together with the uncertainty about regulations on health claims this caused negative expectations about the marketing opportunities for nutraceutical products in Europe (-F4)

Just before the exit of the large companies from the European nutraceuticals industry there were some positive expectations (F4) in 2002 regarding Directive 2002/46/EC on the labeling of food supplements. The European nutraceuticals industry was expecting improvements in the complex regulatory systems by which it was controlled until then. However because individual member states were free to interpret and to incorporate Directive 2002/46/EC into their own national laws, there

were still many regulatory differences between the different EU countries because of different interpretations of Directive 2002/46/EC.

Not only in the EU there was criticism on the regulatory framework (-F4) by which nutraceuticals were controlled. Also in the US there was criticism (-F4), be it from a completely different nature. In the US criticism came from several physicians and from The Foundation for Innovation in Medicine (FIM), run by Dr. DeFelice, who coined the term nutraceutical in 1989. Their criticism focused on the large degree of freedom regarding the use of health claims under the DHEA. According to Physicians and the FIM this large degree of freedom was hampering knowledge development and scientific substantiation of nutraceutical products (-F2). Many claims used on nutraceutical products were backed by little scientific evidence and the US nutraceuticals market was called a "cowboy industry" with many misleading nutraceutical products on the market (The Associated Press, 26-1-1993; Reuters Health Medical News, 15-5-2000). This had a negative influence on the credibility of the nutraceuticals industry (-F7). To increase scientific substantiation of nutraceutical products Congressman Frank Pallone, supported by Dr. DeFelice and the FIM, introduced in 1999 The Nutraceutical Research & Education Act (NREA) into US Congress. The aim of the NREA was to establish a clinically research based nutraceuticals industry by prescribing a period of exclusive marketing protection over a health claim for the person or company that demonstrated the health benefits of a dietary supplement, medical food, or other food. The bill however was not accepted by US congress and nutraceutical products in the US would still be regulated under the DSHEA and nutraceutical manufacturers in the US still enjoyed the same degree of freedom regarding the use of health claims.

Despite most countries in Europe were enforcing stricter regulations than in the US, the lack scientific substantiation of nutraceutical products was also visible in Europe. From the beginning of the 2000s more and more suspicious products were entering the European market with scientifically unsubstantiated health claims (IV5,8). This lack of scientific substantiation (-F2) negatively influenced the credibility (-F7) of the European nutraceuticals industry. Due to different regulations and new distribution channels, such as websites on the internet and Facebook, the market was getting more diffuse and it became more difficult to enforce regulations and ban scientifically unsubstantiated nutraceutical products off the market (IV5).

Thus several relations between the System Functions were visible during the period 2000 – 2005. First positive expectations within F4: guidance of the search stimulated large companies to start entrepreneurial activities (F1) in Europe. In the US the same mechanism as in the foregoing period was going on: regulations (F4) had created a market for nutraceuticals (F5) and stimulated entrepreneurial activities (F1). Then in Europe uncertainty about regulations and the future of the industry (-F4) took over and stopped entrepreneurial activities (-F1) and investments in nutraceutical projects (-F6). The lack of regulations in Europe, which influence on F5 and F6 persisted until 2009, is graphically represented in Figure 6.1.

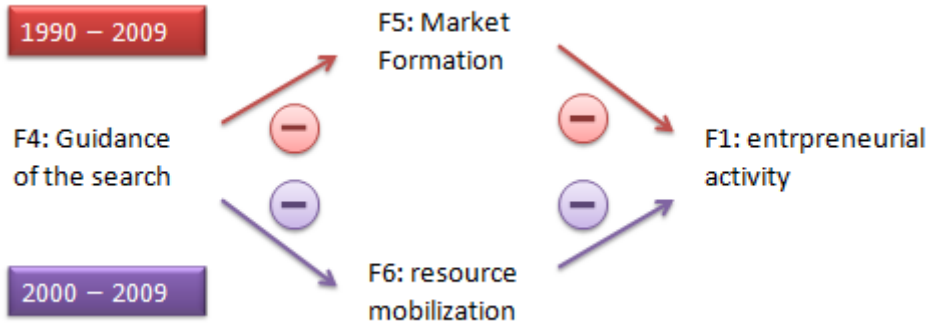

Figure 6.1 Effect of the lack of regulations in European nutraceuticals IS

Lastly there was the recognition of the lack of scientific substantiation (-F2) of many nutraceutical products in both Europe and the US. Despite many activities were observed in Europe and the US within F2: knowledge development, this knowledge development failed to lead to a high level of scientific substantiation of nutraceutical products on the market. This negatively affected F7: creation of legitimacy / counteract resistance to change in Europe and the US. The effect of the lack of scientific substantiation of nutraceutical products in the Europe and the US over the period 1990 – 2009 is graphically represented in Figure 6.2.

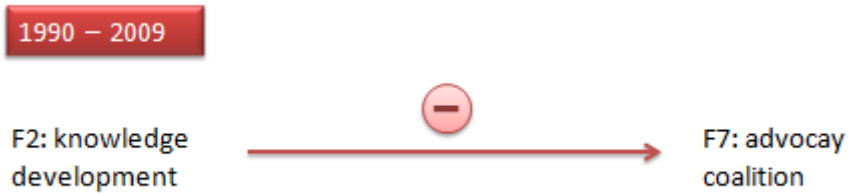

Figure 6.2 Effect of the lack of scientific substantiation of nutraceutical products on F7

Table 4.2 gives an overview the key characteristics of the seven System Functions over the period 2000 – 2005 in Europe and the US.

Table 4.2: Key characteristics of the System Functions within the European and US nutraceuticals innovation system 2000 – 2005

System functions	Europe	US
F1: entrepreneurial activities	• Large companies enter nutraceutical industry around 1999 and exit around 2003, • No entrepreneurial activity between 2000-2002	• Entrepreneurial activities reach steady state
F2: knowledge development	• Knowledge development does not lead to scientific substantiation of nutraceutical products	• Knowledge development does not lead to scientific substantiation of nutraceutical products • Number of patents far exceeds research publications
F3: knowledge diffusion	• Conferences and meeting about unclear regulations	• Many coalitions between companies and/or research institutes

		• Many mergers/acquisitions
F4: guidance of the search	• Optimism in growing nutraceutical industry turns into uncertainty due to the lack of clear regulations	• General expectations are positive • Some experts question the large degree of freedom regarding health claims
F5: market formation	• Lack of one European market	• Nutraceuticals market was created in foregoing period
F6: resources mobilization	• No investments in nutraceutical projects between 2000 – 2004	• Investments in nutraceutical projects reach steady state
F7: creation of legitimacy / counteract resistance to change	• Lack of scientific substantiation negatively affects credibility of nutraceuticals industry	• Lack of scientific substantiation negatively affects credibility of nutraceuticals industry

6.3 2006 – Present: Regulations ensure scientifically substantiated nutraceutical products

In 2006 Regulation (EC) 1924/2006 on nutrition and health claims made on foods came into force in the EU (F4). The goal of this Regulation was to harmonize individual member states' regulations on nutrition and health claims made on foods and to ensure a high level of protection for consumers, which in its turn could have a positive effect on F7: creation of legitimacy / counteract resistance to change. Under Regulation (EC) 1924/2006 a list would be created with permitted health claims that would be allowed to be used. Despite Regulation (EC) 1924/2006 marked the end of the lack of harmonized regulation regarding nutraceuticals and health claims in the EU (F4), companies were uncertain about what health claims they could use and were expecting Regulation (EC) 1924/2006 was going to have a profound negative impact on the marketing of nutraceuticals in Europe (-F4). Industry organizations such as the Dutch NPN had indicated that Regulation (EC) 1924/2006 marked the start of a period of uncertainty for European nutraceutical companies (-F4) and as a result entrepreneurial activities decreased (-F1). After a long 5 year process of scientific evaluation by the EFSA of the health claims submitted by the European nutraceuticals industry, it is expected that European Parliament will vote on the approval of the list of approved health claims in 2012. The uncertainty regarding future business opportunities (-F4) especially affects smaller companies within the European nutraceuticals industry: the high level of scientific substantiation under Regulation (EC) 1924/2006 requires significant funds to carry out research such as clinical trials.

From 2009 a decrease of uncertainty (F4) amongst nutraceutical companies in Europe is visible. This can be related to the increased clarity about the implementation of Regulation (EC) 1924/2006. Additionally, due to Regulation (EC) 1924/2006 scientifically unsubstantiated health claims will become more difficult to use and will make it more difficult for the earlier mentioned free-riders to market their products. This can create a scientifically substantiated nutraceuticals market (F2, F5) and can create new entrepreneurial activities (F1). Accordingly larger companies were again seeking opportunities in the European nutraceuticals industry (F1) after leaving the European nutraceuticals industry around 2003 (IV8). This is also visible in the increase of investments (F6) in the European nutraceuticals industry after 2006. These investments include investments by pharmaceutical firms such as CNS Pharmaceuticals AG (M2 EquityBites, 12-11-1999). These firms have the experience and funds to carry out clinical trials. In addition, after 2008 the number of granted patents triples to 93 new patents registered at the EPO in 2009 (F2). This also supports the involvement of large companies in the European nutraceutical industry; large companies are more focused on patenting

than small firms (IV2,3). Furthermore the increased clarity about the future of the industry (F4), which would again attract large companies to the European nutraceutical industry (F1), is also supported by the strong decline of the occurrence of both positive and negative events within Function 4: guidance of the search.

Where in the EU an increase of investments (F6) can be observed in the last few years, in the US a decrease in investments (-F6) is visible. However, the decline in investments does not seem to have influenced the start of new nutraceutical entrepreneurial activities; Function 1: entrepreneurial activities did not show any decline in the start of new nutraceutical projects such as product launches. The liberal nutraceuticals market in the US had grown in 2006 to US $21.3 billion. In Europe on the other hand where a higher level of scientific substantiation for the use of health claims is required the market had grown in 2007 to US $8 billion.

Besides these regulatory differences (F4) which have had an important influence on the fulfillment of F1: entrepreneurial activities and F5: market formation, both nutraceuticals innovation systems have also known numerous incidents (-F7), often relating to contamination of fish oil supplements or contra-indications for the use of fish oil supplements. Furthermore in the US much attention has been paid in the media in 2006 to a law suit regarding fraud against Enzyte, a male enhancement supplement. Also other law suits had been observed within the US nutraceuticals IS, however no law suits were observed within the European nutraceuticals IS. Despite the media attention to the fraud and other lawsuits (-F7), and also the regular negative opinions on fish oil in the media (-F7), the publicity did not stuck with consumers for a long time and had little effect on sales (IV5,7).

Concluding, during this last period, 2006 – present, Regulation (EC) 1924/2006 has had a two-way influence in Europe: at first negative expectations and uncertainty about the future of the industry prevailed (-F4) and as a result entrepreneurial activities decreased (-F1). Then in 2009 the number of events within F4: guidance of the search started to decrease which is a sign of decreased ambiguity and increased clarity about the future of the industry. Furthermore, Regulation (EC) 1924/2006 also creates a research driven market, and thus positively influences F2: knowledge development. The increased scientific substantiation of nutraceutical products in Europe positively affects (reduces) consumer skepticism. Also, Regulation (EC) 1924/2006 creates a uniform European nutraceuticals market. As a result F1: entrepreneurial activities started to rise again in Europe in 2010 and 2011 and the European nutraceuticals IS is at the beginning of a market with scientifically substantiated nutraceutical products. These influences are graphically represented in Figure 6.3.

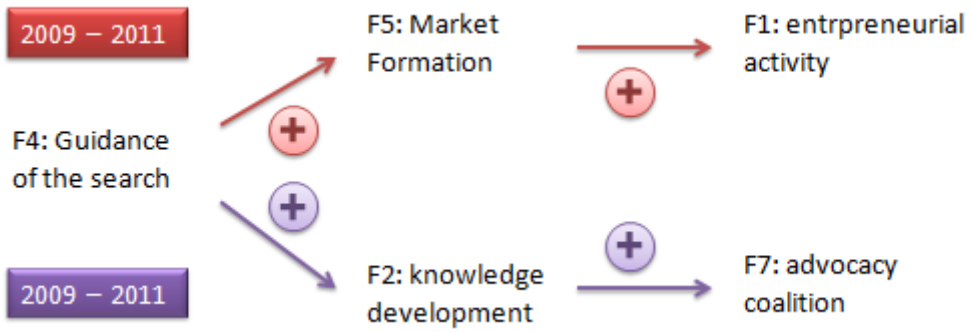

Figure 6.3 Effect of Regulation (EC) 1924/2006 on European nutraceuticals IS

In the US nutraceuticals IS little has changed; entrepreneurial activities (F1) were widely taking place and also the other System Functions were fulfilled. F6: resource mobilization did show a decrease of events after 2006 but this did not affect other System Functions.
Also negative incidents regarding nutraceuticals within F7: creation of legitimacy / counteract resistance to change did not negatively affect the other System Function in either Europe or the US. Table 4.3 gives an overview the key characteristics of the seven System Functions over the period 2006 – present in Europe and the US.

Table 4.3: Key characteristics of the System Functions within the European and US nutraceutical innovation system 2006 – present

System functions	Europe	US
F1: entrepreneurial activities	• Uncertainty regarding Regulation (EC) 1924/2006 causes entrepreneurial activities to cease after 2006. • Entrepreneurial activities rise again in 2010 and large companies re-enter nutraceutical industry	• Entrepreneurial activities on steady state
F2: knowledge development	• Number of newly issued patents drops after 2006 • Number of newly issued patents increases again in 2009	• Research and patents mentioning the term nutraceuticals on steady state
F3: knowledge diffusion	• After 2008 activity within F3: knowledge diffusion strongly decreases	• Many coalitions between companies and/or research institutes and many mergers/acquisitions
F4: guidance of the search	• Regulation (EC) 1924/2006 comes into force and first causes uncertainty and then clarity	• General expectations are positive
F5: market formation	• One European market is formed by Regulation (EC) 1924/2006	• Nutraceuticals market was created in foregoing period
F6: resources mobilization	• Few investments	• Investments decline after 2006
F7: creation of legitimacy / counteract resistance to change	• Moderate controversy about nutraceuticals	• Moderate controversy about nutraceuticals

The comparison shows the regulatory framework (F4) can be identified as the common influencing factor in the development of a market (F5) and the development of entrepreneurial activities (F1).
In the US a liberal regulatory framework regarding the use of health claims created a market for nutraceuticals (F5) and stimulated entrepreneurial activity (F1). In Europe the lack of harmonized regulations, and after harmonization the strict regulatory framework (-F4) made it more difficult for a nutraceuticals market to develop (-F5). Consequently entrepreneurial activity (F1) remained low. As a result the market for nutraceuticals was larger and grew faster in the US than in the EU.
The comparison did not show differences in consumer skepticism regarding nutraceuticals (F7), which was used to measure acceptance problems with nutraceuticals. In both the European and US

nutraceuticals IS consumers had expressed their skepticism regarding health claims made on nutraceutical products. This expressed skepticism was only observed several times but could not be related to the fulfillment of other System Functions.

Furthermore the most significant difference between the European and US nutraceutical innovation system is that as result of the regulatory differences the scientific substantiation of nutraceutical products will be higher in Europe than in the US. Consequently consumers will be better protected against misleading products and can expect higher quality nutraceutical products on the European market.

7. Conclusions

The problem studied in this research was framed as the lagging behind in size and growth of the European nutraceuticals market compared to the global nutraceuticals market and US nutraceuticals market, which is the largest and most rapidly expanding nutraceuticals market in the world. Earlier studies showed that the regulatory system for nutraceuticals in Europe and consumer acceptance of nutraceuticals in Europe were the main causes of the lagging behind of the European nutraceuticals market. The aim of this study was to compare the European and the US nutraceuticals developments on innovation systems level to better understand the strengths and weaknesses of the European nutraceuticals innovation system (IS). Also, the aim was to design policy recommendations to overcome the weaknesses of the European nutraceuticals IS. Because the term 'nutraceutical' was coined in 1989 and the first nutraceutical products entered the European market mid 90s, the studied timeframe was the period 1990 – 2011.
This chapter will provide the answer the two research questions:

> RQ1: *What are the strengths and weaknesses of the emerging nutraceuticals innovation system in the European Union compared to the emerging nutraceuticals innovation system in the United States over the period 1990 – 2011?*
>
> RQ2: *What recommendations can be given to policy makers in the European Union to overcome the weaknesses of the emerging European nutraceuticals innovation system?*

Firstly the European and US nutraceuticals IS were analyzed using the technological innovation system (TIS) approach. This innovation systemic approach enabled to analyze the European and US nutraceuticals IS over time. Also the TIS approach enabled to study the specific problems of the European regulatory system and consumer acceptance of nutraceuticals (which was taken into account by looking at consumer skepticism) as part of the entire European nutraceuticals IS. The TIS approach discerns seven System Functions with interact with each other. The better the seven System Functions are fulfilled, the better the performance of the IS is expected to be. Due to vast amounts of data available, this research has only included data regarding the nutraceuticals market. Thus, the domain was narrowed down from the entire European nutraceuticals IS to the European nutraceuticals market.
Secondly, to overcome the weaknesses of the European nutraceuticals IS for the European Union policy recommendations are given based on the outcomes of RQ1.

7.1 Conclusions European and US nutraceutical innovation system analyses

The section will answer the first research question:

> *What are the strengths and weaknesses of the emerging nutraceuticals innovation system in the European Union compared to the emerging nutraceuticals innovation system in the United States over the period 1990 – 2011?*

According to the comparison between the EU and the US nutraceuticals IS over the period 1990 – 2011 it can be concluded that regulations regarding the use on health claims on nutraceuticals was

one of the most important factors influencing the development of both the European and US nutraceuticals IS.

In the US nutraceuticals IS the main strength over the period 1990 – 2011 was the rapid development of regulations to control health claims on nutraceuticals. The fulfillment of F4: guidance of the search in the form of the Dietary Supplement Health and Education Act (DSHEA) was the most important enabling factor for the development of a market for nutraceuticals (F5) in the US. Under the DSHEA nutraceuticals were recognized as dietary supplements and manufactures of nutraceuticals enjoyed significant freedom regarding the use of health claims on nutraceutical products. By allowing health claims on nutraceuticals, new marketing opportunities for nutraceutical manufactures arose and a market for nutraceuticals was created (F5). The creation of a market stimulated the fulfillment of F1: entrepreneurial activities; after the introduction of the DSHEA in 1994 the US nutraceuticals industry showed a large number of entrepreneurial activities. Furthermore, a strong growth of the nutraceuticals market was observed.

In Europe the lack of regulations on health claims between 1990 an 2006, and thus the lack of fulfillment of F4: guidance of the search was one of the main weaknesses of the European nutraceuticals IS. It took until 2006 before a regulation regarding the use of health claims was designed on a European level: Regulation (EC) 1924/2006 on health claims. It took another 6 years until full implementation of this regulation. Until then the lack of regulations on health claims had as a result that the development of a market for nutraceuticals in Europe (F5) went problematic. The individual European countries applied different national regulations and this resulted in the lack of one uniform European nutraceuticals market. The fragmented European nutraceuticals market made it difficult for nutraceutical manufactures to market their product internationally. As a result, large food and pharmaceutical companies which entered the European nutraceuticals industry around the year 2000 could not obtain significant market shares and most of these companies left the nutraceuticals industry around 2002/2003. Consequently, besides F5: market formation, F1: entrepreneurial activity also lagged behind.

Additionally, expert interviews showed that from 2000 onwards the ongoing lack of regulations caused uncertainty about the future of the European nutraceuticals market (-F4). This uncertainty made nutraceutical companies hesitant to invest in new nutraceutical projects and thus negatively affected the fulfillment of F6: resource mobilization in Europe. The negative influence of the lack of regulations on the European nutraceuticals IS persisted until 2009.

Another weakness of the European and even more for the US nutraceuticals innovation system was the lack of scientific substantiation (-F2) of many nutraceutical products. This lack of scientific substantiation was *not* the result of the lack of fulfillment of F2: knowledge development. In the US the large degree of freedom under the DSHEA regarding the use of health claims meant the DSHEA did not provide incentives for nutraceutical research. Thereby the DSHEA was hampering scientific substantiation of nutraceutical products (-F2). The lack of scientific substantiation of nutraceutical products encouraged consumer skepticism and had a negative influence on the credibility of the nutraceuticals industry (-F7). What is notable in this respect is that despite the large number of activities within F2: knowledge development, this knowledge development failed to lead to a high level of scientific substantiation of nutraceutical products on the US nutraceuticals market.

In Europe the lack of scientific substantiation (-F2) of many nutraceutical products was the result of the lack of a European inspection agency that could effectively ban scientifically unsubstantiated nutraceutical products off the market. New sales channels such as websites, Facebook, and Ebay created opportunities for companies to market scientifically unsubstantiated nutraceutical products

to consumers. Because of the new sales channels these nutraceutical companies were difficult to trace by (national) inspection agencies. Also in Europe the scientifically unsubstantiated nutraceutical products entering the market encouraged consumer skepticism towards nutraceutical products, which negatively affected F7: creation of legitimacy / counteract resistance to change.

The so far weak European nutraceutical innovation system changed significantly when in 2006 the European Commission enacted Regulation (EC) 1924/2006 regarding the use of health claims. Regulation (EC) 1924/2006 was based on the precautionary principle, in which consumer protection has a high priority, and had as goal to harmonize different national regulations. It had a two-way influence on the European nutraceuticals IS: firstly, the nutraceuticals industry was uncertain about the health claims the industry could use in the future. This uncertainty negatively affected the fulfillment of F4: guidance of the search and had a negative influence on entrepreneurial activities (-F1) in the European nutraceuticals IS. Secondly, when around 2009 it became clear how the European nutraceuticals market would look like after the full implementation of Regulation (EC) 1924/2006, uncertainty decreased and entrepreneurial activities (F1) started to rise again. By assuring a high level of consumer protection by demanding a high level of scientific substantiation of health claims on nutraceuticals, Regulation (EC) 1924/2006 created a research driven market, and thus positively influenced F2: knowledge development. Also, because Regulation (EC) 1924/2006 harmonized the different national regulations, it created one uniform European nutraceuticals market and positively influenced F5: market formation. Furthermore, the high level of consumer protection results in a European market with nutraceutical products with scientifically substantiated health claims. This reduces consumer skepticism towards nutraceutical products, and accordingly positively affects F7: creation of legitimacy / counteract resistance to change. Therefore Regulation (EC) 1924/2006 can be regarded as the main strength of the European nutraceuticals innovation system: it has created a European market with only scientifically substantiated products. Ergo, these nutraceutical products can really benefit consumers.

Besides these influences, Regulation (EC) 1924/2006 is expected to have some other consequences as well. At the moment entrepreneurial activity (F1) in the European nutraceuticals innovation system mainly comes from small companies. Because the approval of new health claims requires significant scientific research and evidence such as clinical trials, it is expected that entrepreneurial activity in the future will to a greater extent come from large companies (mainly originating from pharmaceutical and food companies) which have sufficient funds to pay for such studies. The small companies that cannot get health claims on their products approved are not expected to completely disappear. It is expected that small companies will divert their strategies towards endorsement practices to promote the health benefits of their products at general practitioners, alternative medicine doctors, and start public relations activities. In this way the small companies are still able to inform consumers about the health benefits of their products without expensive research and the use of health claims.

Concluding, over the period 1990 – 2006 the main weaknesses of the European nutraceuticals innovation system was the lack of European regulations regarding the use of health claims on nutraceuticals, and thus the lack of fulfillment of F4: guidance of the search. This influenced the lack of fulfillment of F5: market formation and the lagging behind of F1: entrepreneurial activity. The ongoing lack of regulations created uncertainty about the future of the European nutraceuticals market (-F4) which had a negative effect on the fulfillment of F6: resource mobilization.

In the US the opposite happens. The early creation of regulations regarding the use of health claims (F4) created a market for nutraceuticals (F5). As a result many entrepreneurial activities (F1) take place which allowed for a strong growth of the US nutraceuticals industry.
Another weakness of the European and also the US nutraceuticals innovation system was the lack of scientific substantiation (-F2) of many nutraceutical products which lead to consumer skepticism and thereby negatively affected F7: creation of legitimacy / counteract resistance to change.
The main strength of the European nutraceutical innovation system is Regulation (EC) 1924/2006. At first it created uncertainty in the European nutraceuticals industry about the health claims the industry could use in the future. In 2009 this uncertainty reduces. By harmonizing national regulations on health claims Regulation (EC) 1924/2006 positively influenced F5: market formation. Market formation in its turn positively influenced F1: entrepreneurial activity. Furthermore, by demanding a high level of scientific substantiation, Regulation (EC) 1924/2006 stimulates F2: knowledge development. By assuring a high level of scientific substantiation of nutraceutical products, consumers will be protected against scientifically unsubstantiated nutraceutical products. Thereby consumer skepticism is reduced and F7: creation of legitimacy / counteract resistance to change is positively affected.
Innovative activities in the European and US nutraceuticals industry in the past focused on bringing new products to the market without scientific substantiation, and were thus more marketing focused. In the US there are no signs that this will change. In Europe, however, the introduction of Regulation (EC) 1924/2006 in 2006 created a more research oriented nutraceuticals industry: innovation could from then on focus on product innovation based on science with scientifically substantiated nutraceutical products as a result.
The next section discusses the implications of these results and gives recommendations to policy makers in the European Union.

7.2 Policy recommendations

The policy recommendations to overcome the weaknesses of the European nutraceuticals innovation system have been dealt with in the second research question:

> *What recommendations can be given to policy makers in the European Union to overcome the weaknesses of the emerging European nutraceuticals innovation system?*

Regulation (EC) 1924/2006 on health claims is the first big policy measure at European level that has had a profound influence on the European nutraceuticals industry. It has had a positive effect on F5: market formation which in its turn will positively affected F1: entrepreneurial activity. However, Regulation (EC) 1924/2006 has some consequences for the nutraceuticals industry which need to be taken into account for Regulation (EC) 1924/2006 to be successful. First, Regulation (EC) 1924/2006 threatens small nutraceutical companies in Europe in their existence because it becomes difficult for them to bring new nutraceutical products with health claims market due to the required scientifically substantiated of health claims. Because of their limited financial resources they cannot pay for research to scientifically substantiate the health claims on their products and thus from their perspective Regulation (EC) 1924/2006 is hampering innovation. Since the current European nutraceuticals industry mainly consists of small companies, the nutraceuticals industry is pressing for a more liberal regulatory regime in which a system with gradation in health claims is implemented. A gradation in health claims would make it possible for nutraceutical manufacturers to also use health

claims that have not been scientifically proven. A disclaimer, like in the US, would then state the degree of scientific uncertainty regarding the health claim. The European nutraceuticals industry argues this would create an incentive to innovate and will stimulate entrepreneurial activity (F1) because new products can be marketed at an earlier stage with limited scientific substantiation. However, the first goal of Regulation (EC) 1924/2006 is to assure a high level of consumer protection. A gradation system in health claims does not correspond with this first goal of consumer protection, and the implementation of a grading system in health claims is therefore not recommended to policy makers in the European Union (EU).

The interviews revealed that nutraceutical companies that cannot get health claims approved on their nutraceutical products are expected to direct their marketing strategies towards endorsement practices. These endorsement practices will entail the start up of public relations activities to inform consumers about the health benefits of nutraceutical products. The interviews also revealed that nutraceutical companies that cannot get health claims approved on their nutraceutical products are expected to seek contact with natural therapists and other forms of alternative medicine providers to still be able to communicate with consumers, be it not directly through marketing activities. In order for consumers to make informed choices about nutraceutical products it is important that national governments provide consumers with objective information through public relations activities. Thus, there should be public relations agencies in the individual European countries that provide consumers with complete and unbiased information about nutraceuticals so consumers can make informed choices about the use of nutraceuticals and their potential health benefit. This can decrease consumer skepticism and increase consumer acceptance of nutraceuticals in Europe.

The most important policy measure to be taken for Regulation (EC) 1924/2006 to be successful is the establishment of a European inspection agency that monitors the nutraceuticals market and can effectively ban products that make scientifically unsubstantiated health claims off the market. Because of the current absence of an inspection agency at European level, such products can still exist and can only be banned from the market when another company presses legal charges. Manufactures of scientifically unsubstantiated nutraceutical products lack the high investments for scientific substantiation of health claims. Thereby it becomes very difficult for companies that do invest in expensive clinical research to bring products on the market for a competitive price. In this way the European nutraceuticals market is disrupted and innovation in products that are proven to be effective is hampered. As a result the industry is bringing few quality products to the market.

The presence of a European inspection agency will contribute to entrepreneurial activity (F1) by ensuring fair competition, and will benefit F7: creation of legitimacy / counteract resistance to change by increasing consumer thrust in nutraceutical products by assuring a high level of scientific substantiation of the health claims on nutraceutical products on the European market.

Concluding, Regulation (EC) 1924/2006 is the first step to a European market with scientifically substantiated nutraceutical products. To achieve a scientifically substantiated European nutraceuticals market the EU and should establish an inspection agency that monitors the market and can ban nutraceutical products that make scientifically unsubstantiated health claims off the European market. Furthermore the individual European countries should have public relations agencies that provide consumers with complete and unbiased information about nutraceuticals and their potential health benefits. Lastly, the EU should not implement a grading system in health claims since this would decrease the scientific substantiation of nutraceutical products on the European market.

8. Discussion

This research studied the problem of the lagging behind in size and growth of the European nutraceuticals market compared to the US and global nutraceuticals market, and more specifically the problem of the regulatory framework in Europe and the lack of consumer acceptance of nutraceuticals in Europe. The emerging European and US nutraceuticals innovation systems were mapped and compared with each other using the TIS approach. The strength of the TIS approach lies in using a specific technology as a starting point, and focusing on the system level as the core unit of analysis (Suurs and Hekkert, 2009; Hekkert et al., 2007). Comparing the European and US nutraceuticals innovation systems created a better understanding of the strengths and weaknesses of the European nutraceuticals innovation system. This chapter will discuss whether the study was adequately set up and whether the obtained results were accurate and able to answer the research questions. Furthermore this chapter will discuss starting points for future research.

Discussion of results in relation to previous studies

Previous studies on the lagging behind in size and growth of the European nutraceuticals market compared to the US and global nutraceuticals market have assumed that consumer acceptance was one of the main reasons for the slow growth of the European nutraceuticals industry (Granato et al., 2010; Lähteenmäki et al., 2010; Ares and Gámbaro, 2007; Verbeke, 2005; Menrad 2003; Urala and Lähteenmäki, 2003; Weststrate et al. 2002, among others). This study took consumer acceptance of nutraceuticals into account by looking at expressed consumer skepticism regarding nutraceuticals in the dataset. The comparison between the EU and the US nutraceuticals innovation systems showed little differences regarding consumer skepticism and no strong indications were found that supported the assumption that consumer acceptance was one of the main reasons for the slow growth of the European nutraceuticals industry. In the US nutraceuticals innovation system more lobbying activities (F7) in favor of nutraceuticals were observed. However, most of these lobbying activities consisted of product specific public relations campaigns and could therefore not directly be related to a more positive attitude of the American consumer towards nutraceuticals. Both in the EU and the US nutraceuticals innovation system there were negative opinions (-F7) towards nutraceutical products and the associated health claims. However, a large difference in the amount of skepticism towards nutraceuticals products (-F7) had not been observed. Moreover, the introduction of Regulation (EC) 1924/2006 could increase European consumers' thrust in nutraceutical products and the European nutraceuticals industry (F7) because no scientifically unsubstantiated health claims on nutraceutical products are allowed anymore on the European market.

Other studies found that firms encounter several problems due to regulations that might hamper the nutraceuticals innovation process and market access (Gilsenan, 2011; Bech-Larsen and Scholderer, 2007; Yeung et al., 2007; Coppens et al., 2006; Kwak and Jukes, 2001). This earlier work is in line with the results of this study which showed that the lack of regulations in Europe regarding the use of health claims on nutraceuticals caused the lack of fulfillment of F4: guidance of the search, which created the lack of fulfillment of F5: market formation which in its turn negatively influenced the fulfillment of F1: entrepreneurial activity, and entrepreneurial activity is necessary for a market to grow.

Reflections on method

By framing the problem of the European nutraceuticals innovation system as the lagging behind in terms of market size and growth (in Euro's), with specific the problems of the regulatory framework and lack of consumer acceptance of nutraceuticals in Europe, the TIS approach was a suitable method for this research. TIS studies in general are better in describing the enabling and constraining factors than in explaining why the TIS developed as it did. The emergence of a technological innovation system is too complex to determine causal relationships by studying the entire system. Therefore this study was not meant to determine causal relationships; it was designed to study general patterns of change and interactions within the TIS. By taking the entire nutraceuticals IS into account, it was possible to study the specific problems regarding regulations and consumer acceptance not in isolation but as part of the entire nutraceuticals IS, which created a more comprehensive understanding of origins of these problems and their influence on the European nutraceuticals innovation system.

However during data collection several difficulties occurred. First, public data on the dependent variable 'market size' of the European and US nutraceuticals market was limitedly available. The data that was available came from different sources, which used different definitions of the term 'nutraceutical'. This made it difficult to compare the data. Only rough estimations of the growth of the European and US nutraceuticals market could be made. Second, the operationalization made it difficult to assign several unforeseen events to one of the System Functions. Such events were people that switched jobs between companies, law suits, and endorsement practices. This problem was solved by retrospectively adding these events to the most appropriate System Function and see whether general patterns within System Functions had changed. No major changes of patterns occurred: it was a limited number of events in relation to the total number of event observed in both analyses. However it cannot be excluded that data has been biased and therefore in future studies it is recommended to include these events in the operationalization, which will be discussed later in this discussion.

Despite these difficulties, the TIS approach has been successful in describing the lagging behind in size and growth of the European nutraceuticals industry compared to the US nutraceuticals industry. Because of the differences in market size and growth of the European and US nutraceuticals industry the comparison between the two created more insights in the European nutraceuticals IS than when only the European nutraceuticals IS was considered. These insights helped to describe the strengths and weaknesses of the European nutraceuticals industry. In both cases a common factor, the regulatory framework, enabled or restrained the growth of the nutraceuticals industry. Thus, because of the comparison, the regulatory framework can with a larger degree of certainty be related to the difference in size and growth between the European and US nutraceuticals industry.

The objective was to measure the fulfillment of the System Functions by including all events that could have had an influence on the nutraceuticals innovation system. Initially, the historical event database of the European nutraceuticals innovation system consisted about 5000 articles which were analyzed and resulted in 533 events. For the historical event database of the US nutraceuticals innovation system over 10.000 press articles were found in the LexisNexis database that contained the term 'nutraceutical' when searching within the geographical area of the US. Due to time constraints the results were narrowed down by selecting 'Nutraceuticals' under the header 'Market', so only articles that were tagged in the LexisNexis database as relating to the nutraceuticals market

were analyzed. This resulted in a more manageable amount of 4000 articles that needed to be analyzed. To make a sound comparison possible between the European and the US nutraceuticals innovation system, the sources for the European historical event database needed to be narrowed down to articles in the LexisNexis database regarding the nutraceuticals market too. This meant that 68 out of 533 events needed to be deleted from the European historical event database to make a sound comparison, since the articles in which they had been found did not belong to the nutraceuticals market according the LexisNexis database. To increase the *construct validity* of the European nutraceuticals innovation system analysis, data was triangulated by including interviews with experts from the European nutraceuticals industry. This helped to verify whether the observed results of the European TIS analysis were correct, and to create a better understanding of the perspectives of the different actor groups and unravel their underlying assumptions and motives regarding to nutraceutical technology. No interviews could be arranged with people from outside the Netherlands. Nevertheless, most Dutch interviewees were also closely involved in developments regarding the European nutraceuticals IS that occurred on a European level. Unfortunately for the US nutraceuticals IS analysis no interview data could be obtained.

Narrowing down of the European and US historical event databases by only selecting articles in the LexisNexis database regarding the nutraceuticals market has influenced the construct validity: it was intended to measure the development of the European and US nutraceuticals innovation systems, however strictly speaking only the European and US nutraceuticals market has been taken into account. Accordingly the domain of the study to which the results apply is narrowed from the European and US nutraceuticals innovation systems to the European and US nutraceuticals market. Nevertheless it needs to be considered that the European and US nutraceuticals market to a great extend overlap with European and US nutraceuticals innovation systems and thus the results can to a great extend be extrapolated to the entire nutraceuticals IS.

It is difficult to determine whether *internal validity* is met, also, explorative case studies such as this research are not so much concerned with testing causal relations but more with the broader problem of making inferences between variables (Yin, 2009). The internal validity of the study has also been negatively affected by selection bias that occurred while building the historical event databases of the European and US nutraceuticals IS. This selection bias occurred when the domain of the study was narrowed down to the nutraceuticals market as described above, and the fact that only English language news has been analyzed. In the European historical event database there is a chance that important events have been missed due inability of analyzing news written in languages other than English or Dutch. However, for events occurring on the European level (such as regulations) this bias was minor since events that have had a European wide influence on the development of the European nutraceuticals innovation system, such as EU regulations or European lobbying activities, are generally published in several languages, including English.

The *external validity* is the degree to which the results of this study can be generalized and can be established by comparing the outcomes of the study to similar cases. However, since no similar cases have been found that apply the TIS approach it is difficult to determine the external validity of the results. The emerging nutraceuticals industry is a technological specific innovation system and the results of this study that describe the strengths and weaknesses of the European nutraceuticals innovation system do not simply apply to other domains too. Therefore this study compared the cases of the European and the US nutraceuticals IS with each other to take into account the external validity. In both cases a common factor, the regulatory framework, enabled (US) or restrained (Europe) the growth of the nutraceuticals industry. Also, the same mechanism was observed; the

fulfillment of F4: guidance of the search, influenced the fulfillment of F5: market formation, which influenced the fulfillment of F1: entrepreneurial activity. Since in both cases the same mechanism has been identified, the external validity is increased. However the generalizability is limited since only two cases have been compared.

By carefully documenting the process of data collection and data analysis and documenting the data in the historical event database a high level of *reliability* of the historical event database is assured. However the identification and assignment of events to the System Functions is dependent upon the interpretation of the researcher which makes the TIS approach susceptible to bias. The reliability of this study could be increased by including an extra researcher in the process of assigning the events to the System Functions. Furthermore the historical event database is included in the appendix on a CD-ROM and all interviews have been audio recorded to increase the reliability of the results.

Relevance of the research

The *societal relevance* of this study lies in the policy recommendations given in the conclusions. Especially the creation of a European inspection agency that monitors if no illegal health claims are made can have a large societal impact since this can ensure that only nutraceutical products with proven health benefits will reach the European market.

Furthermore regarding the theoretical relevance, this study has shown that the TIS approach can be a valuable tool in analyzing the dynamics in emerging innovation systems in the life-science field. The TIS approach is a well known tool in the analyses of emerging innovation systems in the energy sector, but is rather new in analyses of emerging innovation systems in the life-sciences field. The power of the TIS approach lies within the mapping of events over time, which helps to structure the vast amount of data and enables a dynamic analysis of an emerging IS.

However, it is important for future studies to take several aspects into account when applying the TIS approach in the life-science field. First, a fair amount of people had been found that switched jobs between companies. This activity could be added to Function 3: Knowledge diffusion since the transfer of an employee to another company entails the transfer of knowledge possessed by that person as well.

Second, life-science industries are often characterized by strict regulations, which are measured within Function 4: Guidance of the search, as positive and negative sentiment towards regulations. This study found that regulations play an important role in the development and diffusion of a technology in the life-science field. It needs to be ensured that possible enabling or restraining regulations for the success of a technology are included in the analysis, not only the sentiment expressed regarding regulations. Therefore all regulations regarding the technology, including their contents, need to be considered. The aim is to determine the positive or negative contribution of the regulation on the technological innovation system. Thus, for future studies applying the TIS approach in the life-science field it is recommended to include a new System Function: Regulations. This enables to differentiate between expectations, which are guiding and belong to guidance of the search, and regulations, which are institutional factors that are often compulsory and determine the framework conditions with which a technology has to comply. Another argument to include a new System Function: regulations, is that expectations about a technology are not always consistent with the regulations that are designed by governments. By measuring expectations and regulations within a separate System Function clarity is increased on how each these Functions (i.e. guidance of the search and regulations) influences the emerging IS. After all, the essence of F4: guidance of the

search is providing clarity about consumer needs and technological possibilities (Hekkert and Negro, 2009).

Function 7: creation of legitimacy / counteract resistance to change, also requires special attention. This function is about creating legitimacy for a new technological trajectory. Several law suits had been found against firms in the US nutraceuticals industry. Lawsuits can have a major influence on the perception of a technology by consumers and other actor groups within an innovation system. Therefore for future studies applying the TIS approach in the life-science field it is recommended to include law suits regarding the producers or developers of a technology within Function 7: creation of legitimacy / counteract resistance to change. Also several activities had been found on the boundary between providing information and marketing activities. Examples of such activities are infomercials and the informative websites by the industry. These activities generally aimed at showing the benefits of nutraceuticals and increasing the sales of nutraceuticals. By providing information these endorsement practices were more than just merely marketing activities. Because such activities create legitimacy among actors in the innovation system, endorsement practices are recommended to be included within Function 7: creation of legitimacy / counteract resistance to change, in future studies applying the TIS approach in the life-science field.

Concluding, by applying the TIS approach to the case of European and US nutraceuticals innovation system this study has contributed to innovation literature by adding to the understanding of emerging technological innovation systems in the life-science field in general. It has demonstrated that regulations are of high importance and suggested to incorporate regulations in future TIS studies in the life-science field in a separate System Function. Together with incorporating job switches within Function 3: Knowledge diffusion, and lawsuits and endorsement practices within Function 7: creation of legitimacy / counteract resistance to change, these additions should contribute to a more comprehensive understanding of an emerging life-science technology. Future TIS studies on emerging life-science technologies can now focus on how to operationalize these new variables and verify the added value of these new variables for future TIS studies in the life-science field.

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List of tables and figures

Appendix A: Interview questions European nutraceutical innovation system analysis

Welkom, voorstellen + korte uitleg studie
-vragen of je gesprek mag opnemen, na uitwerking interviewverslag opgestuurd ter correctie etc…

Actor specifiek

- Wat is uw rol in het nutraceutical en voedingssupplementen Innovatie systeem? (wat zijn uw verrichtingen, doelen, verantwoordelijkheden etc)
- Op welke momenten heeft u een rol gespeeld in nutraceutical en voedingssupplementen innovatie in EU? (vroege fase, later, op elk moment)

Laat ingevulde Nutra IS systeem plaatje voor EU zien en vraag om voor elk blok wele actoren er actief zijn. Daarnaast specifiek:

- Zijn er grote bedrijven in het innovatiesysteem actief? Zo ja welke?
- Wat zijn tegenwoordig de belangrijkste nutraceutical producten op de markt?
- Welke reguleringen zijn belangrijk met betrekking tot nutraceuticals?
- Kloppen de verbanden in het plaatje?
- Ontrbreekt er nog iets in het plaatje?

Functie analyse

Vragen mbt Functie 1: Entrepreneurial activities (ondernemingsactiviteit)

- Hoe is het gesteld met het ondernemingsklimaat van de nutraceutical industrie?
- Welke nieuwe ontwikkelingen/ondernemersactiveiten verwacht u in de toekomst? (andere producenten, personalized nutrition etc.)
- Wat vind u van de innovativiteit van de Europese nutraceutical sector?

Vragen mbt Functie 2: Knowledge development (kennisontwikkeling)

- Wanneer is het onderzoek mbt nutraceuticals begonnen?
- Waar vind onderzoek mbt tot nutraceuticals vooral plaats? (universiteiten, bedrijven, TNO, etc)
- Spelen patenten een belangrijke rol in de Europese nutraceutical industrie?
- In 2009 verdrievoudigd het aantal nieuwe patenten bij de EPO. Heeft u een verklaring voor deze ontwikkeling?
- Welke kennis ontwikkelingen in de afgelopen 20 jaar zijn belangrijk geweest voor de ontwikkeling van nutraceuticals? (onderzoeksresultaten, technologische ontdekkingen)
- Is er een gebrek aan kennis dat het succes van Nutraceuticals innovaties belemmert? Zo ja, waar zou toekomstig onderzoek zich op moeten richten?

Vragen mbt Functie 3: Knowledge diffusion (kennis verspreiding)

- Hoe is het gesteld met de kennisoverdracht mbt nutraceuticals van universiteiten naar bedrijven?
- Welke partijen zijn hoofdzakelijk betrokken bij kennisverspreiding mbt nutraceuticals in EU?
- Waar lag in het verleden de nadruk op bij congressen en conferenties mbt nutraceuticals en waar ligt tegenwoordig de nadruk op?
- Op welke manieren denkt u dat het beste kennis over nutra verspreid kan worden naar gerelateerde partijenen?

Vragen mbt Functie 4: Guidance of the search (regelgeving)

- Zijn er op Europees niveau projecten die nutraceutical innovaties stimuleren?
- Hoe zijn de verwachtingen in het verleden geweest mbt de ontwikkeling van een markt voor nutraceuticals?
- Heeft het verschil in reguleringen tussen de Europese landen in het verleden een remmend effect gehad op de innovativeit en het ondernemingsklimaat van de sector?
- Heeft de langzame ontwikkeling van reguleringen op Europees niveau in het verleden een remmend effect gehad op de innovativeit en het ondernemingsklimaat van de sector?
- Hoe worden de huidige reguleringen ervaren? (met name Regulation (EC) 1924/2006)?
- Meer dan 95% van de claims op voedingssupplementen is afgewezen. Wat voor impact heeft dit gehad op de sector?
- Zal 1924/2006 een positieve uiwerking hebben op innovatie?
- Wat zouden de EU overheden/overheidsinstanties beter kunnen doen mbt regelgeving in zijn algemeenheid? Gedaan kunnen hebben?
- Wat zouden de EU overheden/overheidsinstanties ter ondersteuning van de industrie kunnen doen? Gedaan kunnen hebben?

Vragen mbt Functie 5: Market formation

- Hoe is het gesteld met de bereidheid tot investeren in nutraceutical bedrijven?
- Wat zijn de voornaamste remmende en stimulerende ontwikkelingen geweest op de ontwikkeling van een markt voor nutraceuticals in Europa? Wat had er anders moeten gebeuren?
- Wat voor effect hebben deze ontwikkelingen gehad op de bereidheid tot investeringen in de Europese nutraceutical industrie?

Vragen mbt Functie 6: Resources mobilization

- Welke resources met name belangrijk? (Financial, human, social etc)

Vragen mbt Functie 7: Creation of legitimacy / counteract resistance to change (lobby activiteiten)

- Zijn er veel incidenten geweest mbt tot nutraceuticals? Zo ja wat is de invloed hirevan geweest op de (Europese) markt? (bv. dioxine visolie)
- Hoe staat de consument tegenover nutraceuticals?
- hoe is het gesteld met de geloofwaardigheid van de industrie?
- Zijn er vanuit de industrie veel activiteiten ondernomen om het imago te verbeteren?
- Zijn er mediagebeurtenissen (Tv, krantenberichten) die invloed hebben gehad op het imago van de nutraceutical industrie?
- Wat vindt u van de rol van wetenschappers, media, politiek, etc mbt lobby rondom nutraceuticals?

Algemene vragen

- Wat zijn de sterke punten van het nutraceutical innovatiesysteem? (zowel technologisch als beleidsmatig, hoe bedrijven met elkaar omgaan, of op markt opereren, etc.)
- Wat zijn de zwakke punten van het nutraceutical innovatiesysteem?
- Hoe kan de markt voor nutraceuticals succesvoller worden gemaakt?

Overig:

- heeft u nog vragen of opmerkingen over nutraceuticals innovaties in EU?
- heeft nu nog vragen of opmerkingen over mijn onderzoek?
- Weet u nog andere partijen/personen die u mij aanraad om te interviewen?
- Heeft u gegevens over de grote van de de Europese nutraceutical markt?

Appendix B: References European nutraceuticals innovation system analysis (1990 – 2011)

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Appendix E: Historical event databases European nutraceuticals innovation system and US nutraceuticals innovation system

In the enclosed CD-ROM the historical event databases of the European nutraceuticals innovation system and US nutraceuticals innovation system can be found.