AN INTRODUCTION TO THE MEDICAL FOODS INDUSTRY

A Market Research Project conducted in collaboration with Coller IP

REBECCA PULLON

University of Oxford

Supervised by: Jackie Maguire and Robert Gleave

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Executive Summary

Medical foods are defined as foods that are specially formulated to meet the underlying nutritional deficiencies of a specific disease, first produced over fifty years ago. This report investigates the market for medical foods and relevant patenting activity, to provide initial information for newly emerging companies considering entering this market. The medical foods market has grown significantly in the last fifteen years, bringing it to the exciting and emerging field that it is today. Many large food and healthcare companies are moving into the medical foods area, notably Nutricia, Nestle and Abbott Laboratories. There are also smaller companies who primarily focus on the development of medical foods, such as Targeted Medical Pharma and Pamlab. The United Sates is the pioneer of medical foods, where the term is more readily understood than in the rest of the world, yet one of the main barriers to market expansion still appears to be the lack of understanding and awareness of medical foods, both by the consumer and medical professional. Market drivers for medical foods include the rise in aging population, a shift to enteral nutrition and a demand for personalised medicine.

The patent landscape for medical foods is a challenge to define because there is no single classification code that identifies a medical food. Relevant patent applications are instead often classified by active ingredient, and as a nutritionally modified food. A search by classification code therefore necessarily includes those relating to dietary supplements and other nutraceuticals, but it appears that the trends in patenting activity of this wider nutritional foods industry can be considered to be representative of the medical foods subset. A keyword patent search for “medical foods” has some limitations, but shows an overall increase in recognition of the medical foods industry.

Within this report, further information is provided about the definition of medical foods, market trends and influencing factors, and patent search strategies. From this analysis, the strengths, weaknesses, opportunities and threats of the medical foods market can be drawn.

In conclusion, the market and industry for medical foods is expanding, seen through the shift of major food and healthcare companies to include medical food products, and an increase in patenting activity. The market is following in the wake of other nutritional foods, with strong market drivers, and looks well placed to continue to develop rapidly.

Contents

1 Purpose

This report is prepared as part of a market research project between Coller IP and the University of Oxford, to investigate the nature of the medical foods industry. Industry dynamics are assessed through analysis of market trends and drivers, and investigation of patent activity. This report is intended to provide initial information to future investors or companies interested in entering this field[1].

2 Introduction to Medical Foods

A medical food is a specially formulated food that meets the nutritional requirements of a specific disease. The concept is more than fifty years old, born out of catering for the nutritional deficiencies of certain genetic diseases, to become an emerging discipline that surrounds the medical foods industry of today. The nutritional needs of the human body have been the subject of research for many years, and a focus on adequate nutrition, to keep people healthy, has led to the decline of multiple nutritional deficiency diseases such as rickets, scurvy or goitre[1]. It is now known that most diseases impose nutritional requirements that are different to those of a healthy individual; so medical foods were developed through the corporate efforts of the medical community, nutritionists, dietitians and food scientists, to fulfil the underlying nutritional deficiencies of a specific disease[2]. Medical foods have now been developed for many types of diseases, from neurological disorders such as Alzheimer's disease, Parkinson's or depression, to general physiological disorders such as hypertension, viral infections or pain and inflammation. Ailments such as food intolerances, insomnia or fatigue, are also treated by specific medical foods.

The medical food industry lies between pharmaceutical drugs and the food industry, a separation that has historically been clearly defined by law and until 1972, there was no additional recognised categorisation[3]. Medical foods are included in the nutraceutical industry, a wider field that encompasses foods with health benefits or added nutritional value[4]. Also included in the nutraceutical industry are dietary supplements and functional foods which medical foods are often confused with, the latter of which refers to foods with an added substance that provides a beneficial function such as disease prevention or health promotion. Another name for a medical food is a food for special medical use, but "medicinal foods" refers to something different, synonymous with nutraceuticals. Medical foods can be used for medical nutrition therapy, and can be considered as an integrative medicine (as opposed to traditional or alternative medicine) because medical evidence of effect is required.

Medical foods are prepared from GRAS (Generally Recognised As Safe) substances, to be taken eternally (absorption through the gastrointestinal tract) for the partial or exclusive feeding of a patient. There must be medical evidence that medical foods meet the specific needs of a disease state that cannot be achieved with a simple dietary shift. Medical foods are thus distinct from dietary supplements intended for normal, healthy adults, and are not a blanket term for all foods fed to sick patients. They also must only be used under medical supervision. The medical foods journey will continue to be described in the next few sections[5,6].

[1] This report has been made available for research purposes and those entering the field are recommended to carry out further due diligence. Coller IP and the University of Oxford accept no liability for any subsequent actions taken.

2.1 History of medical foods

Medical foods were first developed in the 1950s, originally designed for those with genetic diseases that could not handle certain nutrients[7]. The American Food and Drug Administration (FDA) originally regulated medical foods as drugs, because they were intended to affect the structure or function of the body. One of the first medical foods was Lofenalac, an infant formula produced by Mean Johnson Nutrition in 1957, for the dietary management of phenylketonuria (PKU). Lofenalac was regulated as a drug under the 1938 Federal Food, drug and Cosmetic Act (FFDCA) 201(g)(1)(B), yet it challenged the definition of a drug, partly because the strict regulations concerning the levels of active ingredients in drugs were difficult to achieve for nutrition formulas. In 1972, Lofenalac was the first substance classified as a "food for special dietary use" under the revised FDA definition. This allowed medical foods to be exempt from the strict clinical trial phase required for individual drug regulation, and aimed to encourage innovation in the medical food area.

It wasn't until the Orphan Drug Amendments of 1988 (Act 21 U.S.C. 260ee (b) (3)) that the term "medical food" was coined along with a statutory definition. Medical foods were then made exempt from the nutrition labelling, health claim and nutrient disclosure requirements of most other foods, in the Nutrition Labelling and Education Act of 1990. This further distinguished the medical food category from conventional food products. In 1996 the FDA expressed concern about the number of products under the medical food category, many with inadequate scientific support, so put forward the Announcement of New Proposed Regulations (ANPR). This was withdrawn in 2004, along with other similar notices, because the FDA no longer considered it to be a viable candidate for further Agency action. A revised guidance document was issued in 2007 to answer frequently asked questions about medical foods and further define the category. Medical foods have slowly been similarly regulated across the world, although America is unique in using the "medical food" phrase to describe these products[5,7,8,9].

2.2 Regulating medical foods

The medical foods definition started in the United States, but has spread and taken on different names and forms all over the world. This section briefly describes the regulations for medical foods in a few key countries.

The American Food and Drug Administration (FDA) clearly define a medical food as:

> *A food which is formulated to be consumed or administered enterally through the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.*

Medical foods are substances which diagnose, cure, mitigate, treat, or prevent disease[8,9]. As stated earlier, they are made from GRAS (Generally Recognised As Safe) substances to ensure their safety. Protein-based medical foods are the most common, nutrients are also popular ingredients (such as Omega 3 fatty acids, isoflavones, or chelated zinc), and vitamins and minerals are often added (such as thiamine and folic acid)[10]. Medical foods must comply with all applicable requirements for the manufacture of foods. They are exempt from the labelling requirements for health claims and nutrient content claims, but must contain the same necessary information as any other product, and can be labelled for specific medical conditions, unlike dietary supplements. Medical foods do not have to undergo premarket approval by the FDA, they do not require specification as an IND (Investigational New Drug), and do not have

to be registered individually with the FDA. However, medical foods are required to support all medical benefit claims with appropriate laboratory and clinical science[11].

The FDA classifies medical foods into four major categories[12]:

1. *Nutritionally complete products* – usually contain a protein source, carbohydrate source, and fat source with possible vitamins, minerals or electrolytes. These are taken as a complete food, so do not need to be supplemented with other food sources, most commonly used for patients who are tube feeding.
2. *Nutritionally incomplete products* – these contain a single food group, such as carbohydrates only or vitamins only. It is necessary to consume additional food sources for a complete diet. This food group may be taken by patients who are at home and still able to eat normal foods.
3. *Formulas for metabolic (genetic) disorders* – The majority of medical foods treat metabolic disorders, targeting signalling pathways. They are typically formulas with unique nutrients removed or added.
4. *Oral rehydration solutions* – these help the body absorb nutrients by shifting the osmolarity of an oral solution so that the gastrointestinal tract retains fluid. They typically contain sodium, chloride, potassium citrate, dextrose and water.

The medical food definition is often confused with that of a drug and a dietary supplement, and understandably so since there is some overlap. Table 1 shows the distinction between these three categories as defined by the FDA.

The term "medical food" is unique to FDA regulations, but the same sorts of substances have become regulated all over the world. The European Food Safety Authority (EFSA) distinguishes dietary "foods for special medical purposes" (FSMPs) under the Foods for Particular Nutritional Uses Directive 2009/39/EC (an amendment of Directive 1999/21/EC). These foods are specifically formulated, processed and intended for the dietary management of diseases, disorders or medical conditions. They must be used under medical supervision, and are specifically for those individuals whose nutritional requirements cannot be met by normal foods. The Directive gives guidance to the minimum and maximum levels of vitamins and minerals and details the labelling requirements, specifically that the label must unambiguously mention whether the product is intended to be the sole source of energy and nutrients for the person. The EFSA also assigns food for special medical purposes into three categories relating to whether the food is intended for exclusive or partial nourishment, and whether is consists of a nutrient-adapted formulation or not[2,13,14,15].

Australia and New Zealand similarly define "foods for special medical purposes"; foods that manage the diets of people with certain diseases, disorders or medical conditions, again for people whose nutritional requirements cannot be met by normal foods. The composition, labelling and sale of food for special medical purposes are regulated by Standard 2.9.5 of the Food Standards Code. Most medical foods are manufactured abroad and then imported into Australia and New Zealand, so the standard aligns as much as possible with the relevant regulations of the European Union and the United States of America[16,17].

Canadian regulations are not so clear, with medical foods under the wide banner of "foods for special dietary use" 9.9 [B.24.001, FDR]. These are foods specially processed or formulated for a person who either: has an existing physical or physiological condition resulting from disease or injury; or can obtain a particular effect by a controlled intake of foods[18]. In Japan, medical foods are regulated under the "foods for specified health uses" title, a subcategory of "foods with health claims", regulated under Article 5 of the Food Sanitation Act, 2001[19].

Table 1: The distinction between of pharmaceutical drugs, medical foods and dietary supplements[5,8,11].

	Drugs	**Medical foods**	**Dietary supplements**
Governing regulation	Federal Food, Drug and Cosmetic Act	Orphan Drug Act (amendments, 1988)	Dietary Supplements Health & Education Act
IND required	Yes	No	No (needed for health claims)
Pre-market scientific testing	Preclinical and clinical studies (phases I, II, III)	Medical evaluation in patients with the specific disease being targeted	No
Ingredients	Mostly synthetic, can be nutritional	Nutritional, not in ordinary diet	Nutritional
NDA/BLA required	Yes	No	No
Claims	Negotiated with FDA and dependent on pivotal clinical trial data	Dietary management of a specific disease	Support healthy function
Intended target population	Diseased - for patients with a specific indication or symptoms	Diseased - for meeting nutritional requirements of a specific diseased population	Normal, healthy adults
Safety and pharmacovigilance	Need to establish through clinical trials and post market surveillance	GRAS and post market surveillance	General expectation of safety and through monitoring of consumer complaints
Physician supervision	Required if prescription drug, not for OTC medications	Required	None
Dosing	Any	Oral or enteral	Oral
Distribution	Hospitals, retail pharmacies	Hospitals, retail pharmacies	Health food stores, mass market

Medical foods are regulated differently around the world. Europe and other jurisdictions distinguish medical foods under regulations for nutritional foods or foods for dietary use, but the FDA has no such classification so regulate them under the Orphan Drug Act. Some medical foods are also recognized as medical nutrition therapy (MNT) by the Older Americans Act, Administration on Aging[8]. A similar trend is seen with the functional foods industry where Japan, Canada and others have a distinct category, but Europe and the USA focused on concept rather than function, so classified it under existing food categories. Despite this, medical foods are becoming a recognised class all over the world.

2.3 Examples of medical foods

There are many medical foods available for medical professionals to prescribe for patients. A few examples of widely prescribed medical foods are described below, detailing the disease they aim to treat, and the mechanism by which that occurs.

Axona (Accera)
Axona was developed by Accera (USA) as a medical food to provide the necessary nutrients for patients with Alzheimer's Disease (AD). AD is the leading cause of dementia[6], a neurodegenerative disease characterized by a decline in the ability of the brain to metabolize glucose, even in its early stages. Glucose is the primary fuel source for the brain, so a deficit causes cerebral atrophy and consequently, the symptoms associated with AD. Axona is made from caprylic triglyceride and other medium-chain triglycerides, which are converted to ketone bodies by the liver, an alternative energy source for cerebral neurons[20]. Ketone bodies are naturally occurring compounds and are mainly produced by the liver from fatty acids. Axona has been clinically shown to improve cognitive function in some patients with AD and does not increase metabolism[21,22]. This product is now being developed in partnership with Nestlé Health Science.

Axona is a powder, taken orally dissolved in water once a day. Improvements in cognition and alertness are anticipated to peak 2 hours after consumption, and there are few side effects. An estimated 30,000 people are already using Axona.

Limbrel (Primus Pharmaceuticals)
Limbrel is a medical food developed for the nutritional management of the metabolic processes associated with osteoarthritis. It was launched in 2006, developed by Primus Pharmaceuticals[23]. Osteoarthritis is the mechanical loss of function associated with the degradation of articular cartilage and bone in synovial joints. Damaged joints release excess phospholipids, which increase the production of prostaglandins and leukotrienes, leading to an inflammatory response. Limbrel contains flavocoxid, a commonly occurring ingredient in foods, which inhibits the enzymes responsible for the production of inflammatory irritants, lipoxygenase and cyclooxygenase, therefore reducing the pain and inflammation associated with osteoarthritis[5,24].

Limbrel comes as a capsule, containing 250 or 500 mg of flavocoxid and 50 mg of citrated zinc bisglycinate. It is only available by prescription.

Deplin (Pamlab)
Deplin was developed as an adjunctive therapy to antidepressant drugs in treating depression, by Pamlab Inc. Major depressive disorder is the fourth leading disease burden worldwide and while considered treatable, reoccurrences are common[25]. Depression is long understood to be related to the imbalance of neurotransmitters in the brain such as dopamine, norepinephrine or serotonin. Folate is a water soluble

essential vitamin that is a crucial co-factor for neurotransmitter synthesis, and numerous studies have shown that more than 50% of those who are depressed and don't respond to antidepressants, have a folate deficiency[26,27,28]. Deplin contains L-methylfolate (MTHF), the only biologically active form of folate which is able to cross the blood-brain barrier, and thus allows the continued production of neurotransmitters. This differs from the action of anti-depressant drugs which work to allow neurotransmitters to remain available to the brain. There has been some dispute about the effectiveness of Deplin, especially as an adjunctive to antidepressants. Few clinical trials have been carried out, the most recent study[25] showed impressive results but there was no placebo group[29,30].

Deplin comes in two dosage forms (7.5 mg and 15 mg tablets), taken once a day. Initial studies have found Deplin to be well tolerated and showing no side effects. The cost for a 30 day supply of Deplin is $80-$100.

Lofenalac (Mead Johnson Nutrition)

Lofenalac was one of the first medical foods developed in the late 1950s by Mead Johnson Nutrition. It was designed for the dietary management of pehylketonuria (PKU), a genetic defect in the metabolism of phenylalanine hydroxylase enzyme which converts the amino acid phenylalanine (Phe) to tyrosine[8]. Phe is in protein and many other foods, so a patient with PKU experiences rapid accumulation of toxic concentrations of Phe in the blood if left untreated, leading to neurocognitive damage[31]. Lofenalac is produced from an enzymatic hydrolysate of casein that is low in phenylalanine (0.08%). It is supplemented with proteins, carbohydrates, vitamins and minerals, so provides nutritional support without requiring the breakdown of Phe. Lofenalac is designed to replace milk, and comes as a powder to be dissolved in water. Lofenalac is no longer produced for management of PKU as other medical foods and drugs have been developed in the last forty years, such as three other casein hydrolysate-based products developed in the UK: Albumaid XP (Powell and Scholefield Ltd.), Cymogran (Alan and Hanbury's Ltd.) and Minafen (Cow & Gate).

A list of other medical food products currently available can be found in Appendix A.

3 The Medical Foods Market

3.1 Size and nature of market

The size of the medical foods market is unclear and hard to estimate. The Global Industry Analysts projected global sales to be just less than $9 billion in 2011 [6]. Medical food revenue in the United States was estimated at $2.1 billion in 2011 by the bioStrategies Group, and expected to grow at a rate of 10% [6]. The FDA also predicts strong growth in the medical foods industry due to the use of medical foods in long-term care and an aging population. There is a scarcity of public data in the medical foods sector which make market assessment challenging.

3.2 Active companies

Many companies are moving into the medical foods area, including large food and healthcare companies such as Nutricia, Nestle and Abbott Laboratories, and smaller companies specialising in medical foods such as Targeted Medical Pharma and Pamlab.

Nutricia specialise in the delivery of advanced medical nutrition to all age groups, and are the largest specialist nutrition company in Europe. They form the medical division of the Danone group since their acquisition in 2007. Nutricia have been pioneers in the concepts of specialised medial nutrition, developing nutrition products to help support patients with specific diseases. Currently, they have a few specific medical food products on the market, such as Souvenaid for patients with Alzheimer's disease, and are rapidly developing more products in this area [32,33].

Nestle is the largest food and beverage company in the world, with products sold in more than 130 countries. Nestle aims to become the world's leader in nutrition, health and wellness. Nutrition in particular has always been at the core of Nestle, since their initial focus on milk products more than 150 years ago. In 2010, Nestle Health Science was created to focus on the prevention and treatment of chronic medical illnesses based on scientific research and personalised nutrition. One of their aims is to break into the industry between nutraceutical drugs and nutritional foods. Therefore, since their beginning, Nestle Health Science have acquired or begun partnerships with seven companies, including Vitaflo, CM&D Pharma, Prometheus Laboratories, Pamlab, Vital foods, Accera and Nutrition Science Partner. Some of these specifically focus on medical foods, and others are similarly researching links between nutrition and disease [34,35].

Abbott Laboratories are diversified healthcare company, based in the United States. They have four core business focuses which include medical diagnostics, medical devices, nutrition, and pharmaceuticals. Within their nutrition division, Abbott Laboratories aim to offer science-based nutrition products for every stage of life. Medical foods make up a large portion of this business focus, products named "specialist feeds" under their therapeutic nutrition category [36].

Targeted Medical Pharma are a small company, founded in 1999, that develop prescription medical foods for the treatment of chronic disease, such as pain syndromes, peripheral neuropathy, hypertension, obesity, sleep and cognitive disorders. They specialise in technology that promotes the production of neurotransmitters despite reduced concentrations of amino acids. Targeted Medical Pharma currently market ten medical foods which are manufactured and distributed by Physician Therapeutics across North America, Japan and the Middle East [37].

Primus Pharmaceutials Inc. are a company which aim to be the pioneers of prescription metabolic products. They develop branded prescription drugs and medical foods that are effective in chronic or recurring diseases, such as Limbrel for targeting nutritional needs of osteoarthritis. Primus Pharmaceuticals are currently based in the United States, but open to international distribution options[38].

Pamlab are now owned by Nestlé Health Science, they are a biomedical company that specialise in personalised medicine by developing medical foods. They have an interest in pharmacogenetics, combining genetic information with pharmacology to ultimately create personalised medicine. Currently Pamlab have a handful of medical food products on the market, such as Deplin (depression) and Metanx (diabetes), and anticipate more products to follow[39].

Accera have just begun a partnership with Nestlé Health Science. They are a biotechnology company, focused on treating central nervous system disorders, particularly Parkinson's disease and Alzheimer's disease. Currently their only product on the market is Axona, a medical food for Alzheimer's disease which has quickly gained public recognition. Other products in the pipeline include a medical food to target memory impairment, and drugs for Parkinson's and Huntington's diseases. Accera are based in the United States, but are looking for worldwide commercial partners, particularly to market Axona[22].

There are many other companies involved in the production of medical foods, such as NattoPharma[40,41], Prismic Pharmaceuticals Inc.[42] and Soho Flordis International[43]. Many of the smaller companies that focus on medical foods (such as Pamlab, Targeted Medical Pharma and Prismic Pharmaeuticals) have prepared fact sheets and pamphlets about medical foods, available on their websites. There are other informational websites such as www.medicalfoods.com that provide current clinical data and applications about medical foods, aiming to educate both patients and physicians about the important links between nutrition and disease[44]. The Medical Nutrition Industry[45] brings together companies that focus on specialised nutritional products and services. Activity in the medical foods industry is primarily observed in the United States, perhaps because medical foods are easily defined, but is not limited to them.

3.3 Market trends

Trends currently observed in the medical foods industry include a movement to mainstream medical use, and growing awareness of medical foods.

Medical foods are now offered in tablet and capsule form, which enables them to be easily distributed by prescription. Online ordering is beginning to occur, although medical foods must still be prescribed by a physician. Some healthcare plans in the United States, and often Medicare or Medicaid, reimburse medical food products which is also aiding the move to mainstream medical use[8,9].

Medical foods are becoming recognised products, particularly in the United States, less so elsewhere. This is seen through the organisation of a Medical foods conference in 2011, hosted by the National Organisation of Rare Diseases (NORD); websites and corporations designed to increase communication between medical food providers and inform patients and physicians about medical foods[44,45]; and companies producing pamphlets and information sheets about medical foods, such as Targeted Medical Pharma, Pamlab and Nutricia.

3.4 Factors influencing the market

There are many factors that influence the medical foods market. These are separated into market drivers, opportunities and issues.

3.4.1 Drivers

The main drivers identified for the medical food industry are as follows:

1. *Rise in aging population*
   The life expectancy has been steadily increasing over the last few decades, and the older population is growing at a significantly higher rate than the total population. Over the next half a century the proportion of older persons is projected to more than double[46]. Unfortunately the healthy life expectancy has not increased as fast as life expectancy, putting strain on healthcare services[47]. Surgical areas of cardiothoracic, ophthalmology and urology are particularly expected to be burdened[48]. This raises the question of how to keep people healthy for longer. Medical foods and other nutritional substances are becoming valuable solutions, especially when long term effects of medication are important[4].

2. *Shift to enteral nutrition*
   There has been a shift to using enteral nutrition methods (absorption through the gastrointestinal tract) rather than total parental nutrition (absorption not through the GI tract, for example, intravenous administration) for a number of reasons. Enteral administration is safer compared to parental options as there is less risk of infection, and offers physiological benefits such as the maintenance of small intestine mass and pancreatic function. Technology advances have allowed enteral drug administration to become cost-effective. Enteral feeding devices have improved, such as pumps becoming lightweight, constructed from materials that alleviate cracking in high-stress applications, they are easy to use and easy to clean. A variety of feeding tubes are also available (varied length, diameter and material) which allow convenient access and administration of liquid products. Nutrients can also be delivered in various formats, such as tablets of capsules instead of sterile liquids or rehydratable powders. This is due to technological advances in the availability of some chemical constituents to allow microencapsulation[2,49].

3. *Demand for personalised medicine*
   One of the outstanding issues of medical treatment is that each person responds differently. Personalised medicine is about catering for a smaller, subset of the population by incorporating genetic information into treatment strategies. Ethnic and socioeconomic factors also contribute to developing personalised medicine. Genomic data is being linked with a variety of industries, and much research is being undertaken to minimise side effects for an individual based on their genetic disposition. The area of nutrition is no exception, as it was an interest in providing the nutritional needs of genetic defects that first spurred the birth of medical foods over fifty years ago. Drugs often have severe side effects, so developing nutritional alternatives to treat the underlying cause is a way to personalise medicine, and in addition, possibly incorporate genetic information. Pamlab is using an interest in pharmacogenetics to drive their development of medical foods[40]. The personalised medicine driver is also seen in the shift from institutional care to community care. Emphasis is placed on building a service that caters to an individual's needs, empowering a community to look after each other, rather than solely relying on formal institutionalised care[49].

3.4.2 Opportunities

There are several other research and commercial opportunities that contribute to a favourable risk to benefit ratio for medical foods, and are believed to create an environment that will foster the continued use and expansion of medical foods[8].

- Some drug therapies are not completely successful in the treatment of disease.
- Medical foods are cheaper to produce than drugs because of the difference in regulatory requirements. When medical foods were awarded orphan drug status by the FDA, it reduced the costs and time associated with bringing medical foods to market, particularly in regards to the clinical trial stages[10].
- Natural, plant-based ingredients have been shown to be successful in managing metabolic processes associated with many conditions or diseases. This leads people to seek for natural, nutritional supplements and alternatives to other medication.
- Medical foods are composed of GRAS ingredients, which generally have a low toxicity, so there is already an element of safety for the food. In contrast, drugs can be harmful and cause severe side effects.
- Advances in food technology allow expansion in medical food manufacturing[10].

3.4.3 Issues

As with all products, there are some issues preventing the spread and uptake of medical foods. Most importantly there is a general lack of awareness and understanding of medical foods in the medical community. This prevents doctors from prescribing and using medical foods. The general public also lack understanding of medical foods, and their attitudes affect their willingness to consume a new product. A study on the socio-economic influences for the functional foods market found that an individual's beliefs (such as in the food-disease prevention concept, or impacts of personal health), and knowledge of benefits, significantly affect their choice to consume a product[50]. It is expected this is similar to medical foods and other nutritional products.

Another issue is that some scientific support is required for the regulation of medical foods. While not as extensive as drug regulation, medical evidence takes time and slows innovation. Finally, some health services and insurers don't cover the cost of nutritional products for disease prevention or management[10]. This means the final decision making regarding the consumption of medical foods is with consumers and patients, even if physicians describe them.

4 Patent Investigation

One way to investigate the main trends in the medical food industry is to identify what Intellectual Property is being filed, as it is representative of the areas and ideas that companies recognize as important to protect. The aim of the current research is to identify a set of patents that represent the medical foods industry, allowing the development of a patent landscape and thus the identification of the main trends.

4.1 Search strategy

Thomson Innovation software was used to search for patent documents relevant to the medical foods industry in the last ten years, since recent activity is of the most interest. Patent applications filed in the United States and Europe, and international (PCT) applications were considered, because major innovation in the medical foods industry has been observed in these territories. A primary search was conducted using classification codes that had been identified as relevant to medical foods, and then key words were added to see if that refined the results set further.

4.1.1 Patent classification

Patent classifications are used to organise and index the technical content of patent specifications, so that an area or topic of technology can be identified easily and accurately[37]. Each region defines their own set of classification codes. Of particular note are the International Patent Codes (IPC) which are governed and maintained by the World Intellectual Property Organisation (WIPO). One or more of the 70,000 IPC classifications are applied to all international (PCT) applications. Recently, the Cooperative Patent Classification (CPC) system was introduced, a scheme jointly developed by the European Patent Office and the United States Patent and Trademark Office. The CPC classifications are largely based on the previous European Classifications (ECLA) and combine features of the European and US patent classification systems to provide a united, detailed scheme with more than 210,000 subdivisions[51,52].

4.1.2 Medical food classifications

Some key products and their corresponding patents were identified in the medical foods industry to extract classification codes that are regularly used for medical foods. The table below (see table 2) lists these patents with the IPC codes that have been assigned to them.

It was observed from patents of known medical foods, that they are often classified by the active ingredient in the food, and sometimes as a food formulation for a specific purpose or consumer group. There is no unique or distinct classification for a medical food, the codes are varied across the medical food patents, and the words “medical food” are not always used in the description of the invention.

The CPC codes were also analysed and those that seemed to be relevant to medical foods highlighted. From the combination of IPC codes from known medical food patents and relevant CPC codes, the following table (see table 3) is believed to be the most representative set for classifying medical foods. There are two main categories, firstly classifying the product as a food with modified nutritive qualities (A23L); and secondly by the ingredients that compose the medical food (A61K).

Table 2: Five patents that were identified as examples of medical foods, corresponding to products currently on the market. The publication number and brief details are given as well as all the IPC codes assigned to the patent.

Publication number	**Brief Description**	**Assignee**	**Patent filed in other countries**	IPC Codes
US7514469B2	Formulation for Limbrel, for osteoarthritis	Unigen Pharmaceuticals Inc.	AT, AU, BR, CA, CN, DK, EP, ES, HK, JP, KR, MX, NZ, RU, US, WO	A61K31/553 A61K 31/7048 A61K 31/353 A61K 31/352 A61K 31/05 A61K 31/35 A61K 31/08
US7838042B2	Updated formulation for Fosteum, for osteoporosis	Albion International Inc.	DE, EP, US, WO	A61K 33/00 A61K 33/26 A61K 33/30 A61K 33/32 A61K 33/34 A01N 59/00
US7674482B2	Amino acid based medical foods, targeting neurotransmitters	Targeted Medical Pharma	AU, EP, JP, US, WO	A61K 36/00 A61K 36/16 A61K 31/14 A61K 31/221 A61K 47/00 A23L 1/30 Many more
US7943163B2	Method of manufacturing medical food for diabetes	Response Scient Inc.	US	A61K 31/381 A61K 31/15 A61K 9/50 A61P 3/10
US6835750B1	Treating Alzheimer's Disease (Axona)	Accera Inc.	AT, AU, BR, CA, CN, DK, EP, ES, US, WO, JP, MX, NZ, RU, ZA	A61K 31/12 A61K 31/20 A61K 31/205 A61K 31/215 A61K 31/22 A61K 31/221 A61K 31/23 A61K 31/25 A61K 45/06

Table 3: The IPC/CPC classification and corresponding description for those codes believed to be common among patents for medical foods[52].

IPC/CPC code	Description
A23L 1/29	Modifying nutritive qualities of foods; Dietetic products
A23L 1/296	...Complete food formulations for specific consumer groups or for specific purposes
A23L 1/30	...Containing additives (includes vitamins, inorganic salts, minerals, amino acids)
A61K 9/00	Medicinal preparations characterised by special physical form
A61K 31/00	Medicinal preparations containing organic active ingredients
A61K 33/00	Medicinal preparations containing inorganic active ingredients
A61K 36/00	Medicinal preparations of undetermined constitution containing material from algae, lichens, fungi or plants, or derivatives thereof, e.g. Traditional herbal medicines
A61K 38/00	Medicinal preparations containing peptides

4.1.3 Generation of patent sets

Initial searches were carried out using the classification codes that had been identified as relevant and common to medical foods. Since these fall into two main categories, patents relating to each were investigated individually and then were combined to review the intersection of the two sets. These were investigated to see if the results would yield a set that only encompassed medical foods, or at least relevant and representative of the movement of the medical food industry.

Two classification code searches were therefore carried out using the IPC/CPC codes identified as relevant and common to medical foods.

- The first search (search 1) searched for all patent documents that had the classification codes A23L 1/29* and A23L 1/30* assigned, to identify patents relating to food with modified nutritive qualities. (* is a truncation operator).
- The second search (search 2) was a subset of search 1, requiring the patents to also have one of the codes associated with medicinal preparations containing ingredients commonly found in medical foods, A61K 31/00* or A61K 33/00* or A61K 36/00* or A61K 38/00*.

It was found that the classification codes used in these searches also encompass pharmaceutical drugs, dietary supplements, functional foods, food devices and methods for preparing normal foods. No search combination was found that uniquely returns medical foods, and sometimes it is hard to distinguish which patents actually describe medical foods and ingredients for medical foods.

For comparison, a key word search was also performed. It has been noted that patents relating to medical foods often include the "medical food" phrase in the description of the invention, especially if it is an ingredient that can be utilised for many products. It was found that searching for the "medical food" phrase returned unusual patents, such as relating to protective garments, so the word search was limited by broad classification codes to exclude those completely unrelated patents.

- Therefore this third search (search 3) searched for the phrase, "medical food" in all text fields, and A23L* or A61K* in all assigned IPC/CPC codes.

4.2 Themescape maps of IP landscape

Thomson Innovation's Themescape mapping tool was used to create landscapes for the patent sets returned from each search criteria. Landscape maps are constructed from key themes, words or phrases that are common to patent documents in the document set. The data is transformed using the Thomson Innovation software to represent the data in a two-dimensional landscape map. In general, areas of activity that are technically similar are placed close together on a map whilst unrelated areas are further apart. The peaks represent areas of concentrated patenting activity, for which a key word or theme can be identified. Landscapes were prepared for all searches using word themes from the title, abstract and claims.

5 Analysis of Patent Results

5.1 Search 1: Classification codes for nutritional foods

Search 1 used classification codes for foods with modified nutritive qualities, and returned 37020 records in 13420 DWPI (Derwent World Patent Index) families with publication dates within the last ten years. Note that a DWPI family is a group of patents containing the same technical content usually claiming the same priority dates[53]. This includes overseas patents and divisional applications. We are interested in the rate of innovation in the medical foods industry, so it is appropriate to analyse the results by patent family, rather than individual patent documents.

Analysis of this document set reflected that this is representative of the wider nutraceuticals and functional foods industry, of which medical foods is included. This is expected since the search terms included all foods with modified nutritive qualities. Figure 1 shows the number of patents filed per company. Of note are Nestec who have filed almost twice as many patents in this set as Nutricia and any other company. Nestec incorporates the research and development centre of Nestlé, taking care of much of the intellectual property of the company[54]. For information on Nutricia and Abbott Laboratories, who also significantly feature in this set, please see Section 3.2. Other companies that have not yet been identified as in the medical foods industry are described below:

Unilever have many patents filed in the nutritional food sector. They are a large company with laboratories all over the world and invest 1 billion euros into research and development each year. Unilever spans a wide range of health sectors, including community education, with an overall focus on health, wellbeing and sustainability. A strong nutrition policy has been part of Unilever since 2000, acting to improve the nutrition of all their products and advocate healthy heart, healthy weight and healthy growth and development. Medical foods do not feature specifically in Unilever's products at the moment, and it's unclear if they have plans to move in this direction[55].

DSM is also a large contributor to this area. DSM is the leading global producer of ingredients and vitamins for the pharmaceutical industry, also utilised for medical foods. They are a large company but currently do not directly deal with medical foods, although their inclusion is in DSM's future business plan[56].

Anjinomoto is a Japanese based company that aims to contribute to human health globally through sustainability, securing food resources and promoting healthy lifestyles. They have a core focus on amino-acids which form the base of their pharmaceutical products. It is unclear whether these are medical foods or not[57].

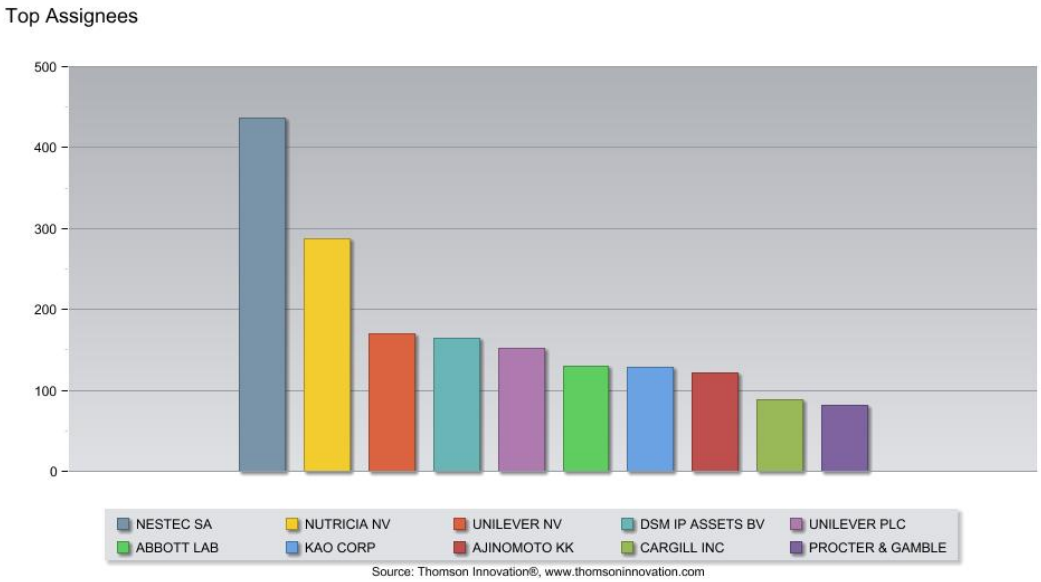

Figure 1: Number of DWPI patent families filed per Assignee/Inventor for wide nutritional food industry (search 1).

In summary, this search identified companies that are active in manufacturing nutritional foods. The patent landscape is dominated by large food companies that are active all over the world, with dedicated resources for research and development in nutrition. It is evident that about half of these companies produce medical foods, and others are beginning to recognise the medical food industry and move in that direction. While this set does include medical food products, it reflects a much wider movement in the nutraceutical industry, so a narrower search is necessary to more purely segment the trends relevant for medical foods.

A brief analysis of the patent landscape (not shown) reflects the broad spread of the companies' interests, particularly Nestec, Unilever and DSM that are involved in many sectors. Nutricia's patents are gathered around products composed of probiotics and targeted towards infants. Abbott Laboratories also appear to focus on milk and infant products on this landscape. A keyword search for different diseases in the DWPI titles of the patents, showed that nutritional foods in all areas can be used to treat or prevent diseases. Diabetes is the most commonly targeted disease and related patents are clustered around a peak that focuses on treating metabolic disorders.

The rate of patent filing for this search is shown in figure 2. The application year of the earliest DWPI family member has been used because we believe that this best reflects innovation rate since it plots when the invention was first patented. The filing rate appears reasonably steady with a slight increase, particularly in 2010. This consistency is expected because of the large and well-established nutritional food industry that this set represents. Note that the data for 2012 is not yet complete as patents are published 18 months after the initial filing date.

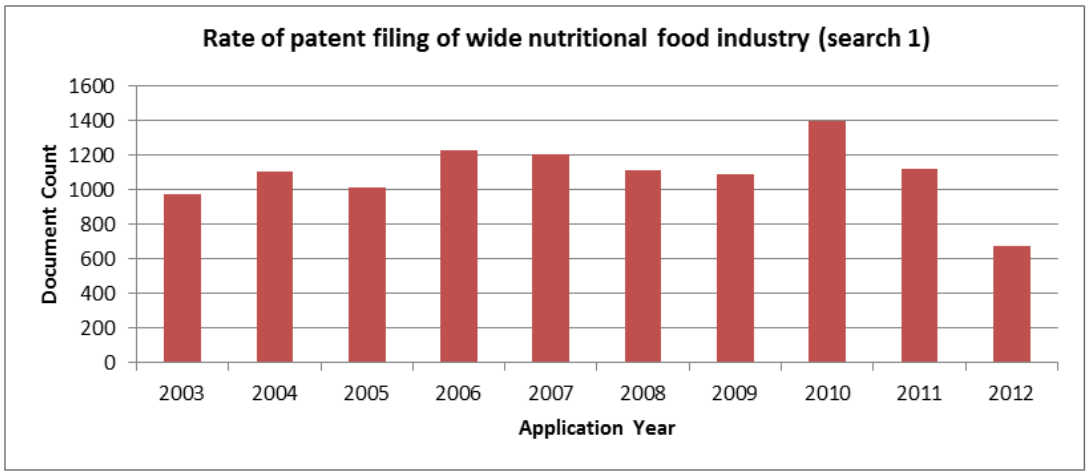

Figure 2: Rate of patent filing (application year of earliest DWPI family member). Note that data for 2012 is incomplete as patents are published 18 months after the initial filing.

5.2 Search 2: Classification codes for nutritional food and certain ingredients

Search 2 was a sub-search of search 1, additionally including classification codes relating to medicinal preparations containing ingredients that were identified as commonly found in medical foods. This search returned 8709 patents in 2944 DWPI families.

It is believed that the set returned by this search is a closer representation of the medical foods industry compared to set 1, although still includes some pharmaceutical drugs, dietary supplements and other functional foods. However, because the search has been limited by classification codes relating to ingredients and a much small patent set has been returned, the trends observed in this set seem to be more reflective of what is expected in the medical foods area, and what has been suggested by other sources. The set is difficult to refine further because medical foods are classified by ingredients, do not have a unique code, and because it is an emerging field, it is expected that at the time of patenting an ingredient or other invention, the possibilities for using it as a medical food may not have been apparent, but could become evident in the future. To that end, it is difficult to ascertain on a macroscopic scale, which patents actually do relate to medical foods.

A sub search for the phrase "medical food" in any text field yielded 90 DWPI families. This indicates that even within this set that is largely believed to reflect the trends of medical foods, the identification of an invention for use in or as a medical food is not widely used so cannot be relied upon to identify relevant patents. It is also acknowledged that outside of the USA, the term "medical food" is not widely used.

The top assignees to patents in this set are shown in figure 3. These are similar to the results in set 1, indeed the top five companies (Nestec, Nutricia, Abbott Laboratories, Ajinomoto and DSM) were all large contributors to the wider nutritional foods industry. This further emphasises the trend of large health and food companies moving into the medical foods sector.

The rate of application filing is fairly steady (see figure 4), with between 200-250 patent families originally filed each year. This steady trend is somewhat surprising, as other market research has shown the nutraceutical industry rapidly gaining popularity with strong market drivers. The rate of patent filing is either behind this trend, the market expansion is not due to or generating new inventions, or there is a shift within the set where a larger percentage of patents filed relate to nutritional foods.

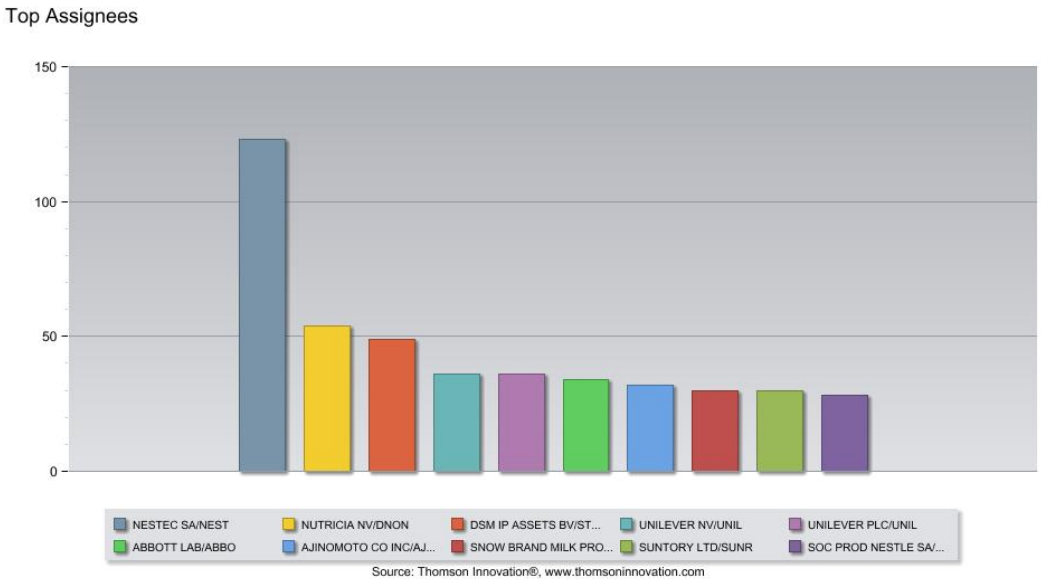

Figure 3: Patent count per assignee for the narrower nutritional foods (search 2).

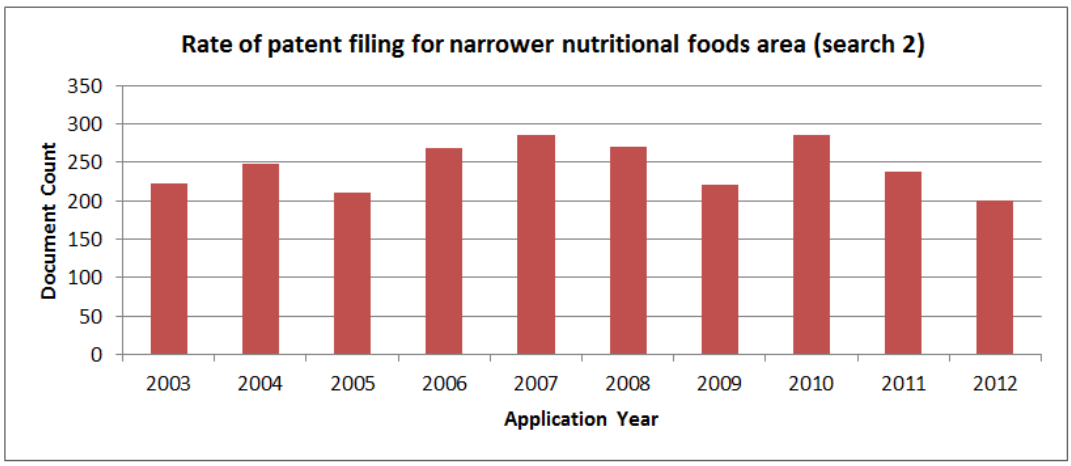

Figure 4: Rate of filing for Search 2 results (application year of the earliest DWPI family member). Note that data for 2012 is incomplete as patents are published 18 months after the initial filing.

Thomson Innovation's Themescape mapping tool was used to portray a landscape for this set of data (see figure 7). The peaks reflect areas of high patenting activity, grouped by word themes. Analysis of this map shows that the peaks are largely grouped by ingredient. These are all likely to be classified as GRAS substances since they are naturally occurring, such as plant materials, fruit extracts, herbal extracts, oils and fats. Other observations from the landscape map are as follows:

- Some peaks include action for a specific disease, for example in between the natural extracts, there is a peak that groups of all the natural extracts used for their anti-inflammatory actions.
- The companies are sparsely spread over this landscape. However Nutricia and Nestlé both have high patenting activity around the use of oils, fats and probiotics for therapeutic action.
- Targeted Medical Pharma has 5 DWPI patent families on this map, all grouped together (north of "Inflammation disorders" peak). These all refer to compositions aimed to enhance neurotransmitter activity, taken orally. Targeted Medical Pharma have 7 DWPI patent families in total, therefore supporting the market research findings that their purpose is focused on developing medical foods.

- A sub search was performed to see if diseases grouped on the landscape. It was found that the diseases were quite spread (and sparse). Diabetes was again the most commonly quoted disease application in patents, and was largely grouped around the peak for controlling blood glucose. Results from searching arthritis and asthma vaguely clustered around the two anti-inflammatory peaks.

5.3 Search 3: Medical foods keyword search

A keyword search was also carried out, searching for the phrase "medical food" in any text field of patents published in the last ten years. The search was limited to patents with classification codes A23L* and A61K*. 1850 records were returned in 926 DWPI families.

A startling observation from the results of this search is the presence of the Swiss company Mondobiotech. They are responsible for 312 of the 926 DWPI patent families, all focusing on the use of naturally occurring peptides as therapeutic agents to treat rare diseases. Mondobiotech is primarily a drug company, founded in 2001 with the sole purpose of finding treatments for rare diseases, and they use mathematical algorithms to search and match peptides to diseases. They do varying amounts of development of the drug, but always licence their patented "Medicinal Product Candidates" to strategic partners for regulatory approval and commercialisation. These products are not medical foods. However, they are primarily composed from peptides (many of which are classified as GRAS substances), target a specific disease, and in the United States are regulated under the Orphan Drug Act, yet not as a medical food as far as one can tell. All the patents have been returned in the search because in the description they include the phrase "medical food" in reference to the possibility of using the invention in an infant product, sometimes called a medical food[58].

It is interesting that Mondobiotech filed all 312 patents in 2008. The reason for this is unclear. Perhaps motivated by becoming a public company in 2009, or maybe their research had progressed far enough that they could start to patent and licence their inventions and expand. Mondobiotech now have five wholly owned subsidiaries in Switzerland as well as one in Liechtenstein and the United States, and this year acquired Pierrel Research International AG[59]. In summary, Mondobiotech has patented many peptides, and although they are not described as medical foods the potential for these "drugs" to move into the medical food industry is high. It is therefore not appropriate to remove them from this patent set, but they do skew the results because of their filing strategy.

Apart from Mondobiotech, the main companies in this search set are Nutricia, Du Pont and Abbott Laboratories (see figure 5). Nutricia and Abbott Laboratories have featured in the previous searches under nutritional food classification codes, but this is the first time that Du Pont have appeared significantly on this landscape. Du Pont is another large company with activity in over 90 countries, and is involved in many industries one of which is food and beverages. Within their food sector they have a focus on improving the nutritional value of food, therefore produce many nutritional foods and dietary supplements. Some of their products are ingredients that are sometimes used in medical foods, such as probiotics or vitamins, but Du Pont currently do not appear to market medical foods[60,61].

The patent landscape of this keyword search shows patents by Du Pont grouped by another of their research areas, the construction of polynucleotides (see figure 8). These are used particularly for the formation of fatty acids or oils, which can be included in medical foods or other pharmaceutical products. Mondobiotech take up a large portion of the landscape, all relating to the use of peptides for treating disease.

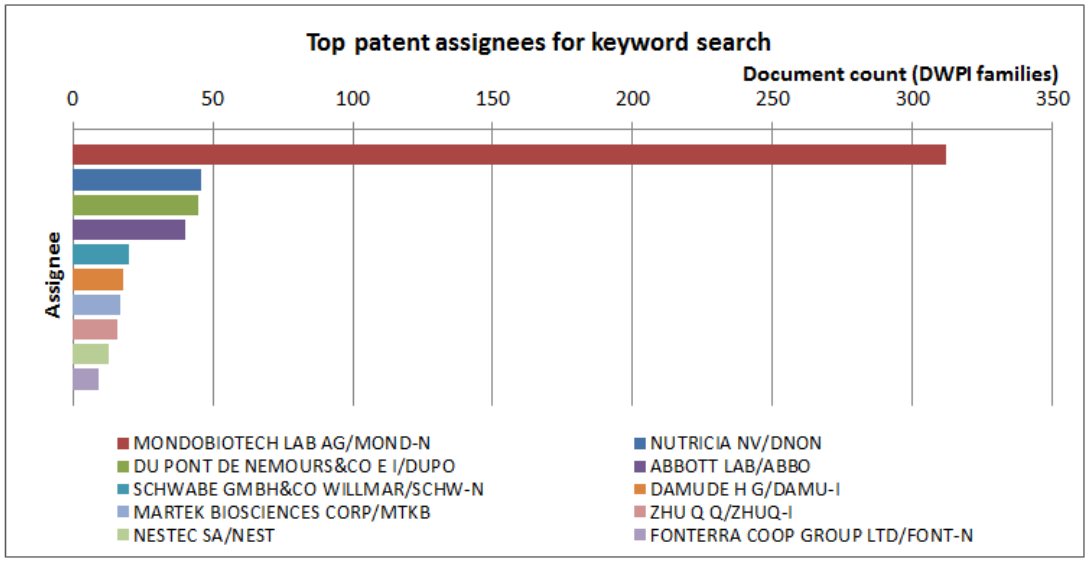

Figure 5: Rate of filing for search 3 results (application year of the earliest DWPI family member).

Nutricia are also grouped, surrounding the peaks of nutritional compositions containing nucleosides and lipids, often to treat frailty and neurotrauma diseases, and foods in liquid form.

The peaks of the patent landscape are mostly grouped by ingredient, similar to the set from search 2. Key active ingredients identified from the landscape include fats, oils and lipids; nucleotides, nucleosides and agrobacterium; peptides; and probiotics.

The rate of patent filing is shown in figure 6. Notice the large peak in 2008 which is where Mondobiotech filed 312 patents. Taking this into account, there is a general increase in the rate of patenting, doubling from 2009 to 2011. We believe this indicates that the application of medical foods is being increasingly considered when companies are patenting their products, reflecting a general increase in the recognition of the medical food industry.

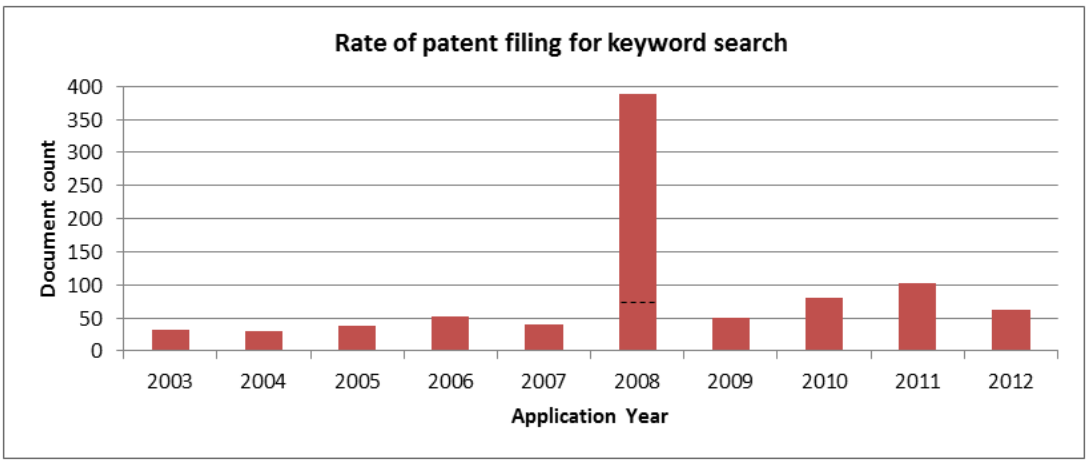

Figure 6: Patent count per assignee in medical foods keyword results (by DWPI assignee). The dotted line in 2008 indicates the patent count for that year excluding Mondobiotech. Note that data for 2012 is incomplete as patents are published 18 months after the initial filing.

Overall, this search set gives some information about the rate of recognition of the medical foods industry. However, it also highlights limitations of a key word search. Primarily, it relies on the patent attorney identifying the invention as related to medical foods and thus including the words in the patent; analysis on this basis is therefore not guaranteed. This key word search has missed out on those ingredients that are used in drugs and medical foods but not necessarily named for the latter, or where a medical foods application may not have been considered at the time of filing but becomes apparent several years later and thus is now relevant. Patents that aren't specifically related to medical foods have been included, because the phrase is mentioned in their description as an alternative name for one possible use of the invention. "Medical foods" is also unique to food regulations in the United States, so this search will most likely have missed relevant patents that originated elsewhere in the world. Due to these limitations of this search, it is believed that the second search is the most representative of the current trends in medical foods. This is not dependent on keywords, uses classification codes that are common for medical foods, and the wider nutritional foods that were included in the results have similar market drivers and trends to medical foods.

PATENT LANDSCAPE – CLASSIFICATION CODE SEARCH 2

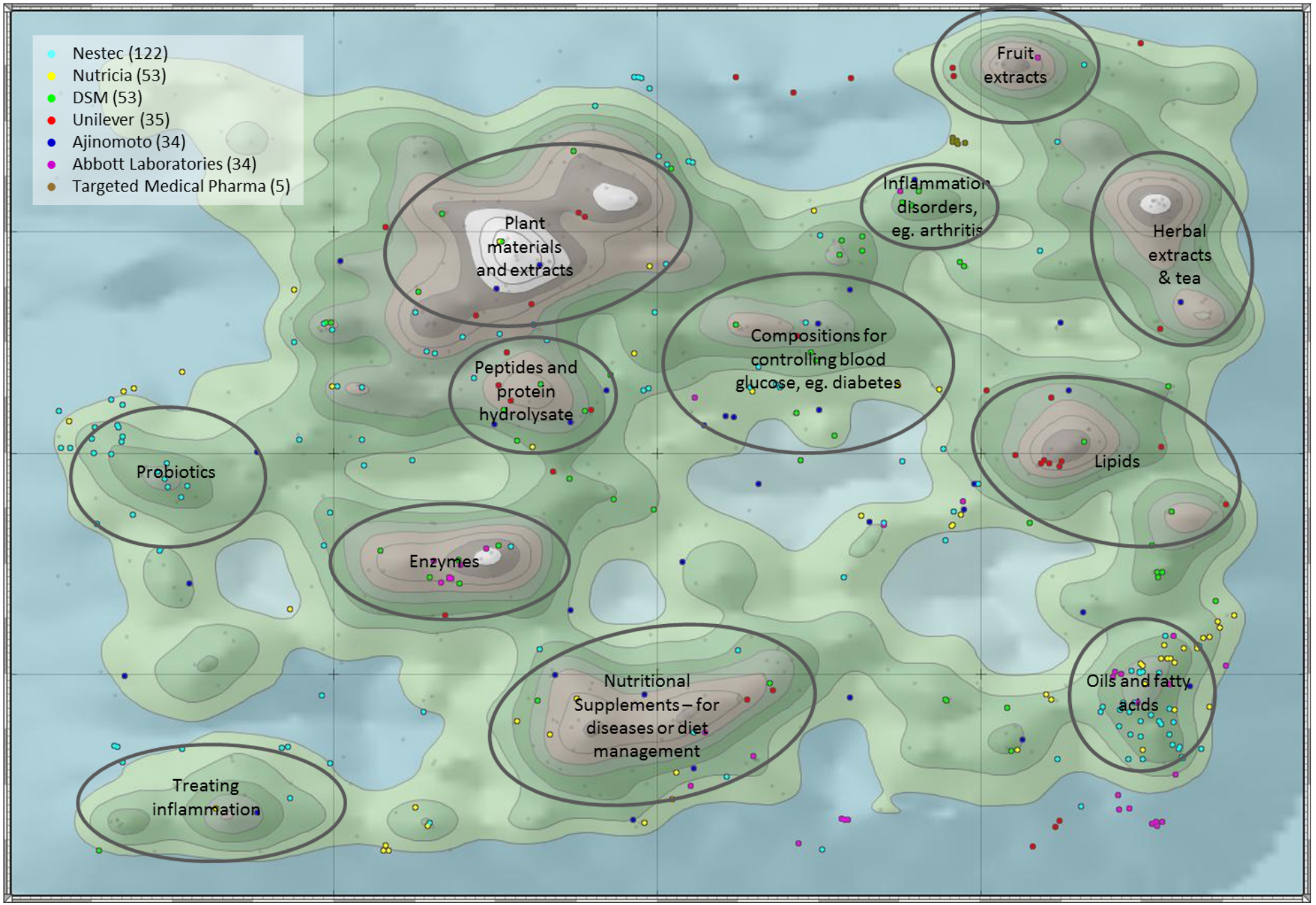

Figure 7: Patent landscape for nutritional foods (search 2), generated using Thomson Innovation software.

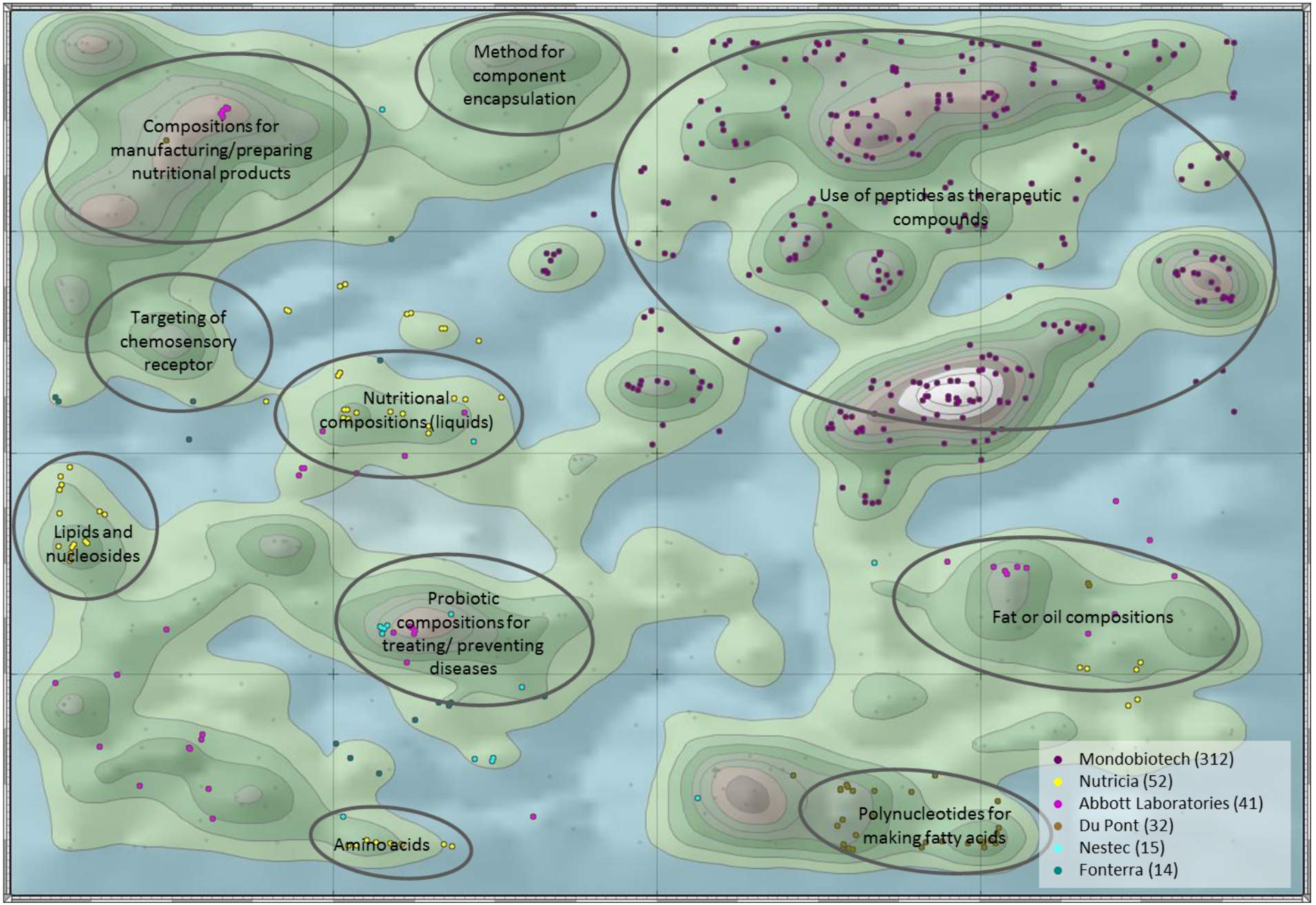

Figure 8: Patent landscape for medical foods keyword (search 3), generated using Thomson Innovation software.

6 Conclusions

The market and patent landscape analysis as described in this report indicate that there is increasing interest in the medical foods industry.

The ***strengths*** of this market include the growth in patenting activity and increased recognition of medical foods over the last fifteen years. Companies are able to protect innovative products by patenting, for example ingredients or method for formulation. Extensive patent activity has been observed in this area, particularly in the United States. Medical foods are also becoming more accessible for use as a prescribed substance, and via marketing by large food and healthcare companies starting to market specifically in this area. Other strengths are the robust market drivers that suggest the medical foods market is well placed to continue developing rapidly. These drivers are similar to those of the wider nutritional foods industry and include an emphasis on healthy living by the aging population, a shift to enteral nutrition and a demand for personalised medicine. Finally, the concept of medical foods has become widely regulated around the world, which encourages global innovation and provides a strong foundation for the medical foods industry.

Market analysis has also revealed some ***weaknesses*** of the medical food industry. A major weakness is the lack of understanding and awareness of medical foods by medical professionals and consumers. This prevents physicians from prescribing medical foods and consumers are less likely to seek medical foods if they are not educated about medical foods, particularly if a large cost is associated with it because their healthcare system or insurance does not cover the cost. Another weakness is the challenge of defining the medical foods market and industry. The patent landscape activity is unclear due to the absence of a specific classification code, and the overlap with dietary supplements and other nutritional foods. Therefore there is a difficulty in determining the freedom to operate. The regulatory requirement for medical evidence of medical foods is another weakness. This takes time and restricts innovation rate compared to dietary supplements or functional foods, however it is less regimented than that for a pharmaceutical drug.

Despite the apparent weaknesses in the medical foods industry, many ***opportunities*** are also present. Advances in enteral feeding technology have resulted in a preference for this administration method compared to other parental methods. Medical foods are required to be administered enterally, so can make use of the emphasis of this delivery method. New microencapsulation technology also allows the easy administration of medical foods. Another opportunity arises from issues with drugs use, primarily severe side effects and incomplete success of treatment. Medical foods are cheap to produce and a safe alternative. The small size of the market also provides opportunities for expansion, as it seems likely that market saturation has not been reached, especially outside the United States.

As with any industry, there are also ***threats*** to the medical foods industry. One apparent threat is that the market is currently cornered by a small number of large companies, with large patent portfolios, which provides a limitation for new innovators. The medical foods industry is also competing with other nutritional food products at a consumer level, and with drug companies with large sales and marketing operations. In many countries the healthcare budget is also shrinking which threatens the availability and priority of medical foods.

Overall, analysis of the medical foods market and patent landscape has allowed a number of conclusions to be made. It seems likely that the medical foods sector will expand to form a significant part of the wider healthcare industry.

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Appendix A

There are many medical food products currently available, that treat a wide range of diseases. Some of the products available are listed in the table below (see Table 4) with the specific disease/s that they target. This is not a complete product list, but aims to give an indication of the range of products being developed, with a focus on the companies that have been mentioned in this report.

Table 4: Some medical food products currently available for purchase.

Company	**Product**	**Disease targeted**
Abbott Laboratories	Ensure	Cancer, Celiac disease
Abbott Laboratories	Glucerna	Diabetes
Abbott Laboratories	Juven	Diseases that cause weight loss (eg. Sarcopenia) (Juven acts to support lean body mass)
Abbott Laboratories	Oxepa	Acute Lung Injury (ALI), Acute Respiratory Distress Syndrome (ARDS) and/or Systemic Inflammatory Response Syndrom (SIRS)
Abbott Laboratories	ProSure	Cancer (to help manage weight loss)
Abbott Laboratories	Pulmocare	Pulmonary disease
Abbott Laboratories	Suplena	Chronic kidney disease (stages 3 and 4)
Abbott Laboratories	Vital HN	Chronically impaired gastrointestinal function (eg. maldigestion, malabsorption)
Accera	Axona	Alzheimer's disease
Axcan Pharma	Ultrase MT	Cystic fibrosis
Nutricia	Souvenaid	Alzheimer's Disease
Pamlab	CerefolinNAC	Cognitive Impairment
Pamlab	Deplin	Depression
Pamlab	Metanx	Diabetes
Pamlab	NeevoDHA	High-risk pregnancy
Primus Pharmaceuticals	Fosteum	Osteoporosis
Primus Pharmaceuticals	Limbrel	Osteoarthritis
Primus Pharmaceuticals	Vasculera	Chronic Venus Insufficiency
Targeted Medical Pharma	AppTrim	insulin resistance and other forms of metabolic dysfunction
Targeted Medical Pharma	GABAdone	Insomnia
Targeted Medical Pharma	Hypertensa	Hypertension
Targeted Medical Pharma	Lister V	Viral infections and other diseases causing impaired immune function
Targeted Medical Pharma	Pulmona	Asthma and pulmonary hypertension
Targeted Medical Pharma	Sentra AM	Fatigue and cognitive dysfunction
Targeted Medical Pharma	Sentra PM	Sleep disorders associated with depression
Targeted Medical Pharma	Theramine	Pain and inflammation syndromes
Targeted Medical Pharma	Trepadone	Pain and inflammation syndromes, particularly arthritis
Upsher-Smith	Folgard RX 2.2	Cardiovascular disease, stroke
Vitaflo	Vitaquick	Dysphagia (swallowing difficulties)