Title: At the boundaries of food and medicine: The role of the regulation on the transformation of the probiotic applications in Europe and the United States from 2000 until present time

Dissertation in Business Administration and Bioentrepreneurship

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Abstract

The field of health-related new product development (NPD), in particular nutraceutical and functional foods (NFFs) is one of the most interesting areas of research and innovation, since variety of different products can be designed to enhance public health, reduce the probability of specific types of diseases, and even prevent and treat some illnesses (MarkHerbert, 2004; Menrad, 2003). *Probiotics* (friendly live microbs) present a rather young, but very versatile product group, that has been introduced into the international market as a part of the NFFs concept. NFFs emerged at the boundaries of the food and pharma industries, as a result, the position of the regulatory system within existing categories became vague and quite unclear (Arora, 2015). In this industry, there are rising concerns that the overly strict and outdated regulatory framework hampers innovation, and delays state of the art technology becoming available for consumers. Considering the economic, social and technological challenges in the probiotic industry, and a lack of studies on innovation in this industry, an in-depth understanding of the relevant regulation and its influence became the objective of the present study, which could be valuable for governments and policymakers, as well as to firms and other stakeholders. Thus, this thesis focuses on probiotics, marketed with health claims (HC), and is based on empiricall and quantitative secondary data covering the last 23

years. It aims to answer the following research question "What role has regulation played in shaping the market for probiotic applications in Europe and the U.S. since 2000?". Probiotics industry is highly innovative industry and NPD represents a science-based innovation trajectory, carried out by a network of interrelated actors with various interests and perspectives. To guide the investigation, the National Innovation System Framework by Kuhlmann and Arnold (2001) will be adopted in this context. The academic literature view on the ultimate impact of regulation on innovation indicates that regulatory influence is a tradeoff between between innovation-inducing factors and innovation-constraining ones including compliance costs generated by regulation (Pelkmans et al., 2014). In order to study the main relationship and interactions between regulation and innovation, the conceptual model based on the BERR report (2008), further modified by Pelkmans & Renda in 2014 will be used. It shows that this relationship between regulation and innovation is complex, multi-dimensional, ambiguous and dynamic (BERR, 2008). The academic literature suggests several regulatory mechanisms and dimensions to influence firms' decisions to innovate: stringency, uncertainty, compliance cost, timing, information and flexibility. From the holistic examination of the probiotics innovation systems, the probiotic industry, the regulation, and the relationship between the regulation and innovation, the results show that the probiotic industry in the U.S. developed as a leader in development of supplements and therapeutic applications, such as LBPs and medical foods, while the probiotic industry in Europe developed as a lagger behind focusing mainly on functional foods and less on development of supplements and therapeutic applications. Hence, this dissertation identifies that the regulatory agencies, the level of stringency of the safety and health claim regulation, together with their views and the way of exercising their power determine the different direction of the probiotic innovation and product trajectory, of often same industry players on global level into contest the convergence of products and regulations to more pharmaceutical resemblance.

1. Introduction

Due to the growing recognition between diet and health, nowadays there is an expanding interest in the benefits of foods promoting health and reducing the risk of diseases within the food industry and amongst health care professionals, consumers and society in general (Moors 2012). Some of the most dominant health conditions include energy/performance, healthy aging, immunity, digestion, cardiovascular, joint support, weight loss, and diabetes (Bagchi et al., 2017).

The health-related products industry is very dynamic and is currently a US$150+ billion sector worldwide, growing overall at over 10% per year with functional foods and beverages leading the way, followed by nutraceuticals and dietary supplements at a somehow lower growth rate (Bagchi et al., 2017). In 2004 the global market sized ranged from US$30 to US$60 billion, representing 1-3 % of the total food market (Kotilainen et al., 2006). Currently the leading markets are the U.S. and Japan, followed by Asia Pacific and the European Union. This industry is going through almost constant change and evolution, partly due to the changing regulatory environment and partly due to the ever-changing attitudes of everyday consumer regarding health and wellness. (Hilton J., 2017).

In researching for this Master Thesis what health-related foods with live microorganisms (probiotics) are it became evident that the "health-food sector" is a diverse concept: it is defined differently, regulated differently, and encompasses different types of products in different countries. The terms functional foods, nutraceuticals, supplements, natural health products, medical foods are used variously and interchangeably across different countries to refer to products with health-enhancing attributes.

Generally speaking, the health food sector is characterized by two broad categories of products: so, called "functional foods" and "nutraceuticals". Since the late 1980s and early 1990s, the sector of Nutraceuticals and Functional foods (NFF) has emerged at the boundaries of the pharmaceutical and food industries (figure 1.1).

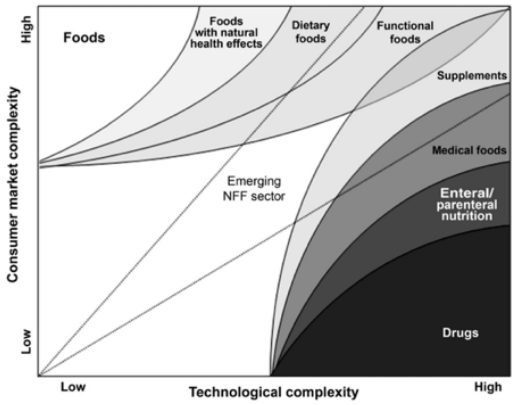


Figure 1.1. The emerging Health Foods and the NFF sector (ref. Bröring S., 2010)

Functional foods are operationally defined as "natural whole foods along with fortified, enriched, or enhanced foods that have potentially beneficial effect on health when consumed as part of diet on a regular basis at effective levels" (Crowe et al. 2013). Such foods provide health benefits, beyond basic

nutrition on the multiple body functions in a way that is related to either an enhanced health condition and well-being or a decreased risk of disease" (Martirosyan et al. 2016).

Nutraceuticals, also known as food supplements or natural health products are defined as "any substance or a product isolated or purified from foods that provide medical/health benefits, including the prevention and/or treatment of a disease" (Cencic and Chingwary 2010) and may include ingredients such as vitamins, amino acids, probiotics, etc., and are often marketed and sold in pills, powders and other medicinal forms. The definition of a nutraceutical is still in the grey area between food, food supplements and pharmaceuticals. (Bull et al. 2000; Nasri et al. 2014).

These definitions show that there is something 'extra' in functional foods, an opportunity for product differentiation, that presents a constant trigger for innovation. Thus, the emerging NFF segment offers an arena for a variety of different products. These vary from the simple fortification of existing foods with functional ingredients, to the emergence of personalised nutrition based on the scientific knowledge of genomics. NFFs have advanced to the point at which they can be designed to enhance public health by improving the general conditions of the body (e.g. pre- and probiotics), reduce the probability of having specific types of diseases (e.g. cholesterol-lowering products), help patients with special nutritional needs (infant feeding formulas) and could even be used to prevent and treat some illnesses as medical foods or therapies (MarkHerbert, 2004; Menrad, 2003; Side, 2006).

2. Problem definition

For foods to be marketed as a functional, it has to meet certain conditions that include conformation and meeting food safety regulation of a particular country or if exporting then meeting international food safety standards, free access, and proof of health benefits when consumed normally as a balanced diet. One of the major features of the NFFs are the health claims and labeling that are too specific without scientific evidence and facts. They are at times merely used as a gimmick for promotion. The "messages" or "claims" shown on the labeling of nutraceuticals and functional foods (NFFs) are highly important as they help consumers to identify the specific health benefits provided by the consumption of these products, as well as encourage consumers to make adequate food choices (Hieke et al., 2016). In addition, health-related claims are considered an important issue for food industry, as its use in food marketing is broadly widespread and promote the innovation and the competitiveness among food companies, which must ensure that every food product is adequately labeled before its commercialization (Tollin, Erz, & Vej, 2016).

Food companies are generally interested in making health claims in the labeling of their food products whenever is possible. The field of health-related new product development (NPD) is one of the most interesting areas of research and innovation in the food industry (Bigliardi and Galati, 2013; Siro et al., 2008). However, it is a complex and costly process that resembles R&D in pharma industry, while the marketing is about fast-moving consumer goods (FMCG).

The strict requirements which food companies must meet in order to include these claims in the labeling of their products, the limited financial resources necessary to make new applications for approving new health claims, and the steady change in the food sector (product categories, list of ingredients allowed to be incorporated in new functional food products, etc.) are considered the major challenges to face by the food industry and could have a negative impact on the product innovation (Bröring et al., 2017, Khedkar et al., 2016, Khedkar et al., 2016).

As an increasing number of claims started to appear in the labeling of NFFs, international regulation was required in order to (1) avoid misleading advertising and unfair competition in the food industry, (2) allow the free movement of functional products in the global market, and (3) ensure a high level of consumers protection by giving them all the information necessary to make adequate food choices with full knowledge (Bagchi et al., 2017).

NFFs are subject to regulation regarding any health claim attributed to the product and, in turn, how the product is labeled. Manufacturers cannot make medicinal claims e.g. that the product can prevent, treat or cure an illness or condition. Wording on these products need to be more generic, along the lines of claiming that the product can assist in promoting a healthy life, as part of the pursuit of a healthy lifestyle and/or through following a healthy diet (EU-Japan Center, 2016). Although the European, American and Japanese claims are partly similar in nature, the approval and use procedures as well as the regulatory framework are quite different.

Thus, the objectives of the present study are focused on describing (1) the changing status of the international regulatory framework for food health-related claims and (2) the state of the art regarding the functional food and nutraceutical products, marketed with health claims (HC) as an opportunity to observe the influence of the regulations on innovation.

This paper is a study to examine empirically and quantitatively the impact of the transition of the European, resp. U.S. regulation on health-related products enhanced with live microorganisms (probiotics) since 2000 until now and to answer the following research question "What role has regulation played in shaping the market for probiotic applications in Europe and the US since 2000?".

Food ingredient category of *probiotics* presents a rather young group in contrast to the more classical functional ingredients like vitamins and minerals, widely adopted by consumers in both Europe and the U.S. since 1990s (Sloan, 2004). Probiotics are defined as "live microorganisms, as they are consumed in adequate numbers to confer a health benefit on the host", with ongoing controversy as to whether microbes must be viable for efficacy in all cases (Charalampopoulos at al., 2003; Charalampopoulos, et al., 2010).

The present work is focused on United States (US) and Europe as the main representative countries with public and internationally available regulation of two continents (America and Europe). Japan was the first country in proposing the term "functional food", its classification and its regulation. In addition, it was the cradle of the functional food market. Japan is the global leader where probiotics are commercially available as both foods, neutraceutical and drug. It is the first country to implement regulation on functional foods and nutraceuticals in 1991. After the introduction of the functional food system in 1991, many

clinically proven foods for specified health uses (FOSHU) have been developed and launched in the market. Most of the health claims relate to improving gastro-intestinal health using probiotics. US and Europe are also considered important global powers in terms of functional food products with significantly different approaches regarding food and claims regulation (De Boer & Bast, 2015a). However, the regulatory authorities in the U.S. and Europe viewed probiotics with health claims more as medicinal products and the regulatory system was de-constructed outside the original purpose of the NFFs, and placed them in unclear healthcare, regulatory and marketing category.

3. Innovation systems

3.1. Definition

Over the course of more than 70 years of innovation research, a range of definitions have been developed for the concept of innovation. Schumpeter (1934) was one of the first to define economic innovation and his interpretation of the concept still lives on in the work of scholars like Dosi (1990), who defines innovation as "the search for, and the discovery, experimentation, development, imitation and adoption of new products, new production processes and new organizational setups". Innovation systems are defined as frameworks for understanding innovation, which have become popular particularly among policy makers and innovation researchers first in Europe, but now anywhere in the world. The concept was introduced by Lundvall in 1985. The components of an innovation system are the actors, networks and institutions (Carlsson and Stankiewicz, 1991) contributing to the overall function of developing, diffusing and utilizing new products (goods and services) and processes (Bergek, 2002; Carlsson and Stankiewicz, 1995; Galli and Teubal, 1997).

Innovation activities of companies are typical examples for complex processes with a long-term perspective which are characterised by multiple feedback-loops and interactions with a great number of actors located within and outside the companies (Edquist, 1997). Therefore innovation activities represent an ideal area to use system theory approaches for the analysis of such processes. Since the 1980s a series of different approaches and empirical studies can be registered which are rooted in the works of Schumpeter. A number of different innovation system concepts have been put forward in the literature such as national innovation system (Lundvall, 1992), regional innovation system (Cooke et al., 1997), sectoral innovation system (Breschi & Malerba, 1997) and technological innovation system (TIS) (Carlsson & Stanckiewicz, 1991).

Although each variant emerged from the same roots in innovation studies and evolutionary economics, their developers also created their own research program with a somewhat distinct epistemology and methodological approach (Coenen & López, 2010). However, they share characteristics and can all be represented as sets of institutional actors and interactions, having as their ultimate goal the generation and adoption of innovations at some level of aggregation (country, region, industrial sector, technology, etc.).

It is almost universally accepted that technological change and other kinds of innovations are the most important sources of productivity growth and increased material welfare - and that this has been so for centuries. Innovations are new creations of economic significance. They may be brand new but are more often new combinations of existing elements. Innovations may be of various kinds (e.g., technological and organizational). The processes through which technological innovations emerge are extremely complex; they have to do with the emergence and diffusion of knowledge elements (i.e., with scientific and technological possibilities), as well as the 'translation' of these into new products and production processes (Edquist, 1997).

This translation by no means follows a 'linear' path from basic research to applied research and further to the development and implementation of new processes and new products. Instead, it is characterized by complicated feedback mechanisms and interactive relations involving science, technology, learning, production, policy, and demand. Innovation processes occur over time and are influenced by many factors (Edquist, 1997).

Because of this complexity, firms almost never innovate in isolation. In the pursuit of innovation they interact with other organizations to gain, develop, and exchange various kinds of knowledge, information, and other resources. Depending on the stages of technological development the organization covers, it can be interlinked to other parties both in the same stage of technology development, e.g. research alliances, and in earlier or subsequent stages of technology development, e.g. licensing or manufacturing.

3.2. Different players (based on the model of Kulmann & Arnold)

Innovation activities of companies are typical examples for complex processes with a long-term perspective which are characterised by multiple feedback-loops and interactions with a great number of actors located within and outside the companies (Edquist, 1997). Kuhlmann and Arnold (2001) proposed a conceptual model of a national innovation system, depicted on figure 3.1. The components of the model emphasize the market and non-market knowledge interactions between firms, institutions, and other human resources involved in a national system (Doherty et al., 2001).

The Conceptual Model highlights the importance of six components, necessary for innovation: (1). Demand includes the need for innovations on the part of consumers and other producers in the economy; (2). The industrial system is all sizes of firms in the economy, including large companies, SMEs, and new technology-based firms. The firms might be suppliers, customers, or competitors; (3). Intermediaries are research institutes and other brokers of information or knowledge, such as government agencies; (4) The education and research system includes higher education, job skills training initiatives, and also research conducted by public sector organizations; (5). The political system involves the government and its policies, especially those that involve science, technology, and innovation policy. The regulatory frameworks are like norms, routines, established practices, rules or laws that govern the relations and interactions among actors;

(6). Infrastructure includes standards and norms, venture capital, intellectual property rights, and other supporting structures for potentially innovating firms.

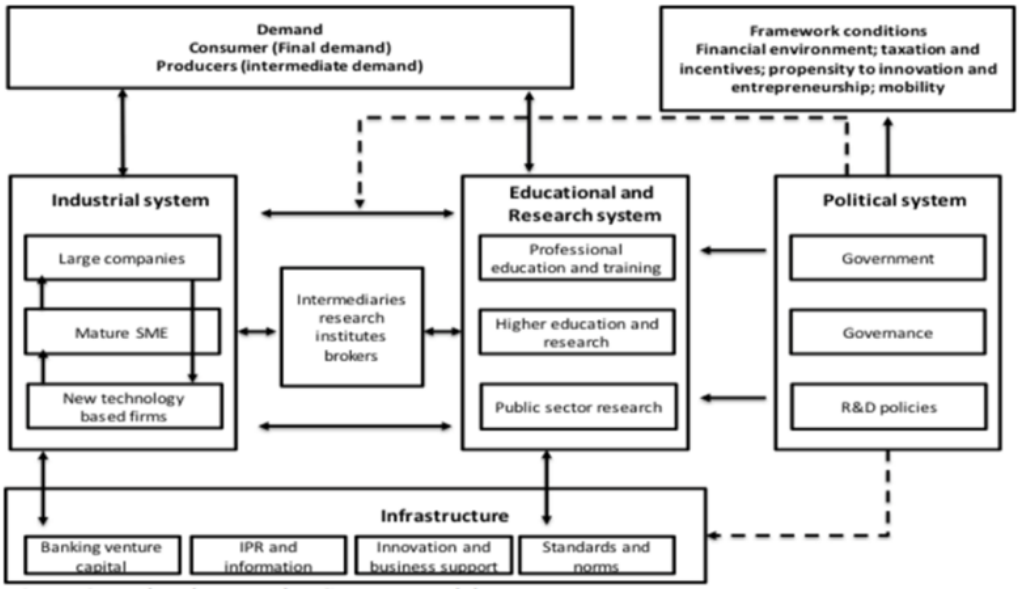


Figure 3.1. National innovation system model, Kuhlmann and Arnold (2001)

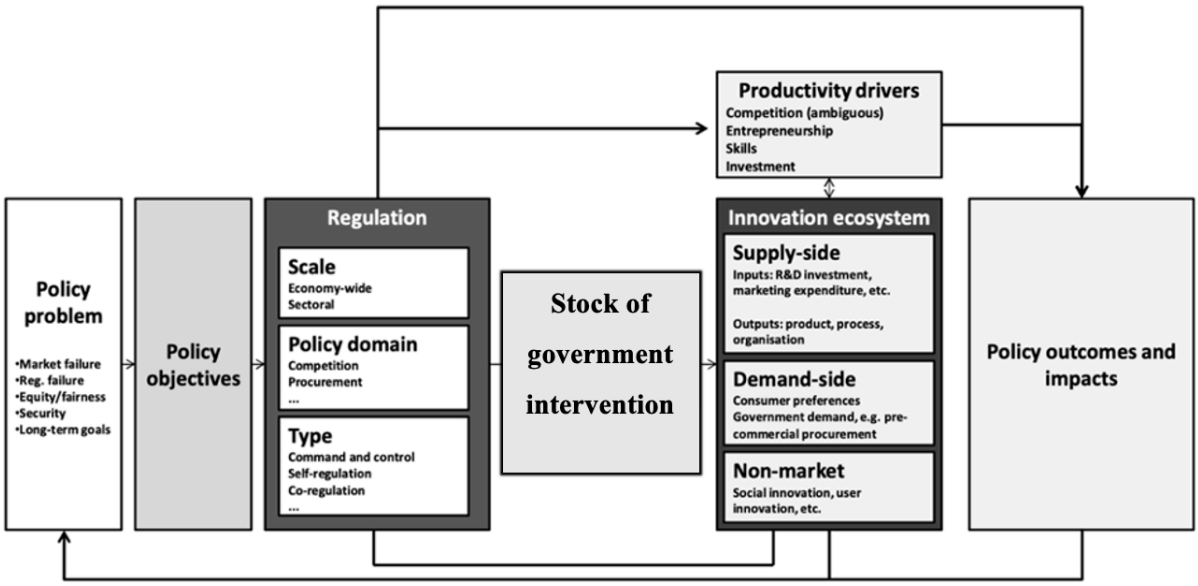
These components all interact within broad framework conditions, which include fiscal and tax policy, worker mobility rules, and other incentives that affect the occurrence of firms' innovation. The innovative capabilities of a firm depend on its ability to communicate and interact with a variety of external sources of knowledge (e.g. other firms, suppliers, users, scientific institutes, service and supporting institutions) as well as on the ability to co-ordinate a variety of interdependent sources of knowledge within the firm itself (e.g. R&D, production, marketing/sales) (Doherty et al., 2001).

Through their innovative activities firms often establish relations with each other and other kinds of organizations; therefore it does not make sense to regard innovating firms as isolated, individual decision-making units. The behavior of firms is also shaped by institutions that constitute constraints and/or incentives for innovation, such as laws, health regulations, cultural norms, social rules, and technical standards.

3.3. Main relationships and interactions between regulation and innovation.

A research paper published by UK BERR in 2008 explored the main relationships and interactions between regulation and innovation. In this report BERR developed a conceptual model to map the relationship between regulation and innovation, which was further modified by Jacques Pelkmans and Andrea Renda in 2014.

In this model, the relationship starts from the left-hand side by defining the policy objectives and proceeds with the decision of the government to use the regulatory framework rather than taxis or public spending to achieve it. The intervention through the regulatory framework may take three forms: introduction of new regulation, revisions to current regulation or removal of an existing regulation. The regulatory intervention may apply to across the whole economy (economy-wide) or be sectorial regulation (e.g. consumer protection, competition, intellectual property). They may also involve amendments to formal rules and requirements or entail the use of alternatives such as self-regulation (e.g. voluntary codes of conduct). All these different changes in the regulatory framework, in turn, alter the total stock of government policies (regulatory, tax and spending policies), and also the scale and nature of the interactions between them. Government interventions through the regulatory system interact with other government market-based and regulatory-based policies to affect changes in the innovation system by altering the incentives and risks of innovation as well as the costs and benefits.



Source: Authors' elaboration on BERR (2008).

Figure 3.2: Schematic of the modified regulation-innovation relationship based on the BERR report (2008) by Pelkmans & Renda in 2014.

Regulation may impact directly on innovation as well as indirectly by influencing other productivity drivers: e.g. strengthening competition, raising skill levels, encouraging more investment or promoting greater entrepreneurial activity. Government interventions may affect both the supply-side and demand side of the innovation system, business behaviour and decisions resulting in changes in innovation inputs (e.g. R&D investment, marketing expenditure) and outputs (e.g. products, processes and organisational structures). On the demand-side, regulatory interventions may alter consumer preferences for particular technologies

and products and services leading to changes in the pace and direction of innovation (Pelkmans & Renda, 2014). Changes in the innovation system may, in turn, affect policy outcomes. Alone, or through other four productivity drivers (i.e. competition, skills, investment and enterprise), innovation may have an effect on social and environmental objectives such as improved health and safety or better environmental quality. Such outcomes might lead to the need for more policy interventions, if policy problems persist. Finally, the development of new technologies, products and business practices may give rise to new markets and market failures, which require modifications, where appropriate, to the current regulatory framework and, in some cases, the introduction of new rules. By incorporation "feedback effects" the conceptual model captures the dynamic relationship between regulation and innovation.

The empirical studies based on economics and the conceptual model in the BERR 2008 report with modifications by Pelkmans & Renda in 2014 reveal the complexity of the study of regulation. The findings of the empirical studies highlighted that the relationship between regulation and innovation is complex, multi-dimensional, ambiguous and dynamic. Pelkmans & Renda assumed that the decision to engage in innovation is a rational one, and as such depends on whether the expected "net benefits" of the innovation activity is positive. Everything that affects basic conditions for entrepreneurship and innovation should thus be included in this rather complex picture. More specifically:

- The R&D and development phases of innovation are certainly affected by:
  - ◊ General rules applicable across sectors, such as competition rules, public procurement rules, infrastructure policy, bankruptcy legislation, and also education policy, which can affect the emergence of skills conducive to entrepreneurship, productivity and innovation.
  - ◊ Supply-side and demand-side innovation-specific regulation, such as patent laws, technology transfer legislation, tax credits on R&D, standardization, pre-commercial procurement regulations, obligations to cross-license (e.g. cases of blocking patents), etc.
  - ◊ Sector-specific rules, in particular for what concerns their stringency, timing and flexibility.
- All phases of the regulatory process affect R&D and development: however, while the agenda-setting phase is relevant, as it implies the definition of the general content of the regulation, often the legislation phase can have an even more significant impact on the timing, stringency and flexibility of the regulation itself. Moreover, the extent to which the regulation creates compliance burdens (both administrative burdens and substantive compliance costs) is also a very relevant element, as it can alter the overall expected benefit from the innovative activity. Finally, all phases of the regulatory process contribute to legal certainty, which is another key element of the decision to engage in innovative activity.
- The commercialization phase is affected by a partly different set of rules, which include the following:
  - ◊ General rules such as competition rules, consumer protection rules, trade regulations, unfair competition and B2B unfair commercial practices rules, etc.

- ◊ Sector-specific rules related to technology transfer, sectoral competition rules, administrative procedures related to the launch of new products, including authorizations, licenses, etc.

Stringency, uncertainty, compliance cost, timing, information and flexibility are identified as most influential characteristics of regulation. Among these characteristics, regulatory stringency is recognized as the most important factor influencing technological innovation.

3.4. A critical assessment of regulation with relevance to innovation

Regulation: Definition and main features

The term regulation is a generic term and comes from the Latin word "regula", which means "order" or "rule" (Zaharieva, 2017). "Regulation" refers to the diverse set of instruments by which governments set requirements on enterprises and citizens to maintain all activities valued by the community under a legal and sustainable framework (Selznick 1985). It is used by governments to influence choices, decisions, and public interest. Regulation include all laws, formal and informal orders, subordinate rules, administrative formalities and rules issued by non-governmental or self-regulatory bodies to whom governments have delegated regulatory powers (OECD, 2018). Based on the regulatory objectives, the regulations can be divided into economic, social and administrative regulation, all of which have effects on innovation.

Economic regulation is intended to improve the efficiency of markets in delivering goods and services and aims to avoid "market failures" generated by the behaviour of individual market players. "Market failures" include cases of significant market power (and abuse thereof), public goods, externalities, and asymmetric or incomplete information. "Economic regulation" gathers abuse of dominance and antitrust regulation, market entry regulation, mergers and acquisition regulation, price regulation, quantity regulation, as well as the economic regulation of natural monopolies and public enterprises (OECD 2021, case studies).

Social regulation protects the environment, as well as wellbeing, safety and the rights of society at large. "Social regulation" covers liability law, labour market regulation, bankruptcy law, intellectual property regulation, product quality and safety regulation, environmental regulation, worker health and safety regulation, data protection regulation and information security regulations (OECD 2021, case studies).

Administrative or institutional regulation governs the practical functioning of the public and private sectors. It can include regulations relating to taxes, business operations, distribution systems, health care administration and intellectual property rights (OECD 1997). "These are paperwork and administrative formalities (the so called bureaucracy/„red tape"), through which governments collect information and intervene in individual economic decisions. They can have substantial impact on private sector economic performance." (OECD 1997, Reg. Reform).

For each type of regulations, several different kinds of policies can be employed. "Regulatory policy" consists of the set of rules, procedures and institutions introduced by government for the express purpose of developing, administering and reviewing regulation (OECD, 2018).

Main types of regulatory interventions

Regulations may be rigid or flexible, gradual or disruptive. Government regulators may focus on creating rules to protect established interests, rather than creating rules that allow market participants and new entrants to innovate (Castro, 2011). Regulatory approaches can range from explicitly preventing the development and adoption of certain technologies, to adopting a "wait and see" approach to discover which perceived risks materialise, or piloting of innovative approaches such as the adoption of fixed-term regulatory exemptions (e.g. regulatory sandboxes) for innovative entrants that uphold protection for citizens and the environment.

Anticipatory governance. The rapid pace of innovation means that governments need to develop anticipatory governance approaches to allow for an earlier identification of risks and opportunities brought by technological developments (OECD, 2021, OECD Science; Tõnurist & Hanson, 2020). This can notably be achieved by means of structured horizon scanning, scenario planning and earlier and more active engagement with stakeholders, including innovators – all of which can also help governments prioritise innovations where regulatory reform is needed to unlock their benefits for society or minimise associated risks (OECD, 2021, case study).

Wait and see approaches. A rather common reaction at the beginning of the technological development consists in observing how the technology develops without taking any regulatory action (during this period, innovators operate within the existing regulatory regime). While such an option could be a wise choice in the early stages of the technological development, this should be replaced by formal regulatory strategy once the evidence have been collected (through public and stakeholder engagement in particular).

Issuing guidance. Innovators often face difficulties in identifying and interpreting applicable rules, in particular when innovation is straddling or blurring the boundaries of traditional market definitions. Then governments can rely on soft law mechanisms such as regulatory guidance to help innovators understand how the regulatory framework applies for a specific technological development and reduce the potential regulatory uncertainty as to how to comply with existing requirements. When a government formally decides to wait before issuing a regulatory decision, businesses may face regulatory uncertainties (e.g. on how to navigate the interdependences between the regulatory regimes) undermining incentives to innovate. Issuing guidance may help overcome this drawback by providing clarification and insights on how the regulatory landscape applies (governments could also use guidance to warn business about potential enforcement action in certain conditions are not met).

Guidance can take two forms. Informal guidance is on case-by-case basis with preliminary warnings, informal statements, and initial guidance on existing regulations in relation to the technology and no-action

letters. Formal guidance relies on more formalised mechanisms to clarify the broader application of existing regulatory frameworks. It uses tools ranging from principles, policy guidance documents, best practices or white papers. However, both approaches could be considered as 'soft law' and might be subsequently challenged by the judiciary (OECD, 2021, case study).

"Command and control", also sometimes called "means-based" or "technology-based" is one of approaches commonly used in social regulations to prevent negative impact on the society. The regulatory agency sets out in detail the desired regulatory outcomes to be achieved, which may include clear rules on the inputs and technologies to be used, and the types of business processes, practices and models by which the regulated entity must operate. This regulation creates certainty for the government, the regulated entity, and the public, because a body of experts have carefully developed the safest and most efficient mode of operation for the sector. In essence it exercises influence by imposing standards backed by criminal sanctions.

Although it is relatively easy for the regulator to observe and evaluate, and therefore to determine compliance the "command and control" might be highly expensive form of regulation, not only increasing the costs of products to the public, but also stifling of innovation. It may produce highly complicated and inflexible rules which may lead to over-regulation, legalism, delay intrusion on managerial freedom, and strangling competition and enterprise. In addition, setting appropriate standards and level of required information many be difficult, due to the severe informational demands. However, "Command and control" regulation proves to be the most effective to achieve the objectives of social regulations (Pritchett W, 2016).

Nowadays, governments are confronted with rising concerns whether the existing regulatory frameworks, often of the type "Command and Control" are best adapted to the growth of the probiotic industry. Realizing the weakness of the "Command and control" EU policy and the increasing economic hurdles, certain national policymakers started to reform their policies to enable innovation and achieve economic growth. There is an urgent need to gain a systematic understanding of the impact of the regulation on the industry. Such understanding will provide a reference to regulatory authorities to reform the country's regulatory framework when necessary.

Self-regulation. As noted by OECD (2009) "self-regulation *typically involves a group of economic agents, such as firms in a particular industry or a professional group, voluntarily developing rules or codes of conduct that regulate or guide the behaviour, actions and standards of its members. The group* is responsible for *developing self-regulatory instruments,* monitoring compliance and ensure enforcement". Examples of self-regulation include: codes of practice; industry-based accreditation arrangements; and voluntary adoption of standards. However, self-regulation may lack transparency and fail to reflect properly the preferences of economic agents. First, in the absence of a common regulatory framework, competition issues may arise, which is not desirable from an industry and government perspective given the associated cost and uncertainties. Second, businesses might self-regulatate to develop barriers to entry, asking for new entrants to comply with excessive and burdensome rules (which could be partly designed on purpose). In this context, the success of this approach

critically hinges on the capacity of governments to "*closely monitor practices and engage in regular reviews of technical standards and codes of practice in an open and inclusive way to avoid inappropriate market distortions*" (OECD, 2021, Recommendation).

Co-regulation. An approach that can be used to circumvent part of the difficulties associated with self-regulation is co-regulation. In the EU, "*an EU legislative act entrusts the attainment of the objectives defined by the legislative authority to parties which are recognised in the field (such as economic operators, the social partners, non-governmental organisations, or associations)*" (OECD, 2021, Recommendation). First, it offers a certain degree of flexibility under the control of governments, which is desirable to deal with the pace of technological developments. Second, it relies on a close collaboration between business and governments, which creates avenues for access to first-hand and detailed evidence on technological developments and makes sure that it complies with general public policy objectives.

Outcome-based regulation. Outcome-based regulation contrasts "Control and Command" regulation, and "*usually defines measurable outcomes that regulated firms must achieve. In focusing on outcomes rather than on inputs, it offers flexibility to businesses on how to meet to objectives, as long as they can demonstrate that the desired outcome has been achieved. Such approach theoretically allows regulated entities to choose the most efficient way to achieve the regulatory goal, while lowering compliance costs"* (OECD, Reg. Policy 2021). Outcome-based schemes appear well-suited to address the dynamic and the uncertainties of technological developments by providing flexibility to innovators. (Coglianese, 2017).

Process-based regulation. This regulation is so named because they require businesses to develop processes that ensure a systematic approach to controlling and minimizing production risks. They are based on the idea that, given the right incentives, producers are likely to prove more effective in identifying hazards and developing lowest-cost solutions than is a central regulatory authority. They are particularly useful where there are multiple and complex sources of risk, and ex post testing of the product is either relatively ineffective or prohibitively expensive. In the United States, the FDA's Hazard Analysis at Critical Control Points (HACCP) program regulates food safety. Producers are required to document and analyze the different stages of the production process, identifying key points at which hazards arise and putting into place site-specific strategies to manage them. The benefits of HACCP, compared with previously used regulatory approaches, have been estimated to be in the range of USD 1.4 billion to USD 2.6 billion, with up to 58 000 illnesses from contaminated seafood avoided annually. HACCP approaches have been recommended by the UN-based Codex Alimentarius Commission and other countries (OECD 2002, Reviews of Reg. Reform).

Information approaches. Education and persuasion can be used to achieve the community's objectives. Strategies which attempt to address perceived problems by providing more information, or changing the distribution of information can improve market functioning by enabling people to make better informed decisions). Examples include: information and education campaigns, labelling requirements, or requirements to disclose other information to the market. These instruments are often characterized as being "light-handed" because the degree of direct government involvement in decision making or directing

behaviour is more limited than with other instruments. They do not put legally binding rules on the behaviour of consumers or businesses. In relation to the criteria for efficiency, the benefits of these types of instrument will only be realised if the appropriate information is made available to those who need it. It is therefore necessary to ensure that these instruments are well targeted, which will also help to minimise costs (OECD, 2009).

Outright/effective ban. As the final step of the regulatory spectrum, governments may decide to implement an outright (or effective) ban, either to protect existing markets through regulation or to protect citizens against the potentially negative consequences of a technological development.

Standardization. Standardization is specific form of regulation as clarified by BERR (2008). Standards may define desired "performance" or "outcomes" criteria, enabling innovators freedom to design their products and services; Measurement standards can convey technical information in a transparent and consistent way enabling innovators to benchmark the performance of their products/services/processes and compare it against their competitors; Compatibility/interface standards can help innovators to ensure that new products/services/technologies are compatible with existing ones thereby promoting open and competitive markets; Quality standards can communicate to consumers that new products, services/technologies meet socially desired minimum levels of quality and safety (e.g. health and safety and environmental standards); Variance reduction standards can promote conformity between products, services and technologies brought to market thereby enabling producers to exploit economies of scale and enabling users to have confidence in their choice of product. Technology standards can be used by firms as an "insurance" hedging against the risky process of developing new products. This insurance mechanism fosters incremental innovation and product growth especially for those further away from the technological frontier. The use of technology standards significantly enables a firm's incremental innovation while also reducing its incentive to deliver radical innovation (Foucart R. et al., 2021).

As pointed out by (Coglianese, 2016), regulations often combine different types of approaches. Given the sheer pace and the cross-cutting nature of technological changes, it is even more likely that the appropriate response will require a mix of regulatory approaches. As an example, self-regulation might well go hand in hand with co-regulation or guidance to provide some frameworks to business and mitigate the potential risks raised by the technology. Self-regulation can even be mandated by regulators through a regulatory measure. Governments might also want to publish guidance or code of practices to complement performance-based approaches. Similarly, it could be useful to combine regulatory sandboxes with regulatory guidance to reduce the level of uncertainty faced by business when launching a technological innovation.

Despite the broad enthusiasm outcome-based regulation has recently garnered across governments, it must be underlined that none of the above-mentioned regulatory approaches are optimal per se. The relative efficiency of each regulatory solution depends, inter alia, on the expertise of governments, the ability to measure performance, the innovation stage and the pace of the technological

development. Against this background, governments should carefully scrutinise the different alternatives, paying close attention to the strengths and weaknesses of each option (OECD 2021, case studies).

Regulatory dimensions:

Ashford (2000) suggests that for innovation to occur, entrepreneurs must have the willingness, opportunity/motivation, and capability or capacity to innovate, and that regulation can affect all three aspects. The economic literature (starting from the seminal work of Ashford and later with the so-called "Porter hypothesis") has long recognized that regulation can be a powerful stimulus to innovation and entrepreneurship. The ultimate impact of regulation on innovation is an empirical, case-by-case question, and depends on the balance between innovation-inducing factors and innovation-constraining ones including compliance costs generated by regulation (Pelkmans et al., 2014).

Regulation influences innovation through mechanisms, while some of them are identified as specific to particular regulations, others appear to apply to all. There are five categories of mechanisms: compliance costs, incentives, market conditions, capacity/capital, or information/signalling (McEntaggart et al., 2020).

- compliance costs: compliance cost mechanisms are triggered by any requirement a business needs to comply with as a result of their ongoing activities; compliance cost mechanisms provide a channel through which regulation has a direct impact on individual businesses;
- incentives: incentive mechanisms refer to the ways regulatory changes affect the way businesses assess the costs and benefits of their future activities; incentive mechanisms provide a channel through which regulation directly impacts businesses; market conditions can also generate incentives for businesses;
- market conditions: market conditions mechanisms refer to the ways regulation affect the market environment in which businesses find themselves without impacting businesses directly; this includes any policy impact on the level of competition in the market, consumer demand, the physical, human or financial capital available in the market, or the flow of information and knowledge across organisations and within networks;
- capacity/capital: capacity/capital mechanisms refer to the ways market conditions or regulation modify the financial capital (e.g. the ability to use patents as collateral for loans) or the human capital (e.g. staff expertise, motivation) that business organisations and networks have at their disposal for innovation or other endeavours; this excludes compliance costs, which by virtue of their extensive use in the literature, are considered a separate mechanism;
- information/signalling: information/signalling mechanisms refer to the ways regulation signals to organisations and networks what is desirable or not (Sunstein 1996); such mechanisms account for the impact that the meaning carried by regulations (distinct from any material costs and benefits) have on business behaviour. The argument here applies widely, in the sense that any legislation or standard provides information, and that information may sometimes be relevant to innovation if it gives direction towards a particular technological trajectory (McEntaggart K et al., (2020).

Compliance costs & Incentives. Compliance cost refers to the cost for demonstrating compliance with regulation before entering the market. Compliance cost consists of testing costs and other expenditures for developing and manufacturing products likely to pass the regulatory requirements. The cost of conformity is related to the stringent level of regulation. Regulation enforces compliance cost and results in firms needing to divert resource expenditures to meet regulatory requirements (Stewart, 1981). The diverted investment reduces the available resource for innovation activities within the firm. For example, businesses may have limited budgets and if these are used to ensure compliance with a new regulation then there may be insufficient funds to finance further innovation (e.g. through investment in capital equipment, research and development and skills and training). Put another way, the opportunity cost of allocating limited resources to complying with regulation can imply 'lost' innovation (BERR 2008).

Economic theories on the role of regulation on innovation are principally based on the work of Carlin and Soskice (2006) and (Blind, 2012). They differentiate clearly between compliance cost or negative incentive impact, and the positive incentive impact of regulation. Carlin and Soskice (2006) demonstrated that regulation impact innovation introducing: 1) compliance costs, which reduce the available resources for investment in R&D, therefore lowering the innovation level; and 2) changes in incentives for investments in R&D, which can be both negative or positive, depending on the type of regulation.

The net impact of regulation on innovation depends on the relative strength of compliance effect and the incentive effect. A positive impact on innovation is expected if compliance costs are low or even zero and the incentives are positive and a negative impact especially in case of high compliance cost and low or even negative innovation incentives (Blind, 2012). An increase in compliance costs could also lead firms to innovate, or, on the contrary, could disincentivise them from investing in R&D. The same can be said for increases in incentives or uncertainties (McEntaggart K et al., (2020).

Firms may show inability to achieve compliance with existing products and services, but under the assumption that the regulated firms stay in business, regulation may stimulate two types of innovation. Stewart (2010) distinguished circumventive innovation and compliance innovation. Circumventive innovation can be realized when the scope of the regulation is rather narrow and therefore allows companies to escape the exposure of the regulation. Compliance innovation can be obtained when the scope of the regulation is rather broad, so the resulting product or process innovations remain consequently in compliance within the scope of the regulation. According to Stewart (2010) regulation that requires compliance innovation will result in incremental innovation, radical innovation, or "dud" inventions with no commercial viability.

Firms that make relatively minor improvements to existing products and processes, improving preexisting attributes to meet the minimum standards for compliance produce incremental innovation. When firms take the more costly and risky pathway to produce new products and processes known as radical innovation both the innovator and the society can obtain higher benefits. On the other hand, the likelihood of the radical innovation to produce "dud" inventions with no commercial viability or no

invention at all is high too, making the incremental innovation the preferred choice by firms. Regulations that are most effective at stimulating innovation will tend to require compliance innovation and, at the same time, will minimize the compliance burden and mitigate the risks of producing "dud" inventions Stewart (2010).

Capital/Capital intensity. With increasing capital intensity more resources are available for investments in R&D, which allows the innovation in firms to foster. Some regulatory schemes, such as patent protection, may create additional incentives to invest in R&D (Carlin and Soskice, 2006), whereas price restrictions and product market regulation may reduce incentives for innovators (Crafts, 2006).

Market conditions. The literature points to a range of contextual factors that will impact the relative strength of a mechanism, such as the sector to which the regulation applies, but also the level of competition in a market, the size and nature of firms that are affected and the nature of the products and services affected. Other ways in which regulation affect the market environment in which businesses operate without impacting businesses directly includes any policy impact on the level of competition in the market, consumer demand, the physical, human or financial capital available in the market (McEntaggart K., 2020).

Specific norm can simultaneously promote or hinder innovation, depending on other factors. Blind (2012) explains that market entry regulation may entail both effects. On the one hand, it may hamper innovation by prohibiting market entry of potential innovative newcomers. On the other hand, limited competition may also be beneficial for incumbents by allowing them to engage and invest in frontier innovation activities, and to increase their R&D spending, enjoying temporary monopoly positions.

The idea that capturing monopoly rents is the crucial reward for innovators has been the core argument of the Schumpeterian growth theory, positing that a more competitive marketplace lowers incentives for firms to innovate by reducing their profit margins (Franco F., 2021). More liberal market entry regulations can contribute to an increase in competition, which generally impacts positively on innovation. Liberal market entry regulations may also encourage more entrepreneurs (and potential innovators) to enter the market. However, allowing more new entrants is likely to reduce profits for incumbents, meaning that there is less for them to invest in R&D (McEntaggart K et al., (2020).

The debate on market structure and innovation is among the most researched issues in economics. Two of the most prominent economists of the past century, Joseph Schumpeter and Kenneth Arrow had completely opposite views of the best market conditions that would contribute to stimulating innovation. According to Schumpeter, "the introduction of new methods of production and new commodities is hardly conceivable with perfect – and perfectly prompt – competition from the start. And this means that the bulk of what we call economic progress is incompatible with it. As a matter of fact, perfect competition is and always has been temporarily suspended whenever anything new is being introduced – automatically or by measures devised for the purpose –even in otherwise perfectly competitive conditions" (Pelkmans et al., 2014).

On the other hand, Kenneth Arrow focused on a different view of dynamic efficiency, by looking at the incentive, for market players, to achieve superior levels of productive efficiency (mostly reductions in unit costs of existing products) over time, which would allow them to beat rivals in reasonably competitive environments. Every time inventors can appropriate part of the social benefit of the invention they introduce, their private incentive will be aligned with the public interest. Since this is more Since this is more likely to happen under competitive conditions, given the pressure exerted from rivals, more competition also means more innovation (Pelkmans et al., 2014).

Firms innovate to defend their competitive position as well as to seek competitive advantage. A firm may take a reactive approach and innovate to prevent losing market share to an innovative competitor. Or it may take a proactive approach to gain a strategic market position relative to its competitors, for example by developing and then trying to enforce higher technical standards for the products it produces. Regulation provides also flow of information and knowledge across organisations and within networks in terms what is desirable or not to do and that information may sometimes be relevant to innovation if it gives direction towards a particular technological trajectory (Sunstein 1996). Also, the work of David Teece (1986) has shed a different light on the dynamics of innovation. He focuses on a contracting, "Williamsonian" approach to innovation policy. In particular, Teece considers that most innovative products have to be integrated in a nexus of complementary products to really unleash their full potential. Thus, the modularity of modern products and the possibility of integrating innovation into existing system goods becomes one of the essential drivers of product innovation in a given economy (Pelkmans et al., 2014).

The work of Philippe Aghion et al., has shed more light on the potentially beneficial impact of competition on innovation and growth. These include: (a) a "Darwinian effect" or "innovate to survive", generated by intensified product market competition that forces managers to speed up the adoption of new technologies in order to avoid loss of control rights due to bankruptcy; (b) a "neck-and-neck competition" effect, especially observed when innovation is incremental and forms compete to overtake one another in a constant competitive race; and (c) a "mobility effect" that emerges when skilled workers are able to easily switch to new production lines (Pelkmans et al., 2014).

A number of other factors might contribute to the relationship between regulation and innovation. According to Pelkmans and Renda (2014) and Ravet (2017), sector-specific characteristics are among the most important ones. In many instances, the literature suggests that smaller firms are likely to be disproportionately impacted by increases in compliance costs and changes to market conditions, and that, while many regulations tend to negatively impact on innovation in the short term, a number of them have a beneficial impact on the long term (McEntaggart K et al., 2020). Less clear is the influence of firm age. On the one hand, young companies trying to enter new markets or just having entered existing markets have less experience with the requirements set by regulatory bodies, on the other hand they have more flexibility to react to upcoming regulations.

Information. Information measures whether a regulation promotes more or less complete information in the market (Stewart, 2010). Regulation can either promote more complete information about products and processes in the marketplace or induce uncertainty. Each affects the compliance burden of a regulation and the probability that compliance innovation will result in "dud" inventions. In general, more complete information aids innovation. One example is regulation that reduces information asymmetry. Information asymmetry occurs when one side of the market - typically the consumer side - has less information about a product than the producer side. When information asymmetry is present, regulation that helps alleviate the asymmetry may offset its own compliance burden somewhat. An important case is when regulation promotes more complete information by acting as a certification of the quality of the product for consumers, thereby adding compliance value for producers (Stewart, 2010).

The literature also highlights that other characteristic of the regulation, such as flexibility, stringency, prescriptiveness, clarity, uncertainty will impact the extent to which it influences innovation.

Timing. The time given for businesses to comply with a new regulation or standard can play an important role in determining the overall impact on innovation. First, businesses need time to understand proposed changes in the regulatory framework and the implications for their businesses. Then, they need time to identify and implement the appropriate changes to their business to ensure compliance, which may involve the development of new technologies or the adoption of very different business practices and models (Stewart 2010). However, it is important to note that there is a trade-off between the benefits of innovation and the benefits of compliance. While granting firms long time frames to comply may encourage firms to develop superior more innovative technological and non-technological solutions they inevitably delay the benefits of regulation since businesses are not all complying immediately. Here too, timing is a double-edged sword: too little time might discourage innovation and determine an unsustainable increase of compliance burdens, too much time might crystallize innovation efforts due to the lack of pressure to meet the requirements (Blind, 2012).

Flexibility. One classification of flexibility is the authority structure of the regulation. All regulations are aimed to achieve a desired outcome but differ in the way it can done by firms. The degree of flexibility in the implementation of regulations has a strong influence on companies' inclination towards radical or incremental innovations (McEntaggart et al., 2020). Flexibility also describes the number of implementation paths firms have available for compliance (Stewart 2010). Performance- or outcome-based regulation is more flexible and stimulates innovation more than purely prescriptive regulations such as "command-and-control" regulations. The flexibility of a regulation determines the cost burden and the probability of producing "dud" inventions (Stewart, 1981).

The literature generally indicates that more prescriptive regulation leaves less space to innovation, or that it determines the path that innovation should take. Since "Command-and-control" regulations prescribe specific materials or technology requirements they give no market prospect to those who want to experiment with alternative solutions (Renda et al., 2012). A firm may be obligated to lower the price of its output or may be required to reduce pollution emissions, because these regulations are behavioral

obligations. Regulation that sets goals or outcomes but does not prescribe means has been associated with more innovation. In contrast, the performance-based regulations where the regulator does not dictate the materials or processes but rather sets ultimate production standards, the regulated entity has the flexibility to determine the most efficient way to meet that standard (Renda et al., 2012).

Incentives-based regulations make a particular behavior more profitable for a firm to pursue. The firm can weigh the regulatory incentives for the encouraged behavior against other market incentives and then decide to what degree (or when) to behave as desired by the regulator.On an industry-wide level, the greater flexibility afforded by incentives-based regulation can minimize the compliance burden for the industry as a whole, because those firms for which behavioral compliance is relatively less costly will assume more of the burden of the regulation, instead of the burden being evenly distributed across all firms, including those with higher compliance costs (Stewart, 2010).

Another measure of flexibility pertains to the stage of the specificity of the regulation. Regulation can either use specification or performance standards to define the desired outcome of the product. Specification standards or technical standards govern the material composition or the technical configuration of a product or process. Performance standards set a benchmark for the performance of the product or process. They are more flexible than specification standards in that they allow firms to choose their own path to compliance. Not only can this reduce the compliance burden, but it can also directly reduce the probability that the firm will produce a "dud" invention, assuming, in both cases, that the firm is a more effective decision maker than the regulator (Stewart, 2010). Also, the early development of a formal open standard during the development of a new technology gives the first mover a competitive advantage, whereas, in the long run, it increases competition and lowers the cost of the innovative technology (Renda et al., 2012).

Stringency. Stringency measures the degree to which a regulation requires compliance innovation and imposes a compliance burden on a firm, industry or market. More stringent, non-prescriptive regulations–especially environmental regulations–can encourage innovations that help improve commercial competitiveness. According to Ashford et al. (1985) stringency is "the most important factor influencing technological innovation". A regulation is judged to be stringent if firms need to significantly change their behavior or develop new technology to comply with the regulation. Many studies use compliance costs as a proxy for regulatory stringency. Accordingly, stringency comes with significant costs (Renda et al., 2014). A significantly stringent regulation can act as a double-edged sword: when distance between regulatory requirement and the status quo is excessive, firms not able to comply (for technical and financial reasons) with the new requirements might go out of business. When this is the case, the innovation-enhancing potential of stringent rules is replaced by discouraging effect on existing firms (Renda et al., 2014). A gradual increase of the stringency of a regulation over time or "moving target" regulation is more apt to result in incremental innovation, only because it does not demand radical innovation, so firms tend to take the least costly and risky path. In contrast, "disruptive regulation", disrupts the existing products and processes of firms and industries and forces them to undergo radical re-engineering. The main disadvantage of disruptive

regulation is that it imposes a high compliance burden on firms, as well as resulting product and processes will face uncertain commercial viability and increased likelihood of "dud" inventions (Stewart, 1981). The (voluntary) use of technology standards is widely perceived to accelerate the diffusion of innovative technologies. Technology standards can be used by firms as an "insurance" hedging against the risky process of developing new products. This insurance mechanism fosters incremental innovation and product growth especially for those further away from the technological frontier. The use of technology standards significantly enables a firm's incremental innovation while also reducing its incentive to deliver radical innovation (Foucart R et al., 2021).

Swann (2000) concludes that: Standardization helps to build focus, cohesion and critical mass in the emerging stages of technologies and markets. Standards for measurements and tests help innovative companies to demonstrate to the customer that their innovative products possess the features they claim to have, but also acceptable levels of risks for health, safety and the environment. Standards codify and diffuse state of the art in science and technology and best practice. Open standardization processes and standards enable a competition between and within technologies and contribute therefore to innovation-led growth.

Surveys of innovating firms find many enterprises say that standards are a source of information that helps their innovation activities. While many say that regulations do also constrain their innovation activities, these constraints do not necessarily prevent innovation. In addition, standards can help: (i) the exploitation of economies of scale; (ii) the effective division of labour; (iii) the building of competencies; (iv) to reduce barriers to entry; (v) to build network effects; (vi) to reduce transaction costs; and (vii) to increase trust between trading partners. Technology standards can be used by firms as an "insurance" hedging against the risky process of developing new products. This insurance mechanism fosters incremental innovation and product growth especially for those further away from the technological frontier. The use of technology standards significantly enables a firm's incremental innovation while also reducing its incentive to deliver radical innovation (Foucart R et al., 2021).

Recently, Blind (2013), in its paper for NESTA, shows the positive and negative impacts often correlated with different types of standards. In 2006, Standards Australia published a comprehensive overview of the impact of standard on the Australian economy, finding that there is apparently a positive relationship between economy-wide total factor productivity and the "stock of standards", either when this is kept as a separate variable, or combined with a stock of R&D variable. A selection of a rigid, non-scalable standard can inhibit both incremental and disruptive innovation, and as such is highly damaging to social welfare and progress. "If a particular product or technical standard is imposed too early in the process of developing a new product, then the effect on innovation may be negative. On the other hand, a standard that comes along too late may result in unnecessary costs or duplication or 'lock-in' technologies that were not the most efficient and potentially detrimental to innovation (Renda et al., 2015).

Clarity. A lack of clarity in (either prescriptive or goal-based) regulations can impact on innovation by creating uncertainty about the future (e.g. ability of firms to comply with regulation, greater exposure to

liability claims). This is especially likely to reduce innovation in firms operating in sectors where innovation requires significant investment and longer timescales or where firms are operating in less financially secure markets (McEntaggart K et al., 2020).

Uncertainty. Before a regulation is implemented along one or more of these dimensions, it is typically preceded by uncertainty. Policy uncertainty occurs when a firm or industry anticipates the enactment of a regulation at some time in the future. Policy uncertainty has a mixed effect on innovation, although often it will precipitate the effects of the innovation dimensions of the regulation itself, regardless of whether the regulation is eventually enacted or not. In line with Birnbaum (1984) the term "regulatory uncertainty" is used to refer to the unpredictability of the actions of governmental agencies which create and enforce regulation. Ashford et al. (1985) conclude that, "a pre-regulation period allows industry time to develop compliance technologies, process changes, or product substitutes, while allowing leeway for it to adjust to ensure continued production or future commercial innovation." Under certain circumstances, uncertainty can be beneficial as firms try to anticipate or avoid future regulation by exploring alternatives.

Ashford et al. (1985), claim that "Although excessive regulatory uncertainty may cause industry inaction on the part of the industry too much certainty will stimulate only minimum compliance technology. Similarly, too frequent change of regulatory requirements may frustrate technological development." However, uncertainty about the actual shape or form of impending regulation is likely to hamper innovation. The process of developing new products and improved processes is a very risky and costly process and regulatory delay and uncertainty can add to this. As Ashford et al. (1985) conclude, "Faced with uncertainties which create risks that the technology developed will not ultimately be needed or will be unnecessarily costly, potentially innovative industries will simply adopt low-risk existing technology. Thus, only diffusion will occur."

Regulation, in practice, is a source of temporal uncertainty. Regulation makes the innovation process longer. The very existence of pre-market, market and post-market regulations poses potential obstacles for transforming an upstream discovery into an applied technology and eventually a commercially viable product or service (Lesser, Neil, 2014, Deloitte).

Policy uncertainty, but also compliance uncertainty caused by an existing regulation, do appear to cause both negative and positive effects on future innovation regulation. Compliance uncertainty can take two forms. In the first, a firm may be uncertain as to whether a product or process will comply with pre-existing regulation. This first form can also occur when the details of the regulation are unclear or difficult to interpret. In the second form, a firm may be uncertain about the length of the delay before a product or process comply with regulation in order to reach the market—otherwise known as "regulatory delay" (Braeutigam, 1981). In both forms, a regulation creates uncertainty about a return on investment, thereby increasing its compliance burden (Stewart, 2010).

Uncertainty may also concern the risk involved in the regulatory requirements. Firms' preliminary investment in a new product might be lost entirely if the project subsequently fails to meet regulatory requirements (Stewart, 1981). The risk associated with regulation could be either technical or administrative.

Stern (2017) distinguished uncertainty into technical uncertainty and uncertainty about the content and format of information. Technological uncertainty refers to the situation that the regulator has a lack of technical or scientific understanding of a particular type of product and its use in the human body, especially for innovative products. Content and format uncertainty occurs in the absence of clear guidelines for the protocols for evaluating a new product.

Under certain circumstances, uncertainty can be beneficial as firms try to anticipate or avoid future regulations by exploring alternatives. Ashford et al. (1985) claim that "although excessive regulatory uncertainty may cause industry inaction on the part of the industry too much certainty will stimulate only minimum compliance technology. Similarly, too frequent change of regulatory requirements may frustrate technological development. (Ashford, 1985). Another important factor is uncertainty on the content of the scope of future (upcoming) polices. Policy uncertainty reportedly has a mixed effect on innovation, although often it will precipitate the effects of the innovation dimensions of the regulation itself. Likewise, the compliance burden may affect firms prior to enactment if, in anticipation, they begin diverting resources toward compliance. If policy uncertainty is high and the optimal decisions with and without the regulation are contradictory, then firms may suspend investment and innovation until a policy uncertainty is reduced to a more comfortable level (Ishi & Yan, 2004).

Likewise, the stringency may affect firms prior to enactment if, in anticipation, they begin diverting resources toward compliance. If policy uncertainty is high and the optimal decisions with and without the regulation are contradictory, then firms may suspend investment in innovation until a policy uncertainty is reduced to a more comfortable level (Ishii & Yan, 2004).

From available experience and evidence, it seems that regulation can spur innovation through stringent requirements provided that the distance to be covered by targeted stakeholders is not excessive, and that the outcome is specified in a technology neutral, non-prescriptive way, which allows for experimentation of various solutions and, as such, innovative compliance (Renda et al., 2014).

In summary, the analysis of the impacts of regulations on innovation should take all these dimensions into account (Blind 2012). Each dimension plays a large role in determining the impact of regulation on innovation. Greater flexibility and more complete information generally aid innovation, whereas with stringency, there is a trade-off between the compliance burden and the type of innovation desired, as more radical innovation will generally causes a higher cost (Stewart, 2010).

4. Methodology

The purpose of the methodology section is to explain the reasoning behind the decisions taken during the research. Hereby is provided a logical explanation of the choices occurred regarding the use of the methodological approach, theory and data collection. Furthermore, the structure of the thesis is presented, to give a clear description of the purpose of each of the sections and to explain how all the components of the paper are used to answer the research question. A graphical representation is provided

to clarify the rationale of the overall structure and to highlight the major focus and effort that the research is addressing. Finally, the reliability and validity of data is argued for, and a brief description of the limitations of the choices made, how they affect the whole project research and how they delimit its scope is presented.

Methodological approach

Theory is a standardized principle on which basis the relationship between two or more concepts and variables can be explained. There are two levels of theory, first abstract theory that follows inductive level approach and second is empirical level that follows deductive theory approach (Rahi S., 2017).

Inductive level. Collis and Hussey (2013) defined inductive approach as a process where theory is developed by observation on what researcher has observed during his research. Moreover, it may call a process which can induce or inferences a thought about a specific object or variable. In accession to this Collis and Hussey have explained the induction process in which a relationship between meanings and actions of human subjects are used to be observed and investigated (Rahi S., 2017).

Deductive level. According to Collis and Hussey (2013) in a deductive approach you don't get a theory from observation. Theory already existed and was proved by researchers. Moreover, you can explain a research based on empirical observation and theory generated on conceptual and theoretical structure. Generally researcher intends to test a theory by collecting the fresh data from respondents and observe the findings by applying various statistical tests. This method is generally recommended for specific studies in which researcher work on particular concept by creating assumptions and then verifying those assumptions. Deductive reasoning in contrast to the inductive reasoning is narrower in nature and is concerned with testing or confirming theories through empirical studies (Rahi S., 2017).

Abductive level, also referred to as abductive approach is set to address weaknesses associated with deductive and inductive approaches. In abductive approach, the research process starts with 'surprising facts' or 'puzzles' and the research process is devoted their explanation (Bryman, 2015). 'Surprising facts' or 'puzzles' may emerge when a researchers encounters with an empirical phenomena that cannot be explained by the existing range of theories. According to Peirce (1878), abduction or abductive reasoning, may produce new knowledge, and thus may be related to scientific reasoning. Abduction consists in studying the facts and devising a theory to explain them. It is the first starting of an hypothesis and the entertaining of it, whether as a simple interrogation or with any degree of confidence (Pierce C.S., 1931-1958). Pierce's attempt to distinguish between abduction and induction whereby he describes the former as proceeding from facts to an explanatory hypothesis whereas the latter proceeds from a hypothesis towards supportive facts.

For Walton (2001), abduction is different than deduction and induction because the conclusion is just a hypothesis, a best guess, based on the given knowledge and evidence at that moment. For this reason, abductive inferences are defeasible, meaning that they are "subject to retraction if further investigation of the facts in the case shows that another of the alternative explanations is 'better'. Moreover, abductive reasoning resembles a continuous deliberation process that needs to be open to revision as new evidence

of the factual circumstances of the case enters into the calculations. Abductive reasoning is similar to the reasoning of a detective looking for the best data that would give the best explanation possible. The decision for what counts as the best explanation in a given context is based on the criterion of plausibility, rather than possibility, as in deductive inferences, or probability, as in most inductive inferences (Walton, 2001).

The research approach adopted for this study is qualitative and abductive. The utility of the approach as realized from this study can be streamlined to the following aspects; the centrality of a researcher's observation pertaining to a certain phenomenon; the development of hypothesis (proposition) based on this observation; the reliance on a credible background theory in an attempt to explain the proposition; the use of deductively and inductively sourced data in validating the explanation of the proposition; the creation of new knowledge based on the validation of the explanation of the initial proposition. Abductive approach implies looking for and exploring potential explanatory patterns within the facts of a phenomenon to reveal a path from facts to ideas and theory, or expressed differently basically it seeks theory. This approach can further new and useful hypotheses (Åsvoll, 2014).

An explanatory research study strategy seeks to develop an accurate theory which could be adopted to describe practical generalization. While study of a descriptive nature seeks to answer the questions that likely starts with; who, what, where, when and or how of the research study topic and questions. An exploratory study is adopted when the research study seeks to find out about the topic of interest what is happening, to ask questions and evaluate findings from a different perspective (Saunders et al., 2009; Nabee & Walters, 2018).

4.1. Research Philosophy

The term research philosophy refers to a system of beliefs and assumptions about the development of knowledge. Developing knowledge in a particular field is what we are doing when embarking on research and our research philosophy will reflect the interpretation of the results and the way in which they are presented (Saunders et al., 2019). There are seven different philosophical assumptions, reported in the literature, such as Ontology, Epistemology, Axiology, Rhetoric, Methodology, Strategies of Inquiry and Methods.

The ontological philosophy describes the nature of reality about the concept of knowledge, whereas Epistemology deals with the connection between the researcher and that being researched (Rahl S., 2017). In business management and literature, the approaches of objectivism and subjectivism are usually adopted to the ontological philosophy to produce acceptable knowledge (Saunders et al., 2019).

Objectivism is the belief in an external reality whose existence is independent of knowledge of it; the world exists as an independent object waiting to be discovered. Objectivists understand facts as an objective entity to reality, that cannot be changed by human interpretation. Subjectivism is a belief that you cannot know an external or objective reality apart from your subjective awareness of it; what we agree exists, exists for us, of and in our intersubjective awareness. Subjectivists accept that humans perceive facts differently and have different ways of interpreting the same observation. This dissertation is inclined to

agree with subjectivists. The empirical data will therefore be accepted in respects to individuals' beliefs that cannot always be perceived as general truths (Saunders et al., 2019).

Five major philosophies exist: positivism, critical realism, interpretivism, postmodernism and pragmatism. Positivism relates to the philosophical stance of the natural scientist. This entails working with an observable social reality and the end product can be law-like generalisations similar to those in the physical and natural sciences. Critical realism focuses on explaining what we see and experience in terms of the underlying structures of reality that shape the observable events. Critical realists tend to undertake historical analyses of changing or enduring societal and organisational structures, using a variety of methods.

Interpretivism is a subjectivist philosophy, which emphasises that human beings are different from physical phenomena because they create meanings. Interpretivists study meanings to create new, richer understandings of organisational realities. Empirically, interpretivists focus on individuals' lived experiences and cultural artefacts, and seek to include their participants as well as their own interpretations into their research. Postmodernism emphasises the world-making role of language and power relations. Postmodernists seek to question the accepted ways of thinking and give voice to alternative worldviews that have been marginalised and silenced by dominant perspectives. Postmodernists deconstruct data to expose the instabilities and absences within them. Postmodernis taxiology is radically reflexive. Pragmatist ontology, epistemology and axiology are focused on improving practice. Pragmatists adopt a wide range of research strategies, the choice of which is driven by the specific nature of their research problems (Saunders et al., 2019).

Critical realists attempt to provide an explanation for observable events by looking at the underlying causes and mechanisms that shape them. Critical realists embrace epistemological relativism, a mildly subjective approach to knowledge. Knowledge is considered a product of its time and social facts agreed to by other people rather than existing independently. The notion of causality can hence not be reduced to quantitative methods and statistical correlations, but a variety of methods are acceptable. The axiological position of a critical realists guides him or her to believe that knowledge of reality is a result of the social actors involved, making them strive to minimize biases and be as objective as possible (Saunders et al., 2019). It is hence the approach of a critical realist that is taken to understand the regulation and underlying dimensions leading to the observable phenomenon: probiotics products with different applications evolved in time. Saunders et al. (2019) also draw attention to the fact that a critical realist position is very much in line with the purpose of business research in general, which often is to understand the reason for phenomena as a precursor to recommending change (Saunders et al., 2019). Correspondingly, as the purpose of this dissertation is to explore how regulation shaped the application of probiotics technology in time and space, from 2000 until now in two different markets – the EU and the US.

4.2. Research design

To answer the research question " What role has regulation played in shaping the market for probiotic applications in Europe and the US since 2000?", first a literature review on innovation, innovation

system and regulation is carried out, to introduce the concepts and find out what impact regulation has on innovation. The NIS approach, based on the model of Kulmann & Arnold (2001) is used to provide a structural analysis of the European and the US probiotics innovation system (ISs). To study the main relationship and interactions between regulation and innovation, the conceptual model based on the BERR report (2008), further modified by Pelkmans & Renda in 2014 is used.

The research approach adopted for this study is qualitative and abductive, that uses a comparative case study to answer the research question and to establish relationships of regulations to innovation system within the each IS and gain more in dept-insight into both ISs. Triangulation is a common feature of case studies. It is a term used to describe the use of multiple different data collection techniques to improve the credibility and validity of research findings. Four types of triangulation are proposed by Denzin (2012). Data triangulation, which includes matters such as space, time, and people; investigator triangulation which incorporates multiple researchers in a study; theory triangulation which encourages various theories to interpret a phenomenon; and methodological triangulation which promotes the use of several data collection methods including interviews and observations (Denzin, 2012). This dissertation is based on a single, critical case study. Two out of the four triangulation types will be adopted to answer the research question. Namely, that of data triangulation as space and time is taken into consideration to study evolution of innovation and regulation; and theory triangulation as literature from various papers will be relied on to assess.

The study was conducted as a desk research including a review of existing literature The literature surveyed to provide secondary data covered academic journals, trade journals, magazine and newspaper articles, market reports, proceedings, books and other publications. Web page content was used, as necessary to gain information on probiotics, probiotics market, probiotics innovation and the legislations regarding probiotics in both Europe and the United States and to establish the relationship between the regulation and innovation. Only material in English was reviewed.

Literature was collected using numerous search engines (for example, Science direct, Google, Google Scholar, PubMed, Marketing data from different sources) in addition to CBS library databases and internet libraries of international development organizations. Key words in the search involved probiotics, prebiotics, live microorganisms, health foods, functional foods, medical foods, drugs, but as the terminology in the international setting is poorly defined, also nutraceuticals, supplements, bioactive ingredients, and other variations were used. For this comparison a qualitative research design based on secondary desk research is used.

Chapters in pills. Chapter 1 discusses the introduction. Chapter 2 defines the problem and the research question. Chapter 3 discusses the theoretical framework of the study. It defines the innovation system concept, a model for mapping the different players involved in the probiotics system, the regulation concept and the relationship between the regulation and innovation with critical assessment. Chapter 4 presents the methodology. It includes the methodological approach, the research philosophy, the research design, the data collection, data analysis, and the credibility of the research in terms of reliability validity,

reliability and generalisation. Chapter 5 introduces the probiotics industry, presents the results of the analysis of the probiotics innovation system in the EU and the US, the regulation related to the probiotics case, and the relationship between regulation and innovation. Chapter 6 shows the implications for management and for policy. Chapter 7 gives conclusions to answer to the research question and the limitations. Chapter 8 lists the references and finally chapter 9 includes tables and figures.

4.3. Credibility

Reliability. The concept of reliability refers to "the accuracy and precision of the measurement and absence of differences in the results if the research was repeated" (Collis and Hussey, 2014). Producing findings with high reliability can be a challenge in interpretivist research because of the subjectivity that comes with the high degree of researcher involvement in qualitative research methods (Collis and Hussey, 2014). In practice, this means that different researchers may collect different data and come to different findings at the end because the researcher's background, identity, values and interests can influence the collection and analysis of the data (Denscombe, 2014).

To counteract a potential negative impact on the reliability of the results, the researcher remained conscious of her own role in the research so that potential bias in the findings could be eliminated or, at least, minimised. The researcher was also aware of the innate human tendency to validate one's own beliefs, known as confirmation bias (Hallihan and Shu, 2013): researchers may unconsciously emphasise those perspectives that fuel their pre-existing views, while disregarding options that do not support these personal assumptions. In this study, the researcher tried to avoid confirmation bias and produce reliable results by consciously treating all data equally, being honest in the analysis of the collected data and avoiding any temptation to manipulate the data (Denscombe, 2014). Moreover, discussions and consultation with the research supervisor further contributed to avoiding researcher bias.

Validity. Like reliability, validity is a way of assessing the quality of the chosen research design and methods. If the research findings truly measure the phenomenon they claim to measure, the findings can be judged valid (Collis and Hussey, 2014). On the basis of the appropriateness of the chosen methods of data collection and analysis, the data collected for the purpose of this study is highly likely to be accurate and appropriate (Denscombe, 2014). The validity of this study is further underpinned by the level of attention paid to ethical issues in the research design and the researcher's conscious attempts to eliminate researcher bias throughout the entire research process.

Generalisability. As this research study is underpinned by the interpretivist research philosophy and the data is not statistically analysed, generalisation is not the aim of the study (Collis and Hussey, 2014). However, the findings are nonetheless likely to be generalisable to other settings similar to those that have been studied. The researcher has attempted to capture the characteristics and complexities of adopting design as a strategic tool in organisations and has gained a comprehensive and deep understanding of this phenomenon. Thus, the richness of the collected data has enabled the generation of patterns, concepts and

theories that ought to be true and applicable in other organisations that set out to become design driven (Denscombe, 2014).

5. Probiotics Industry

5.1. Probiotics and definitions

The world "**probiotic**" is a relatively new word meaning "for life" and originates from the Latin word "pro" and Greek word "βιωτικος-biotikos" as opposed to "antibiotic" which denotes "against life" (Guarner et al., 2005). The idea that micro-organisms could be beneficial for human health was first developed by Elias Metchnikoff in 1900. He proposed that aging is caused by toxic bacteria in the gut and that good bacteria producing lactic acid could prolong life. At the time, Metchnikoff's theory was ground-breaking and later inspired others to begin investigating a causal relationship between intestinal health and micro-organisms such as bacteria and yeasts. This eventually led to the worldwide development, manufacturing, sales and consumption of fermented milk drinks and products, first in Japan, followed by Europe and the US (Ipa Europe, 2017).

Whilst the definition of probiotics has evolved throughout the years, the most recent and generally accepted among the scientific community, states that probiotics are "live microorganisms that, when administered in adequate amounts, confer a benefit to the health of the host " in 2001 by the Food and Agriculture Organization (FAO) and the World Health Organization (WHO), which was reaffirmed in 2014 (Joint FAO/WHO, 2006; Hill et al., 2014).

The "Biotic family". The biotic family is a group of dietary nutrients that can provide health benefits, such as gut health. Postbiotics are the most recent addition to the 'biotics family' that already consists of *Prebiotics* (food for 'good bacteria'), *Probiotics* ('good bacteria') and *Synbiotics* (a combination of food for 'good bacteria' and 'good bacteria').

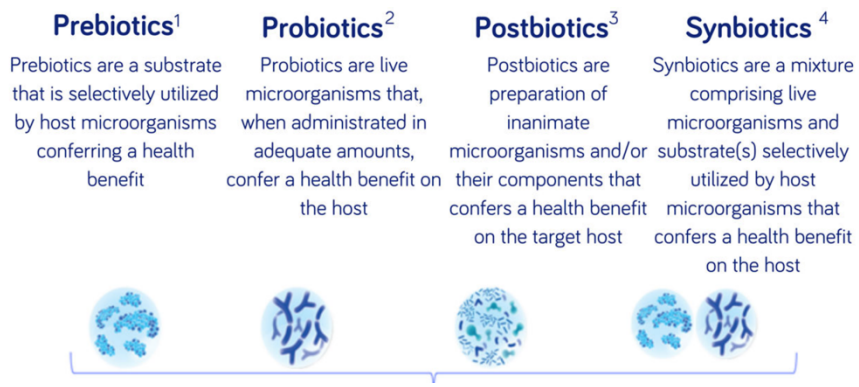


Figure 5.1. Biotic family (reference: https://www.nutricia.com/latest-news/postbioticsdefinition.html)

Fermented products are considered healthy and contain, due to fermentation, live micro-organisms that may be related to known probiotic microorganisms. Traditional fermented foods and the human gut was used to isolate *Lactobacillus* and *Bifidobacterium* strains (LABs), shown to provide probiotic benefits in good quality clinical studies. These strains have the largest coverage area with probiotic properties, as well as some members of *Bacillus* and *Escherichia coli* and yeasts (see ref. xx in figures). Probiotics should be considered as transient micro-organisms that have beneficial effects as they pass through the gut. The probiotic products may have added generic or documented probiotic strains or prebiotics. Generic probiotic strains include *Lactobacillus acidophilus*, *Bifidobacteria* and *Lactobacillus casei*. Documented probiotic strains are labelled with additional alphanumeric strain designation and include for example *Bifidobacterium BB-12* (Chr. Hansen) or *Bifidobacterium lactis DN 173010*, also known as Bifidus *ActiRegularis* (proprietary Danone, Activia), (Ipa Europe, 2021).

LABs have been listed either as Generally Regarded as Safe (GRAS) at the strain level by the United States Food and Drug Administration (FDA) or as Qualified Presumption of Safety (QPS) at the species level by the European Food Safety Authority (EFSA). A long history of use and their proved safety allowed their application as food or food supplements from a regulatory point of view (Martín & Langella, 2019).

Gibson and Roberfroid (1995) defined the term prebiotic as "non-digestible food ingredients or substances that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacterial species already resident in the colon, and thus attempt to improve host health" (Roberfroid et al., 2010). Examples include galacto-oligosaccharides (GOS), lactulose, inulin and fructo-oligosaccharides (FOS) which affect human health by keeping microbial populations balanced. Up-to-date research indicates that they can assist specific members of the gut microbiota and also probiotic microorganisms added from the diet, by helping them grow within the gut environment.

The mixtures of probiotics and prebiotics, referred as synbiotics or symbiotics "beneficially affect the metabolism of the gastrointestinal tract, thus improving the host immune system and welfare" (Roberfroid et al., 2010). A product can only be called synbiotic if it is perfectly characterised and has been proven to induce a beneficial effect greater than the sum of those generated separately by its component parts (Markowiak et al., 2017). Postbiotics were defined as a "preparation of inanimate microorganisms and/or their components that confers a health benefit on the host". Effective postbiotics must contain inactivated microbial cells or cell components, with or without metabolites, that contribute to observed health benefits (Salminen et al., 2021).

Some adjacent new fields to the mentioned above include Next-generation probiotics and Live biotherapeutic products (LBPs). The term "next-generation" probiotics refers to those beneficial species that make up part of the human gut microbiota (*Faecalibacterium prausnitzii, Roseburia intestinalis, Eubacterium spp., Bacteroides spp.* and *Akkermansia muciniphila*). It is only since "omics" technologies became available that organisms could be characterised as part of the community. NGPs are commensal bacteria and do not have a long history of safe use, and their safety is not thus considered as proven. Submission through GRAS, QPS, and novel food frameworks may enable a path to commercialisation, and for pharmaceutical

applications (O'Toole et al., 2017). Paraprobiotics (ghost probiotics) are "non-viable microbial cells (intact or broken) or crude cell extracts (i.e., with complex chemical composition), which, when administered (orally or topically) in adequate amounts, confer a benefit on the human or animal consumer" (Tavernity et al., 2011).

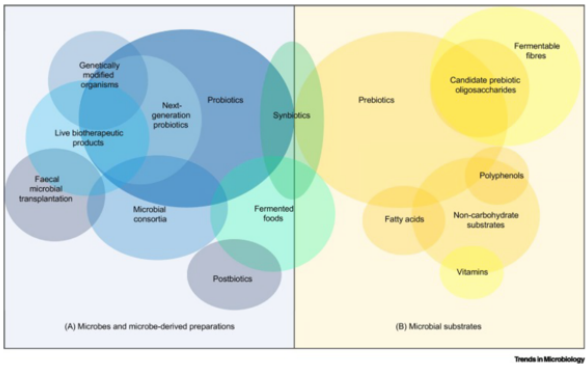


Figure 5.2. Probiotics, Prebiotics, and Adjacent Fields (reference: "Shaping the future of probiotics and prebiotics: Trends in Microbiology", 2021).

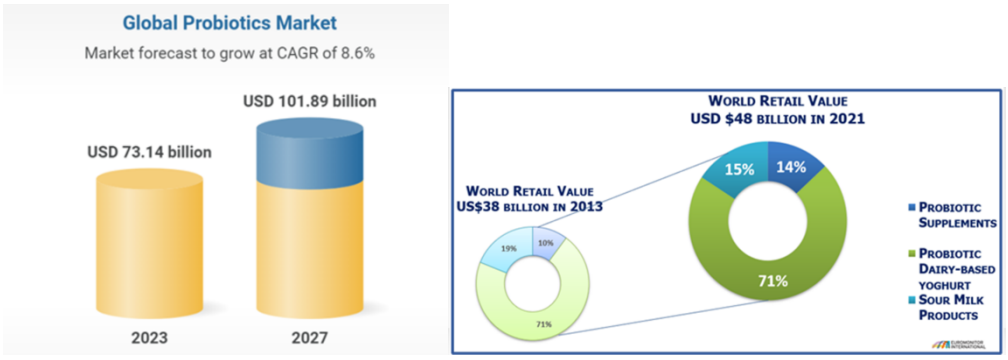
The broad spectrum of the term "probiotics" has led several scientists to introduce subdivisions and the corresponding new terms considering the potential illness or system targeted. A subset of probiotic products may thus target disease, i.e., they will not address the general population but patients with a specific disease amenable to be treated by a particular probiotic product. In this sense, one can mention for instance either "psychobiotics","immunobiotics" and "oncobiotics" to treat psychiatric illness, immune system conditions or cancer (Martín & Langella, 2019). The Food and Drug Administration (FDA) introduced the term LBP since 2010 and subsequently specified, to clearly distinguish between the drug and food categories, that a product that is no longer used as a food with specific characteristics of nutritional content, taste and flavour, but for other physiological purposes, becomes a drug. In 2019 the term was adopted by the European Pharmacopeia (Ph. Eur.) that recognise LBPs as medicinal products containing live micro-organisms (bacteria or yeasts) for human use. LBPs are being developed either as single bacterial strains or as multi-strain consortia (KTN Microbiome, 2021).

5.2. Probiotics Industry

5.2.1. Global overview

Probiotics present natural ways and safe alternatives to pharmaceuticals to maintain health and wellbeing, and probiotic foods and supplements can help support human digestive health and immune functions, thus contributing to general wellbeing. Probiotics can help restore and maintain the beneficial micro-organisms in our digestive system, as well as help to resist to the growth of harmful micro-organisms (Wang et al., 2021). Functional foods with probiotics domination were first commercialized and got approved health claims in Japan in the 1990s (Heasman & Melentin, 2001). In 2003 the probiotics market

in Western Europe was leading Japan at over US$4 billion with over $1 billion, while North America at under US$0.3 billion was an underdeveloped market (Euromonitor data on ipaeurope.org). The global probiotics market is continually expanding at an estimated annual rate of 7% and is worth approximately US$15 billion per year (Van den Nieuwboer et al., 2016). According to a new study by Research and Markets it grew to US$73.14 billion in 2023, as Asia Pacific dominated the industry in 2022 with a share of over 40.0%, followed by the US and Europe (Research and Markets, 2023, Probiotics market size).



A) B)

Figure 5.2. A) Global Probiotics Market (Research and Markets, 2023); B) Probiotic consumption share (Euromonitor, 2021).

Probiotics play an essential part in preventative and therapeutic healthcare. The human probiotics market can be broadly segmented by application into two categories: nutrition & wellness and therapeutics. The health and wellness segment comprise health-enhancing functional foods & drinks, nutraceuticals (supplements), personalized food and diet solutions, and medical foods. The therapeutics include medical devices, biotherapeutics and drugs (Grandview Research, 2023).

Functional foods and supplements. Probiotic yogurts are representing 70 % of the total market value of dairy functional foods, as sour milk and probiotic supplements take 15 % market share each (IPA Europe, 2021). The probiotic products are also incorporated by application in other dairy foods (infant formula, kefir, cheese), plant-based yoghurts and milks, non-dairy beverages (soy, oat, wheat, rice, probiotic fruit and vegetable drinks, wine, beer), baked goods, chocolate, cereals, pickles, some meat products, nutrition bars, ice-creams, dietary supplements and drug formulations (Fieldman M., 2016).

Food supplements contain probiotic cultures, usually in a dry form, and are formulated in an appropriate galenic form, e.g. sachet, capsule, drops or tablets. From 2009 to 2014, the supplement market grew by 37.2% and despite early interest in Japan and Western Europe, quickly became dominated by the U.S., which sustained a scalding 10% constant value CAGR from 2004 to 2016. There are nearly 5024 products globally, with 40 different probiotic species and 42 different delivery technologies – these very niche sectors within the probiotics space provide unique opportunities for suppliers and manufacturers looking to grow their share of the market (Lumina Intelligence, 2021).

Medical foods. They are formulated specifically to manage nutritional deficiencies that affect disease progression, tested for effectiveness in clinical trials and are used under medical supervision (Today's Dietician, 2012). Personalised diets and food for specific target groups are thought to be effective in helping manage Alzheimer's disease, heart disease, IBS, diabetes and depression among others (Grandview Research, 2017). There is a growing interest in the application of probiotic technologies in personalised medical foods which bridge the gap between a food and a pharmaceutical.

LBPs as a medicine. The therapeutic medicine is produced by the healthcare industry, in particular the microbiome industry, which is a nascent but rapidly developing field. LBPs are recognized as a new class of medicines which contains live organisms, such as bacteria. These probiotic drugs can prevent, treat and cure the disease conditions of humans and potentially transform how we treat many diseases. The reintroduction of probiotics as clinically relevant therapies re-establish and maintain a healthy balance in the gut. In particular, the first wave of pivotal clinical successes were concentrated on products for the prevention of recurrent *Clostridium difficile* infection (*CDI), (Peyton D & Badham C, 2022).* Rebyota, developed by Rebiotix Inc. and Vowst (Ser-109), developed by Seres Therapeutics became the first in class enema, respectively oral LBPs approved by FDA in 2022 and 2023. Rebyota was authorized for commercialization by Ferring Pharmaceuticals, and Vowst for co-commercialization by Nestlé Health Science and Seres Therapeutics (Microbiome Times, 2023).

Currently, there are several companies actively engaged in R&D to bring medical foods, biomarkers and new interventions, including probiotics, prebiotics, synbiotics, and novel live biotherapeutic products, as the U.S. is the leading therapeutic market, followed by Western Europe.

5.2.2. Region Insights - The European Probiotics Market

The most active area within the functional foods market in Europe has been probiotic dairy yogurts and milks. In 1997 these products accounted for 65% of the European functional foods market, valued at US$ 889 million). Between mid-1990s and early 2000, the European market had several established suppliers and manufactures of probiotic strains to be used as ingredients or ready probiotic solutions for their own brands or private label. Chr. Hansen launched successfully several LABs strains used in food and dietary supplements since 1995 (Johnson D. , 2017).

In 1986 Morinaga Milk (JP) launched its first probiotic yoghurt B'A with bifidus culture: B. longum BB536 and Yakult Honsha (JP) introduced "Yakult", a fermented-milk drink with with lactobacillus culture: L. casei Shirota in 1994 (Heasman & Melentin, 2001). Danone (FR) launched Activia (Bio) yogurt and Actimel fermented-milk drink, and Nestlé (CH) launched LC1 spoonable yogurt. Me-too products followed. Finland's largest dairy company Valio started to sign technology licenses for L. rhamnosus GG, and several companies in Europe and later in U.S. started to market own products ranging from yogurts, fermented milks to pharmaceutical products. Central to the development and growing application of probiotics and prebiotics, both individually and in combination were claims to

improve gut health and thereby general well-being, lowering blood cholesterol and strengthening the body's natural defenses (Young, 1996).

The most popular format, however, is the "daily-dose" drink, Danone (Actimel [DanActive in the United States]) and Yakult (both of which use a strain of *Lactobacillus casei*), which since 2001 became the market leaders. The functional dairy products with probiotics claimed health benefits for the gut health and digestion, lowering bad cholesterol and strengthening the body's natural defense mechanisms (Heasman & Melentin, 2001). BioGaia and Probi from Sweden contributed with new strains such as L. reuteri and L. plantarum 299v for development of dairy, probiotic-based fruit drinks and probiotic supplements first with gut health and then with wide range therapeutic applications (Heasman & Melentin, 2001).

Meanwhile, a small but growing number of life-science companies started to develop technologies that modulate the human gut, such as new and novel microbial strains, NEXT-GEN precision probiotics, active compounds and formulations for use as food ingredients, supplements with health benefits for a gut health and variety of other health applications (Heasman M.,2001). There was also remarkable repositioning by food companies, especially suppliers declaring their commitment and investments to health, nutrition and functional food development with probiotics, such as Danisco and DSM (nutraingredients.com., 2003).

Western Europe enjoyed a liberal marketplace starting in 2002, when it began allowing the free promotion of digestive health claims in probiotic yogurt (Feldman M., 2016). In 2002 and 2007, probiotic yogurt was the "driving force of overall yogurt in Europe", and the market saw over 18% annual growth between 2002 and 2003 (Euromonitor market data on ipaeurope.org; Feldman M., 2016). It doubled to almost US$6 billion from 2002, and until 2009 EU was the top market for yoghurts and probiotic supplements, leading Japan and the U.S., before the EFSA's new claims review policy took effect and ultimately resulted in the ban of health claim use in such products (Euromonitor market data on ipaeurope.org; Feldman M., 2016). Several existing companies within ingredient supply/distribution or agro-food created/enforced their Health & Nutrition Units to put focus on R&D of new and novel high-quality and well-researched probiotic strains supported by human clinical data, safe to consume, and IP and trademark protected, as well as improving the efficacy of the existing products. These are Danisco (DK, 2001), Chr. Hansen (DK, 2006), Gnosis by Lesaffre (FR, 2007), DSM (NL, 2007), BASF (GE, 2010), Nestlé (CH, Nestlé Research Centre, 2012), Danone (FR, Nutricia Research, 2013), (KTN Microbiome Innovation, 2021). During the period 2009-2016, double digit growth in probiotic sales has been recorded elsewhere in the world (+138,5% in North America, +74,9% in Asia Pacific area). Between 2012-2013, the worst year on record the probiotic market for yoghurts and fermented milk declined by nearly 8%, and 5% food supplements in 20 EU markets. By 2016 the dairy probiotics have lost more than €1 billion in projected sales (Euromonitor market data on ipaeurope.org). From December 2012, the terms "probiotic" and "prebiotics" were banned on packaging, prohibiting manufacturers to mention them and explicitly claim an associated health benefit (ipaeurope.org). Worldwide in 2012, probiotic supplements grew by 7.8% and became "the fastest growing supplements globally" (Euromonitor market data on ipaeurope.org).

Otherwise, probiotics supplements had a steady growth since 2001 with small but growing number of life-science companies, albeit not at the strong rates of yogurt, as consumer awareness increased (Feldman M., 2016). As probiotic yogurt has suffered a regulatory backlash, the producers of probiotics supplements in the region are capitalizing on new and novel microbial strains, NEXT-GEN precision probiotics, active compounds for the application, formulation and therapeutic expansion to other health benefits beyond gut health such as immunity and feminine health to generate and/or maintain sales. Newer probiotic health claims are mostly generated from the addition of synergistic ingredients (such as vitamin C for immunity) that have been approved by EFSA for health benefits (Feldman M., 2016).

The companies, most active in probiotic supplements with their country and year of establishment include: Winclove Probiotics (NL, 1987), Essum AB (SE, 1989), Bifodan (DK, 1992), Institut AllergoSan (AT, 1992), Protexin pharma (UK, 1998), The Healthy Bowels (UK, 1999), Astel Medica (spin-off from Univ. of Liège, 2000), Biosearch Life (ES, 2000), SOFAR S.p.A (IT, 2001), AB-BiOTICS (Spin-off from Univ. of Barcelona, 2004), OptibiotixHealth (2006, UK), BioCare Copenhagen (Dk, 2012), ImmuneBiotech (SE, 2013), TargEDys (FR, 2014), Mybacs (CH, 2018), (golden.com/search/probiotics).

Since 2018 the European probiotics market was on a growth trajectory and reflect the increased use of the term 'probiotic' in several European countries on label and communication. In 2020, the market experimented a shift to e-commerce sales, and this growth between 2021 and 2022 was driven by Europe globally. The track of the online sales shows that about 48% of the products are foreign, labelled with probiotic claims, as european consumers have become very engaged with pro/pre/post biotic products (source Lumina intelligence on ipaeurope.org).

5.2.3. Region Insights - The U.S. Probiotics Market

Before 2002 industry-wide probiotic sales figures were difficult to document in the U.S. There are many small probiotic distributors and a limited number of fermentation facilities. In most cases, probiotics are imported from outside the U.S. and then formulated and packaged in the county. Probiotics are difficult to promote. First, there are legal restrictions on labelling foods with statements related to health promotion. Claims for the prevention, cure or mitigation of disease are limited to the eleven which were FDA-approved. A claim about probiotics is not one of them. Structure/function claims are the domain of dietary supplements, a category of foods specifically defined in the DSHEA Act of 1994 (Sanders, 1998). A cleverly packaged yoghurt might be legally marketed as a dietary supplement if labelling requirements are met, but this approach may invite FDA scrutiny. Additionally, it is difficult to communicate the benefits of probiotic bacteria to consumers because they do not know what LABs are and feared them. There is a lack of scientific consensus on the benefits of probiotic cultures, especially when considering specific effects (Sanders, 1998).

Since 2002, in U.S. a decisive shift in probiotic consumption of yogurts and supplements by consumers occurred as both started to grow exponentially. An uptick in the official certification of active microbes in 2002 propelled yogurt to be marketed as a probiotic product. Much of the probiotic activity in

the U.S. was "crossover" from other regions. Cross activity from Europe was introduced by Nestlè (LC1 supplement) and Danone (Actimel, later renamed as DanActive, and Activia), and from Japan by Yakult (daily drink fermented milk shots). Probiotics awareness specifically received its first boost in the United States with the ubiquitous advertising for Dannon's probiotic-rich yogurt, Activia, in the early 2000s, by the actress Jamie Lee Curtis. Lifeway Foods, offered probiotic cultured non-dairy functional kefir beverages as food and a dairy functional kefir "Basics Plus" as an immune-supporting dietary supplement beverage (Klinegroup, 2016).

In 2005, in the US, probiotic bacteria are added to some fermented dairy products, such as yogurt, and are also sold as dietary supplement capsules. However, the US market for probiotics, especially in foods, is modest. The lack of scientific consensus on health effects contributes to hesitancy of US food companies to change this situation. (Vanderhoof & Young, 2008). The primary probiotics available in the United States are containing *L. acidophilus, Lactobacillus* GG, *L. reuteri, Bifidobacterium* species, and *S. boulardii.* A great majority of preparations include numerous combinations of commonly recognized healthy bacteria and the products that contain poorly defined or unidentifiable organisms. A major lack of knowledge exists, even among physicians, about the individual differences among bacteria (Vanderhoof & Young, 2008).

Beginning in 2007, more clinical evidence on health benefits, a deeper scientific understanding of the human gut microbiota, and higher consumer awareness on the health proposition of probiotics supplements has led to increasing sales. The U.S. market is becoming much more open-minded in terms of alternative therapies, including probiotics. In 2007, there were 300 probiotics available on the market. Probiotics supplements have seen the highest innovation in formulation, delivery forms, packaging and market positioning. In fact, probiotic supplements were expected to grow 60 percent between 2015 to 2020, compared to 25 percent for sour milks products and a small 4 percent for yogurt (Feldman M., 2016).

In 2010 the U.S. probiotic supplements market came over the sales of the EU market and became a leading supplement market globally (ipaeurope.org). It is consolidated with the combined revenues of the top three companies, Chr. Hansen, Danisco and Lallemand, which make up 70 percent of the total probiotic cultures market. Lallemand is a specialist in dietary supplements. Both Chr. Hansen and Danisco focus on food and dietary supplements. Global expertise, technical capabilities, own manufacturing facilities and sales have proven to be effective in securing market leadership for these companies (Rajagopal N., 2012).

Sixty percent of yogurt probiotic brands in the US are controlled by General Mills Inc., Stonyfield Farm and The Dannon Company. In contrast, the dietary supplement segment is fragmented due to low-entry barriers, attracting numerous supplement manufacturers and distributors. Probiotics are also gaining momentum in the oral care and nutricosmetic domain, although the biggest contribution of sales revenue of probiotics comes from dairy-based food products (Rajagopal N., 2012).

The markets for digestive probiotics and nutritional probiotics (with prebiotics and digestive enzymes) have grown by double digits and in 2013 include brands such as Align (Procter & Gamble), Culturelle (Royal DSM), Accuflora (Church & Dwight), Phillips' Colon Health and One-A-Day Trubiotics

(Bayer Group), Sustenex and Digestive Advantage (Schiff/Reckitt Benckiser), Centrum Pronutrients Probiotics (Pfizer), One-A-Day Trubiotics (Bayer), Nature Made Digestive Health Probiotics (Otsuka), and Provella (Upsher Smith). In the natural and specialty retail channels shelf-stable and refrigerated probiotics are popular with brands such as Ultimate Flora by Renew Life Formulas and Raw by Garden of Life. Strong promotion and advertising from manufacturers, coupled with consumers' increased acceptance and understanding of the many digestive and related health benefits of probiotic products, represents the successful recipe that continues to fuel sales of both current and newly launched brands. Probiotic beverages are the second-largest digestive health market segment, but also the fastest-growing segment. These include kombucha and kefir brands. While kombucha is made from fermented tees, kefir is available both as dairy-based and plant-based alternatives. PepsiCo Inc. with its Tropicana Essentials Probiotic juices, and the acquirement of KeVita company in 2016 became well-positioned (Kline Group, 2018).

While the EU market for probiotic yoghurts and fermented milk reported a significant loss in projected sales with more than € 1 billion during the period 2009-2017, double digit growth in probiotic sales has been recorded elsewhere in the world (+138,5% in North America, +49,1% in Latin America, +74,9% in Asia Pacific area), (Euromonitor data on ipaeurope.org). Until 2013 the U.S. yogurt market was growing and reached a top at $ 3.9 billion, but after this a weak decline in yogurt and steep increase in supplements led to narrowing the gap between both categories. Between 2013 and 2015 the U.S. became the largest growth market for probiotic supplements in the world in front of China and Europe. (Feldman M., 2016).

Increasingly, manufacturers are segmenting their probiotic lines to target individual consumer needs by offering a customized approach to digestive health and added benefits for other conditions. Brands such as Ultimate Flora by Renew Life Formulas and Dr. Formulated by Garden of Life offer products specifically for women, men, prostate health, and many other conditions. Family Flora markets pediatric probiotics, while Nature's Bounty launched new probiotics aimed at improving cardiovascular health and healthy cholesterol levels. Even CVS' private-label probiotics line includes several customized products, including immunity defense, aging, and active living formulations. Many probiotics make general claims as "support immune health" and "maintains digestive health", but all include standard disclaimer that "the claims have not been evaluated by the FDA. The product is not intended to diagnose, tret, cure, or prevent any disease." (Kline Group, 2018).

In 2019 well-established probiotics for the digestive health became Florastor by Biocodex, Florajen by Clarion Brands, Family Flora by America's Naturals, Renew Life, Digestive Smart, PARAzyme by Clorox Company, Renew Life, Doctor Formulated, Raw, Garden of Life, Primal Defence by Nestlé, Olly by Unilever (Mahecha L., 2019).

5.2.4. Comparison of the EU and the U.S. market for probiotics since 2021

In 2021 the global market for probiotic yogurt reached US$ 33.2 billion. The EU (Western Europe) ranks 2nd, after Asia Pacific with US$ under 4.8 billion, representing 25% of the global consumption. In

2021 the global market for probiotic sour milk reached US$ 7.42 billion. EU represents over 47% of global sales of sour milk, valued at € 3.0 billion in 2021. In 2021, the global market for probiotic supplements reached US$ 6.97 billion. The EU market ranks 3rd for probiotic supplements globally with around € 1.66 billion with a growth rate of 9% for the period 2018-2021 (ipaeurope.org). Italy is the 3rd largest market globally with US$ 750 million (€ 560 million) after North America and Asia Pacific. Italy, France, Spain, Germany and UK are the top markets.

The Europe's probiotic market is consolidated with a strong dominance of major players such as Yakult, Danone, PepsiCo, and others. Dairy products such as drinking fermented milks, and set yogurts and drinks dominate. The market's biggest players include Yakult, Danone SA, Morinaga, and Nestlé SA. The Europe Probiotics Market size is expected to grow from US$ 13.32 billion in 2023 to US$ 15.81 billion by 2028, at a CAGR of 3.49% during the forecast period (Mordor Intelligence, 2023). The U.S. market was valued at US$ 17.47 billion in 2022 (Grand View research North America, 2022). The sales of probiotic products in the US increased by 33% and continue to increase since the pandemic, as the consumers are inclined toward nutrient boosters to improve their immunity. (Mordor Intelligence, 2023). The market is highly competitive and fragmented with the presence of numerous players. The major players are focusing on expansion, new product launches, mergers and acquisitions, and partnerships, along with new product developments, as strategic approaches to boost their brand presence among consumers (Mordor Intelligence, 2023).

Currently, there are several companies actively engaged in R&D to bring medical foods, biomarkers and new interventions, including probiotics, prebiotics, synbiotics, and novel live biotherapeutic products and even re-formulate supplements to LBPs, as the U.S. is the leading therapeutic market, where the efforts of multinational companies are focused.

6. Innovation in probiotics

6.1. The European probiotics innovation system

New product development where probiotic is a functional ingredient leads to a product with a "border-line" status and represents a science-based innovation trajectory, carried out by a network of interrelated actors with various interests and perspectives. Figure 6.1., based on the model of Kuhlmann and Arnold, (2001) gives a simplified overview of the European probiotics innovation system with key components depicted in several blocks after analyzing various information collected through different secondary data. Though it is difficult to show all detailed linkages in the system, effort has been put to project the best scenario. In the NIS of Europe, there are four broad levels, viz. political systems, education and research, industrial system, and support services or infrastructure.

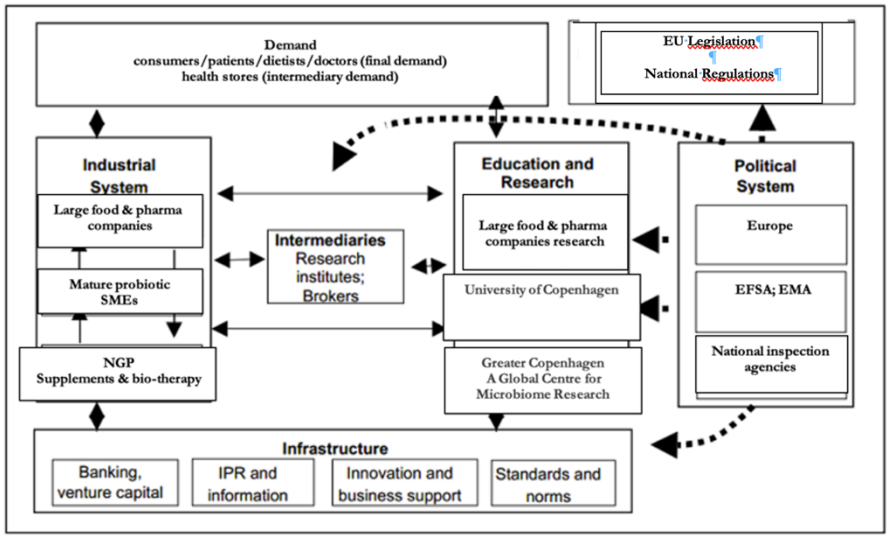


Figure 6.1. The European probiotics innovation system, based on the model of Kuhlmann and Arnold, (2001).

Political system. In Europe there are two main regulatory statuses for human health-related products: foods and pharmaceuticals, depending on the type of the claim of the product. European legislation for probiotics is not harmonized and they are regulated under both common directives and national regulations. Foods are assessed and evaluated by the European Food Safety Authority (EFSA). Drugs are evaluated by the European Medicines Agency (EMA). The European Commission takes the final decision on market authorizations and registrations (eur-lex.europe.eu.).

The two most common legislations regarding foods and drugs are Regulations and Directives. The General Food Law (Regulation (EC) No 178/2002) apply to all food products, and the regulatory status of their sub-categories lead to multiple legislations and laws. A directive 2002/46/EC apply only to food supplements and a Regulation on Nutrition and Health Claims (Regulation (EC) No 1924/2006, (NHCR) is applicable to all food and supplement developers who wish to claim specific nutritional or health benefits of their products. Drugs respectively comply with the human medicines regulation (directive 2001/83/EC with amendments), (eur-lex.eu.).

Industrial System. In the EU industrial system companies across the supply chain range from raw materials to microbial value-added ingredients to contract manufacturers, branded product marketers, distribution, retail and direct-to-consumer sales companies, stemming from different industrial backgrounds: food and agriculture, pharmaceuticals, chemistry, biotechnology, and personal care.

Besides a limited number of large multinational companies, producers of microbial starters and (novel) probiotics to other business (B2B) end-users (B2C) are mainly SMEs. Their competition is driven by the ability to deliver products with known and well characterized genomic sequences and proven safety, stability, and functionalities through manufacturing and storage. There are very clear trends that the large agro-food industries are moving their efforts increasingly toward added value products for specific target groups (people with obesity, cardiovascular problems, diabetes, high blood pressure, etc.) or even individuals. Food industry research programs slowly start resembling approaches used in the pharmaceutical

world, while pharmaceutical companies realize the potential of nutrition slowing down disease progression or improving therapeutic outcome. As a consequence, the demand for new and improved probiotic strains and starter cultures is expected to grow significantly (Genobox project, 2015).

Education & Research. R&D activities both at multinational companies and at smaller SMEs focusing on genome sequencing and annotation of microbial organisms are starting to play an ever more important role. The survival rates of probiotic strains are key for the success of any probiotic product, as they are strain specific and must be tested for each probiotics strain/dairy matrix (Genobox project, 2015). Strain selection being a critical aspect of developing probiotic-based functional foods faces problems from an industry standpoint, because strains cannot be easily produced industrially due to low yields in the growth media or poor survival to freezing or freeze-drying. Selection of strains needs to take into consideration factors such as safety, technology, performance, and health benefits. Strain selection must be made in light of the health claims that will be made or for the consumer group that is targeted, therefore, to use strains having demonstrated clinical effects is critical (Frost & Sullivan., 2009).

Multinational food companies possess necessary resources for product development and marketing as well as well-known brands. These companies also gain opportunities to differentiate and create competitive advantages if developing science-driven, higher-margin products in this segment, where retailers' private labels find it difficult to compete.

The key focus of the functional foods market in Europe has been the development of probiotic and prebiotic dairy foods, accounting for 65% of the total European functional foods market. Within this sector, probiotic cultures have been incorporated in yogurts and fermented milk products in mini-drink formats. Of all the dairy markets, that for yogurt with its existing health image, is well positioned to capitalize on the growth in healthful foods. Yogurt additionally benefits from being a food that tastes good and is enjoyable. Pro/Pre-biotic yoghurt comprises of all variants of dairy-based yoghurt with added generic or documented probiotic strains or prebiotics.

Leading players operating in the probiotic ingredients market are Chr. Hansen Holding A/S (Denmark), Koninklijke DSM NV (Netherlands), Archer Daniels Midland Company (US), Kerry Group (Ireland), International Flavors & Fragrances Inc. (US), Novozymes A/S (Denmark), Lonza (Switzerland). Chr. Hansen and Danisco (now acquired by IFF-DuPont) are the European and the world leaders in both the market of ingredients (starters and probiotics), claiming about 80% of total revenue. The annual turnover of these companies increases each year and a significant percentage of their turnover is spent on R&D (6% for Chr. Hansen and 7% for Danisco) which demonstrates the importance of R&D activities for these companies.

SMEs of biotech origin specializing in research, development and manufacturing of probiotic strains and customized formulations are Winclove Probiotics (Netherlands), Probiotical S.p.A (Italy), Probi (Sweden), BioGaia (Sweden), Protexin Healthcare (UK), Daflorn Ltd (Bulgaria), AB-biotics (Spain).

Pharmaceutical actors are also interested in the sector due to the shorter development time, lower product development costs compared to drugs and revenue stream to offset lost sales as drug patents expire

and new blockbusters fail to materialize. Furthermore, they also possess an established experience in clinical trials to substantiate health claims (Siró et al., 2008). Novartis, Sandoz, Menarini group, Bayer AG **,** Pfizer/GSK, Sanofi **all have** consumer health care unit and **probiotic supplements in their brand portfolio** with well-documented microbial strains**.**

The interest of microbiome is not limited to the scope of the Pharma industry, and the Food industry is actively contributing to the research on microbiome. Indeed, the Food industry holds a significant part in the emerging of microbiome clinical trials. However, since the reinforcement of the European Food Safety Authority (EFSA) regulation on health claims in 2012, the number of food clinical studies is stagnating. Yet some Food companies such as PiLeJe are developing their products as a drug and therefore follow the same path as Pharma companies with clinical studies to prove the efficiency of their products (Casal E at al., Biofortis Mérieux NutriSciences; Bévierre M-O. at al., Cepton Strategies. Microbiome times (2019).

Besides human health, another microbiome research area is emerging in the food industry, which is the food quality in the production plant. How to control the microbial ecosystems in food production to optimize sensory flavor of the products better? How to control spoilage bacteria? The Researchers in the food industry need to better understand the relationship between shelf-life and microbial behavior. Pharma and food industry interest in Microbiome and human health is booming. Europe is at the forefront of human microbiome research, as it promotes the emergence of new biotech companies and developing microbiome-based products (Bévierre M-O., 2018).

Research is conducted at the R&D units of private firms, departments at universities, public and private intermediary research organisations and centers/hubs, focused on microbiome, health, and nutrition, as well hospitals where the clinical trials are performed. Many food companies have science-based collaborations with universities and intermediaries (e.g. research institutes) to conduct well designed clinical studies to prove product efficacy and substantiate health claims, gain rapid access to new scientific and technological knowledge and to benefit from economies of scale in joint R&D. Universities are a strong educational and research partner, as health-related food, nutrition research and microbiome research are an expanding field (Moors E., 2012).

For strategic reasons companies also collaborate to combine research competences or market know-how, to share distribution channels or to protect (mutual) supply agreements. These collaborations can take various forms, ranging from contracts over licensing to joint-ventures are becoming increasingly important, for example in sharing the risks and costs of the research for the health claim dossiers (Moors E., 2012).

Universities are a strong educational and research partner, as health food, nutrition research and microbiome research are an expanding. **The multi-disciplinary microbiome hub** Greater Copenhagen's ecosystem includes 80+ companies, organisations, and institutions working actively within the field of the microbiome including top universities such as DTU Food, University of Copenhagen's Department of Food Science and Department of Nutrition, Exercise and Sports; Lund University's Department of Food

Technology, Engineering and Nutrition. The region's industry, academia and clinical environments collaborate across disciplines to bridge basic and applied science, and to establish connections and generate knowledge. All efforts have the ultimate purpose of enabling microbiome-based innovations for the benefit of health and the environment (microbiome-business. greatercphregion.com.)

The key organisations in Europe working to promote prebiotics and probiotics include European the Europe International Probiotics Association (IPA) and Dairy Association (EDA) IPA Europe represents the industry in discussions, institutions, and national authorities. The International Association for Probiotics and Probiotics (ISAPP) is dedicated to promoting the science behind probiotics. EHPM is the leading European trade association representing the health product manufacturers and distributors sector. EHPM helps in developing an appropriate EU-wide regulatory framework for its members' products and promotes industry best practices for product quality and safety. EHPM cooperates actively with the European Commission, the European Parliament, national governments, relevant trade associations and consumer groups, leading scientists and international contacts to reach consensus.

Infrastructure - funding. Funding mechanisms created by the EU and the European Commission to support and foster Research and Technological Development of functional foods (FFs) in the European Research Area (ERA) are the Framework Programmes (abbreviated: FP2-FP6). Since 2007 EU has given a special priority to the area of the microbiome and the live microbes to find applications and to generate more knowledge on the microbiome, nutrition, various hosts of microbes, and their relation to health and disease. 216 projects were funded under the FP7 (2007-2013) and Horizon 2020 (2014-2017) to promote metagenomics (genetic sequencing) and to advance the knowledge of microbes. Together, all projects related to the microbiome and probiotics involved an investment of more than €498 M. **Horizon Europe** with a budget of over €95 M will support further the R&I to foster advances in microbiome-related research (Hadrich D., 2018).

Besides EU-funded research, several national governmental and private initiatives are fostering R&D and product development within the microbiome. In 2013, the Flemish Government in Belgium allocated a budget of € 0.7 M to support an ambitious Flemish Gut Flora project. The MetaGenoPolis (MGP) project housed at the University of Lyon, France (2013-2017) has received a budget of € 19 M to develop microbiome-based therapeutic products from The National Institute for Agricultural Research and the French Initiative for Future Investments. The APC Microbiome Institute was established in 2003 as a partnership between University of Cork, industry, academia and other public partners. The institute is governing a € 70 M budget for 2013-19 from the Science Foundation Ireland and industry funding. The Germany federal state funded the Leibniz Institute on Aging with $6.2 M (€ 6.6 M) until 2019. In UK investments have been on the rise, with UKRI and BBSRC investing extensively in microbiome-linked diseases and nutrition research (BBSRC Funding - Quadram Institute of Bioscience with ~ $14 M).

Nestlé and Danone invested heavily in the R&D of foods fortified by medical technology and probiotics, targeting the gut microbiome in particular. In 2011 the Nestlé Institute of Health Sciences (NIHS) was set up on the campus of the Swiss Federal Institute for Technology in Lausanne, followed by

a clinical development unit in 2012. NIHS would develop the scientific basis for personalised nutrition in the areas of gastrointestinal health, metabolic health, and brain health and support product development for the Nestlé Health Sciences, a subsidiary also established in January 2011, which offers nutritional solutions for people with specific dietary needs related to illness, disease or the challenges of different stages of life.

Danone was investing significantly in R&D for specialised food products for target groups, such as babies or the elderly. In 2013 Nutricia Research Utrecht in the Utrecht Science Park was inaugurated to be the main development hub of the group in this field. In 2017 Danone was investing €240 M to build a new plant for its Early Life Nutrition business. In 2016, Nestlé invested in Enterome (FR), developing novel pharmaceuticals and diagnostics to support personalized therapies in microbiome-related diseases such as Inflammatory Bowel Disease (IBD), cancer and metabolic diseases. Enterome was backed by leading venture capital investors (Seventure Partners, Lundbeckfonden Ventures, Health for Life Capital & Omnes Capital) and strategic investors (Nestlé Health Science, BMS, Shire & INRA Transfert). This strategic investment would enable Nestlé to expand its microbiome portfolio ranging from diagnosis to therapeutics and nutritional therapies. Enterome has established partnerships with leading pharmaceutical companies and academic research institutes, including Johnson & Johnson Innovation/Janssen Biotech, Takeda and Abbvie in inflammatory bowel and gastro-intestinal diseases; Bristol-Myers Squibb in immuno-oncology; and the Mayo Clinic and Geisinger hospitals in metabolic disorders.

Microbiotica, a spin off form the the Sanger Institute in 2016 and a leading player in personalized microbiome-based therapeutics received a £4m investment from Seventure Partners in 2018. Until 2022 the firm completed a £50 M ($67 M) Series B financing round, which was the largest microbiome-related financing in Europe to date (uktech.news., 2022).

In 2020 Cargill (US) invested in the Health for Life Capital II fund with existing partners such as Danone, ADM and French Lesaffre. Seventure Partners and French institutional investors were committed to investing $5.8 Bn for microbiome innovation by December 2022. The French Microbiome Foundation funds several microbiome projects anually since 2011. UK companies such as Unilever, Reckitt-Benckiser, and Croda have made significant public investments in microbiome research, as several other European companies such as Maat Pharma, Enterome, and DeepBiome were leading in the microbiome therapeutics area (Frost & Sullivan, 2021).

6.2. The U.S. probiotics innovation system

Figure 6.2, based on the model of Kuhlmann and Arnold, (2001) gives a simplified overview of the US probiotics innovation system with key components depicted in several blocks after analyzing various information collected through different secondary data.

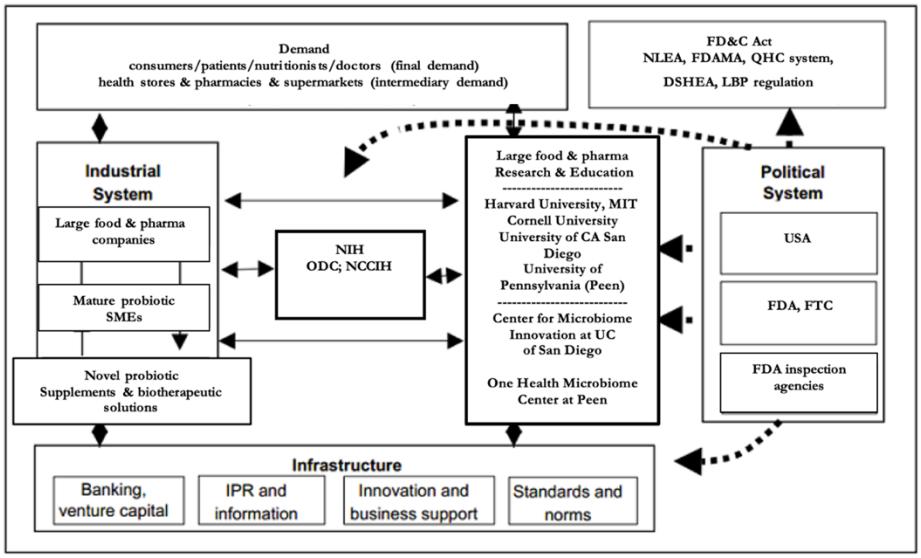


Figure 6.2. The U.S. probiotics innovation system, based on the model of Kuhlmann and Arnold, (2001)

Political system. In the political system the Congress is the lawmaking brunch of federal US government, while the US Food and Drug Administration (FDA) is the executive department responsible for the regulation and approval of all foods and drugs under The Federal Food, Drug, and Cosmetic Act (FD&CA) from 1938. It is a set of laws that authorize the FDA to oversee and regulate the production, sale, and distribution of food, drugs, medical devices, and cosmetics. The FDCA intends to protect the general public from adulterated and misbranded products manufactured and sold in the US (Lam C et al., 2022).
Under the U.S. legislation the probiotics regulation depends on the intended use and may be regulated as food, food ingredient, dietary supplement, medical food, live biotherapeutic agent and drug.

The Nutrition Labelling and Education Act (NLEA) of 1990, the Food and Drug Administration Modernisation Act (FDAMA) of 1997 and The system of qualified health claims (QHC) of 2003 are used to regulate the labeling of nutrient and health claims on foods and supplements (Lalor F. et al., 2011). In the US, dietary supplements are regulated by the FDA under the Dietary Supplement Health and Education Act (DSHEA, 1994) and the Federal Trade Commission (FTC) and need to comply the Good Manufacturing Practice guidelines (Brown, 2017; de Simone, 2019; Fusco et al., 2021). Under the DSHEA probiotics are considered 'Dietary Supplements' (DS) and regulated as grandfathered pre-DSHEA ingredient or a new dietary ingredient. 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 (FDA.gov, 2012).

Industrial system. The US industrial system include globally diversified players, regional players as well as many country-niche players having their own niche in food & beverages and probiotic supplements. There is a large number of startups and spinoffs currently in pre- and clinical stage development of biotherapies and supplements (grandviewresearch, 2021). The key focus of the functional market in US has been the development of probiotic supplements and live bacteria bio-therapies, although the biggest contribution of

sales revenue of probiotics comes from dairy-based food products. Sixty percent of yogurt probiotic brands in the US are controlled by General Mills Inc., Stonyfield Farm and The Dannon Company. (Rajagopal N., 2012).

Chr. Hansen (DK), Danisco (DK) and Lallemand (CA) make up 70 percent of the total probiotic cultures market. Lallemand is a specialist in dietary supplements and both Chr. Hansen and Danisco focus on food and dietary supplements. Global expertise and technical capabilities have proven to be effective in securing market leadership for these companies. All three also have their manufacturing facilities and sales established in North America (Rajagopal N., 2012).

Education & Research. The major players on the market, which are also recognized as the most prolific patent assignees in USA are Nestlé S.A., Groupe Danone S.A., Sanofi Aventis SPA. Chr. Hansen A/S, Unilever N.V., Kraft Foods INC, Danisco A/S, and Yakult Honsha Co. Ltd. Between 2007 and 2019 food & drink/nutrition companies occupied the top positions, perhaps because microbiome research has emerged in part from food and nutrition research over the last 20 years. Nestle (via its R&D subsidiary, Nestec S.A) became by far the most prolific patent filing organisation, followed by Nutricia (part of the Danone group specialising in infant nutrition). Pharma and biotech companies are also present on the market, such as Abbott from the big pharma space, and smaller biotech organisations such as Synthetic Biologics Inc, Seres Therapeutics Inc, Ixcela Inc, Microbiome Therapeutics LLC and Salix Pharmaceuticals Inc. Given that the technology area is still young, it is not surprising that biotech plays a greater role in the microbiome space than large pharma. At this point in the development of a novel technology space, pharma will likely be collaborating or investing in the biotech companies, but not necessarily undertaking in-house R&D, which has comparatively greater risk. Indeed this patent trend aligns with the growing importance of public-private partnerships and university spin-outs in progressing microbiome R&D.

The technology areas of interest include topical areas such as: Beneficial Gut Microbiota; Clostridium Difficile Associated Diarrhoea, early infant diseases and microbiota (such as Bifidobacterium lactis), the gut-brain-axis. Diseases of the gut such as Crohn's Disease, Ulcerative Colitis, Chronic Fatigue and Irritable Bowel Syndrome (IBS) are the most common therapies, followed by Clostridium Difficile Associated Diarrhoea allergy especially in the early infants, cancer diagnostics and cancer therapeutics, metabolic syndrome (including type-2 diabetes) and obesity. The past five years between 2016 and 2022 have witnessed a significant increase in the number of patents granted for novel microbiome technologies.

Academic and industry collaborations have boosted innovations and the launch of new microbiome-based technologies. Majority of microbiome patents are related to functional foods and include formulations using prebiotics and probiotics. Patenting in microbiome-based therapeutics is also on the rise, though patenting FMT (fecal microbiota transplantation) and other microbe-based drugs can be challenging. US is leading in the patent landscape, with the highest R&D innovation and commercial activity in microbiome-based technologies before Europe, China, Japan, and Australia. Looking at the filing of microbiome-related patents by geography, the United States is leading the way with nearly half of the patent fillings identified 307 out of 669 versus the European Patent Office with 61 filings out of 669.

An important intermediary organization is the National Institutes of Health (NIH), which is the primary federal government agency for biomedical research. In particular their office of dietary supplements (ODS) and National Center for Complementary and Integrative Health (NCCIH) have been involved with probiotics, providing a lot of information on their web pages to both consumers and health care professionals. (ods.od.nih.gov, 2023; nccih.nih.gov., 2023). In the US, dietary supplements are regulated by the FDA under the Dietary Supplement Health and Education Act (DSHEA, 1994) and the Federal Trade Commission (FTC) and need to comply the Good Manufacturing Practice guidelines (Brown, 2017; de Simone, 2019; Fusco et al., 2021).

In the United States, universities often form a core around which technology-based firms and research institutes gather in more informal localized innovation centers (OECD, 1997). Examples of the most active universities in the microbiome field include Silicon Valley in California (University of California San Francisco (UCSF) and University of California San Diego (UC San Diego), a Boston area (Harvard University and Massachusetts Institute of Technology (MIT) and a communications cluster in New Jersey (near Princeton University and the former Bell Laboratories), Cornell University, and University of Pennsylvania (Peen). The University of California San Diego (UC San Diego), its Center for Microbiome Innovation (CMI) and the Penn State One Health Microbiome Center at Pennsylvania State University are one the largest and most active units in the field, that cultivates and disseminates long-lasting microbiome applications and knowledge (Arial, 2022).

The key organisation in US working to promote prebiotics and probiotics include the International Probiotics Association (IPA). The Council for Responsible Nutrition (CRN) is the leading trade association representing dietary supplement and functional food manufacturers and ingredient suppliers. IPA created several task forces. The Codex Task Force is a long-term project (started in 2017) which include discussions within the Codex framework to build Guidelines and Standards for Probiotics that meet the FAO/WHO definition (2001 & 2002), for use in foods and dietary supplements. The intention is to work toward harmonization on a broader scale, including the many modern aspects of probiotics manufacturing, in addition to establishing unambiguous identification, characterization, safety, and efficacy.

The FSMA task force is a collaboration with the united Natural Products Alliance (UNPA) with the objective to create a FSMA model for probiotics. The Task Force Objectives include: (1) Explore integration points with existing training and/or certification programs and considerations for design of new ones for probiotic industry; (2) Evaluation of resources from IPA and exploration of new resources IPA can create to equip this task force with needed materials to support any training or certification programs; (3) Establish solid coordination and communication with FSMA personnel at Food and Drug Administration (FDA) within the U.S. Department of Health and Human Services (HHS); (4) Educating regarding compliance requirements for finished products, helping industry understand the extent of the exemption for supplement manufacturers and regulatory implications for ingredient manufacturers and foreign supplier verification programs.

IPA has also several committees. The Education & Communication Committee (ECC) recommends, develops and leads the education and marketing strategy to raise awareness, visibility and knowledge about probiotics among key stakeholders, reinforces the industry role of IPA, and increases demand for high quality probiotics. The role and function of the Manufacturing Committee is to help advance probiotic manufacturing standards within the probiotic sector by advocating on behalf of consumers and the probiotics industry, facilitating communication between industry members and regulatory bodies, and representing the industry on issues of interest/concern. The role and function of the Regulatory Affairs Committee is to help advance probiotic science with regulators by advocating on behalf of consumers and the probiotics industry, facilitating communication between industry members and regulatory bodies, and representing the industry with regulators on issues of interest/concern. Regulatory Affairs Committee speaks in the name of probiotic industry and is heavily involved in shaping regulations across the globe. The Regulatory Affairs Committee is the largest of the IPA committees, with a lot of industry representation. Several smaller task forces have been established from this committee to work on initiatives, including ANVISA and the U.S. Taskforce (for FDA).

In 2016 IPA has submitted a citizen petition to the FDA to require the labeling of probiotic ingredients in dietary supplements as colony forming units (CFUs) instead of by weight. IPA produced several guidelines such as guidelines to qualify a microorganism as probiotic (2017); the manufacturing guidelines (2019); best practices labeling guidelines for dietary supplements with the CRN, (2020) and regulatory manuscript (2022), (internationalprobiotics.org). Since 2023, the IPA scope expandes to include the '**biotics**', comprised of Postbiotics, Prebiotics and Synbiotics within the human, infant and companion animal segments of food and dietary supplements. The International Association for Probiotics and Probiotics (ISAPP) is dedicated to promoting the science behind probiotics.

Infrastructure – funding. The National Institutes of Health (NIH) is the primary federal government agency for biomedical research in the USA. In 2002 NIH invested €134 M on projects related to dietary supplements, but the support for the human microbiome field at NIH was modest at an estimated level of $5 M/year. NIH began a major initiative with the establishment of the 10-year HMP program, providing extensive support for human microbiome research with 21 of 27 NIH Institutes and Centers (ICs) funding this area through their extramural research programs.

The first phase Human Microbiome Project (HMP1) launched in 2007 focused on identifying and characterizing human microbiota. The second phase, known as the Integrative Human Microbiome Project (iHMP) launched in 2014 with the aim of generating resources to characterize the microbiome and elucidating the roles of microbes in health and disease states. Over 10 years (FY2007–2016), NIH provided ~ $880M of support in this research area, above the $215M invested in the HMP program from the start. By FY2012, NIH support for human microbiome research outside of the HMP eclipsed the annual HMP investment and reached or exceeded $100M/year due to the quick growth of research in the individual ICs (NIH team, 2019). The Danone Fellowship Grant was established in 2010 to provide funding for novel studies of yogurt, probiotics, and the gut microbiome. The 2022-2023 program marks eleven years and over

half a million dollars' worth of grants awarded to empower creative minds and nurture scientific advances (Hugnes L., 2023)

A second major American project, the National Microbiome Initiative (NMI) was launched in 2016 by the White House under the Obama administration. It was a consortium with the objectives of supporting interdisciplinary research, developing platform technologies, and expanding the microbiome workforce. Federal contributions to the project were around $121M over the next two years, and $400 million in total cash and in-kind contributions from 100 companies, foundations and academic institutions. Among these, the Bill and Melinda Gates Foundation of Seattle committed $100 M over the next four years to investigate and develop tools to study human microbiomes and whether the gut microbiome can be manipulated using microbial solutions to treat infections instead of antibiotics. JDRF dedicated $10 M for over 5 years to address microbiome research related to type 1 diabetes.

The University of California was funding $12 M in the Center for Microbiome Innovation to enable technology developers to connect with end users. One Codex was launching a public portal for microbiome data, allowing for researchers, clinicians, and other public health professionals to have more access to microbiome data. The BioCollective, LLC**,** along with the Health Ministries Network, were investing $250,000 toward building a microbiome data and sample bank and engaging underrepresented groups in microbiome research. The University of Michigan, with support from the Howard Hughes Medical Institute and Procter and Gamble, was investing in the Michigan Microbiome Project $3.5 M to provide new research experiences for undergraduate students. US has a remarkably high amount of federal funding towards microbiome products and enabling technologies. NIH has funded close to 3000 microbiome projects since 2018 with ~$3.5 billion (Handelsman J., May 13, 2016).

With research increasingly showing that the microbiome played a large part in overall human health, more startups were launching in the field and venture investors have pumped $1 billion into U.S. companies working on gut microbiome projects from 2015 to 2020 with over 100 deals, according to Crunchbase data (Hall C., news.crunchbase.com)

"In 2015, Nestle invested $65 million in the start-up Seres Therapeutics and took an 18% stake when the company went public. Within 1 year Nestle invested twice in Seres, the last for over $120 M to develop and commercialise medicines aimed at restoring a healthy bacterialogical balance in the human digestive system. "In 2016 "microbiome investment has surged again despite a decline in overall venture funding. The $616.9 M raised for microbiome companies to date so far in 2016 is more than all of the venture investment in the microbiome space in 2011 through 2015 combined," according to a Wall Street Journal article by Brian Gormley. In 2016 Johnson & Johnson subsidiary Janssen Biotech division paid as much as *$241 M* to the Boston, Mass.-based Vedanta *Biosciences* to take over the development a promising bacterial treatment as the company becomes the latest Big Pharma name to push into the microbiome therapy space" (McDermit R., 2015).

In 2018 Ferring Pharmaceuticals Inc. acquired Rebiotix and with several other alliances, [it] is a world leader in microbiome research, developing novel microbiome treatment for *Clostridioides difficile* (*C. difficile*)

is a bacterium that can cause CDI, a potentially life-threatening disease resulting in diarrhea and significant inflammation of the colon. RBX2660 is a potential first-in-class microbiota-based live biotherapeutic being studied to deliver a broad consortium of diverse microbes to the gut to reduce recurrent *C. difficile* infection. In the United States, CDI is associated with 15,000-30,000 deaths annually.

In 2022, the U.S. FDA granted approval of Rebyota to Ferring Pharmaceuticals Inc. as the first fecal microbiota product. Rebyota is approved for the prevention of recurrence of *Clostridioides difficile* infection (CDI) in individuals 18 years of age and older. It is for use after an individual has completed antibiotic treatment for recurrent CDI. The application was granted fast track, orphan drug and breakthrough therapy designations (press release on ferring.com., 2021). In 2023 the U.S. FDA granted approval of SER 109 to Nestle and Seres to be delivered through a pill ingested twice daily. SER 109 has been granted orphan drug and breakthrough therapy designations by the U.S. Food and Drug Administration for targeting multiple recurrent clostridium difficile, according to Seres' release. So that it can benefit from incentives such as protection from competition once on the market 7 years of the BLA application approval (Osborne R., 2023).

7. The role of Regulation in Probiotics

From the 1990s, an increasing number of scientific reports appear in the literature detailing the specific health benefits of probiotic micro-organisms; this led to an increasing clamour to allow the use of specific claims in the labelling, marketing and advertising of products containing probiotic micro-organisms. These considerations not only applied to probiotic products, but also encompassed the overall area of functional foods, which fall into the grey area between foods and medicines. As a reaction to this, some countries developed their own legislative systems to ensure food safety and consumer protection and to address the issues raised by this relatively new category of products. Inevitably, differences have arisen between the approaches used in different jurisdictions, and this chapter shall cover the approaches in two regions of the world, starting with the European Union (EU), and going on to discuss the United States (Tamime A. & Thomas L., 2018).

7.1. The legislative situation in the European Union

The EU's horizontal legislation considerations addressing aspects of food safety, novel foods and food ingredients, and food labelling shall be addressed before going on to deal with the regulation of nutrition and health claims. The latter have the greatest impact on probiotics products in the EU and shall be discussed in some detail (Tamime A. & Thomas L., 2018).

Relevant EU food safety legislation. Regulation 178/2002 lays down some general principles and requirements on food safety in the EU (EU, 2002). Article 14.1 of this Regulation requires that food put on the market should be safe. The Regulation goes on to specify that food safety in this context

encompasses short-term, intermediate and long-term effects on consumers, and also any possible effects on subsequent generations (through teratogenic effects). Prior to its adoption, food manufacturers were required to ensure their products met the specific requirements of EU legislation but, unlike the laws of an increasing number of member states, the law did not include the broad requirement that food put on the market should be safe (Tamime A. & Thomas L., 2018).

Novel food regulation in the European Union. The Novel Foods Regulation 258/97 (EU, 1997), which came into force on 15 May 1997, requires novel foods and novel food ingredients that have not been previously used to a significant degree within the EU to undergo a safety assessment before being placed on the market. One could have an interesting discussion on the precise legal meaning of the words 'significant degree' in the definition, but doubtless clarity on this shall emerge over time. The categories of foods listed in the scope of the regulation include novel food ingredients and novel food processes, as well as novel foods themselves. Up to the beginning of 2015, about 180 novel food applications were made, with about 80 such products authorised for use in the EU; however, only one of these applications and notifications relates to a probiotic product (Tamime A. & Thomas L., 2018).

Some milk products containing probiotics were on the market prior to the Novel Foods Regulation coming into force and so were not affected by this regulation, because commercial foods in use in at least one member state before the EU regulation came into force were allowed on the EU market under the 'principle of mutual recognition'. One example of such prior approval of a probiotic is the strain Lactobacillus rhamnosus GG, which was approved by the Advisory Committee for Novel Foods and Processes (ACNFP) in 1992 in the United Kingdom (UK) (Anonymous, 1992). It should be noted that its approval was as a novel starter culture and not as a novel probiotic. This was the first micro-organism to undergo a formal novel food evaluation by the UK ACNFP, and there was discussion in the Committee as to whether the proposed use was actually novel (Tamime A. & Thomas L., 2018).

GMO. Genetically modified organisms (GMOs) are organisms, such as plants, animals and micro-organisms, the genetic characteristics of which have been modified artificially in order to give them new or improved properties. To ensure the safety of GMOs, the EU has established a detailed legal framework covering the area. Given the controversy in recent years regarding GMOs, it is likely to be some time before probiotics developed using genetic modification will appear on the EU market. It has to be borne in mind that, as part of the selection and evaluation of probiotics, improvements of the performance of some of the strains are made; however, to date those that have been developed and are in use have been using non-GMO selection techniques (Tamime A. & Thomas L., 2018).

EU food-labelling provisions. Following much discussion and debate, a new regulation, Regulation 1160/2001 on the provision of food information to consumers, was adopted and published in November 2011 (EU, 2011). Among its purposes, this repeals the earlier food-labelling Directive 2000/13. This regulation entered into force on 13 December 2011 and its provisions applied from 13 December 2014; the provisions on mandatory nutritional declaration applied from 13 December 2016. This new regulation retained the provisions as regards the general principle underpinning food labelling that

purchasers must not be misled, including by claims that could mislead. Much more specific provisions on the subject of claims were addressed in the regulation on nutrition and health claims that had been adopted earlier, in late 2006 (Tamime A. & Thomas L., 2018).

EU nutrition and health claims. The regulation of nutrition and health claims in the EU has posed a major problem for many existing products, and in particular for probiotics since the late 1980s and early 1990s, at a time when nine of the then twelve member states had either national legislation or guidelines on claims. These national provisions gave rise to a situation that had the potential to create barriers to the completion of the open market. The EU Commission produced draft proposals for a regulation, which was worked on for some years, but this effort came to nought, foundering on the contentious issue of health claims. Some countries wanted a total prohibition on health claims completely, while others were prepared to accept them provided, they were subject to strict criteria. Barriers to, and difficulties in, intra-community trade continued to arise as a consequence, while 'health claims' continued to appear on foods, and some viewed them as a problem as they were unregulated (Tamime A. & Thomas L., 2018).

The legislative stalemate at European level acted as a stimulus to national authorities to produce quasi-legal 'guidelines' and "voluntary agreements." These initiatives were generally regarded as stopgap measures, until legislation was to be adopted at the EU level. Each EU Member State had its own regulation concerning nutrient and health claims on foods (Tamime A. & Thomas L., 2018). Sweden developed first its Code in the labeling of food with health claims in 1990. These health claims were related to diet-related diseases or risk factors in connection with the relevant nutrient in food. In the Netherlands, the Nutrition Centre (1998) in conjunction with regulatory authorities, industry and consumer organizations, implemented in their Code behind planned product-specific health claims on foods and drinks (Guittard C., 2006).

The Confederation of the Food and Drink Industries of the European Union (CIAA) developed a code of practice on the use of health claims in 1999 to help manufacturers from fifteen member states to prepare the documentation necessary for the substantiation of health claims, based on generally accepted evidence and to establish guidelines for clear and faithful communication of health claims to consumers. CIAA believed that the current legislation was inflexible and outdated, creating a lot of legal insecurity (Guittard C., 2006). By 2000 "Codes" were introduced in UK, Belgium, Finland, France and Spain (Swedish National Food Administration, 2000). The most liberal approach regarding health claims in the EU was in Finland, France and the UK. It was considerably more difficult to market a functional food product or supplement in Germany, Italy or Switzerland than it was in the UK or Sweden (Guittard C., 2006).

These codes all contain guidelines and conditions for the use of health claims. Some encourage companies seeking to make innovative health claims to submit full documentation of the scientific evidence that forms the basis of the claim to an expert panel for guidance and approval. Internationally and nationally, the regulatory framework for health claims is in a developmental stage. Although the evolving nature of the regulations makes it difficult to present a "snapshot" of the existing regulatory environment,

this review shows that the regulation of health claims on foods varies widely between countries and areas. Many countries neither prohibit nor regulate health claims; others prohibit claims; while some permit claims. Even then, the details of the claims permitted may differ between countries (Guittard C., 2006). Table 1 in the appendix illustrates the various approaches taken by different countries around the world.

At that time, food manufacturers had to meet very different legislative frameworks concerning approval of functional foods, the nutrition information required on labels and the types of health claims that were allowed. As a result, they had to expend much effort to arrange the marketing of their product properly in each Member State (Caduff and Bernauer 2006, Bech-Larsen and Scholderer 2007). The EU legislation on food labelling from 2000 (Directive 2000/13/EC, as amended) represented the first step of creation of EU harmonized regulation. However, it was only defining and allowing nutritional claims. The association of the food with properties about the prevention, treatment or cure of human diseases were forbidden. It was not clear what was meant about the ban on the disease claims. This led to the proliferation of the number and type of claims made on food labels, resulting in non-uniform health and nutrition claims in the EU. This has resulted in different approaches and in numerous discrepancies both regarding the definition of the terms used and the conditions warranting the use of disease claims (Guittard C., 2006).

Health claims (HCs) have proved controversial and difficult to regulate. Regulators must balance the potential to achieve public health objectives with the fact that health claims can deceive or mislead consumers if not based on scientific data clearly showing the link between a nutrient/food substance with health or disease. Even then, the form and words of a health claim may confuse consumers. But there is a general consensus among regulators that benefits asserted in health claims must be substantiated by scientific evidence. However, the actual process and standard of substantiation remaines a complex and controversial issue. What can be claimed for a product in one country does not automatically mean that the same can be said in another member state. This, combined with the fact that the far majority of consumers had little knowledge with respect to nutrition, required an EU wide visible ruling in order to make it as clear as possible to the average consumer (Guittard C., 2006). Table 2 in the appendix summarizes the various types of claims under consideration and their definitions (Codex Guidelines, 2007a).

The European Food Standard Authority (EFSA) was founded in 2002 and was mainly responsible for food risk assessment. Later EFSA was made responsible for giving scientific advice based upon scientific assessment of the beneficial health effects and associated risks related to food/food supplements intake, whereas the responsibility for risk management and communication was taken on by the European Commission and European Parliament (Tamime A. & Thomas L., 2018). Within European Union (EU) law the legal categorization of a nutraceutical is, in general, made on the basis of its accepted effects on the body. Food supplements are defined in Article 2 of Directive 2002/46/EC, as "Food stuffs the purpose of which is to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, marketed in dose form namely forms such as capsules, pastilles, tablets, pills and other similar forms, sachets of powder, ampoules of liquids, drops dispensing bottles and other similar forms of liquids and powders designated to be taken in measures

small unit quantities". Directive 2002/46/EC at present only covers vitamins and minerals, however, in the next few years the scope will be extended to include other ingredients that are present in food supplements including amino acids, essential fatty acids, fibres and various plants and herbal extracts (Coppens et al., 2006).

There is still very little harmonisation across the EU, particularly with regard to substances which are neither vitamins nor minerals. Botanical and probiotics sourced supplement ingredients are the subject of diverse national legislation. Probiotics are regulated by the Food Products Directive and Regulation if to be marketed as food supplement (Regulation 178/2002/EC; Directive 2000/13/EU) and under Herbal Medicinal Product Directive (2004/24/EC) if marketed as traditional herbal products. For the use of probiotic product as herbal medicinal product, it is recommended to apply and obtain a drug registration, or they will be transferred to the category of food supplements. Finally, registered drugs are covered under the Drug Law (65/65/EC, amended), (Coppens et al., 2006). "Legislation always runs behind reality". The problem of borderline botanical and probiotics sourced products is still not resolved and will remain unresolved, unless there is clear distinction between products defined as medicinal products (according to Directive 2001/83/EC or 2004/27/EC) and food supplements (according to Directive 2002/46/EC), (Keller, 2003, EMEA)

A process for the scientific substantiation of health claims (PASSCLAIM) has been developed to underpin the EU regulatory developments on nutrition and health claims. Through an iterative process of discussion in expert groups and workshops, a set of criteria which define requirements for assessing the quality of scientific data reporting the impact of foods and food components on health and well-being have been proposed and progressively refined. As a basis for the development of the criteria, seven comprehensive reviews were produced covering examples of areas of diet, health and performance in which health claims are likely to be made. An eighth paper reviewed existing processes and regulations. Started in 2001 and completed in 2005, PASSCLAIM has involved more than 160 experts from academia, industry, public interest groups and the regulatory environment. It has been supported by the Fifth European Community Framework Programme for Research and Technological Development and was co-ordinated by ILSI Europe (Aggett et al., 2005).

Major agro-food companies such as Danone, Yakult and Nestle became strong supporters of harmonized European regulation and evaluation of health benefits, because they saw it as a means of "disciplining the competition." A certification of their claims by health agencies, would erect a barrier to market entry for their competitors, to justify their higher prices, and thus finance their research efforts in probiotic product innovation. The uncertainties raised by the appearance of functional foods with probiotics did not only have to do with their regulatory status but also more generally with their health benefits. As the markets developed, it appeared increasingly necessary in the eyes of various actors to evaluate the legitimacy of these claims and making credible their claims to consumers (Nutra Ingredients, 2004). Eventually, in July 2003, the Commission published a new proposal for a regulation on nutrition and health claims, which was under discussion in 2004 and 2005. The resulting Regulation EC No 1924/2006

was finally adopted and published on 30 December 2006 and came into force on 19 January 2007. The original published version was corrected in early 2007, and two subsequent amendments were adopted in 2008 and another in 2010 (EU, 2006, 2008b, 2008c, 2010). Full implementation of all the provisions in this regulation is not scheduled until 2021, but an implementing Regulation 353/2008 was adopted in April 2008 (EU, 2008a).

The Regulation has been eagerly awaited by all parties involved, i.e. by consumer organizations, e.g. the European Consumers' Organization (BEUC) the food industry and the retailers, as well as by national authorities and the European Food Safety Authority (EFSA), (BEUC, 2006). The main objectives of Regulation (EC) No. 1924/2006 was to harmonize the different health claim regulations, replace the national regulations on health claims made on foods to ensure a high level of consumer protection (Asp NG., 2008). It aims to develop an approved list of EU-wide claims, which creates a level playing field on which food manufacturers can compete and innovate, backed by legal certainty, to ultimately bring benefits to the consumer. The Regulation makes approval claims open to use by all food operators. Claims based on proprietary data are reserved for the exclusive use of the owner of the data for 5 years unless, in the intervening period, they are independently substantiated on the basis of data from alternative sources (Binns and Howlett 2009).

The Regulation is mandatory for all new and existing health claims on products within the EU. All claims made in the labelling, presentation and advertising of foods and food supplements, including brand names had to be substantiated. The scope also includes food supplements, foods for particular nutritional uses, natural mineral waters and water intended for human consumption. (Tamime A. and Thomas L., 2018). A claim is defined as any message or representation which is not mandatory under EU or national legislation, including pictorial, graphical or symbolic representation in any form, which states, suggests or implies that a food has particular characteristics (EC 2006, Article 2.2.1).

While nutrient content claims had been addressed to some extent already, the regulation of the field of health claims at the community level was new. Health claims are only permitted if the following information is included in the labelling (or if there is no such labelling, in the presentation and advertising): (1) A statement indicating the importance of a varied and balanced diet and a healthy lifestyle; (2) The quantity of the food and pattern of consumption required to obtain the claimed beneficial effect; and (3) Where appropriate, a statement addressed to persons who should avoid using the food; and an appropriate warning for products that are likely to present a health risk if consumed in excess.

The Regulation defines three different claims: (1) A nutrition claim (NC) "states, suggests or implies that a food has particular beneficial nutritional properties due to the energy, nutrients or other substances provided, not provided or provided in reduced/increased amounts." (2) A health claim (HC) "states, suggests or implies that a relationship exists between a food category, a food or one of its constituents, and health." (3) Reduction of disease risk claim (RDRC) "states, suggests or implies that the consumption of a food category, a food or one of its constituents, significantly reduces a risk factor in the development of a human disease."

Types of health claims. HCs that describe or refer to the role of a nutrient/substance in body functions are called Article 13 claims and are further subdivided into Article 13.1 health claims and Article 13.5 health claims. HCs that refer to a reduction of disease risk, or claims referring to children's development and health, are called Article 14 claims. It should be mentioned that medicinal claims (MC), which claim that food can treat, prevent or cure any disease or medical condition, are still prohibited on foods; such medicinal claims can only be made for licensed medicines. Article 13.1 claims address HCs other than those referring to the reduction of disease risk and to children's development and health. These are based on "generally accepted scientific evidence", considered to be well understood by the average consumer and do not require a full dossier to gain approval. In mid-2006, the the Commission asked member states to submit a list of health claims under Article 13.1 made by the food industry within their jurisdiction, and to this end the competent authorities in each country contacted their food companies.

The deadline for the submission of these national lists was the end of January 2008. The EC received about 44,000, of which 400 for probiotics. By a process of eliminating duplicates and consolidating, the total number of Article 13.1 claims to be assessed was reduced to 4306. However, when claims on botanicals, numbering 1548, were put on hold by the Commission this left a total of 2758 Article 13.1 claims to be assessed. The EFSA opinions on the scientific evidence supporting these claims were published in batches, starting in October 2009 and ending in July 2011. By that time EFSA's panel EFSA's panel on Dietetic Products, Nutrition and Allergies (NDA) had completed its assessment of all the remaining 2758 of these claims and issued 341 opinions on them. Based on these opinions from EFSA, the EC and MSs authorised 229 claims or 5% (Hickey, 2014). Some types, or categories, of claims received a higher percentage of favourable outcomes than others (Hickey, 2014).

An earlier personal review and analysis of 2719 of these EFSA opinions indicated that, of the total, 478 (17.6%) received favourable opinions (i.e. that the claims submitted were borne out by the evidence supplied), while 2212 (81.3%) received unfavourable outcomes, with 30 (1.1%) receiving mixed outcomes. The latter cases are due to the grouping of a number of claims in a single opinion; some of the health claims therein have received favourable outcomes, while others received unfavourable opinions. The remaining 38 health claims relate to the roles of various vitamins, minerals and omega-3 fatty acids on various body functions, which had been evaluated in previously published EFSA opinions; thus, their outcomes cannot be readily analysed without identifying each of the corresponding earlier opinions and their outcomes (Hickey, 2014). Some types, or categories, of claims received a higher percentage of favourable outcomes than others. However, none of the opinions on 359 probiotic claims were favourable (see Table 3, appendix).

In 2012, the European Commission and Parliament promulgated 222 authorised food and health claims, and banned any other claim that was not on the list. Probiotic HCs applications, e.g. relating to improved gut or immune function, have been either rejected or withdrawn due to the uncertainty of the assessment of EFSA. The main reasons for submissions on probiotics receiving unfavourable opinions included: (1) Insufficient information to identify or characterise the substance or ingredient on which the

claim is based; only 13% of the microorganisms were characterised. (2) Insufficient scientific evidence to demonstrate that the claimed effect was beneficial to the maintenance or improvement of the functions of the body (non defined claims such as "gut health", "digestive health", "healthy microbiota", "natural defences" etc. were considered non-specific and non-measurable; claims such as "reduction of gastric acid levels", "reduction of inflammation" were considered with non beneficial physiological effect on population); (3) Lack of precision as regards the wording of the health claim being made (examples include claims using broad terms, such as claims on improved 'gut health'); and (4) Lack of sufficient human studies containing the necessary scientific data to demonstrate the claimed health benefit on human physiology and (5) In some cases, applications on well-characterized microorganisms were also rejected (EFSA meeting with IPA Europe, 2019).

Only one article 13.1 health claim that 'Live cultures in yogurt improve lactose digestion of the product in individuals who have difficulty digesting lactose for the microorganisms *L. delbrueckii subsp. bulgaricus* and *Streptococcus thermophilus* (minimum 10^8 CFU/g) was approved. The HC can be used where the specific cultures listed in the EFSA opinion are present. Overall, in both the first and second batches of opinions, almost all (95% plus) of claims relating to 'other substance' (non vitamin and mineral) claims have been rejected. More specifically: No single probiotic bacteria for digestive and immune health has yet been approved; More relevantly, all the rejected claims would then no longer be allowed to be used after a six month transition period from the decision date published in the Official Journal (anticipated in January 2011).

Article 13.5 claims are of a similar nature to the Article 13.1 health claims but are based on newly developed scientific evidence and/or applications that contain requests for the protection of proprietary data. Up to October 2016, the EFSA panel had evaluated 112 applications; those receiving unfavourable opinions included seven milk-based or enriched-milk products, of which four were probiotic-containing products. Of the total Article 13.5 claims assessed, only four (3.6%) EFSA opinions were favourable for the proposed claims (EFSA, 2016). None of these favourable claims concerned milk-based products or probiotics (see Table 3, appendix).

As mentioned, Article 14.1 includes two types of health claims: (a) reduction of disease risk claims, and (b) claims referring to children's development and health. Article 14 claims are assessed individually and are not grouped or consolidated. To October 2016, 37 Article 14.1(a) health claims have been evaluated, including two that are related to probiotics. Fourteen (37.8%) of these were approved, but not those related to the two probiotic claims. A total of 56 Article 14.1(b) claims were evaluated, including nine related to probiotics. Twelve (21.4%) of the claims were approved but, again, none related to probiotics (Table 5.4). It is noted that International Probiotics Association (IPA) Europe, the European chapter of the IPA, established in Brussels in 2015, claim that more than 400 applications were submitted to EFSA (Thomas, 2016).

Furthermore, since no probiotic claims have been approved and under a 2007 interpretation of the EU Nutrition & Health Claims Regulation 1924/2006, on the basis of these negative opinions, the

European Commission even banned the use of the term probiotics and prebiotics, declaring it a health claim in corporate communications aimed at consumers concerning these foods and dietary supplement products since December 2012. Not surprisingly, the consequences for the market for probiotic dairy products in the EU are quite serious. It is interesting to compare the claims made on the labels of some probiotic fermented milk products on the UK and Irish markets in 2005 (Table 4, appendix) with the label statements made on the same, or similar, fermented milk products on the same markets in 2016 (Table 5, appendix). It will be noted that any references to probiotics have been removed in 2016, but the presence of named cultures is still acceptable. Where health claims are made, these now relate to the presence of named vitamins, and use approved wording for the relevant Article 13.1 claims.

Nonetheless, it has been estimated that the probiotic yoghurt industry in the EU, which had grown by an average 5% per annum from 2000 to 2012, declined by 8% in 2013 and may well lose up to €1.5 billion in revenue by 2020 unless the regulatory situation is resolved. This contrasts with continuing steady growth in other regions of the world (Thomas, 2016). The European Medicines Agency (EMA) was not more open to probiotic-based drugs or medical devices. A few probiotic drugs or medical devices had been marketed well before the introduction of any European marketing authorisation procedure. The EMA has even turned down flat industrial firms requesting guidelines for the development and assessment of probiotic-based drugs, arguing that they did not have enough marketing authorisation requests to open investigations in this area (Nouguez E., 2021).

The Pharmabiotic Research Institute (PRI) was founded in 2010 as Europe's leading gut microbiome regulatory science expertise center to support the development of microbiome-based medicines for the EU market, for the benefit of patients. It applies a unique 'Share & Learn' approach to overcome the complex and various regulatory challenges faced by the relevant stakeholders. Its overall mission is to facilitate the conversation between European regulators and Microbiome medicinal product developers and their partners, and to become the key network driving the new therapeutic and diagnostic innovation in the field of microbiome science (pharmabiotic.org. In contrast to the United States, the European Medicinal Agency (EMA) has yet to produce specific guidelines if probiotics have to be authorized as medicinal product (Cordaillat-Simmons et al., 2020). Importantly, in 2019, the European Pharmacopoeia (European Pharmacopoeia Commission, 2019) released the first guideline dedicated to "medicinal products containing live microorganism(s) as active substance," which are not acting as vaccines, and decided to name them "Live Biotherapeutic Products" (LBPs). It now defines the category at the EU level and provides the standards applicable for the production and quality control of these products (Cordaillat-Simmons et al., 2020).

Prompted by a restrictive interpretation of the term "probiotic" as a health claim and the absence of a legal /regulatory definition of "probiotics" the Internatonal Probiotics Associaton finally opened its European office in 2015. Its mission became: to gain the acceptance of the term "probiotic" throughout Europe as a defined category, and to create a favorable environment for probiotics (ipaeurope.org). The

lack of clarity at EU level has led Member States to adopt different national approaches to allow the use of the term, thereby creating potential adverse effects to the functioning of the European Single Market.

Since 2018 some EU member states, such as Italy and Czechia adopted national guidelines developing certain requirements for qualifying specific strains as probiotics as factual information. Italy reasserted the validity and proportionality of their approach to recognize the "effectiveness" of the probiotics in physiological terms and pointed out that the indication of a probiotic to promote the balance of intestinal flora is in accordance with their guidelines and is not a health claim (IPA Europe European legal framework, 2023). In 2020, the Spanish Agency for Food Safety and Nutrition accepted the term "probiotic" on food labeling produced and commercialized in the country. In 2021 the Netherlands released the "Nutrition and Health Claims Handbook", providing clear indication on the use of the term Probiotic in the Netherlands. The term "probiotic" can now be used in mandatory information, to identify the categories of micronutrients or substances that characterize the product in food supplements. In 2021 Denmark released new guideline in allowing the term "probiotic" as mandatory on food supplement labeling. In 2023 France also clarified that 'probiotic' is considered as a "non-specific health claim" which is allowed if accompanied by a specific authorized claim related to the probiotic action in food. In the case of food supplements, the term 'probiotic' can also be used as a category name to characterize the nature of the substances used in the product (IPA Europe European legal framework, 2023).

"These member states are taking a different position opening a small door to probiotics by distinguishing 'probiotics' as just a category from a real health claim," the 2006 Commission guidance is no longer acceptable, particularly compared to the regulatory approaches adopted outside the EU (Katia Merten-Lentz, a lawyer at the Brussels and Paris Bars & expert on the matter, 2023). In several third countries, like the US and Brazil, probiotics are already considered food or as ingredients, while Canadian authorities even allow the use of health claims about microorganisms represented as 'probiotics' on food labels and in advertising. Likewise, third countries like India, Argentina, and Thailand have adopted specific probiotic regulations and definitions for probiotics (IPA Europe European legal framework, 2023).

In 2022, The IPA Europe together with the European Dairy Association **(**EDA), made a joint statement and asked for a clear engagement of the European Commission and stakeholders on the use of the term probiotic on labelling and communication towards consumers in Europe. ***I***nternational Life Sciences Institute (ILSI Europe "task force probiotics"), the European Federation of Associations of Health Product Manufacturers (EHPM) and Food Supplements Europé (FSE) all stay behind. *'We call for action on the part of the European Commission and relevant stakeholders to build a coherent and consistent framework in Europe, to alleviate avoidable legal burden, with the goal of enhancing the functioning of our European Single Market'.* Building a comprehensive framework will result in trustworthy and accurate information being featured on labels and in other communications to consumers, pursuant to the Regulation on the provision of food information to consumers (FIC, EU 1169/2011), (IPA Europe Joint statement, 2023). *The European probiotic sector needs to become again the driving force for innovative products that add value to human wellbeing, and to contribute to the growth of the European economy (*IPA Europe Manifesto, 2021).

The latest development on the 'probiotic' term saga comes from the Fit for Future (F4F) platform, an advisor body of the European Commission consisting of representatives from member states, other EU institutions, and stakeholders which delivers opinions for simplification, burden reduction, and modernisation of existing EU laws. In a set of suggestions to the EU executive released in December 2022 the platform called on the Commission to "consider appropriate actions to provide for a harmonised implementation and enforcement of the rule guiding industry stakeholders to uniformly implement EU rules related to probiotics content of food products." According to the advisory body, "both consumers and industry will benefit from a harmonised approach," as different national interpretations of the term 'probiotics' might put the internal market at risk of fragmentation.

In a recent survey with 8,000 consumers in eight different European countries conducted by 3 GEM on behalf of the International Probiotics Association – Europe (IPAEurope), revealed the evolution of European consumers' opinions, trends and behaviours regarding probiotic foods and supplements and showed a strong interest in overall health and well-being. It also highlighted the fact that 79% of consumers would like to be more informed on the labelling and in communications about probiotic food and food supplements, and about probiotic microorganisms in food and food supplements. 57% of those surveyed did not feel informed that a product contains probiotics. "Contacted by EURACTIV, a Commission official said that the EU executive is aware that one of the suggestions made in the opinion of the F4F platform concerns probiotics are but did not comment further" (Fortuna G., (2023).

7.2. The legislative situation in the U.S.

As is the case with the EU, the USA does not have any specific legislation on probiotics. The US Institute of Medicine of the National Academy of Sciences has defined functional foods as 'any modified food or food ingredient that may provide a health benefit beyond the traditional nutrients it contains'; however, this is not a legal definition. The approach to regulation is again focused on the area of health claims (Tamime A. and Thomas L., 2018).

In the United States, the US Food and Drug Administration (FDA) is responsible for the regulation and supervision on foods and drugs. All food products, including functional foods, are regulated by the Federal Food, Drug and Cosmetic Act. The United States does not have a category of foods that is called "functional foods", "nutraceuticals" or any specific legislation on "probiotics", like in Europe. In the US, probiotics can be given the status of a biologically active dietary supplement (BAS), a food ingredient, medical food or a live biotherapeutic product (LBP), which is a medicine, depending on whether they are intended for use by healthy or sick people (see figure 1 in the appendix).

Respectively Probiotics are regulated by three different FDA centers: FDA's Office of Dietary Supplement Programs, or ODSP, FDA's Office of Food Additive Safety, or OFAS, or FDA's Center for Biologics Evaluation and Research, or CBER (Yunes RA., 2022). Most probiotics used as food ingredients in the United States have not gone through the approval process before being marketed because they fall under

the GRAS (Generally Regarded as Safe) program and are recognised as completely harmless for human. GRAS status is granted automatically to the substances that have been used historically as food constituents before January 1, 1958. The International Dairy Federation (IDF) has established a list of organisms with a documented history of safe use as the components of food products in their Bulletin No. 377 The Inventory of Microorganisms with a Documented History of Use in Food (Mogensen G., 2002).

Regarding the registration of food supplements in the United States, under the Dietary Supplement Act (DSHEA), food additives used before October 15, 1994, are automatically approved for production. The Council for Responsible Nutrition (CRN) has compiled a list of approved supplements which were in use before October 15, 1994. The strains isolated after October 15, 1994 should be registered as a new dietary ingredient (NDI) (Dickinson, A., 2011). The registration of probiotics in the United States is regulated by the Federal Food, Drug and Cosmetics Act (abbreviated as FFDCA, FDCA or FD&C) (Gilsenan, M.B., 2011).

The FDA has defined four categories of foods: Conventional Foods, Dietary Supplements (i.e. intended to supplement the diet and marketed like conventional foods, although they also have to be labelled as dietary supplements); Foods for Special Dietary Use (i.e. intended to supply particular dietary needs for physiological conditions, overweight, food allergies and infant formula); and Medicinal Foods (i.e. intended for dietary management of a specific disease, under the supervision of a doctor or another health professional). In theory, probiotics could fit into any of the above-mentioned categories but, to date, none would seem to be used in medical foods, and there are very few applications for their use in foods for special dietary purposes. A number of conventional foods contain probiotics, and these are mainly dairy products, such as yoghurts, cultured milks, milk and Cottage cheese. However, the National Yogurt Association has introduced a voluntary Live Active Culture seal for products that contain live starter cultures, and this requires refrigerated yoghurt to contain 10^8 colony forming units (cfu) g^{-1} and frozen yoghurt 10^7 cfu g^{-1} at the time of manufacture. These requirements do not apply to the levels of other cultures named on the label (Sanders, 2003).

Now, however, the main market for probiotics in the USA is in dietary supplements, and they are sold in the form of pills, capsules, powders and drinks. The reason that so many probiotics are sold as dietary supplements would appear to be that prior approval of structure/function claims is not required for this category.

Claims and labelling in the U.S. The FDA currently uses three sets of legislation documents and interim procedures to determine which claims can be used in labelling for a food or dietary supplement:

(1) The Nutrition Labelling and Education Act (NLEA) of 1990 allowed health claims on labels or labeling of food or dietary supplement labels, such as 'any substance that expressly or by implication characterises the relationship of any substance to a disease or health-related condition (US Congress, 1990). Such claims on foods are subject to pre-market authorisation by the FDA, based on extensive review and evaluation of scientific evidence via petition or on its own initiative, based on "significant

scientific agreement" (SSA) standard to determine whether the substance/disease relationship is well established.

(2) The Dietary Supplement Health Education Act (DSHEA), which was enacted in 1994, created another category of statements, generally referred to as 'structure/function' claims that may be made for dietary supplements (US Congress, 1994). The manufacturer is responsible for ensuring the accuracy and truthfulness of these claims; the FDA does not approve them. For this reason, the law stipulates that if a dietary supplement label includes such a claim, it must state in a 'disclaimer' that the FDA has not evaluated the claim. The disclaimer must also state that the dietary supplement product is not intended to 'diagnose, treat, cure or prevent any disease' because only a drug can legally make such a claim. Some report that this requirement is not always followed in practice (Berner & O'Donnell, 1998).

(3) In 1997, the Food and Drug Administration Modernisation Act (FDAMA) provided a second, more quick way for health claim to be used only on foods, but not on dietary supplements (US Congress, 1997). The health claims are based on an "authoritative statement" (AS) from the National Academy of Sciences or another scientific body of the US government.

(4) Since 2003 the USA also has a system of qualified health claims (QHC) under interim procedures, based on scientific evidence below the SSA standard on (a) good to moderate (b) low and (c) a very low level. Only QHC may be made for dietary supplements, as a result of the US federal Court of Appeals case of Pearson v. Shalala. This court decision requires the FDA to allow appropriately QHC that would be misleading without such qualification.

As with approved health claims, qualified health claims should also be based on a relationship between a substance and a health-related condition. In common with all health claims, qualified health claims require that a petition (i.e. an application) be submitted to the FDA. An enforcement discretion letter is issued by the FDA if it does not object to the use of the claim specified in the letter, provided that the products that bear the claim are consistent with the stated criteria. The FDA is committed to having all letters of enforcement discretion posted on their website. Once the letter is posted on the website, all manufacturers are informed how the FDA intends to exercise its enforcement discretion on the use of the specific qualified health claim. The scientific support for qualified health claims does not have to be as good as that for health claims with the SSA standard. The criteria for the scientific review are described in the FDA interim guidance (FDA, 2011). As of late 2016, the USA has 15 qualified health claims (see Table 8, appendix).

Nutrition and health claims in the USA fall into three categories:

Health claims: These describe a relationship between a food, food component or dietary supplement ingredient, and reducing risk of a disease or health-related condition. Nutrient content claims: These describe the level of a nutrient or dietary substance in the product, using terms such as 'free', 'high' or 'low'; or they compare the level in a food to that of another food, using terms such as 'more', 'reduced' or 'lite'.

Structure/function claims: These describe the role of a nutrient or dietary ingredient intended to affect normal structure or function in humans, for example 'Calcium builds strong bones'. They also may characterise the means by which a nutrient or dietary ingredient acts to maintain such structure or function, for example 'Fibre maintains bowel regularity' or 'Antioxidants maintain cell integrity', or they may describe general well-being from consumption of a nutrient or dietary ingredient.

At present, the FDA has approved 12 health claims or nutrient content claims for foods that meet the Significant Scientific Agreement (SSA) standard (see Table 6, appendix) and five FDAMA health claims, authorised based on an Authoritative Statement by Federal Scientific Bodies, (see Table 7, appendix); some of these apply to dietary supplements as well as conventional foods. As well as the requirements for approved claims, the FDA has detailed the requirements for the food making the claim, the food claim requirements and model claim statements. Full details of these claims can be found in the Code of Federal Regulations and in Appendix C of the Food Labelling Guide (FDA, 2009).

The Federal Food, Drug, and Cosmetic Act (the FD&C Act) requires a person or firm that markets a dietary supplement with certain types of claims in the product labeling to notify FDA about the claim within 30 days after first marketing the dietary supplement with the claim. The labeling claims include: (1) structure/function claims (defined as a statement that "describes the role of a nutrient or dietary ingredient intended to affect the structure or function in humans" or "characterizes the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function"); (2) general well-being claims (a statement that "describes general well-being from consumption of a nutrient or dietary ingredient"); and (3)classical nutrient deficiency disease claims (a statement that "claims a benefit related to a classical nutrient deficiency disease and discloses the prevalence of such disease in the US").

In the USA legislation, there is no explicit recognition of any benefits of functional foods as such. Some contend that statements that a probiotic "helps proper digestive function" would be SFC and not necessarily HC; but if claimed "helped reduce the risk of cancer", that would be a health-related claim and, thus, subject to FDA approval (Berner & O'Donnell, 1998).

Some products sold as dietary supplements make structural/function claims, such as 'when taken daily, helps fortify your body's natural defences and helps keep your body at its best' (Actimel, Danone), and 'Helps create a favourable environment for the growth of beneficial flora, which dramatically influences metabolism and physical well-being' (Acidophilus, Cell Tech) (Sanders, 2003). Structure/function claims have historically appeared on the labels of conventional foods and dietary supplements. The Dietary Supplement Health and Education Act of 1994 (DSHEA) established regulatory procedures for such claims for dietary supplement labels (although they can be applied to conventional foods also).

As structure/function claims are not FDA approved, there is no definitive list of such claims. However, such claims may: (a) describe the role of a nutrient or dietary ingredient intended to affect normal structure or function in humans (e.g. 'Calcium builds strong bones'), (b) characterise the means by which a nutrient or dietary ingredient acts to maintain such structure or function (e.g. 'Fibre maintains bowel regularity' or 'Antioxidants maintain cell integrity'), (c) describe general well-being from consumption of a

nutrient or dietary ingredient, and (d) describe a benefit related to a nutrient deficiency disease (like vitamin C and scurvy), as long as the statement also tells how widespread (or otherwise) such a disease is in the USA.

Although structure/function claims do not require pre-approval by the FDA, they must be truthful and not misleading – the manufacturer is responsible for ensuring the accuracy and truthfulness of these claims. The FDA must be notified of dietary supplement claims within 30 days of their first use. If a dietary supplement label includes such a claim, it must state in a 'disclaimer' that the FDA has not evaluated the claim – such a disclaimer is not required on conventional foods. Structure/function claims and disease claims for conventional foods focus on effects derived from nutritive value, while structure/function claims for dietary supplements may focus on nutritive as well as non-nutritive effects. The FDA is likely to interpret the dividing line between structure/function claims and disease claims in a similar manner for conventional foods and for dietary supplements.

The role of the Federal Trade Commission (FTC) and legal challenges. The FTC was established under the Federal Trade Commission Act of 1914 and commenced in early 1915. It has two main purposes: to protect consumers and to promote fair competition. Its role is to protect consumers by preventing unfair, deceptive or fraudulent practices. It challenges companies and individuals that break the law. Its remit covers all business activities and is not confined to food trade matters. It also develops rules to ensure a vibrant marketplace, and educates consumers and businesses about their rights and responsibilities (Tamime A. and Thomas L., 2018). It challenges companies and individuals that break the law. Its remit covers all business activities and is not confined to food trade matters. It also develops rules to ensure a vibrant marketplace and educates consumers and businesses about their rights and responsibilities.

In 2010, it challenged the Dannon company on health claims it was making in the advertising of its DanActive probiotic drink (that it reduced the likelihood of getting colds or flu) and its Activia Yoghurt (that it was clinically proven that if eaten every day, it would help regulate the digestive system in 2 weeks). Dannon agreed to settle FTC charges of deceptive advertising and to drop claims that allegedly exaggerated the health benefits of the two products. Dannon also agreed not to make any other claims about the health benefits, or effectiveness, of any yoghurt, dairy drink, probiotic food or drink, unless the claims are true and backed by competent and reliable scientific evidence. It was noted that while companies usually do not need FDA approval of their health claims to comply with the FTC Act, it strongly recommended that FDA approval of such would help companies avoid such problems. The FTC pointed out that the complaint was a finding that Dannon had actually violated the law and the settlement reached did not constitute admission of a law violation (FTC, 2010).

Another feature of the USA legal system is the use of class actions. A class action is a case in which a group of people, with the same or similar complaint caused by the same product or action, sue the defendant as a group, or the case is taken by an individual on behalf of the group. In 2015, an individual took a case in a US District Court in California against Yakult USA Inc., alleging that the company breached

California's Unfair Competition Law by deceptively claiming that its probiotic beverages containing Lb. casei Shirota helped balance the digestive system which, therefore, supports overall health.

Examples from the website and three advertisements of Yakult were also submitted as evidence. In January 2016, the judge in the case ruled that the plaintiff lacked the necessary standing to seek an injunction on behalf of the putative class because he failed to allege or offer evidence of future harm, as he was unlikely to purchase the product again (Anonymous, 2016). Understanding that he could not proceed with his original case, because he had no intention of ever buying Yakult again, the same individual sought to rectify his problem by buying Yakult again some 10 days after the original hearing and stapled a copy of his receipt to the motion.

The case was heard by the same judge, who ruled that this newly alleged intent to buy Yakult was nothing more than a barely disguised attempt to manufacture standing and dismissed the case (Nakamura, 2016). It is worth noting that this case was decided on the standing of the plaintiff and not on the validity or otherwise of the health claims made for the product.

So what is the situation as regards labelling and marketing claims for probiotic milk based products in the USA at this time? The challenges include conveying the benefits of a food or dietary supplement containing probiotic organisms to avoid wording claims in a manner that would be viewed by the FDA as unauthorised health or drug claims; also, in determining if there is sufficient scientific evidence to support petitioning the FDA to permit a health claim or qualified health claim describing the relationship of a food containing a specific species and strain of probiotics to reduction of the risk of disease.

To date, the answer to this latter question appears to be no. It would be desirable to encourage the FDA to provide specific guidance on substantiation for structure/function claims and health claims for probiotic foods and dietary supplements. Some believe that the problem is the approach of the FDA Center for Biologics Evaluation and Research (CBER) to probiotic research. Their basic role is to evaluate biological drugs, so when they see the word 'probiotic' on a food product, it seems they automatically think 'drug'. The consequence of this is that probiotic drug development in the USA is alive and well, but probiotic foods, and researchers who want to study them, continue to suffer (Sanders, 2012, 2014).

It would be desirable to encourage the FDA to provide specific guidance on substantiation for SFC and HC for probiotic foods and dietary supplements. Some believe that the problem is the approach of the FDA (CBER) to probiotic research. Their basic role is to evaluate biological drugs, so when they see the word 'probiotic' on a food product, it seems they automatically think 'drug'. The consequence of this is that probiotic drug development in the USA is alive and well, but probiotic foods, and researchers who want to study them, continue to suffer (Sanders, 2012, 2014). As a matter of fact, in 2010, the FDA was the first competent authority to propose to consider the status of medicinal products containing live microorganisms used to prevent or treat diseases in humans. In 2016, FDA published guidelines for LBP production. According to the FDA, a product may be classified as an LBP if it contains living organisms, may be used for prevention and treatment of a specific disease or disorder in humans, and is not a vaccine (Paquet, J.C., 2021).

The United States National Institutes of Health (NIH) currently approve LBPs for the treatment of gastrointestinal diseases and allergies, dental disorders, diseases related to the gut-brain axis, and others. In brief, to register a new LBP, a positive balance of benefits and risks should be demonstrated. Proof of the positive benefit/risk balance should be derived from reliable and validated preclinical and clinical trials. The benefit/risk ratio is the basis of a product registration application. Clinical trials are studies conducted in humans that aim aim to evaluated the safety and efficiency of medical, surgical, or behavioural interventions. It is the key commonly accepted methodology to determine whether a new treatment, in the form of a new medicine, diet, or medical device, is safe and efficient when used for humans.

8. Relationship between Regulation and Innovation

Regulation has long been a counterpart of innovation in the health care industry, and recent cases have demonstrated that appropriately designed regulations can both coexist with and promote innovation. Pelkmans and Renda (2014) state that regulations can exert a profound impact on innovation activities in specific sectors as well as in the economy as a whole. If regulatory efforts wish to boost innovation, measures such as harmonization, streamlining and introducing fair competition can be adopted (OECD, 1995). According to Menrad (2004), however, the opposite is more often true, since innovation in the food industry is usually impeded by the institutional framework tied to implementation of regulations. As mentioned earlier, companies may face compliance challenges and seek knowledge from external sources.

Innovation in the health-care sector contributes to health promotion and disease prevention, especially chronic lifestyle-related diseases in aging populations, with the resultant reduction of public health-care costs (Christensen et al., 2009). In most industrialized countries, policy makers strictly regulate this sector to protect the safety and health of consumers. Although regulations can increase costs, restrict firms' freedom of action, and hinder innovation well-designed regulations can induce investment in innovation, process implementation, and new product releases (Palmer et al., 1995; Porter et al., 1995). Thus, regulation has either positive or negative aspects for innovation depending on the characteristics of the business or the technology (Onodera et al., 2018; Blind et al., 2017). To promote innovation, policy makers must understand the multifaceted nature of regulations and design them appropriately to stimulate the market and benefit consumers.

Efficient regulation can help introduce innovation in the health-care sector (Porter et al., 1995). The Japanese regulatory system for foods with health claims (FHC) was introduced in 1991 and the net sales of the FOSHU products were the highest in 2007 at 6.2 billion dol-lars (110 JPY/USD), half of the health claims related to improving gastrointestinal tract (GI tract) health using probiotic lactobacilli, oligo-saccharide, and dietary fiber (Sato et al., 2023). With the lowering or removing of barriers to competition, deregulation often stimulates the market entry of new competitors with alternative technologies or business models (Song et al., 2017).

For example, regulatory reforms implemented by the U.S. FDA have driven the growth of FDA-approved mobile medical apps (Onodera et al., 2018). This suggests that regulatory health-care reform, when properly implemented, can stimulate innovation in technology and the delivery of health care. Introduced in 2015, the less rigid FFC system in Japan, which complemented the FOSHU system was intended to stimulate the health food market through deregulation and result in food products that could potentially promote health, mitigate lifestyle-related diseases, and reduce health care costs for consumers. The clear labeling of nutritional or health information is intended to facilitate consumers' ability to take a proactive approach to their health care and make more informed choices. After the introduction of the new system, many New Functional Foods have been developed because of the more flexible health claims compared to FOSHU and the lack of a requirement for governmental approval. As a result, sales of New Functional Foods reached US$ 1.8 billion in 2018 and are still increasing (Sato et al., 2023).

From the viewpoint of the health food industry, deregulation was intended to reduce companies' costs and risks of product development (Shimasaki et al., 2016; Yuda et al., 2017). In the FFC system, the Japanese government does not evaluate the safety and effectiveness of function claims, and thus has reduced the cost of the process by adopting a notification system with the responsibility of the operator as part of the administrative procedure. Thus, the FFC system not only provides more information about functional food products to consumers but also helps small companies develop functional foods (Tanemura et al., 2017; Yuda et al., 2017; Farid et al., 2019). The FFC system accelerated the entry of new competitors into the market, with the goal of increased market growth. Under the FFC system, the government certified many product health claims - including those related to eyes, joints, mental stress, cognitive function, sleep, physical fatigue, and obesity - that had not previously been approved under the FOSHU system (Yuda et al., 2017).

This raises the question as to how the challenges related to the NHCR have affected innovation and the demand for external knowledge in the EU food sector. The research performed by Moors (2012) revealed many impacts of the Regulation EC 1924/2006 on functional food innovations. Within the functional food industry high development costs seemed to be an important challenge. Furthermore, the data showed that the companies followed either an early mover or a product follower strategy. Regarding the authorities, legal uncertainty reduced when the EU legislation moved towards harmonization and increased transparency. From the demand side, consumer scepticism regarding functional foods had to be overcome in order to increase consumer understanding and acceptance.

High development costs. The new Regulation influences how the food innovation process is organized, thereby influencing development time and development costs, especially when costly and lengthy clinical trials need to be done. Several respondents signalled that the cost of substantiating a health claim and building an accurate dossier is a serious hurdle for innovation. The cost of bringing a novel food to the market varies considerably (globally between 4 and 24 million €, inclusive of R&D costs); there are global regulatory requirements (safety, efficacy studies costing 0.5-4.5 million €) and EU-specific regulatory

costs (i.e. in addition to meeting common requirements of most regulatory systems: 0.3-0.75 million €; CIAA 2009).

The functional ingredient producers play an important role regarding health claims. These companies deliver the ingredients including a health claim and often take care of the health claim dossier. Manufacturers of functional foods for the supermarkets buy these ingredients and add them to their products (e.g. Omega 3 being added to a dairy drink). However, the functional ingredient producers are often SMEs and do not have the resources to submit new health claim dossiers.

The new Regulation affects SMEs relatively more than larger companies. As their turnover is low (< 2 million €), the new regulation on claims will have significant impact on the end cost of the product. The costs of health claim dossiers may be too high for SMEs, accounting for 99% of Europe's food operators, because of their lack of financial resources (FoodDrinkEurope 2011). Furthermore, the large companies also fear the risk to the image of the established brands, if claims prove not to be supported or product performance falls short of expectations (Binns and Howlett 2009). Therefore, a main problem for functional food manufacturers is the return on investment. Required health claim dossiers imply additional development costs, which are lost if the health claim is not approved. Even if the health claim is approved, the question remains, according to several respondents, whether or not the sales on the relatively small European market, compared with the largest and oldest functional food market of Japan, followed by the United States (AGNS 2007), in terms of functional foods consumers, are high enough to earn the investments back.

Furthermore, the small, specialized supplier of functional ingredients expected that the R&D budget will be allocated differently in the future. Some ingredients may not have market potential without claims. These products might be cancelled before reaching the market. The large dairy product manufacturer indicated that they focused on a smaller number of products. As a result, the pipeline was filled with fewer products, but with a stronger market potential owing to the substantiated evidence for the health claim on these chosen products.

Early mover or product follower strategy. Despite high development cost, products with new health claims remain attractive. They provide an "early mover advantage" to companies that market the product first, which may result in higher sales and market leadership. However, it may be easier to follow the product leader when the specific health claim cannot be protected and generic products might appear very shortly after market launch of an inventive product, according to the large food manufacturer.

Since all authorized claims, other than those dependent on protected proprietary data for their substantiation, will be available for everyone to use, generic products are mentioned as a threat to the operator's returns on investment. This makes product imitation more attractive than searching for new health claims. In that case, the product followers use the product leader to collect more information and to observe whether or not the claim is approved and what the market potential of the food product is. This may decrease financial risk. Developing a generic product may imply lower development costs, because the claim may be already on the EU Union List, and there may already be more scientific evidence available.

As a result, a decrease of product innovation and an increasing number of product-followers might be expected.

Legal uncertainty. Delays in claim approval procedures of two to three years provide major disincentives to innovate and bring a product to the EU market, as the industry's return on research investment can be marginal. EFSA uses strict approval criteria and only a few dossiers for new health claims (Article 14) got a positive recommendation. At the moment, the proportion of existing health claims that will be banned from the market is still uncertain, pending the final EU list of claims. The proportion of new health claim dossiers that will get a positive recommendation of the EFSA and will be approved by the EC is also uncertain. Some companies mentioned that after the new Regulation the pipeline was filled with fewer products, but the products had a stronger market potential because the evidence for the claim on these chosen products was more extensive as time and effort were more concentrated.

None of the investigated companies raised their R&D expenditures on functional foods. This may be related to the high legal uncertainty currently. Some respondents of both large and small firms stated that they had reconsidered their investments in new health claims owing to the uncertainty about the feasibility of the health claim dossier and the returns on investment. The two large companies interviewed stated that they may not invest or may less invest in new health claims if the EFSA remains as strict as it is at the moment. The smaller companies stated that they cannot afford these kinds of health claim dossiers anyway and will not develop new claims. For food operators with products carrying claims that do not meet the nutrient profiles on the EU List, there will be a need to reformulate or remove these products from the market. The problem continues to be that it is not exactly known what the profiles will be, so reformulation has to wait. For new product development this means that nutrient composition is at best a guess until at the very least the EU List with Article 13.1 claims is available. Food manufacturers call on the Commission to meet the legal obligations of the Claims Regulation without delay to provide legal certainty to operators in the application of claims on their products. Legal uncertainty adds costs and loss of market opportunities (up to 5 million € in some cases). The current system favours followers or secondary applications that can avoid regulatory costs and time delays (CIAA, 2009). Some companies are changing the recipes of their products. Others have decided to focus more on a smaller product portfolio to spend more time and effort in substantiating the health claims with a greater chance of claim approval. In that way the new regulation framework is forcing companies to improve or change existing products or product ideas and design in the early stage of innovation. However, many food companies are not taking any action now. They are waiting for the EFSA and the end of the transition period. When the uncertainty is reduced, companies may start to adapt their strategies, products and processes.

Harmonization and the efficiency of procedures. The aim of the harmonized Regulation EC 1924/2006 was to create bigger market potential, as the product can be brought on the market in all Member States based on the same documentation, and more efficient procedures by decreasing development time and costs. Before this Regulation came into force, food operators needed to negotiate market-by-market to seek approval to market an innovative product with a health claim, and in some cases

no health claims were permitted. With the new Regulation, food operators only need one approval that covers all EU Member States. However, non-uniformity can also be advantageous because it gives companies the opportunity to enter the market first in countries with less strict criteria for functional foods. All the respondents indicated that they had specialists involved in regulation. The information needed was obtained from governments, food industry associations and relevant websites. Most of the companies were already familiar with previous food regulation and the new EU Regulation was regarded as a follow-up step. Many companies continuously monitor the regulatory requirements and integrate the latest requirements in their product development cycles.

The large manufacturer of dairy products had changed its intellectual property (IPR) strategy to secure the returns on investment; the other respondents had not changed their IPR policy. The respondent from the specialized supplier of functional ingredients stated that patents do not make any sense for the protection of health claims, because the claims themselves cannot be patented and become public information because they are on the label. If a company cannot substantiate their health claims, they might leave the functional food market and focus on other food products. Their products might be "selected" away by preferred products with a health claim. Companies whose health claims are no longer approved will have to find alternative ways of marketing their products and advertising health benefits to consumers, with fresh innovative packaging or product label design, new tastes and slogans that fall outside the scope of the EU health claims regulations. Product differentiation could then be achieved through the inclusion of special ingredients, even without making specific health claims. Claims can be made in different ways, for example, by combining ingredients with approved health claims with other ingredients (NPI 2011). Summing up, products without scientifically substantiated health claims are selected away. This will make it more difficult for free-riders to market their products (Pennings 2012). In this way, the harmonized EU Regulation itself may become a selection mechanism in innovation.

Transparency. Customers of companies demand ingredients and products with health claims. Health claims offer functional food companies the opportunity to differentiate their products on mass markets, adding value to them, so reinforcing their competitive position. By establishing a Community procedure for evaluation of claims and a register for those assessed to be valid, the Regulation provides an even playing field for all food operators, reducing the possibility for large companies to gain credibility for claims solely from their larger market presence (Binns and Howlett 2009). The food industry asked for more dialogue and greater guidance for applicants and the EFSA is now organizing scientific stakeholder meetings, an essential step to ensuring applicants know what is expected of them (CIAA 2010). Currently guidance is also being developed on how authorized claims can be used by Member States. This could provide greater clarity and legal certainty for stakeholders, including the consumers. Industry is not totally reliant on approved health claims and can increase market share by marketing products without claims via smart media offerings (Binns 2009). Some companies apply creative marketing techniques using vague fantasy claims (such as "super fruit"), implying that the product is extra healthy, without claiming anything. In the current regulatory framework, this might occur more often in order to avoid costly and lengthy

health claim procedures and to sell products without a health claim, which does not improve the transparency for consumers.

Consumer understanding. The issue of consumer interpretation of nutritional information has received considerable policy interest. In the new EU Regulation the evidence for consumer understanding of nutrition and health claims is a prerequisite in the claim approval process, next to trustworthiness (i.e. scientific substantiation of the claimed benefit). From a consumer protection point of view, this is an important milestone in nutrition and health communication at the European level (Van Trijp, 2009). After all, the new Regulation avoids consumers spending unnecessary money on products that do not have an additional effect. Regarding health-enhancing functional foods, it is important for consumers that the information is easily accessible. Consumers like to obtain the proof of safety and efficacy of a functional food product from an independent scientific organization, such as the EFSA. Furthermore, regarding trustworthiness of claims, there is a consumer need for an independent quality symbol on the packaging. Reliable information about functional food products should be given by general practitioners, dieticians and TV programs about product quality and comparisons (Moors et al., 2009).

A food market in which available health claims are scientifically substantiated and effectively communicated to consumers guarantees transparency and informed choice and creates a level playing field for fair competition among food operators, further stimulating innovations in the food industry (Van Trijp, 2009). Successful functional food products are then those that are presented to consumers in a form that meets their perceptions and expectations with regard to traditional food characteristics (i.e. the consumer tendency to prefer naturalness in their food, associating "active" components with risk), and communicates the additional health benefits consumers can expect to obtain in a user-friendly context. The challenge is to re-establish the perceived value of food in general by improving its quality with regard to both taste and nutritional value (Binns, 2009). According to Asp (2009), one of the key challenges and opportunities for functional food innovation is to add functionality to traditional foods in such a way that they retain their appeal, and yet deliver added benefits.

9. Implications for management (and/or policy)

Regulation (EC) No 1924/2006 on nutrition and health claims made on foods ("NHCR") governs the use of such claims in labelling, presentation and advertising. In its Preamble, the NHCR aspires to facilitate informed choice, alongside the protection of consumers and the encouragement of legitimate business in the food industry. The following impacts of the Regulation EC 1924/2006 on probiotics sector innovations are revealed.

Lack of transparency. EFSA hasn't been transparent with industry about what they're looking for. The agency made it unnecessarily difficult for companies to know what information to provide in order to gain approval, and where there has been guidance it's invariably come too late. In 2008, the European Commission issued guidance that indicated the authority would reject outright any scientific health claims dossier that didn't contain human clinical data. The instructions came too late for many probiotic food

companies who were already in the process of submitting their claims, as human studies can take three or more years to complete (Vogel, 2010).

The lack of clear criteria and standards on when to classify probiotic products as drugs and therapies, foods or wellness products led to confusion for innovators as to which regulatory pathways to follow. According to industry, probiotics are not drugs and they're not nutrients: they fall somewhere in between. However, EFSA was taking a pharmaceutical approach, and the standards of evidence that went along with that approach were too high, particularly if looking at healthy populations.

Understanding what constitutes sufficient evidence to determine the safety and/or efficacy of microbiome-based products was not straightforward. As it can take 10-15 years for a disease to develop, and the study participants are free of disease at the baseline, it's not surprising or particularly informative to see no benefits after several years of supplementation. It's pulling probiotics out of context and treating them like drugs, which no one is claiming they are. It's also not taking into consideration nutrition science in its entirety. But the absence of data from clinical trials hasn't been the only problem. Many industry claims were made before companies realized that the authority was requiring them to include strain characterization for all microorganisms. That, in turn, led to many EFSA rejections on the grounds of incomplete dossiers rather than insufficient evidence of efficacy. Many claims were thrown out because EFSA deemed the strains were insufficiently characterized. In those cases, the authority did not scrutinize the gut health, immunity and other health benefit data contained in the dossiers (Vogel, 2010).

EFSA's failure to communicate its assessment process has left many companies in limbo, unwilling to develop new products or resubmit claims for fear of further rejection and adverse publicity. France-based industry leader-Danone has twice withdrawn health claims applications for probiotic yogurts Activia and Actimel. There were serious financial and health implications to EFSA's approach. If EFSA didn't start communicating what they wanted, food companies will eventually give up on the expensive claims application process and, in turn, will likely give up on putting the money into researching and selling probiotic products.

EFSA assessment is in danger of killing public confidence in probiotics, and that would mean a smaller health food industry in Europe, reduced spending on research and development, jobs lost, billions of dollars drained from the economy and studies killed. The probiotic food market was estimated to be worth approximately €10 billion in 2008 and held an estimated 10% of the global functional food market, but the industry was only as strong as its health claims. For its part, EFSA insistsed that holding probiotics to the gold standard of clinical trials was necessary to guarantee that public confidence in probiotics is based on true health benefits. Food are not drugs … but the science behind [probiotics] should be sound in any case. This is contrasted with the previous situation in which nothing was regulated and that is why criteria seem to be so strict. EFSA was organizing a fall workshop to address concerns about these criteria.

Moreover, the EFSA assessment introduced legal uncertainty. Meanwhile, industry legal teams were preparing court challenges. There's only two ways around EFSA in this situation: you either do the work or you change the law. In the short term, industry will have to reduce their claims to deal with simple

things like improved fecal consistency, but obviously those claims won't be amenable to creative marketing. Another alternative for companies is to resubmit rejected claims under different articles of the health claims regulations. This really was an international issue, because the world looks to Europe as a leader in probiotics, and it's not unreasonable to expect to see these kinds of regulations exported elsewhere in the world. EFSA's insistence on evidence derived from the gold standard of randomized clinical trials is ill-suited to demonstrating the supportive function that live microorganisms play in human health, critics say (Vogel, 2010).

Regulatory uncertainty. However, an inappropriate demand for medical-style scientific proof has resulted in an impractical authorization process that was alien to the culture of the food industry and beyond its expertise and resources. As a result, in the probiotics case only one health claim was authorized, while 359 health claims were rejected. The vast majority of the small number of authorized health claims are based on established science about the impact of vitamins and minerals on health, instead of innovative scientific research on the role of food in achieving better health results (EHPM, 2021).

Companies are discouraged from investing in innovation. Furthermore, this regulatory uncertainty discourages food supplement companies from investing in innovation. In May 2015, the European Commission announced its plan to carry out a Regulatory Fitness and Performance (REFIT) evaluation of the EU legislation on nutrition and health claims in order to find a solution to this situation. The REFIT process will develop a balanced solution, that would address the requirement for scientific stringency, be practical for the industry and above all else provide consumers with the sort of information that they are looking for on the foods that they purchase and eat.

High level of uncertainty caused by the regulatory framework, currently considering the term 'probiotic' as a health claim, is impacting the growth of the sector, disruption of the internal market, difficulties for companies accessing the EU market as well as confusion among consumers. Although there is consolidated scientific proof of the value of probiotics in various physiological functions of the human body, the EU does not recognize any health or nutritional claim for probiotics. Also, the EU Commission, based on the 2007 Guidance document on the implementation of Regulation No.1924/200617, considers the term "probiotic" as well as the phrase "contains probiotics" as health claims. In line with that, most Member States do not allow the use of the word "probiotc" on the products' packaging. This creates a severe disruption of the internal market, difficulties for companies accessing the EU market as well as confusion among consumers (EHPM, 2021).

The regulatory environment seems to have a major impact on sales in the EU. The EU was the top global market for probiotic yoghurt and supplement sales until 2009, but in 2019 ranks third, after China and the US. For both foods and supplements, the global probiotics market continues to grow from one year to the next, confirming the positive trend, while the forecast for the Western Europe indicates a decline of -2,1%. Moreover, the probiotic yoghurt lost over € 1 billion in sales after 2009 (IPA Europe (manifesto, 2021).

Lack of clarity at EU level. The lack of clarity at EU level has led Member States to adopt different national approaches to allow the use of the term 'probiotic', thereby creating potential adverse effects to the functioning of the European Single Market. It is accepted in some countries but not in others and based on the principle of 'mutual recognition', the product legally produced in a country allowing the use of the term probiotic is in free circulation in the EU. The associations are claiming the opportunity to build a coherent and harmonised approach for the use of the term "probiotic". Food business operators should be able to rely on harmonised rules across the EU to avoid potential barriers within the Single Market. While several national and international authorities worldwide have recognized the potential physiological and health benefits of probiotics and authorized such claims, little progress has been made at the EU level. It is crucial to create a labelling environment that the consumers can trust, and that allows consumers to make informed choices. In fact, consumers are in any case exposed to "probiotics", either because products containing them are legally commercialized, or because conversations on probiotics take place in the public domain but without any frame or criteria (IPA Europe manifesto, 2021).

Need to support Innovation. Innovation is key for the development of the sector and essential in order to provide consumers with products able to meet their current demands for more natural solutions. Unfortunately, investments in innovation are strongly hindered by the current uncertainty around the probiotic category in the European regulatory framework. In fact, the process for claim authorisation provided by the Nutritional and Health Claim Regulation, has proven to be extremely unpredictable for companies: only 12 claims based on new scientific evidence have been officially approved by the European Commission. This incredibly low rate of approval (6%) has led to a substantial reduction of the number of applications submitted to EFSA: in 2019 75% fewer applications were submitted to EFSA compared to 2011. Innovation in the food business has been durably hindered by this situation.

The European probiotic sector needs robust research and innovation, to once again become the driving force for innovative products that add value to human wellbeing, and to contribute to the growth of the European economy. The European voice of the probiotics industry, IPA Europe, is working on the definition, in order to enable the use of the term 'probiotic' as the name of a category. Framing the use of the term 'probiotic', under appropriate criteria and conditions, is a necessary step towards the interest of European consumers and the functioning of the European Single Market. Probiotics are currently one of the most topical issues in the field of science and the food industry. An interdisciplinary approach that invokes regulatory, economic, social and scientific means should be adopted by the EU, in order to assess probiotics in a holistic manner (EHPM, 2021; IPA Europe manifesto, 2021).

Several industry associations such as IPA Europe, EDA and EHPM, believe that the use of the term "contains probiotics" should be permitted in EU, with clear and appropriate conditions of use, that authorities can verify using some simple criteria to distinguish probiotics from other live microorganisms. This will allow consumers to make informed choices. IPA Europe and EDA asked in a joint statement for an evaluation of the current understanding of the term "probiotic" within a regulatory EU framework and the conclusive statement that a food containing probiotic microorganisms will be included on the list of

nutrition claims. The contribution that the probiotic sector can make to deliver on a number of objectives listed by the European Commission in the Farm to Fork are: (1) making relevant and reliable information available to the consumers; (2) Motivating consumers to make decisions on good and healthy diets in a sustainable perspective; (3) Using a more flexible approach to regulatory and non-regulatory measures to promote best practices: (4) Making use of research and innovation.

IPA Europe recommends providing useful guidance for stakeholders and for consumers on the use of the term 'probiotic' in food, beverage, and dietary supplements. This will require reassessment of the EC Guidance of 2007, which indicates that the term 'probiotic' should be regarded as a health claim only. Instead, IPA Europe and EHPM call on a modification of the health claims evaluation process using a graded system to encourage the European Commission to further develop European framework, based also on national good practices and experiences. Companies cannot invest without knowing that the ingredients they use and the health claims they make will be authorised in the EU. This is especially the case for SMEs (EHPM, 2021; IPA Europe manifesto, 2021; IPA Europe legal, 2022).

This graded approach graded approach should be developed corresponding to the different level of supporting scientific evidence. It is believed that it will make a distinction between the probiotic category and the specific health claim requirements and will not contradict the spirit of the EU legal framework. Fostering a favourable environment for probiotics will work to benefit both industry in Europe and European consumers. Through both regulatory and non-regulatory measures, this graded approach will steer the responsible probiotic industry towards practices that make a healthy, sustainable choice the easy one for consumers. A category being named 'probiotic' is factual and thus should not be interpreted differently from other nutrients or substances (e.g. dietary fibre). Therefore, there is no reason to apply a very restrictive interpretation only to probiotics (IPA Europe manifesto, 2021).

Currently, the NHCR can be applied differently, depending on the interpretations of the Member States authorities but also on the typology of probiotic food and food supplements. A set of criteria should be used to identify probiotics microorganisms in food and food supplements, covering the safety and quality, labelling and efficacy aspects. With these requirements agreed at European level IPA Europe can provide clarity to the minimum criteria needed for the proper use of the term probiotic in both food and dietary supplements. When used in compliance with the definition of the category and within the framework of Regulation (EC) 1924/2006, the use of the term 'probiotic' would not require an EFSA health assessment, as long as no reference to a specific health effect is made.

Information and education are essential to make a responsible consumer and contribute to motivating consumers to make food choices based on a rational understanding of their own interests. The EU Regulation on the provision of food information to consumers (FIC, EU 1169/2011) states that "the prime consideration for requiring mandatory food information should be to enable consumers to identify and make appropriate use of a food and to make choices that suit their individual dietary needs". However, this is not the case for probiotic food and food supplements. The lack of a harmonised approach is not

helping responsible players to provide information on probiotics and is not allowing consumers to make informed choices.

The interest in this category of ingredient is hampered by a lack of knowledge and a lack of product information The general principle of food labelling is to provide specific and descriptive information to help consumers make appropriate food choices. This principle is currently not applied to probiotics, as the prevailing view of the European Commission is that the term "probiotic" is considered an implied health claim and is therefore not permitted on the labels and communication of food products and food supplements. The current situation penalizes European manufacturers of probiotic foods and dietary supplements and does not meet the demand of consumers for appropriate information on food products, which was also the scope of Regulation (EC) N°1924/2006 on Nutrition and Health Claims made on Foods.

The food supplements sector has also been affected: fake news and misleading information find greater grip on the media, opinion leaders, sometimes even institutions, which feed the noise and uncontrolled voices on the identity, the functional value and the characteristics of food supplements that prevent consumers from grasping their real social value. Therefore, it is highly important that promoting effective, truthful and professional communication to all stakeholders to clearly define the identity of the food supplement and its functional and social value is central to overcoming visions and erroneous juxtapositions with other products. The effect is that consumers do not have access to the information that they are increasingly looking for on the health benefits of the foods, and particularly the food supplements, that they purchase. As a consequence, consumers are increasingly turning to uncontrolled sources for information, such as the internet – increasing the likelihood of them being misled (EHPM, 2021; IPA Europe manifesto, 2021).

In a time when a simple Google search for 'probiotics' produces over 56.8 million hits, means that most people have heard about probiotics through various channels. An ever-increasing variety of probiotic products are available in different regions of the world, and European consumers can purchase these products from outside Europe via e-commerce: this represents a loss for the European economy.

However, this also shows that consumers are exposed to any kind of product bearing the term 'probiotic'. Thus, it is important to emphasise that some products bearing the term 'probiotic', regardless of whether they claim to have positive effects, do not provide any assessment on the real activity of the probiotic microorganisms. Internet sales or e-commerce is increasing and driven by consumer demand, the distribution model is changing. Experts expect e-commerce to further increase in the coming years. It is important that products sold on e-commerce respect the same rules than the products sold by the traditional distribution channels. E-commerce is an opportunity for the EU food supplements industry. A level playing field to avoid unfair competition from countries with less strict rules stresses the importance for consumers to receive appropriate information and fair advertising. A harmonised approach should be implemented in Europe, with specific criteria for the use of the term "probiotic" in line with the consumer expectations of

receiving better information and to avoid disruption of the European Market (EHPM, 2021; IPA Europe manifesto, 2021).

The industry associations call for action of the European Commission and relevant stakeholders to build a coherent and consistent framework in Europe, to alleviate an avoidable legal burden, enhance the functioning of our European Single Market. A common EU solution should be found within the Nutrition and Health Claims Regulation, by adding the claim 'contain probiotic microorganisms', or similar wording, to the list of nutrition claims. The European regulatory framework should provide safety and quality but at the same time allow business to use recognised and validated innovative technologies for the improvement of the quality of products. The European Institutions must address the challenges the food supplements sector is facing, in order to contribute to a Europe of healthy citizens, who make informed choices about safe, high quality and sustainable food supplements, produced by competitive and innovative companies able to market their products across the EU (IPA Europe manifesto, 2021).

The European Union is entering a new and challenging period, where policymakers play a decisive role in putting food at the centre of their policies. This necessitates the preparation of a European industrial strategy to uphold the competitiveness, quality and sustainability of the European food industry, including the probiotic foods and food supplements. IPA Europe is committed to safeguarding the role of the European food industry as a global leader, while continuing to offer high-quality products to European consumers. It is crucial to create a labelling environment that the consumers can trust, allowing the consumer to make an informed choice. Building a comprehensive framework will result in trustworthy and accurate information being featured on labels and in other communications to consumers, pursuant to the Regulation on the provision of food information to consumers (FIC, EU 1169/2011). This will result in consistent and harmonized information that meets the objective of enabling consumers to identify and make appropriate use of food, as well as making choices that suit their individual dietary needs.

IPA Europe is a strong advocate for, as stated by Commissioner Stella Kyriakides, "having consistent rules in the EU, ensuring that legitimate demands for more information remain compatible with our single market [and] to look into how we can improve consumer information, starting with the possibilities that exist under the current legal framework". A harmonized response across Member States that invokes comprehensive criteria and conditions for use of the term 'probiotic' and builds a clear labelling environment will contribute towards the objectives of the Farm to Fork Strategy.

Building a sustainable food system requires a holistic approach. Clear and coherent criteria attached to the 'probiotic category of food and food supplements will provide clarity and will contribute towards the overall Farm to Fork Strategy objective of improving information on food, based on good practices and experiences. This should result in a more consistent framework of regulatory and non-regulatory measures in relation to probiotics that will adequately address the need for better consumer information, will enhance the correct functioning of the European market and will foster an environment that promotes innovation.

IPA Europe maintains that regardless of developments within Europe, it is important to take the global dimension of trade into account.

The development of international guidelines within the Codex Alimentarius and with the WHO are necessary to sustain quality probiotic products on a global scale, and to ensure fair practices in food trade. Therefore IPA Europe is also a proponent of establishing a definition with minimum characterisation requirements and quality and labelling parameters for probiotics for use as an ingredient in food and dietary supplements on aspects not framed by existing Codex standards (IPA Europe manifesto, 2021).

10. Discussion

Food regulation is extensive and complex, especially for functional foods where health claims are involved. Regulation is becoming more detailed and prescriptive, such as the EU Regulation EC 1924/2006 on nutrition and health claims made on foods, and the The NLEA of 1990, the FDAMA of 1997 and the Qualified health claims introduced U.S. in 2003 are all stringent frameworks and need approval of the health claims. These Regulations are obligatory for all new and current health claims on functional food products. They are based on the precautionary principle, in which consumer protection has a high priority. To assure a high level of consumer protection they are demanding a high level of scientific substantiation of health claims and a health claim dossier, based on in vitro/clinical data, resembling pharma. Regulations has created a research-driven market. Contrary no pre-approval are needed for using structure and function claims, under DSHEA, but the FDA must be notified of dietary supplement claims. Introduced in 2004, this less rigid regulatory system in U.S., which complemented the other health claims system were intended to stimulate the health food market through deregulation and result in food products that could potentially promote health, mitigate lifestyle-related diseases, and reduce health care costs for consumers.

Health claims offer functional food companies the opportunity to differentiate their products on mass markets, adding value to their products, and so reinforcing the competitive position of their products. Furthermore, products with a health claim may be sold for a higher price, making health claims commercially attractive. On the other hand, the cost of developing and submitting a health claims dossier to be approved by the EFSA and the EC, or FDA require a lot of additional effort, time and resources, which appears to be a core problem for functional food operators (Moors, 2012). These costs overrule the expected returns on investments on innovative foods with new health claims. The large number of SMEs in the food sector cannot afford these additional efforts and will probably not develop new health claims on foods but accept a product-follower strategy. Furthermore, the number of approved claims determines the competitive landscape that will occur. If EFSA and FDA will reject the majority of the claims, the development of functional foods products may decline. If they approve most of the claims, mainly large companies will be able to obtain health claims because they have enough financial resources, giving them a better opportunity to increase their innovation output. In US, however the firms have a second option to take under the DSHEA, which lowers the entry market barriers for both large companies and SMEs.

The new EU Regulation in EU had already some influence on existing functional food products: companies have changed their recipes, focused on fewer products or abandoned specific product development projects. However, the majority of companies have not changed their position and are waiting for a change in the health claim re-assessment options of the EFSA and the official Article 13.1 Union List of the EC. Meanwhile, an open ongoing dialogue between industry and authorities will lead to better state-of-the-art knowledge and understanding by authorities and vice versa regarding health claims on probiotic products (Moors, 2012).

When these results are clear in the future, there may be a large change in the number or type of health claims on probiotic foods and supplements. Existing products might have to leave the market, because they are no longer allowed and new health claims might not be developed because the returns on investments may be too low. This might result in a total collapse of products with health claims on the markets and the development of new health claims. Maybe the current claims will be consolidated or only the strongest health claims and companies with enough resources to pay the high costs of health claim dossiers will be left. Small companies may develop creative marketing techniques and vague claims in order to stay in the market and avoid the lengthy and expensive health claim procedures. In other words, the new regulation policy may not only be "restrictive" but also "selective" for future innovative pathways in interaction with regulatory institutions (Moors, 2012).

The uncertainty about the health claims criteria should be reduced in the short term. This will enable companies to make a better estimation of the financial risks and the chances of approval. The first way to realize this is to wait and see which claims are approved to draw lessons from the success and failures of health claim submissions. These results give food operators more insight into the time, effort and quality of evidence needed for a health claim dossier. The EFSA may support this process by clearly communicating its criteria to the companies. Another way to reduce the financial risk of firms is to increase the possibilities for protecting health claims, as some parts of the health claim dossiers can be appropriated via IPR.

During 2012, the transition period during which companies have been granted time to ensure that their marketing is in accordance with the list of approved health claims will expire and food companies will face the challenge of having to adapt their innovation strategies to benefit from the approved health claims and to develop alternative ways of marketing and advertising to communicate health benefits of products for which claims have not been approved. In this way, the new Regulation has a huge impact on innovation. These regulations have an ability to steer complex science and technology, such as the development of functional foods and supplements, providing healthier food choices for consumers. The future of functional foods is dependent on continuous advances in food and nutrition sciences, technical innovation in the food industry, the regulatory framework and the ability to respond to evolving consumer demands (Moors, 2012).

After all, a better performing European and U.S. functional food innovation system can increase the health benefits of functional food consumers by a higher diffusion of functional food products or higher

quality products, the consumers being better protected against misleading products. Furthermore, it contributes to the competitiveness of European functional food firms on the global market, which will have a positive influence on economic activity within the European Union to become once again leaders in this field.

11. Conclusions & Limitations

Probiotics are friendly live microorganisms that are similar to beneficial microorganisms found in the human gut. The investigation of the causal relationship between intestinal health and microorganisms such as bacteria and yeasts, eventually led to the worldwide development, manufacturing, sales and consumption of functional foods such as yogurts and fermented milk drinks, followed by dietary supplements. The traditional concepts of sound health have changed dramatically over the years due to increased growing evidence that probiotics can have beneficial effects on digestive health and immune functions, and therefore maintain health and wellbeing. However, it is really in the last decade that research on probiotics has exploded with the advent of new scientific technologies, but also because of an increasing interest and awareness among consumers and clinicians seeking safe and validated alternatives to pharmaceuticals to assist the general population in maintaining health and wellness.

All-time high interest in the field of probiotics is due to emerging probiotic industry. The "biotic family" was extended from probiotics, and prebiotics to synbiotics and recently to postbiotics. They are available in foods and dietary supplements, even as pharmaceutical formulations (capsules, tablets and powders) and in some other forms as well, but their claims of health benefits may challenge the traditional border between food and medicine. A number of probiotic products have been introduced into the international market as food supplements, dietary supplements, natural health products, functional foods, nutraceuticals, medical foods and many more other categories, as a result, the position of regulatory system for probiotics within existing categories become vague and quite unclear.

The probiotics definition by FAO/WHO from 2001 as "Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" was widely recognized in the scientific community, but did not evolve into neither a legally recognized definition of, nor a standard of identity for, the term probiotic in the US or Europe. The misuse of "probiotics" started to take place for marketing tactics with regard to the functional foods revolution in the early 1990s. Hence, many countries enacted a broad-spectrum stringent framework to develop regulatory policies and labeling claims for probiotic and probiotic-based foods & beverages including safety, efficacy, quality control, health claim regulations and associated penalties to protect consumers from misleading claims (de Simone, 2019).

The introduction of the first functional food system was in 1991 in Japan, which evolved with the involvement and participation of both government and industry in the development of foods with health claims, while in the EU and the US, the approach was more of a reactionary one to products already on the markets there. The global probiotic market is continually expanding at an estimated annual rate of 7% and is worth approximately US$15 billion per year. Dairy functional foods and beverages are by far the biggest

segment for probiotics, currently standing at over US$48 billion in 2021 and the probiotic supplements take 15 % market share. Besides probiotics have found a growing application in plant-based yoghurts and milks, non-dairy beverages, baked goods, chocolate, cereals, pickles, some meat products, nutrition bars, ice-creams, and drug formulations, as well as medical foods and therapeutic applications as live biotherapeutics.

To be able to answer the Research Question: "What role has regulation played in shaping the market for probiotic applications in Europe and the US since 2000?", I would like to discuss first why probiotic applications as drugs were not an option for probiotics until recently. From a legal point of view, probiotics are positioned in a transitional zone between food and pharmaceuticals. It should be mentioned that medicinal claims (MC), which claim that food can treat, prevent or cure any disease or medical condition, are still prohibited on foods; such medicinal claims can only be made for licensed medicines under the EU and the U.S. laws. However, health claims such as nutrient deficiency disease claims under the U.S. legislation of food and reduction of disease risk claim (RDRC) under the E.U. legislation stay a bit closer to medicinal claims (MC) than general well-being claims, making approved food products closer move to medicines.

In the EU, its Member States and U.S. food and pharmaceutical products are subject to different regulation regimes and are – at least in the EU – regulated by differing relevant authorities. Additionally, pharmaceuticals and other medicinal products require pre-market approval by state authorities, while EU and U.S. legislation on foodstuffs (with a few exceptions like e.g. novel foods or food additives) leaves companies free to market their products, if they are safe and do not mislead consumer and afterwards they are subject to post-marketing control by public authorities. Due to the novelty character of probiotics, additional questions arise concerning the safety and efficacy of such products, the required testing and monitoring methods, their impact on consumers' nutritional behaviour as well as the institutional procedures and responsible authorities. These legal environments have attracted non to few market players to develop probiotic therapeutic applications as drugs, although in Europe before 2006 some products were placed as drugs due to the regional views of some authorities to treat the health claims as medical claims. Probiotic functional foods and supplements were developed with an intention to achieve health claims under the food legislation.

To be able to answer the Research Question: "What role has regulation played in shaping the market for probiotic applications in Europe since 2000?", I will discuss the outcome of the very detailed and prescriptive Regulation EC No 1924/2006 on nutrition and health claims. The EU-wide Regulation EC No 1924/2006 on nutrition and health claims, forced in 2007 was mandatory for every food operator willing to have food or supplement claiming beneficial effect. The EFSA's assessment panel issued unfavourable opinions on probiotics in contrast to vitamins, minerals and omega-3 fatty acids. The predominant view was that (1) probiotic health claims were not supported with sufficient scientific evidence to demonstrate that the claimed effect such as "gut health", "digestive health", "healthy microbiota" etc. were beneficial to the maintenance or improvement of the functions of the body; (2) it was a lack of

sufficient human studies containing the necessary scientific data to demonstrate the claimed health benefit on human physiology (EFSA meeting with IPA Europe, 2019). The European Medicines Agency (EMA) was not more open to probiotic-based drugs or medical devices. A few probiotic drugs or medical devices had been marketed well before the introduction of any European marketing authorisation procedure. The EMA has even turned down flat industrial firms requesting guidelines for the development and assessment of probiotic-based drugs, arguing that they did not have enough marketing authorisation requests to open investigations in this area (Nouguez E., 2021).

The EU-wide Nutrition & Health Claims Regulation 1924/2006 resulted in one approved and 359 probiotic claims non-approved. Under the 2007 interpretation, on the basis of these negative opinions, the European Commission even banned the use of the term probiotics and prebiotics, declaring it a health claim in corporate communications aimed at consumers concerning these foods and dietary supplement products since end 2012. Not surprisingly, the consequences for the market were quite serious for the probiotic dairy products in the EU, while supplements were less influenced. The probiotic yoghurt industry in the EU, which had grown by an average 5% per annum from 2000 to 2012, favored as fresh and healthy dairy by consumers and by the uncertain legal environment in the separate member states. However, it declined by 8% in 2013 with loss of over €1 billion in revenue by 2020. This contrasts with continuing steady growth in other regions of the world, sometimes in double digits (Thomas, 2016). In the EU, where health claims are made in the re-formulated products, these now relate to the presence of named vitamins, and use approved wording for the relevant Article 13.1 claims, while in the U.S. products are positioned as dietary supplements and carry structure/function claims. Increasingly, manufacturers are segmenting their probiotic lines to target individual consumer needs by offering a customized approach to digestive health and immune health and added benefits for other therapeutic conditions.

Eventually, regulators in different parts of the world started to recognise the benefits of probiotics under certain conditions and to authorise favourable claims relating to probiotics differently. Since 2018 some EU member states, such as Italy, Czechia, Span, Netherlands, Denmark, France adopted national guidelines developing certain requirements for qualifying specific strains as probiotics as factual information. Italy reasserted the validity and proportionality of their approach to recognize the "effectiveness" of the probiotics in physiological terms and pointed out that the indication of a probiotic to promote the balance of intestinal flora is in accordance with their guidelines and is not a health claim (IPA Europe European legal framework, 2023). Italy is currently the 3rd most developed in the word for probiotic supplement. These EU member states showed that 2006 Commission guidance is no longer acceptable, particularly compared to the regulatory approaches adopted outside the EU (Katia Merten-Lentz, a lawyer at the Brussels and Paris Bars & expert on the matter, 2023). In several third countries, like the US and Brazil, probiotics are already considered food or as ingredients, while Canadian and Swiss authorities even allow the use of health claims about microorganisms represented as 'probiotics' on food labels and in advertising. Likewise, third countries like India, Argentina, and Thailand have adopted specific

probiotic regulations and definitions for probiotics (IPA Europe European legal framework, 2023). Since 2018, the EU probiotics market is on growing trajectory.

To be able to answer the Research Question: "What role has regulation played in shaping the market for probiotic applications in U.S. since 2000?", I will discuss the regulatory environment in which probiotics were introduced from 2000 until the present time. The U.S. has been a hub for open-minded market when it comes to alternative therapies that include probiotics. Some of the unique features of US market for probiotic-based foods and beverages include: generally lack of fermented foods and its lower consumption; strong fear for all bacteria since the discovery of penicillin and understanding of what bacteria can do; increasing incidence of foodborne illness; skepticism of advertising claims for natural probiotic food products, high use of dietary supplements (Vanderhoof and Young, 2008). Regulatory issues remain an area of concern for the probiotic-based foods and beverages in US particularly when it comes to what the industry needs to know and how to protect the consumers from false claims.

Currently, the products are regulated depending on their intended use. The NLEA (1990), the FDAMA (1997) and the Qualified health claims introduced U.S. (2003) are all stringent frameworks and need approval of the health claims. Contrary no pre-approval is needed for using structure/function claims, under DSHEA, but the FDA must be notified of dietary supplement claims 30 days prior to their first use. Receiving a health claim was not an option when probiotics were introduced on the market in the early 2000s, since very few other products have been approved under these regulatory paths. In contrast, the more flexible DSHEA of 1994 was used in larger extend to market dietary supplements, which by now were estimated to reach over 80,000 products. Probiotics could be sold as dietary supplements and make structural/function claims, such as "helps fortify your body's natural defences"; "helps keep your body at its best" (Actimel, Danone), and "helps create a favourable environment for the growth of beneficial flora, (Acidophilus, Cell Tech), (Sanders, 2003). However, the claims that speak to the normal functioning of the human body do not require government approval. As a result, they are used with great frequency on probiotic foods and supplements, making it difficult to differentiate products that are scientifically backed from those with little evidence. Making general function claims requires that the research be designed to have a health impact on the general population, not to mitigate disease in people already sick. Such research is challenging as magnitudes of effects may be small and difficult to discern in the variations inherent to a human study. Studies likely will require large numbers of subjects. Better characterization of the microbiota and host genome of subjects might help differentiate the responders and non-responders (Sanders, 2003).

Despite the later start compared to Japan and Europe, DSHEA shaped the U.S. market for probiotic dairy foods (and interrelated food supplements) to develop faster and to larger market values. The U.S. market for probiotic supplements overtook the EU and Asia-Pacific. Between 2013 and 2015 the U.S. became the largest growth market for probiotic supplements in the world in front of China and Europe, using the DSHEA as preferred regulation to comply with. In the EU, where health claims are made in the re-formulated products, these now relate to the presence of named vitamins, and use approved wording for the relevant Article 13.1 claims, while in the U.S. products are positioned as dietary

supplements and carry structure/function claims. Increasingly, manufacturers are segmenting their probiotic lines to target individual consumer needs by offering a customized approach to digestive health and immune health and added benefits for other therapeutic conditions. In 2021, U.S. is the global leader in probiotic supplements with over US$ 3.0 billion from US$ 3.0 billion, and the consumption gap between yogurts and supplements is narrowing quickly (Ipa Europe data, 2021).

I would like to take also in consideration how the regulatory view shaped the medicalization of the probiotic applications. Although DSHEA gave liberty to the probiotics, since 2010 the view of both regulating authorities, FDA and EFSA became more convincing that probiotic in legal terms is a live biotherapeutic. A probiotic that makes a health claim that resembles a medical claim is classified into "drug" as in medical or therapeutic products and regulated as such (Venugopalan et al., 2010). More specifically LBPs category for probiotics was developed under biological products in 2016 by FDA and in 2019 by the European Pharmacopeia to accommodate their therapeutic uses the first LBPs were approved by FDA in 2022 and 2023. In summary, the U.S. regulation shaped the U.S. market as a leader in probiotic supplements. In addition, the view of the FDA and the possibility to regulate according intended use, shaped the market medicalization of the U.S. in medical foods and is the country, where first LBPs were approved.

Limitations: This research is limited to only Europe and the US. The study covers a long period of time of 20 years, including the newest research and quite a broad number of sources for cross-reference. Only qualitative secondary data was used and was not complemented with primary data to take into consideration the view of the industry players positioned on both markets. Nevertheless, using interviews as data collection method has certain limitations too. The interview provides only indirect information filtered through the views of interviewees. Opinions of the interviewee may only represent certain aspects due to the interests of the respondent (Creswell, 2009). The opinion might also be biased. To minimize the influence of the limitation, a future study may include interviewees through a respondent selection process considering specific criteria or even include survey covering more respondents.

Final Conclusion: The objectives of the present thesis are to examine role of (1) the changing status of the international regulatory framework for food health-related claims and (2) the state of the art regarding the probiotic products, marketed with health claims (HC) as an opportunity to observe the influence of the regulations on innovation.

This paper is a study to examine empirically and quantitatively the impact of the transition of the European, resp. U.S. regulation on health-related products enhanced with live microorganisms (probiotics) since 2000 until now and to answer the following research question "What role has regulation played in shaping the market for probiotic applications in Europe and the US since 2000?".

The U.S. regulation shaped the U.S. market as a leader in probiotic supplements and increasing probiotic dairy products with possibility to bear structure/function claims. In addition, the view of the FDA and the possibility to regulate according intended use, shaped additionally the market toward medicalization in terms of therapeutic approaches such as medical foods and LBPs.

The EU regulation shaped the EU market form a leader in probiotic foods and supplements with possibility to bear specific health claims into a lagger behind Asia-Pacific and U.S. in probiotic foods and supplements, except sour milks with possibility to bear unspecific health claims in the re-formulated products, not related to the probiotic ingredients but rather to the presence of named vitamins, and use approved wording for the relevant Article 13.1 claims. In addition, the view and the action of some member states showed that 2006 Commission guidance is no longer acceptable, particularly compared to the regulatory approaches adopted outside the EU where health claims on probiotics are already approved.

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13. Tables and figures

Table 1. International comparison of various regulatory approaches to health claims taken by different countries around the world (v = yes sometimes still under development, X = no, -= not applicable). Source: European Journal of Nutrition volume 42, Suppl. 1, March 2003. Reference: Tamime A. & Thomas L., (2018).

	JHCI (UK)	Sweden	NL	Belgium	CIAA	Council of Europe	USA	Canada	Japan	Codex
Website	www.jhci.co.uk	www.snf.ieon.se	www.voedingscentrum.nl		www.ciaa.be	www.coe.fr/soc-sp	www.cfsan.fda.gov/~dms/hclaims.html	www.hc-gc.ca/food-aliment/english/subjects/health_claims	Available in Japanese	www.codexalimentarius.net/reports.asp
Voluntary/Mandatory	Voluntary	Voluntary	Voluntary	Voluntary	Voluntary	Voluntary	Voluntary	Mandatory	Mandatory	Voluntary
Origin	Industry, consumers, enforcement partnership	Industry (from primary production to retail organisations), supported by consumer organisations	Council of Europe	Industry	Food industry guidelines	Council of Europe	Manufacturers? Federal scientific bodies, e.g. NAS, NIH etc	Government	Government	Codex members
Definitions	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Health claims	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Enhanced function	✓	✓	✓	✓	✓	✓	✓		✓	✓
Disease risk reduction	X	**✓, for generic claims**	✓	✓	✓	✓	✓	✓	X	✓
Generic claims	✓	✓	X	✓	X	(X)	✓	✓	✓	✓
Product specific	✓	✓	X	✓	X	✓	✓	✓	✓	✓
Communication guidelines	✓	✓	✓	✓	✓	✓	✓		✓	
Nutrition principles	✓	✓	✓	✓	✓	✓	✓		✓	✓
Amount and frequency specified	✓	✓	X	X	✓	✓	✓		✓	
Safety	Refers to existing law	Refers to existing law	Refers to existing law	X	Refers to existing law	Refers to existing law	Refers to existing law	✓	✓ **data required**	✓
Quality assurance	Refers to existing law	In general terms	X	X	Refers to existing law	✓		✓	✓	✓
Guidelines for dossier	✓	X	X	X	✓	X	✓	✓	✓	✓
Process for substantiation	✓	✓	✓	✓	X	✓	✓	✓	✓	✓
Approval procedure	Level of data required	✓	✓	X	X	-	✓ **(except medical food)**	Outlined	✓	-
Administrative procedures	✓	✓	✓	X	X	X	✓		✓	
Use of independent expert panel	✓ (7 experts)	At least 3 experts appointed case by case	✓	X	X	-	FDA, federal scientific bodies		✓ **(Ministry)**	-
Defined wording of health claims	X	X	X	X	X	X	✓		✓ **(6 months)**	X
Start date of code	2000	12 years generic <1 year product specific	1998	Draft 1998	-	-	1990 (NLEA authorised health claims 2000 (Qualified health claims)	Still evolving	Since 1991 Revised 2001	At step 5 of Codex procedure
Health claims approved (to Sept. 2002)	6	8 generic since 1990 1 product specific	2	X	-	-	12 generic since 1993 2 generic health claims since 1997		302 product specific claims	
Financial support	Mainly industry funding/project grants from FSA, moving to membership scheme in 2002	Principals of code basic funding Fees for evaluation of product-specific claims	Fees for evaluation	X	-	-			Fees to be paid for evaluation	
Timescale for approval	X	✓ **(4 months)**	3 months	X	-	-	Yes (> 1 yr under NLEA)		✓ **(6 months minimum)**	

Table 2. Summary of the various types of claims under consideration and their definitions (Codex Guidelines, 2007a). Reference: Tamime A. & Thomas L., (2018).

TYPE OF CLAIM	DEFINITION	EXAMPLE
Nutrition claim	*Any representation that states, suggests or implies that a food has specific nutritional properties including but not limited to the energy value and content of protein, fat and carbohydrates, as well as the content of vitamins and minerals*	
Nutrient content claim	A nutrition claim that refers to the level of a nutrient contained in a food	"Source of calcium", "high in fibre", "low in fat"
Comparative claim	A nutrition claim that compares the nutrient levels and/or energy value of two or more foods	"Reduced", "less than", "fewer", "increased", "more than"
Health claim	*Any representation that states, suggests or implies that a relationship exists between a food or constituent of that food and health*	
Nutrient function claim	A form of claim that refers to the physiological role of the nutrient in growth, development and normal functions of the body	"Food X is a good/excellent source of nutrient A, naming the physiological role of nutrient A in the body in the maintenance of health and promotion of normal growth and development"
Enhanced function claim	Claims that concern specific beneficial effects of foods or their constituents in the context of the total diet on physiological or psychological functions or biological activities. Such claims relate to a positive contribution to health, improvement of a function, or modification or preservation of health	"Certain nondigestible oligosaccharides may improve the growth of a specific bacterial flora in the gut" "Caffeine can improve cognitive performance" "Folate can help maintain healthy plasma homocysteine levels"
Reduction of risk of disease	Claims relating to the consumption of a food or food constituent in the context of the total diet that may help reduce the risk of a specific disease or health-related condition. The claim must consist of two parts: (1) information on an accepted diet-health relationship, followed by (2) information on the composition of the product relevant to the relationship, unless the relationship is based on a whole food or foods whereby the research does not link to specific constituents of the food	"Folate may reduce a woman's risk of having a child with neural tube defects" "Sufficient calcium intake may help to reduce the risk of osteoporosis in later life" "Intake of specific probiotics may help to reduce the risk of rotavirus infection in young children"

Table 3. Analysis of applications and authorisations of health claims under the EU Regulation 1924/2006, to October 2016. Reference: Tamime A. & Thomas L., (2018).

Claim type	Total submitted	Not authorised	Authorised	Probiotic claims (not authorised)
General health claims (Article 13.1)	2104	1875	229	359
Health claims based on new scientific evidence or where protection of proprietary data was requested (Article 13.5)	112	108	4	17
Reduction of disease risk claims [Article 14.1(a)]	37	23	14	2
Claims referring to children's development and health [Article 14.1(b)]	56	44	12	9
Totals	2309	2050	259	387

Table 4. Examples of claims used on labels of some probiotic fermented milk products on the UK and Irish Markets in 2005. Reference: Tamime A. & Thomas L., (2018).

Manufacturer/product	Probiotic micro-organisms	Claim on label
Danone (Actimel)	*Lactobacillus casei* strain Immunitas	Helps support your bodies' natural defenses.
Danone (Activia)	*Bifidobacterium* spp. strain Essensis or Digestivum	*Bifidobacterium* spp. strain Essensis or Digestivum, a natural culture unique to Danone Activia, has been proven to help our digestion work better as it supplements and supports the essential cultures in our intestinal flora. A healthy digestion is essential to a healthy life.
Yoplait (Every Body Probiotic Yoghurt Drink + 15 Vitamins and Minerals)	*Lactobacillus rhamnosus* GG (LGG)	+ LGG, the most clinically researched probiotic in the world proven to enhance your natural resistance and help you maintain a healthy digestive system. + Balance from within LGG + Healthy digestive system LGG
Müller (Vitality)	*Lactobacillus acidophilus* LA-5 and *Bifidobacterium animalis* subsp. *lactis* BB-12 (see Masco *et al.*, 2004)	The good bacteria in Müller Vitality can help maintain the balance of "good" and "bad" bacteria in your digestive system. Vitality is packed with millions of "good" probiotic bacteria *Lb. acidophilus* LA-5 and *Bif. animalis* subsp. *lactis* BB-12. Great at any time of day as often as you like. Contains prebiotic inulin.
Ocean Spray Probiotic Yoghurt	Not listed	Contains millions of friendly bacteria that help to maintain the balance of natural flora in your body, which in turn may aid digestion and general well-being.

Table 5. Examples of claims used on labels of some probiotic fermented milk products on the UK and Irish Markets in 2016. Reference: Tamime A. & Thomas L., (2018).

Product	Cultures named on list of ingredients or label statements	Statement on label
Danone Actimel	*Lactobacillus casei* Danone® (This is the registered trademark used for the specific Danone strain *Lactobacillus paracasei* subsp. *paracasei* CNCM I-1518.)	Start your day with Actimel with Vitamins B_6 and D to support your immune system. It also contains L. casei[1] Danone® cultures. Enjoy as part of a healthy balanced diet and lifestyle.
Danone Activia	Bifidus ActiRegularis® (This is the registered trademark name used in the United Kingdom and Ireland for their strain *Bifidobacterium lactis*[2] DN-173 010.)	Yogurt with Bifidus ActiRegularis, and the ingredients list *Bifidobacterium lactis*[2] (Bifidus ActiRegularis®) and *Lactococcus lactis*[3] cultures Every Activia pot contains carefully selected ingredients and 4 billion Bifidus ActiRegularis® cultures to craft our delicious yogurt.
Yakult	*Lactobacillus casei* Shirota	Contains 10^{10} billion *Lactobacillus casei* Shirota per 100 ml when refrigerated (6.5 billion per bottle). Did you know there are billions of unique *Lactobacillus casei* Shirota bacteria in these small bottles? Millions of people enjoy it as part of their daily life. Yakult has come a long way since it was introduced in 1935 by the Japanese scientist Dr. Shirota. Since then Yakult has been chosen by people around the world. With 6.5 billion *Lactobacillus casei* Shirota bacteria you'll want to drink every last drop. You can enjoy this delicious drink every day.
Milbona ProViact Yogurt Drink	*L. casei*	Fat-free yogurt drink with sugars and sweeteners, with L. casei[1] cultures, Vitamin D and Vitamin B_6. Vitamin D and Vitamin B_6 contribute to the normal function of the immune system. As part of a varied, balanced diet and healthy lifestyle.

[1] L. casei stated on the label should read '*L. casei*'.
[2] *Bifidobacterium lactis* stated on the label; presumed to be *Bifidobacterium animalis* subsp. *lactis*.
[3] *Lactococcus lactis* stated on the label should read '*Lactococcus lactis* spp.'.

Table 6. Health claims approved by FDA that meet the Significant Scientific Agreement (SSA) standard.

Reference	Approved claim	Examples of food requirements
21 CFR 101.72	Calcium & osteoporosis	Calcium bioavailable
21 CFR 101.74	Sodium & hypertension	Low sodium
21 CFR 101.73	Dietary fat & cancer	Low fat
21 CFR 101.75	*Dietary saturated fat and cholesterol & risk of coronary heart disease (CHD)*	*Low saturated fat; low cholesterol; low fat; fish meats "extra-lean"*
21 CFR 01.76	Fiber containing grain products, fruits and vegetables, & cancer	A grain product, fruit or vegetable that contains dietary fiber; low fat
21 CFR 101.77	Fruits, vegetables and grain fiber, particularly soluble fiber, & risk of CHD	Same as above
21 CFR 101.78	Fruits and vegetables, & cancer	Good source for vitamin (A), (C) or fiber
21 CFR 101.79	Folate & neural tube defects	Good source of folate
21 CFR 101.80	Dietary sugar alcohol & dental caries	Sugar-free; sorbitol, manitol, isomalt, etc.
21 CFR 101.81	Soluble fiber & risk of coronary heart disease	Sources of whole oat , or psyllium
21 CFR 101.82	*Soy protein & risk of coronary heart disease*	*At least 6,25 g soy protein per serving*
21 CFR 101.83	Plant sterol/stanol esters & risk of coronary heart disease	At least 1,7 g plant stanol per serving
Docket 99P-2209	Whole grain food & risk of heart disease	Contains 51% or more of whole grains
Docket 00Q-1582	Potassium & risk of high blood pressure	Good source of potassium

Source: FDA Internet site at: www.cfsan.fda. gov/dms/flg-6c.html

Table 7. Five FDAMA health claims authorized based on authorative statement by federal scientific bodies. Reference: Tamime A. & Thomas L., (2018).

Diets rich in whole grain foods and other plant foods and low in total fat, saturated fat, and cholesterol may reduce the risk of heart disease and some cancers.
Diets containing foods that are a good source of potassium and that are low in sodium may reduce the risk of high blood pressure and stroke.
Drinking fluoridated water may reduce the risk of [dental caries or tooth decay].
Diets low in saturated fat and cholesterol, and as low as possible in *trans* fat, may reduce the risk of heart disease.
Replacing saturated fat with similar amounts of unsaturated fats may reduce the risk of heart disease. To achieve this benefit, total daily calories should not increase.

[1] There is also one nutrient content claim authorised under the FDAMA – for choline content of foods. After FDA (2015).

Table 8. Qualified health claims currently in use in the USA (ref. Fiona Lalor, Patrick G. Wall, (2011).

· Qualified claim about cancer risk: tomatoes and/or tomato sauce and reduced risk of prostate, ovarian, gastric and pancreatic cancer; calcium and colon/rectal cancer and calcium and reduced risk of recurring colon/rectal polyps; green tea and reduced risk of cancer; selenium and reduced risk of cancer; antioxidant vitamins and reduced risk of cancer.
· Qualified claims about cardiovascular disease risk: nuts and reduced risk of heart disease; walnuts and reduced risk of heart disease; Omega-3 fatty acids and reduced risk of coronary heart disease; B vitamins and reduced risk of vascular disease; mono-unsaturated fatty acids from olive oil and reduced risk of coronary heart disease; unsaturated fatty acids from canola oil and reduced risk of coronary heart disease; corn oil and reduced risk of heart disease.
· Qualified claims about cognitive function: phosphatidylserine and cognitive dysfunction and reduced risk of dementia.
· Qualified claims about diabetes: chromium picolinate and reduced risk of diabetes.
· Qualified claims about hypertension: calcium and reduced risk of hypertension, pregnancy induced hypertension and reduced risk of pre-eclampsia.
· Qualified claims about neural tube defects: 0.8 mg folic acid and reduced risk of neural tube defects.

Figure 1. The Status of Probiotics in the United States, (Yunes et al., 2022).

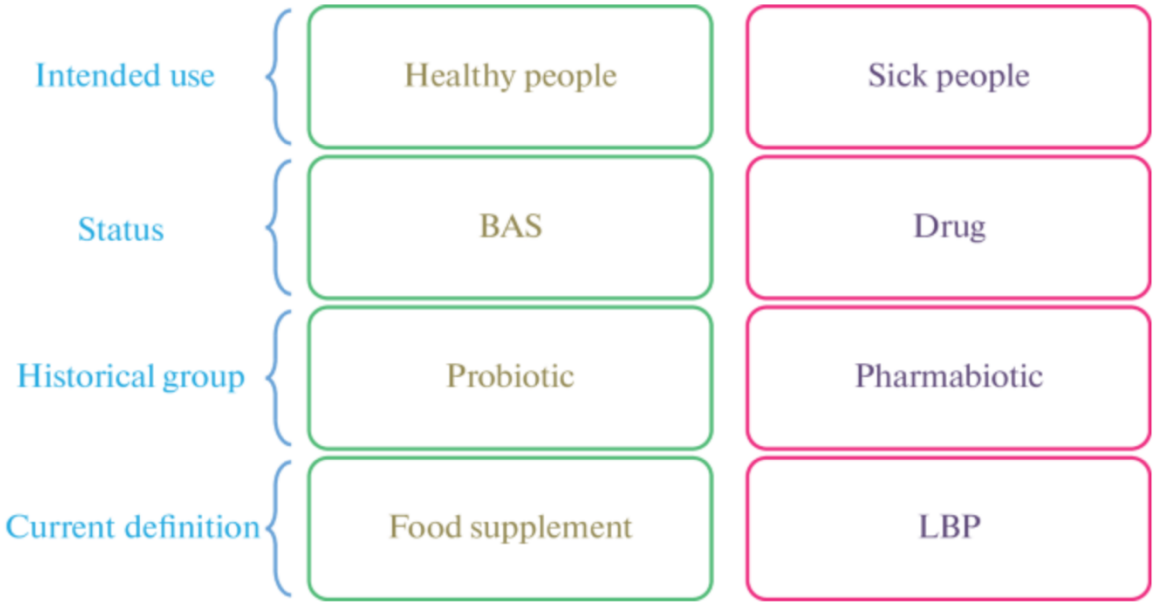
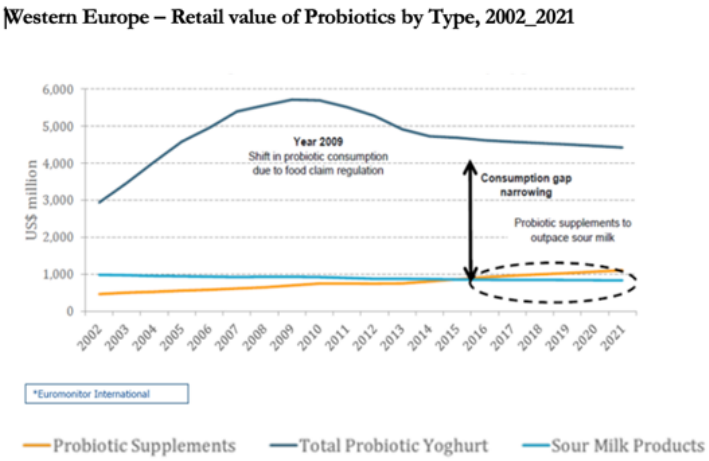


Figure 2. The Probiotics Market Growth between 2002_2021 (Euromonitor market data ipaeurope.org.).

A) The market growth in Western Europe.



B) The market growth in U.S.

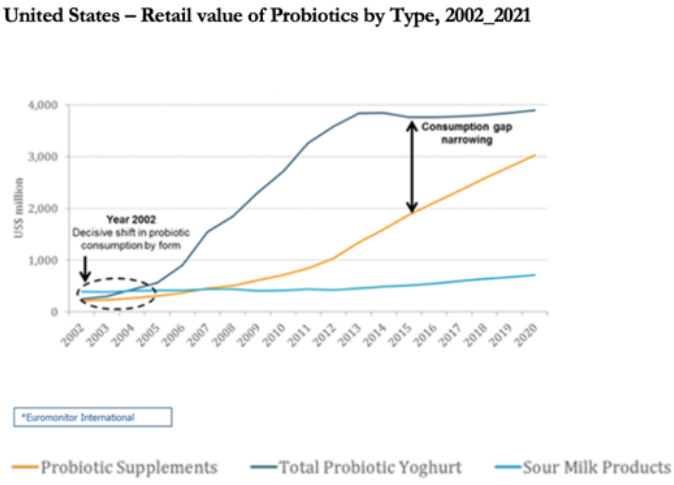
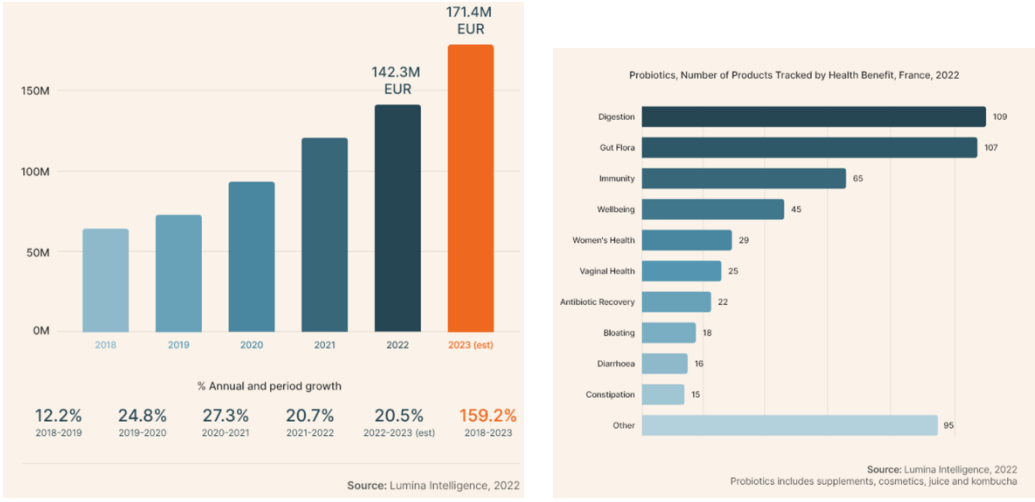


Figure 3. E-com Market growth of probiotics in Western Europe. Italy dominates with 38% of the e-commerce sales, equal to Germany and France combined. In half of the researched EU countries, e-commerce delivers already close to a quarter of the overall retail sales of probiotic supplements (Lumina Intelligence data ipaeurope.org.).

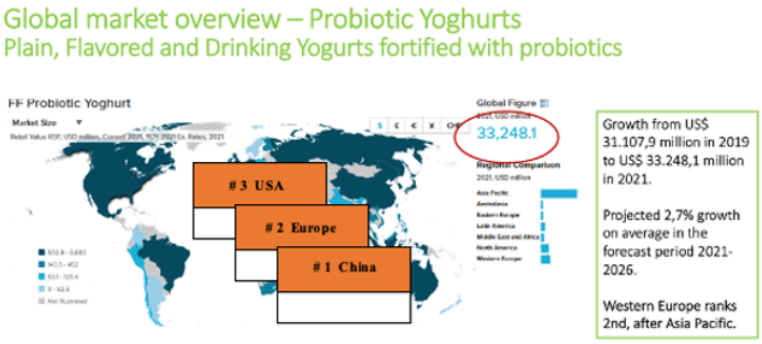


A) The E-com Market size and growth for probiotic supplements in 8-EU countries, 2018_20223. EU countries tracked by Lumina: Belgium, Germany, Spain, Finland, France, Italy, Poland, Sweden; B) Number of products by health benefit in France.

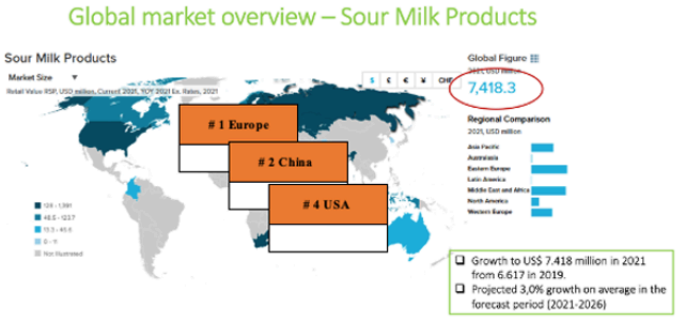
Figure 4. The position of the U.S. and the EU on the global market for probiotics, 2002_2021 (Euromonitor market data ipaeurope.org.).

A) U.S. ranks 1st in probiotic supplements

B) EU ranks 2nd and US ranks 3rd in probiotic yogurts after China



C) EU ranks 1st and U.S. ranks 4rh in sour milks after Middle East and Africa.



Tables to complement the Market Data on probiotics.

Table 1. L. rhamnosus LGG commercialized by Valio and other EU companies in probiotic dairy products (source: Papizadeh et al., 2016, Lactobacillus rhamnosus Gorbach-Goldin (GG): A Top Well-Researched Probiotic Strain, J Med Bacteriol., vol.5, 6: 46-59).

Products	Trade names
Commercial probiotic dairy products on the European market containing *L. rhamnosus* GG (LGG)	A-fil, Actimel, Aktifit, AB-piimä, Bella Vita, Bifidus, Bifisoft, BiofardePlus Biofit, Bioghurt, Biola, Biologic bifidus, Casilus, Cultura, Cultura Dofilus, Dujat Bio Aktiv, Ekologisk Jordgubbs Yoghurt, Emmifit, Everybody, Fit&Aktiv, Fjäll Yoghurt, Fundo, Gaio Dofilus, Gaio, LGG+, Gefilac, Gefilus, God Hälsa, Joghurt, Kaiku Actif, LC 1, LC 1 Go!, Le'Vive+, Milbona, , Onaka, Öresundsfil, Philura, Probiotic drink, Probiotisches, ProViva, Pro X, ProViva, RELA, Verum, Vifit Vitamel, Vitality, Weight Watchers, Yogosan Verum, ViktVäktarna, Vitality, Vivi Vivo Yakult, Yoco Acti-Vit.

Table 2. A review of probiotic strains which are used in probiotic manufacturing companies (source: Papizadeh et al., 2016, Lactobacillus rhamnosus Gorbach-Goldin (GG): A Top Well-Researched Probiotic Strain, J Med Bacteriol., vol.5, 6: 46-59).

Probiotic Species	Strain	Company	Ref.
Bifidobacterium animalis	Bb-12	Chr. Hansen	86, 87, 88
Bifidobacterium bifidum	Bb-11	Chr. Hansen	89
Bifidobacterium infantis	Shirota Immunitas	Danone® Yakult	11
Bifidobacterium lactis	Bb-02 Lafti™ B94	DSM	2, 90
Bifidobacterium longum	BB536 SBT-2928 UCC 35624	Morinaga Milk Industry Snow Brand Milk Products UCCork	3, 11, 85
Bacillus lactis	DR10	Danisco (Howaru™)	91
L. acidophilus	LA-1/LA-5 NCFM DDS-1 SBT-2062	Chr. Hansen Nebraska Cultures Snow Brand Milk Products Rhodia	11, 92-95
L. casei	Shirota Immunitas	Chr. Hansen Danone Yakult (Yakult®)	11, 96
L. fermentum	RC-14	Chr. Hansen Urex Biotech	11
L. helveticus	CECT 4305 LMG 13555 B02		11

Table 3. Commercial examples of probiotic products (source: Siró et al., 2008. Functional food. Product development, marketing and consumer acceptance--a review. Appetite 51(3): 456–467).

Some commercial examples of probiotic products

Brand/trade name	Description	Producer
Actimel	Probiotic drinking yogurt with *L. casei Imunitass*® cultures	Danone, France
Activia	Creamy yogurt containing *Bifidus ActiRegularis*®,	Danone, France
Gefilus	A wide range of LGG products	Valio, Finnland
Hellus	Dairy products containing *Lactobacillus fermentum ME-3*	Tallinna Piimatööstuse AS, Estonia
Jovita Probiotisch	Blend of cereals, fruit and probiotic yogurt	H&J Bruggen, Germany
Pohadka	Yogurt milk with probiotic cultures	Valašské Meziříčí Dairy, Czech Republic
ProViva	Refreshing natural fruit drink and yogurt in many different flavours containing *Lactobacillus plantarum*	Skåne mejerier, Sweden
Rela	Yogurts, cultured milks and juices with *L. reuteri*	Ingman Foods, Finland
Revital Active	Yogurt and drink yogurt with probiotics	Olma, Czech Republic
Snack Fibra	Snacks and bars with natural fibers and extra minerals and vitamins	Celigüeta, Spain
SOYosa	Range of products based on soy and oats and includes a refreshing drink and a probiotic yogurt-like soy–oat product	Bioferme, Finland
Soytreat	Kefir type product with six probiotics	Lifeway, USA
Yakult	Milk drink containing *Lactobacillus casei* Shirota	Yakult, Japan
Yosa	Yogurt-like oat product flavoured with natural fruits and berries containing probiotic bacteria (*Lactobacillus acidophilus, Bifidobacterium lactis*)	Bioferme, Finland
Vitality	Yogurt with pre- and probiotics and omega-3	Müller, Germany
Vifit	Drink yogurts with LGG, vitamins and minerals	Campina, the Netherlands