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Doctoral Thesis

Effectiveness of Regulatory Frameworks in Facilitating Industry Convergence and Innovation: A Case Study of the Functional Food Industry

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Contents

ABSTRACT

This thesis, titled 'Effectiveness of Regulatory Frameworks in Facilitating Industry Convergence and Innovation: A Case Study of the Functional Food Industry', aims to analyze corporate behavior within the functional food industry during a period of regulatory transition. The study adopts a perspective of industry convergence to elucidate the effects of regulations on innovation in the healthcare industry, and to propose a system design that fosters a market conducive to health promotion. The thesis is divided into four chapters.

Chapter 1 presents a background for the research. It expounds upon the concept of the industry convergence and explores the relationship between regulation and innovation within the healthcare sector. It also presents an overview of the functional food industry in Japan, the regulatory system governing it, and the ongoing transition in regulations. Regulation plays a significant role in driving convergence, particularly on the demand side, as deregulation encourages new companies to enter the market and promote convergence. However, limited research exists on how regulation affects supply-side convergence through corporate research and development (R&D) activities. Understanding this intricate relationship is vital for both convergence theory and innovation science. Regulations can impact corporate behaviors by imposing compliance costs and offering incentives for compliance, thereby either promoting or restricting innovation. The impact of regulation on innovation is influenced by various factors on both the regulatory and firm side, making it challenging to fully understand this relationship in a unified manner. By combining convergence theory and regulatory theory, a new perspective can be gained, providing a broader understanding of the relationship between regulation and innovation. To comprehensively examine the relationship between regulations and firms from a convergence theory perspective, a case study focusing on changes in the Japanese supplement industry resulting from regulatory changes is deemed suitable. Empirical and quantitative analyses of company behavior in response to functional food regulations in Japan would provide insights into the impact of regulations on firm behavior and industry convergence. This study specifically centers on two regulations: Good Manufacturing Practice (GMP), which ensures quality and supply safe products, and the Food with Function Claims (FFC), which governs labeling for efficacy demonstration and consumers access to appropriate products.

Chapter 2 provides a quantitative analysis of GMP, the risk-side regulation for quality and safety, along with complementary interviews. The study analyzed the relationships between company characteristics and the adoption of GMP among 90 manufacturers in the dietary supplement industry in Japan. A binomial logistic regression analysis showed three factors that positively and significantly effect a company's adoption of GMP: revenue-based company size (odds ratio = 1.04, $p = 0.019$), possession of a manufacturing license for pharmaceutical products (13.7, $p = 0.003$), and the number of product categories manufactured by the company (3.93, $p = 0.00009$). These findings provided insights into the factors shaping the adoption of GMP, particularly highlighting the role of pharmaceutical manufacturing expertise, knowledge and technology convergence, and the relationship between regulatory compliance and the end-product manufacturer.

Chapter 3 offers a quantitative analysis of FFC, the benefit-side regulation for functionality. Utilizing a dataset of Japanese dietary supplement manufacturing companies (n = 169) and their products (n = 731) in 2019, the study revealed that companies newly entering the FFC system tend to be smaller in scale compared to existing companies ($p < 0.01$, Wilcoxon rank sum test). Furthermore, companies with FFC products exhibited higher revenue growth ($p = 0.01$). The study also found that

external clinical testing type FFC products were evaluated their functionality based on more papers, than in-house clinical testing type ($p < 0.01$). A multiple regression analysis revealed that FFC product sales increased with in-house clinical testing (coefficient: 26.8, $p < 0.0001$), diverse active ingredients (coefficient: 7.6, $p < 0.001$), and claims of new functions (coefficient: 10.2, $p < 0.05$). These findings suggested that the deregulation brought about by the FFC system, led to the entry of predominantly smaller retailers into the regulated market, resulting in increased diversity among market players. The FFC system facilitated the utilization of accumulated knowledge and fostered the development of competitive and high-value products through innovative efforts by companies.

Lastly, chapter 4 delves into the encompassing FFC system, which incorporate both benefit-side and risk-side regulations. The chapter suggested that bundling these regulations structurally facilitated their implementation and that firms' actions to comply with regulations promoted supply-side convergence. Based on the regulatory design requiring a perspective relative to regulations in neighboring industries and a perspective of path-dependency for firms to respond to regulations, a framework regarding convergence starting from regulations was proposed. It is expected that they will lead to appropriate regulation design in the healthcare industry. Additionally, a framework for discussing strategic options for diverse firms was proposed.

Overall, this doctoral thesis examines the impact of regulatory changes on corporate behavior, industry convergence, and innovation. The findings contribute to the fields of regulatory science and convergence theory, offering valuable insights for designing of effective regulatory systems and fostering a market environment conducive to health promotion.

1 Introduction

1.1 Background

1.1.1 Innovation and regulation in healthcare

Due to the increase in chronic diseases and the rising cost of medical care, innovation is expected in the medical and healthcare fields [1]–[6]. In Japan, the government aims to extend healthy life expectancy by promoting self-medication through the use of healthcare products and services. By doing so, it is expected to improve lifestyles and prevent chronic diseases, and to create a 30 trillion yen "healthcare industry" separate from the existing market under the public insurance system [7]. Table 1-1 summarizes the healthcare industry exemplified by the Ministry of Economy, Trade and Industry, comparing medical and non-medical industries.

In the medical and healthcare industries, the role of regulations related to product safety, efficacy, and quality is important in order to protect consumers and avoid market failure [1]. Compared to the medical domain, the newly forming healthcare domain has not yet fully developed appropriate institutions [6]. This is because at the dawn of a newly arising industry, it starts with no institutions and regulations, followed by the gradual establishment of appropriate regulations [8]. Thus, there is a risk of market failure, including disadvantages to consumers and impediments to market formation. Appropriate institutional design is important to achieve consumer protection while allowing companies to innovate in free competition and promoting the healthy development of the industry. In mHealth and other areas, regulatory design is being co-evolved with technological development [6], [9]. How to place regulations to function effectively and, consequently, how to induce innovation is also a point of contention from an innovation science perspective [10]–[14].

Table 1-1 Medical and non-medical sector and health care industry.

Classification of Methods	Non-medical: for healthy people (health maintenance and promotion)		Medical: for patients
		"Healthcare Industry" (by METI [7])	
Taken orally and acts on the body	Food	Functional foods	Pharmaceuticals
Exert an external effect on the body	Miscellaneous Goods / Home Appliances	Health equipment, Measurement equipment (Digital health)	Medical equipment
Obtain information on biological condition			Diagnosis
Maintain and improve the condition by moving the body	sports, exercise, travel etc.	Exercise service Esthetics and relaxation	Rehabilitation, Nursing care

Note: Created by the author based on METI [7].

1.1.2 Functional foods

This study focused on functional foods, particularly dietary supplements. In terms of products to be taken orally, there are pharmaceuticals in the medical domain and foods in the non-medical domain. Functional foods are foods that differ from ordinary foods in that they contain functional physiological components that are expected to have an effect on the body. They are expected to promote health, contribute to preventing diseases in an aging society, and have the potential to reduce the burden on public health, and are also being considered for use as a means of self-medication [15]–[17].

The concept of functional food has its origin in traditional Asian medicine and ancient texts, and was proposed in Japan in the 1980s. In this paper, "functional foods" are used to point the foods that offer health benefits beyond their nutritional value. Terms such as "functional foods" or "nutraceuticals" are widely used in the marketplace. They sometime have referred to as "Nutraceuticals and Functional Foods (NFF) [18]" or "Pharma-Nutrition Interface" [19]. Functional foods include not only ordinary shaped foods and beverages, but also dietary supplements, which are similar in form to pharmaceuticals, such as tablets and capsules.

Dietary supplements contain high concentrations of functional ingredients in tablets or capsules, and provide them the body efficiently similar to pharmaceuticals. The manufacturing process for dietary supplements is different from that of ordinary processed foods, and is rather similar to that of pharmaceuticals. Due to these characteristics similar to pharmaceuticals, dietary supplements are positioned adjacent to pharmaceuticals in food domain [18], [19]. As discussed below, a part of regulations for dietary supplements are also designed with reference to regulations for pharmaceuticals. From the viewpoint of the purpose of this study, clarifying effects of regulations in an industry convergence process, dietary supplements, existing in food domain adjacent to pharmaceuticals (i.e., boundary area between ordinary shaped food and pharmaceutical domains), and affected by pharmaceutical regulations, would be considered as a suitable research object. Therefore, this study focused specifically on dietary supplements.

Product

A dietary supplement is a product marketed in dosage form (e.g., soft and hard capsules, tablets, powders and granules, liquids) that differs from regular food products and contains ingredients with nutritional or physiological effects. A dietary supplement contains one or more of dietary ingredients such as a mineral, a vitamin, an amino acid, a medical herb or other physiological ingredients for use to supplement the diet by increasing the total daily intake. Nutraceuticals are of these nutritional supplements which are used for health purposes other than nutrition. Although there is no common international definition of dietary supplement, it is generally positioned between pharmaceuticals and food under the laws and regulations of many countries [20]. Dietary supplements are similar to pharmaceuticals in that they have a pharmaceutical-like form such as tablet, capsule, etc., and contain ingredients in higher concentrations than ordinary food. Dietary supplements were defined in this study as "foods containing ingredients with specific physiological functionality and having a special form different from that of ordinary foods, such as tablets or capsules", considered their characteristics of "ingredients" and "form" as existing definitions (Table 1-2).

Table 1-2 Definitions of dietary supplements

Definition	References
Foods in the form of tablets, capsules, powders, liquids, and so forth, made from naturally occurring extracts that are fractionated, purified, chemically reacted, or otherwise different in composition from those naturally occurring or made from chemically synthesized products.	Consumer Affairs Agency [21]
Products in tablet or capsule form in which specific ingredients are concentrated.	Ministry of Health, Labour and Welfare [22]

Market

The dietary supplement market is steadily expanding in response to increasing expectations and food innovation [23]–[25]. The functional food industry consists not only specialized producer, but a variety of companies, including food companies, pharmaceutical companies, retails, start-ups using new functional ingredients or local specialty foods, new entrants from other industries, and OEMs. In Japan, the functional food market is 2 trillion yen and dietary supplements market is 1.0 trillion yen. These markets, existing between pharmaceuticals market (10 trillion yen in Japan) and food market (38 trillion yen in Japan) is relatively large in scale among healthcare products.

Proponents of so-called functional foods (i.e., both unmodified foods and dietary supplements, that are also known as nutraceuticals or nutrition supplements) claim that these food products potentially promote health, mitigate lifestyle-related chronic diseases, and reduce public health-care costs. Driven partly by consumers' desire to take a proactive approach to their health care, the global market for dietary supplements has steadily expanded along with increasing consumer acceptance and food technology innovation [23]–[26]. The dietary supplement industry incorporates various business entities, such as pharmaceutical and food companies, small and mid-sized enterprises (SMEs), start-up companies that use novel functional ingredients or local specialty foods, new entrants from other industries, and original equipment manufacturers (OEMs) [27], [28].

Regulation

Functional foods are regulated by the United States Food and Drug Administration (FDA) under the authority of the Federal Food, Drug, and Cosmetic Act, even though they are not specifically defined by law. In the US, functional ingredients added to foods to make them "functional foods" must be approved by the FDA as a food ingredient. In Japan, terms referring to "functional foods" or "dietary supplements" are not defined by law and no legal system exists to comprehensively regulate dietary supplements and functional foods. Some of them are covered by regulation system of foods with health claims as mentioned later. Japanese regulatory is attributed to the historical path-dependency of a repeatedly revised system[27].

Although internationally harmonized regulations have not yet been established, dietary supplements are positioned institutionally in an area adjacent to pharmaceuticals among foods. Based on product characteristics that are similar to those of pharmaceuticals, some concepts of regulations are also introduced based on pharmaceuticals, focusing on quality, safety, and functionality (corresponding to efficacy in pharmaceuticals). With regard to quality, Good Manufacturing Practice (GMP) based controls have been introduced for product manufacturing controls, which are modeled after those for pharmaceutical products. For safety and efficacy, evidence from clinical trials is used in some cases.

Academic research

On the academic side, Functional foods and dietary supplements have been the subject of research in industrial theory. Scholars of regulatory science and innovation management have discussed the influence of technological and regulatory trajectories and the path-dependent or creative mechanism of the dietary supplement industry [8], [29]–[33].

It is discussed that the functional food industry has emerged between the food industry and the pharmaceutical industry, while being influenced by both industries. The process and mechanism for development of the functional food industry have been discussed based on the path dependency of the pharmaceutical and food industries. Papachristos (2013) positioned the functional food industry as a newly emerging industry in the boundary area between the pharmaceutical and food industries, argued that the functional food industry emerged from the combination of resources, technologies, and capabilities owned by the two "parent" systems (pharmaceutical and food) [8]. Curran (2011) studied dietary supplements industry as examples of industrial convergence, highlighting the theory that new industry sectors can form from the fusion of knowledge, technology, and businesses from diverse industries [32], [33]. Convergence is also induced by policies and regulations as triggers. Deregulation is one of the driving forces of convergence [34]–[38].

Regulations on functional foods are still in a formative and fluid stage, and mutual tensions have existed among stakeholders such as regulators, producers, consumers, and academia [39], [40]. While consumers tend to demand free access to products and companies seek to ensure free expression, the regulators aim to ensure product safety and prohibit inappropriate labeling [31]. Under a fluid regulatory system, some companies have accelerated to develop functional food by open innovation based on sharing knowledge and information from cooperative networks of external partners to accelerate R&D efforts in creating functional foods products [41].

Thus, the knowledge and technology resources of the food and pharmaceutical fields are integrated and this industry–academia collaboration results in open innovation in the functional foods sector, and regulation—which has the dual role of promoting innovation and impeding innovation—controls this wide variety of actors [30], [31], [41], [42]. Convergence theory would provide a useful perspective on the discussion of the relationship between regulations and firms and the implications for innovation, in discussing regulations for dietary supplements.

1.1.3 Japan's functional food market

Japan's functional food market is on the scale of 2 trillion yen, and the supplement market is on the scale of 1 trillion yen, making it one of the largest markets in the world [15]. The "Food with Health Claims (FHC)" system has been established as regulation for functional foods. In the market, products that comply with FHC system and those that do not have coexisted. The market size of dietary supplement products compliant with FHC system is approximately 250 billion yen, while the market size of non-compliant products is approximately 700 billion yen. The dietary supplement industry straddles the boundaries of FHC system, and is characterized by its larger scale outside the system (Figure 1-1). Furthermore, the FHC system consists of three segments. The market size for each of these segments is shown in Table 1-3.

In Japan, the markets for dietary supplements with "Foods for Specified Health Use (FOSHU)" and "Foods with Nutrient Function Claims (FNFC)" were quite small compared to that outside the regulation was larger. After the start of the FFC system in 2015, a market for dietary supplements under FFC regulation has expanded rapidly. Regulatory changes in Japan have

impacted significantly on dietary supplements especially. To observe the influence of regulation, dietary supplements in the Japanese market would be suitable research subjects. As shown at appendix 1, the complexity of the Japanese system is attributed to the path dependency of the system, which has been repeatedly expanded and modified. In recent years, regulatory reforms have added to a complexity of the FHC system.

In Japan, functional foods have been institutionalized by the FOSHU system in 1991. In 2015, the "Food with Function Claims (FFC)" system was established. Under the FFC system, a functionality of a product can be labeled by submitting a notification, which is a simpler administrative procedure. In addition to "clinical trials on the product," systematic review (SR) of publicly known literature on the ingredient became acceptable as the basis for the functional claim. The FFC system is a deregulation against the FOSHU system, as it allows for the launch of products that conform to the FHC system at a lower cost than the FOSHU system. On the other hand, FFC also has the aspect of tightening regulations on quality control. The notification guidelines for FFC [21] published by the Consumer Affairs Agency (CAA) stated that “for processed foods in the form of dietary supplements, manufacturing process control based on GMP is highly desirable”. That means CAA effectively made GMP mandatory for dietary supplements under FFC system.

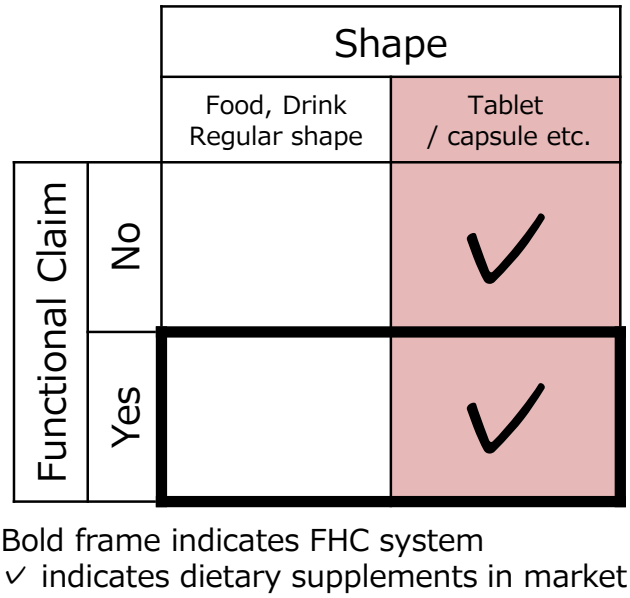

Figure 1-1 Relationship between shape and regulation of dietary supplements in Japan.

Table 1-3 Market segment categorized by shape and regulation, and each market size

Market size in 2015 Unit: billion yen		Food	Beverage	Dietary supplement	Total
So-called health foods (not labeled)		2,961	5,759	7,560	16,280
Food with health claims (labeling allowed)	Food with nutrient function claims	127	273	714	1,114
	Foods with function claims	57	105	138	300
	Food for specified health use	1,196	2,493	131	3,820
Total		4,341	8,630	8,543	21,514

Market size in 2020 Unit: billion yen		Food	Beverage	Dietary supplement	Total
So-called health foods (not labeled)		3,174	6,091	7,185	16,451
Food with health claims (labeling allowed)	Food with nutrient function claims	127	505	801	1,433
	Foods with function claims	281	1,666	1,622	3,569
	Food for specified health use	1,038	2,047	133	3,218
Total		4,620	10,309	9,742	24,671

Source: HB Foods Marketing Handbook 2017 and 2022 (Fuji Keizai)[43]

1.2 Literature review

Prior studies related to this study were broadly divided into two categories: industry theory, which focuses on convergence, and institutional theory, which is concerned with regulation and innovation. In terms of an industrial theory, a functional food industry has been academically studied based on a model of industry convergence (fusion, integration, and blurring of industry domains). In studies focusing on stages and starting points leading to convergence, influencing factors such as knowledge and regulation have been found [44]. In terms of an institutional theory, regulation has been academically discussed from a view point of its aspect: it is necessary to eliminate market failures, but it also has aspects that hinder a market activation and inhibit innovation. Meanwhile, appropriate regulation should lead to market revitalization and consumer benefit. In the healthcare area, as well as in the area of functional foods, research is progressing based on the nature of regulation.

1.2.1 Industrial Theory of Functional Foods

Industry Convergence

In industry theory, functional foods has been discussed an industry resulting from the industrial convergence of pharmaceuticals and foods [8], [29]–[31], [45], [46]. Industry convergence is "a blurring of industries distinguished by products, actors, knowledge and learning processes, technologies, inputs, demand structures, competition, and processes (standards or regulations)". Industry convergence blurs existing industry boundaries and is also an opportunity for innovation because it plays an important role in the formation of new markets and industries. Industry convergence has been observed in many industries, including telecommunications, computer, consumer electronics, cosmetics, and functional foods. Researches for Industry convergence focus on types and processes of convergence to provide some perspectives.

Industry convergence, in terms of the movement of the objects involved, can be categorized as substitutive convergence or complementary convergence [44]. Substitutive convergence represents the process by which industries begin to merge with one another in the exact same location as at least one other industry. For example, smart phones can be thought of as a fusion product of cameras, cell phones, and portable computers via substitutive convergence. In contrast, complementary convergence represents the process by which industries are moved or stretched from their previous separate locations to a new common location. New sectors have not previously been part of their own separate industries. The new industry complements the existing industry. In case of functional foods, complementary convergence of food industry and pharmaceutical industry would bring a new product class with added value and form a new industry. It has complemented existing industries, because it has not replaced the demand for nutrition in the traditional food industry nor the demand for treatment in the pharmaceutical industry [46].

Industry Convergence of functional food sector

Industry convergence studies have discussed various influences on functional foods from the pharmaceutical and food industries [8], [29]–[31], [45], [46]. Bröring (2006) states that technological competence is introduced from the pharmaceutical industry and marketing competence from the food industry [30]. Bornkessel (2014) studies the convergence of the pharmaceutical and food industries in the converging field of functional foods in Europe bibliometrically from the perspective of knowledge, technology, regulation and competence. The study analyzes the status of utilization of food functional claims by industry sector

as a step toward industrial fusion from a regulatory perspective. It points out that food companies are more active in cross-industry collaboration than pharmaceutical companies and leverage their high level of expertise in consumer marketing. Thus, the functional food industry is influenced by different kinds of influences from the pharmaceutical and food industries [47]. Lalitnorasate (2016), in a study of Japanese food for specified health uses, showed that mutual knowledge diffusion and collaboration between the life science and food industries occur to develop the knowledge and competencies required in the health food sector [31].

Industry convergence processes

Industry convergence progresses through multiple stages as shown in Figure 1-2. Hacklin (2009) proposed a model in which convergence occurs in four stages: knowledge, technology, application, and industry, which converge in a co-evolutionary, sequential manner [32]. Similarly, Curran (2010) proposed a convergence process model of four phases, namely science, technology, market, and industry convergence [48]. A model has also been proposed in which industry convergence does not go through all phases, but evolves as a result of new products/services or new business models [33]. In any case, convergence from the supply side involves gradual convergence at the scientific knowledge or technology level to reach the final stage of industry convergence. Since all convergence processes blur the boundaries between industries, firms face with new technologies, consumers, and needs.

Since industry convergence proceed two way, industry convergence can be categorized as supply-side originated and demand-side originated [48]. Convergence on the supply side is mainly due to technological innovation originating from technology and knowledge. The innovative use of new technologies developed from scientific knowledge plays as an important internal factor [32]. An example of convergence on the demand side is bancassurance, which is the result of the convergence of the banking and insurance industries [33]. The new business model may intersect two previously disparate industries. Convergence on the demand side is driven by changing consumer needs and regulatory changes. Convergence by regulation occurs at a faster rate than that caused by changing needs, and its speed is affected by the establishment or relaxation of regulations [49].

Factors that influence the drive for industry convergence include technology and knowledge adoption, as well as regulatory and needs changes [37]. As for studies focusing on regulations, that we focus on in this study, deregulation is the driving force of convergence on the demand side to led to the entry of firms without highly technological development [34]–[38]. Some cases, such as environmental industry, have been identified where knowledge has been fused to respond to regulations and technological development has progressed [49]. Figure 1-2 shows the drivers of convergence.

Corporate Behavior in Convergence

In the functional food industry resulting from the convergence of pharmaceuticals and food, corporate strategies are path-dependent and diverse. For example, based on the Canadian case study of functional foods, companies were classified into three groups in terms of scope of technology development, i.e., whether to utilize existing technology or to develop proprietary technology, and route to commercialization, i.e., BtoB or BtoC [18]. The authors proposed a framework consisting of a spectrum of industry affiliation with Pharmaceutical/chemical companies and Food companies at both ends, indicating innovation strategies in the convergence of functional foods. Pharmaceutical/chemical companies, at one end of the spectrum, consist

mainly of technology-driven BtoB companies that focus on developing new technologies that take advantage of biotechnology and other technologies and commercialize them in the BtoB market. The other extreme, the group led by food companies, consists of low-tech food industries and their affiliates, and focuses on developing consumer-oriented products by leveraging existing technologies, rather than developing new technologies. When these companies lack technical capacity, there may be forward integration in the supply chain, working with ingredient suppliers, not only receiving supply of ingredients, but also receiving applied knowledge, such as formulation of food matrix and regulatory compliance. In between these two poles, there is a group of companies that launch their products to the BtoC market, consisting of R&D projects that combine the development of new technologies with the development of final consumer goods. When adopting this innovation strategy, companies face a resource gap that requires both scientific / technological approach and consumer marketing, which encourages the acquisition of new capabilities and collaboration between companies. Some companies, named "Upgrader", would take an innovation strategy to upgrade existing products by applying new knowledge and technology. They would upgrade products by scientifically demonstrating the physiological and scientific properties of ingredients and products and obtaining functional claims. In this case, resources for clinical data and scientific research are often obtained from CROs.

The ability of firms to confront new demands is restricted by path dependency [50], [51]. Thus, the industry convergence process creates a tension between firms' path dependency. Firms in similar industries have closer cognitive distances and greater absorptive capacity than firms in different industries, so industries may converge after firms adopt or integrate knowledge from other industries [38].

Evaluation Indicators for Convergence

Industry convergence has been quantitatively analyzed using evaluation indicators according to the stage of convergence. Knowledge convergence and technology convergence have been measured by bibliometric methods, such as academic literature and patent analysis. The level of science/knowledge convergence has been measured through research article data and patent data, such as co-citation, co-wording, or co-authorship data [32], [46]. For technology convergence, patent data, such as co-citation or co-categorization data, could be primarily used [31], [33], [46]. Market convergence could be measured through bibliometric information such as newspapers and news articles, industry linkage tables, firm product characteristics and market activity data [32], [38], [52]

Where industries have converged, a variety of data sources have been used, ranging from company micro activity data to patent, press, or IOT data. Despite the variety of methods used, measurements of convergence are still developing [53]. To summarize the above, viewpoints of convergence theory, such as steps of convergence process and influencing factors were organized in the Figure 1-2.

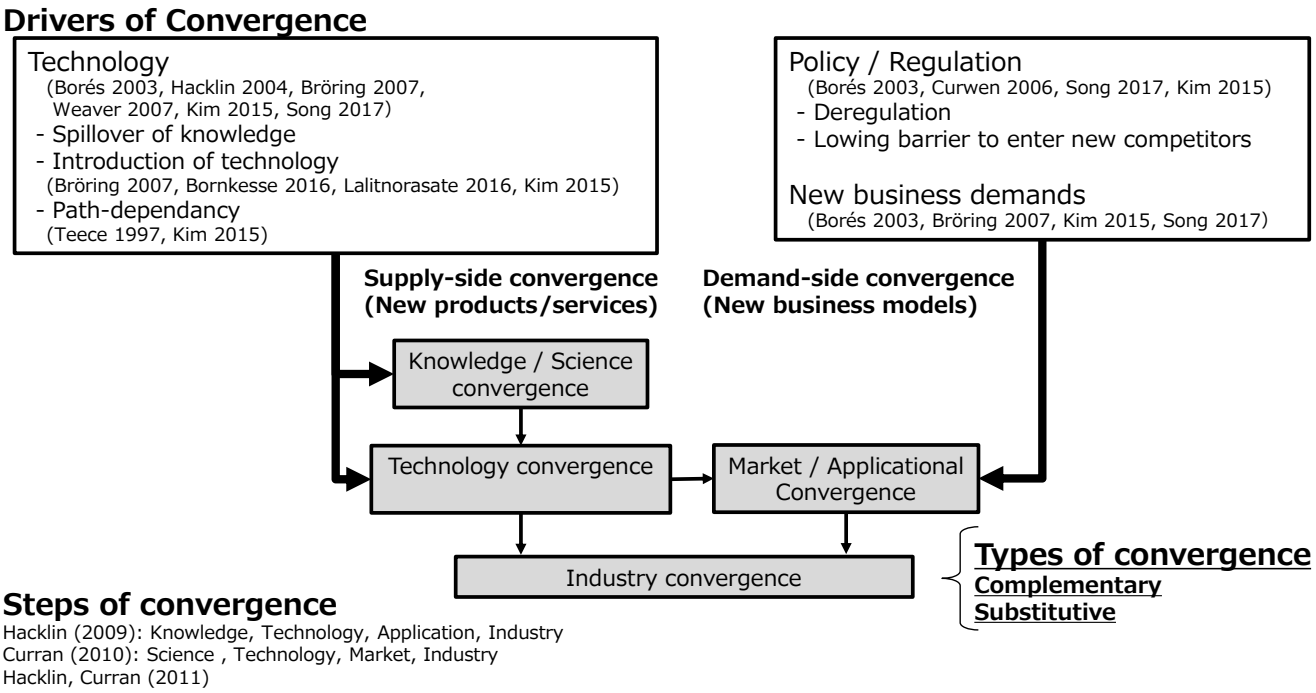

Figure 1-2 Industry convergence framework

1.2.2 Studies about Regulation and Innovation

Types of Regulation

According to the OECD, regulations refer to a variety of instruments by which governments set requirements for businesses and citizens [12], [54], [55]. Regulations include laws, formal and informal orders and subordinate rules issued by governments at all levels, and rules issued by nongovernmental organizations and self-regulatory organizations to which governments have delegated regulatory authority. Regulations are broadly classified into economic, social, and institutional regulations [12], [55]. Economic regulation is designed to avoid market failures caused by the actions of players within a market. Economic regulation intervenes directly in market players' decisions, such as pricing, competition, market entry, and exit. Market entry regulations and price controls are put in place to protect against overly intense competition on the demand or supply side. For pharmaceuticals, price regulation is imposed through official pharmaceutical prices. Regulations on utilities are also put in place in some markets, such as energy infrastructure, where a single supplier or public provision of goods and services is more efficient in terms of static allocative efficiency.

Social regulation aims to reduce or prevent negative externalities and protect public interests such as health, safety, and environment. The influence of social regulation on economic would be significant, although they may be of secondary concern or unexpected. Because of the presence of negative externalities, particularly in the environmental realm, environmental regulation has been a policy issue in recent years, with cases from a variety of sectors being actively analyzed in academia. Pharmaceutical regulation plays important role to prevent patient from exposure to harmful and unsafe drugs whose risks outweigh the benefits [55], [56]. In addition, labor and consumer safety regulations are also social regulations, since products

and production processes can cause harm to consumers and workers. Institutional regulation is regulation based on institutions, for example, regulations on intellectual property rights. Intellectual properties are important factors in innovation and are the subject of research.

Two aspects of regulation on innovation

Historically, regulations have been set up to prevent market failures due to external diseconomies such as pollution, and classically, requiring firms to reduce externalities has been thought to narrow firms' options and thus reduce their profits [57], [58]. Apart from the original purpose for which regulations were set, it has been noted that regulations have a multifaceted impact on corporate behavior and influence innovation. First, compliance with regulations increases the costs borne by firms, limits their options, and reduces the resources available for investment in R&D. As a result, it can stifle technological progress and innovation [58]. In addition, regulations that prescribe, standardize, and require conformity with performance and safety standards for products and services may discourage firms' efforts to develop new products [59], [60]. On the other hand, some regulations, such as patent protection, increase the incentive to invest in R&D. The impact on innovation depends on the compliance costs and the extent of incentive effects. If incentives outweigh compliance costs, there is a positive impact on innovation, and vice versa, there is a negative impact. The impact of regulation on firm innovation can be positive or negative, depending on the characteristics of different industries, firms, and technologies. In order to induce investment in innovation, process implementation, and new product release, regulations must be well designed [10]–[14].

Deregulation, which lowers or removes barriers to competition, often encourages market entry by new competitors with alternative technologies or business models. Conversely, stricter regulation may encourage innovation. In the environmental sector, innovation was spurred by the development of technologies that responded to stricter regulations and the launch of products that responded to those regulations [11], [61].

"Porter hypothesis" regarding Regulation and Innovation

The so-called "Porter hypothesis" is well-known regarding the relationship between regulation and innovation. Porter argued that appropriately designed environmental regulations stimulate technological innovation that leads to cost savings and quality improvements, offsetting the cost of complying with the regulations, and that as a result, firms in countries that introduce environmental regulations ahead of other countries gain a competitive advantage over firms in other countries in international markets [11]. In other words, challenging regulations are the catalyst for innovation, and the technology developed gives firms a competitive advantage. The Porter hypothesis is classified into three hypotheses: a narrow version, a weak version, and a strong version [11], [62]. The narrow version of the hypothesis is concerned with how to design regulations. It holds that environmental regulations that allow for corporate ingenuity are more likely to induce innovation. They argued that flexible, outcome-specific regulations, such as pollution taxes and tradable permits, provide greater incentives for firms to innovate than normative, process-specific regulations, such as technology-based standards.

The extent to which regulation affects innovation is a point of contention between the "weak" and "strong" versions of the hypothesis. The "weak" version of the hypothesis is that environmental regulations induce innovation that reduces environmental impacts by changing inputs and the relative prices of goods and services produced. However, whether this innovation results in improved competitiveness of firms or is socially beneficial is not questioned. The "strong" version of the

hypothesis is that well-designed environmental regulations induce innovations whose benefits outweigh the costs of complying with the regulations by broadening firms' perspectives and encouraging them to pursue previously unnoticed opportunities for innovation. It is argued that the exogenous "shock" of environmental regulations can make firms aware of the existence of various inefficiencies and attempt to correct them, thereby enabling them to reduce costs and, ultimately, innovate, which may improve their financial situation.

The Porter Hypothesis was controversially criticized by neoclassical economists such as Palmer, who argued that if it is possible to increase profits by tightening environmental regulations, no rational firm would structurally miss such an opportunity. The Porter hypothesis has since been tested in various cases [12], [55], [57]. The "narrow" version has limited support, the "weak" version has strong support, and the "strong" version is not well supported [57], [58]. Depending on the time scale, the impact on innovation may vary [55]. A number of studies suggested that environmental regulations would have a positive impact on innovation in the long run, even when they have a negative impact in the short run [55], [58]. In some cases, environmental regulations have induced innovation by indirectly increasing innovation spending of upstream firms in the supply chain [63], and the innovation impact of regulations can extend beyond the directly regulated firms to the wider industrial ecosystem.

Influencing Factors of Regulation and Company on Innovation

The impact of regulations other than environmental regulations on innovation has also been examined. Blind organized the relationship between regulation and innovation based on the broad categories of economic, social, and institutional regulation[12], [55]. Economic regulation affects innovation both promotively or restrictively. For example, regulations on prices increase the incentive to innovate if they ensure that innovating firms have a certain minimum revenue or reduce demand-side risk. Market entry regulations are positive for established firms because they reduce competitive pressure and encourage allocation of resources to risky innovation activities, but negative for industry-wide innovation because they discourage market entry by innovative new entrants [55]. In this case, deregulation promotes innovation by lowering the barriers to entry.

Many previous research about effects of social regulation on innovation has focused on analyzing environmental regulation because of the social, economic, and policy, importance of environmental issues. Outside of environmental regulations, there has been only a limited number of areas where the relationship between social regulations and innovation has been analyzed, with research focusing on regulations related to the protection of workers' health and safety and regulations related to product and consumer safety [12], [55]. While occupational safety regulations limit firms' innovation activities by burdening them with compliance costs, they also create temporary market entry barriers and create incentives for existing firms to develop processes that are safer for workers by providing monopoly benefits. Although empirical evidence is insufficient, the net effect is that regulation acts somewhat negatively on innovation. While product and consumer safety regulations limit firms' innovation activities by burdening them with compliance costs, they also create incentives to develop innovative new products that will gain consumer acceptance and promote diffusion. Although limited and ambiguous evidence, the net effect is that regulation acts somewhat positively on innovation[12], [55]. Flexible regulations, such as incentive-based regulations and performance standards, tend to promote innovation by maximizing implementation room for firms to implement cost-effective and commercially attractive solutions [11], [12]. Regulations that promote more complete market information also promote

innovation by reducing information asymmetries on the consumer side and promoting innovative solutions on the producer side [55].

In a review of the impact of government regulation on innovation in the United States, Stewart (2010) noted that there are three aspects of regulation that affect innovation: flexibility, information, and stringency [64]. Flexibility represents the number of implementation paths available to firms for compliance. Information assesses whether regulations promote complete information in the marketplace. Regulations that reduce information asymmetry may offset some of the burden of compliance by responding to the regulation. In terms of consumer-firm information asymmetry, regulations may promote more complete information by acting as proof of product quality to consumers, thereby providing additional compliance value to producers. For example, in pharmaceuticals, regulatory pre-approval screening may serve as proof of quality and efficacy of new drugs, thereby increasing the value of new drugs in the marketplace, increasing firms' return on investment, and lowering compliance costs [64]. On the other hand, information asymmetry between regulators and firms leads to uncertainty about the return on investment of regulatory responses and increases compliance costs.

Stringency measures the extent to which regulations require compliance innovation and impose compliance burdens on firms, industries, or markets. Each aspect plays a role in determining the impact of regulation on innovation. In general, greater flexibility and more complete information promote innovation, while stringency increases the burden of compliance and discourages innovation. Firm behavior in response to regulation also depends on the scope of the regulation. If the scope of the regulation is narrow, firms may adopt strategies to modify their products or processes to fall outside the scope of the regulation. This is called evasive innovation, as opposed to compliance innovation, in which firms change products or processes to comply with regulations [64].

An analysis examining the impact of recent deregulation in Japan on firms' R&D activities points out that the impact from regulation varies depending on product characteristics and the size of the firm. In addition, a comparison of internal R&D expenditures and external R&D expenditures points to the possibility that deregulation may change the use of resources in research activities and promote open innovation through the externalization of R&D.

The Relationship between Regulation and Innovation with Firm Behavior

Thus, the direction (promotive or restrictive) and intensity of the impact of regulation on innovation depend on the type, scope, and nature of the regulation (flexibility, information, and stringency), as well as factors on the part of the regulated firm (industry area, firm attributes, product characteristics, etc.). The scope of regulatory impact can range from technologies directly related to the regulation to indirect effects on firm performance or the behavior of other firms in the value chain or firms outside the industry. The duration of regulatory impact can also range from short to long term, taking into account time lags. It should also be taken into account that the impact of regulations on innovation is not invariant over time. While the short-term impact can be restrictive for innovation, the long-term impact can be promotive. Since various factors, including those on the regulatory side and the firm side, are relevant, a unified understanding is not yet fully developed.

While a detailed analysis of the firm side based on individual firm attributes and behavioral principles is considered necessary, most previous studies on regulation and innovation have used industry-level aggregate data in specific regulations and industries. Few analyses have examined the impact of regulations on individual firm behavior and focused on innovation.

Each firm makes decisions about its behavior with respect to regulations under these influencing factors, balancing compliance costs with incentives to develop technology. Compliance costs not only reduce resources available for R&D investment, but also discourage innovation by causing existing firms to leave the industry and discouraging new entrants. In addition, inflexible regulations deprive firms of room for technological development. On the other hand, incentives for technological development include the competitive advantage gained from direct compliance with regulations, as well as the expectation of several indirect effects, such as productivity gains from savings in resources made relatively more expensive by compliance costs.

To summarize the above, the relationship between regulation and innovation and firm behavior in the Figure 1-3.

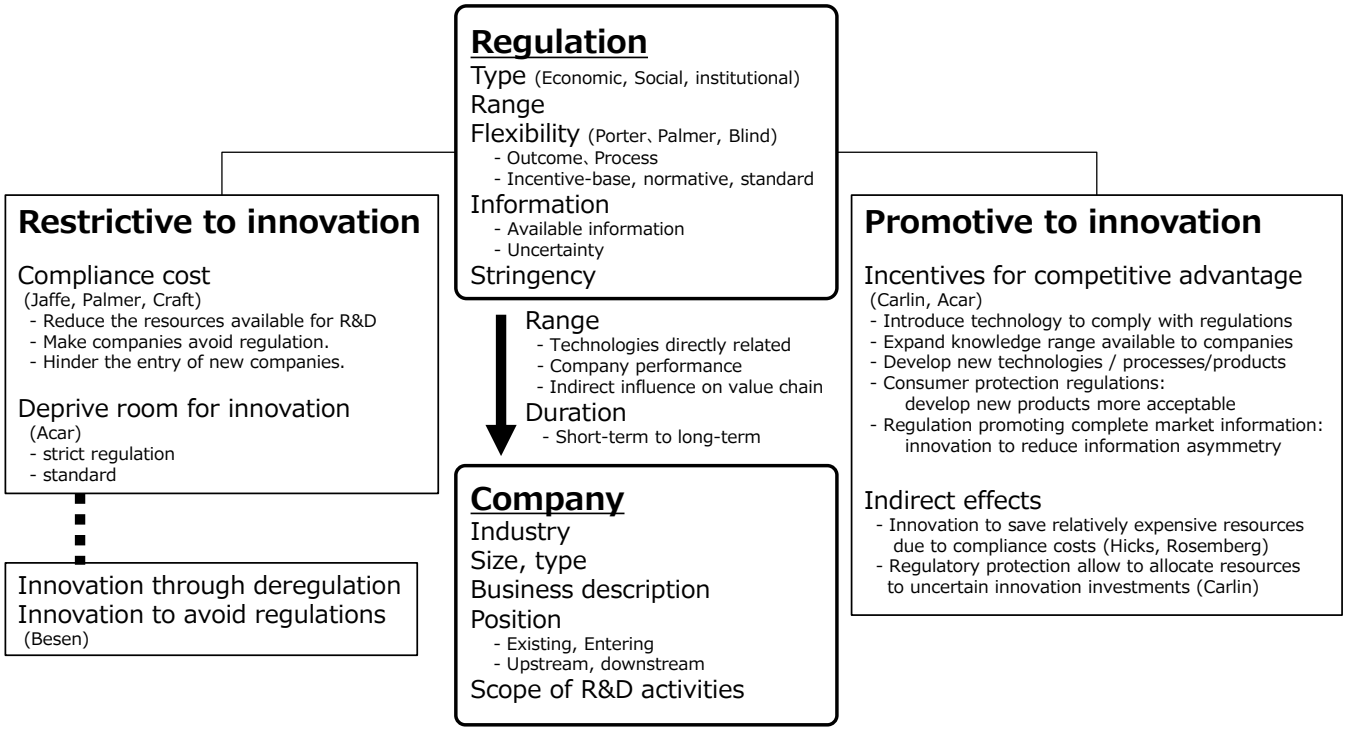

Figure 1-3 The Relationship between Regulation and Innovation with Firm Behavior

1.2.3 Regulatory Studies of Healthcare Sector and Functional Foods

Regulation in the medical and healthcare industry

In most developed countries, the medical sector is heavily regulated by policy makers to protect consumer safety and health [1]. The reasons for government regulation and intervention in the medical domain can be categorized by aspect of ensuring market efficiency or not [65].

Regulations aimed to ensure market efficiency

Regulation from the perspective of ensuring market efficiency can be divided into cases where competitive markets do not achieve efficiency even when they function effectively, i.e., when market failure occurs, and cases where competitive markets themselves do not function effectively.

Market failure can be caused by information asymmetry, externalities, and natural monopolies due to imperfect competition. The medical sector is characterized by a strong asymmetry of information, since services and products were originally provided by doctors, pharmacists, and other highly knowledgeable professional [1]. Regulation in medical sector has a function to ensure accountability for both performance levels and value for money as well as to improve performance and quality [66]. Akerlof (1970) observed that, without regulation, the information asymmetry between consumers and producers could result in unfair competition [67]. Products used in the medical sector (e.g., medical devices and pharmaceuticals) are closely related to safety, health, and ethical aspects, and because of their strong externalities, they are subject to strong regulation to ensure their quality, safety and efficacy. This is because the occurrence of external diseconomies poses a direct and immediate threat to the life and safety of consumers and patients. In response to information asymmetry, regulations such as pharmaceuticals approval systems, licensing systems for healthcare professionals, advertising regulations, etc. exist. The pharmaceutical market has been intervened by various regulations, as various market practices related to the distribution of pharmaceuticals favor existing firms and impede competition [65], [68], [69].

In the medical domain, payers such as the government have been involved in transactions rather than bilateral market transactions between consumers and producers under the insurance system. In Japan, most medical services and related products have provided under the public insurance system and related regulations exist. The prices of products and services paid for by public insurance, i.e., pharmaceutical and medical equipment, inpatient and outpatient medical services, laboratory tests, surgery, and other services, have been officially fixed and are examples of strong price regulation. By regulating reimbursement, governments, as a matter of policy, have controlled health care costs or provided incentives to health care providers [68], [69].
Entry regulations have existed against medical institutions that provide health insurance-based care. As one example, joint stock companies have been prohibited from operating hospitals in order to eliminate profit-motivated management and to curb opportunism in Japan. The licensing system for hospital beds is an example of quantitative regulation. The purpose of the regulation of hospital beds is to control supplier induced demand caused by information asymmetry and to control the cost of health care. These regulations that restrict the decision-making process itself, such as provider entry, price, and volume, are called direct regulations.

Other regulations in the medical and healthcare industry

Regulatory setting perspectives other than efficiency include equity, demerit goods, and ensuring stability [65]. In the medical area, how and to whom to distribute finite medical services or products is an important issue and a basis of regulations from the perspective of equity. Illegal drugs, some of which may be used in medical, without regulation, a free market may be created and cause socially undesirable conditions. From a moral and ethical standpoint, such products are considered demerit goods and their trade on the market is regulated. Medical and health care services and products need to be in stable supply for sick patients and for those who receive care. Several regulations are aimed at ensuring security of supply.

Thus, products and services related to medicine and health care have been regulated by the government because of the need to focus on the public interest, rather than letting the market mechanism function autonomously. In the medical domain, the government has also been involved in transactions as a payer, setting many strong direct regulations. In addition, regulations with objectives such as equity other than efficiency play an important role in the health care sector, since efficiency is not the only value criterion for this sector [65], [68]. In contrast, the health care industry, the subject of this study, basically assumes that products and services are traded in a free market competitive environment. The purpose of regulation of the healthcare industry has been focused on preventing market failures, especially those caused by information asymmetries, and indirect regulation has been set up.

Innovation in the medical and healthcare industry

Christensen (2009) argued that the intent of the scheme of regulation of the medical domain evolves through three stages [1]. Namely, 1. to promote the formation of an industrial base, 2. to stabilize and strengthen the relevant enterprises to ensure fair and equal access to products and services and to guarantee their safety and efficacy, and 3. to promote competition so as improvement of convenience and lowing price of products and services. In the first phase, governments may provide grants or research funding to industries or research that are found to be unable to stand on their own. The goal of most current regulation in the medical industry is to stabilize and assure in the second phase. Most regulations in the medical industry have focused on ensuring the safety and effectiveness of suppliers and products, and there are three major regulations [1]. That is, pricing for products and services, regulation of access, and permits and certifications. Christensen argued that an appropriate relationship between regulation and innovation is essential for dramatic improvements in cost and access in the third stage, and pointed out that deregulation should not aim to promote competition simply, but aim to promote competition with disruptive innovation. It was further argued the effectiveness of a strategy to initiate innovation from places beyond the reach of regulation, based on examples of disruptive innovation occurring in markets that are on the periphery of the regulatory domain, and subsequently breaking down regulations in the domain. Innovations in the healthcare area on the periphery of medical domain could be a trigger for innovations in the medical domain.

Regulation in the health care domain is social regulation that aims to protect consumers from negative externalities of health and safety. The relationship between regulation, firm behavior, and innovation in social regulation has been the subject of much empirical research, especially in environmental regulation, which has been found to often promote innovation in the long-term as reviewed above. In contrast, there has been little research on the relationship between social regulation and innovation in the health care domain. Comanor (1986) showed the effect of regulation on firm behavior for the pharmaceutical products industry, showing that the tightening of new pharmaceuticals reviews in the U.S. in 1962 reduced R&D productivity in the firms and led to delays in bringing new pharmaceuticals to market[70]. Safety regulations would slow down radical innovation because high-risk products would be banned. Meanwhile, these regulations give consumers confidence in the safety of products and a gradual acceptance of new products and services [12].

Innovations in the health care sector is expected to contribute to health promotion and disease prevention, especially chronic lifestyle diseases in an aging society, which in turn will reduce public health care costs [1]. In this context, there is a growing number of innovations in the relatively weakly regulated health care domain, on the periphery of the strongly regulated medical

domain, aimed at extending life expectancy, improving quality of life, diagnostic and treatment options, and increasing the efficiency and cost-effectiveness of the health care system, among others [1], [2]. Policymakers need to understand the multifaceted nature of regulation and design regulations appropriately so that they stimulate industry, promote innovation, and protect and benefit consumers [10]–[14]Deregulation that lowers or removes barriers to competition often stimulates market entry by new competitors with alternative technologies or business models. Conversely, stricter regulations may promote innovation. In the environmental domain, innovation was spurred as companies developed technologies to meet tightened environmental regulations and launched regulation-compliant products [11], [61]. In the healthcare domain, regulatory reforms implemented by the U.S. Food and Drug Administration (FDA) have spurred the growth of FDA-approved mobile medical apps [6]. This suggests that in the healthcare domain, properly designed regulations can promote technology innovation. In some areas such as mHealth, cases where regulators and companies are working together to design institutions in a co-evolving manner is observed [6]. It is suggested that appropriate institutional design can promote innovation in newly forming healthcare industries around existing healthcare domains that are protected by strong regulations.

Regulation of Functional Foods

Regulations regarding functional foods vary across different countries. In the European Union (EU), the European Commission is the main regulatory authority, while the United States has the Food and Drug Administration (FDA), Korea has the Ministry of Food and Drug Safety (MFDS), Taiwan has the Taiwan Food and Drug Administration (TFDA), China has the Chinese Food and Drug Administration, Singapore has the Health Sciences Authority (HAS), and Japan has the Consumer Affairs Agency (CAA). Each country has its own set of regulations and guidelines for functional foods [71]. Functional foods are considered a separate category from pharmaceuticals, and each country has specific laws and regulations that pertain to functional foods. The labeling requirements for functional foods differ between countries, with some countries requiring the specification of the product's form (such as tablets or capsules) on the packaging. However, this requirement may not exist in all countries.

Functional foods are typically marketed as supplements or sources of boosted nutrients rather than cures or treatments for specific diseases. Marketing them as medical treatments is generally prohibited in the countries examined. To ensure the safety and quality of dietary supplements, manufacturers often adopt the Good Manufacturing Practice (GMP) system. GMP systems vary between countries, with the USA, Korea, Taiwan, and China having dedicated GMP systems for dietary supplements manufacturing. Japan and Singapore do not require a specific GMP for dietary supplements. Regulatory authorities commonly create a "positive list" of permissible ingredients for functional foods, ensuring their safety. While limitations on ingredients may exist, the positive list aids manufacturers in obtaining certification or validation for their products in global markets. Some countries also provide a "negative list" indicating ingredients that are not allowed to use for food. Regarding intellectual property, the Japanese Patent and Utility Model Examination Standards have been revised to protect the originality of known food products in 2016, after FFC system started. Manufacturers can obtain intellectual property rights for new attributes and uses discovered in known foods. The patentability depends on factors such as the novelty of the attribute, the description of tests, and the method of utilizing publicly known foods.

Overall, regulations governing functional foods contain product categorization, shape description, product purpose, positive lists, GMP systems, and intellectual property. Similar to pharmaceuticals, these regulations aim to ensure quality, safety,

functionality (efficacy), information disclosure, and labeling [24], [25], [72]–[77]. These regulations are set in the context of information asymmetry [67] between consumers and the firms that are the producers. Compared to companies, consumers have less information about the quality, safety and functionality of functional foods. The regulations aim to protect consumers and ensure a sound state of competition in the market for companies [26], [28], [78]–[80].

Consumer protection from quality issue

Information asymmetry in terms of quality poses a safety risk to consumers due to the characteristics of dietary supplement products. It is difficult for consumers to perceive the state and quality of the ingredients in a dietary supplement product from its appearance. The quality of the ingredients themselves, the addition of multiple ingredients, and impurities can affect the quality of dietary supplement products. In that dietary supplements contain ingredients in high concentrations, products with quality defects pose a high safety risk. In fact, alongside the growth of the market and industry, quality issues such as inappropriate manufacturing process management and insufficient ingredient amounts have emerged [81] [82] [83].

Quality regulations allow consumers to access safe, quality-assured products. Quality certification provides a basis for consumer confidence [84]. To protect consumers from risks, quality assurance standards have been implemented. For example, the pharmaceutical industry adopted Good Manufacturing Practices (GMP) as a means of quality assurance and control [74]. This regulatory standard ensures pharmaceutical manufacturers' compliance with defined manufacturing and packaging procedures. For companies, regulatory compliance is costly [85], [86], but it increases product quality [87], reduces customer complaints, and increases trust [74]. And also, internal effects such as increased productivity, employee motivation and training effects [75]. In addition, external effects, such as improved customer relations and product promotion have also been noted [88]–[90].

Information about health benefit

The mild effects of functional ingredients in dietary supplements on the body make it difficult for consumers to correctly perceive the potential health benefits of consuming functional foods. While information about benefits is of great interest to consumers [84], [91], [92], consumers have difficulty in being fully informed and information asymmetry exists. Unreliable information impedes consumers' decision-making process. Information on these health benefits is regulated as health claims in terms of expression and labeling.

Obtaining health claims has burdened companies a variety of cost, such as research and development costs to demonstrate and confirm the long-term health benefits of functional foods and administrative processing costs [93]. Meanwhile, obtaining health claims contributes to increasing the value of their products [84], [91], [92]. In the functional foods product segment, a market latecomer may develop and produce similar functional foods at a low cost, because it is difficult to effectively protect food ingredients by patents, differing from pharmaceutical ingredients, which have patent protection[94]. This effect could prevent existing manufacturers from allocating resources for research on new functionalities of food. Therefore, according to Hobbs et al., restrictions for labeling health claims could suppress so-called free riders—those who benefit from competitors' efforts and the lack of regulation—and promote innovation [80].

Conversely, strict regulations may reduce the efficiency of development and production, increase the cost to firms of developing new products and obtaining health claims, increase the price of products, and inhibit innovative activity and market

competition [93]. R&D investment amount in the food industry is lower than that in the pharmaceutical industry, and resources for R&D are often inadequate. To compensate for this, the potential for open innovation based on sharing knowledge and information from external networks was suggested [41].

Administrative processing costs would be affected by the kind of process of obtaining health claims. They fall into several categories, including notification, approval, etc. [71], [80], [93]. Hobbs (2014) discussed the gains and losses of the approval system and the generic (by notification and other methods). In the method that allows unique labeling under the approval system, a single company can produce multiple products with unique labeling, thereby increasing consumer awareness. While this leads to consumer protection, it places a burden on companies and regulators in the area of functionality, where there is less willingness to purchase. Meanwhile generic labeling could allow multiple companies to launch similar products, consumers would have more opportunities to be exposed to the labeling of functionality [80], [93].

Relatively weak regulations requiring the low level of evidence would make it easy for companies to enter the market [95]. But in an inadequate regulatory environment, low quality products produced at low cost may be introduced into the market, and adverse selection may result in these products occupying the market. Chauhan et al. noted that healthy market competition requires appropriate regulations for product health claims [78]. Appropriate regulation of functional foods has been needed from the perspective of consumer protection and market competition [80][79][96]. To summarize the above, the aspects for functional foods regulation were organized in the Figure 1-4.

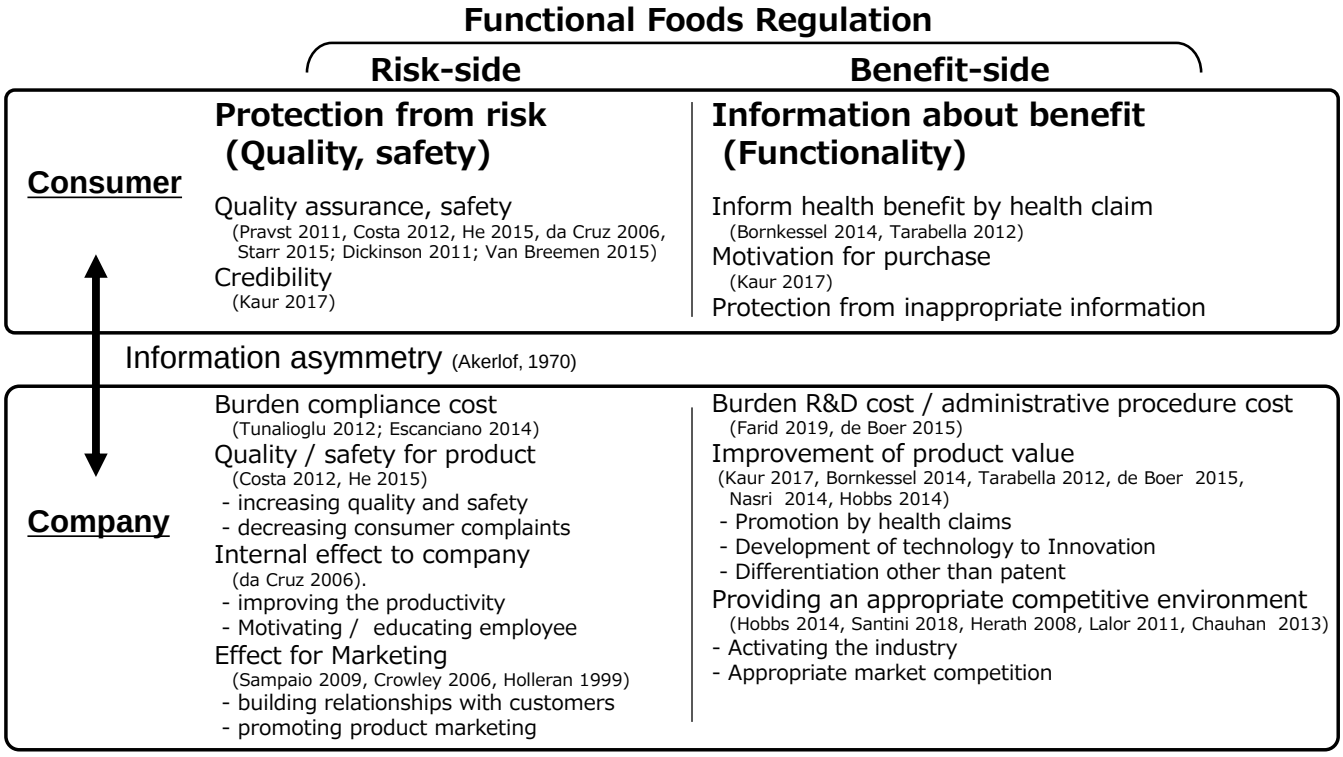

Figure 1-4 Functional foods regulations on risk-side (quality and safety) and benefit-side (functionality).

1.2.4 Summary of review and academic issues

This section provided a summary of previous research in convergence theory and a summary of previous research in regulatory science on regulation and innovation, and presented the academic issues in this area.

Convergence Theory and Regulatory Theory

In convergence research, the actors causing convergence, especially firms and their behavior were focused. The industry convergence process consists of several steps and can be categorized into knowledge and technology convergence on the supply side and market convergence on the demand side. Knowledge convergence is prompted by external contingent knowledge spillovers due to knowledge boundary erosion. Technology convergence is triggered by technology adoption. Market convergence is facilitated by deregulation and changing needs.[30] Regulation is an influencing factor on convergence, especially on the demand side, and deregulation encourages new companies to enter the market to promote convergence [34]–[38].

Research on the relationship between regulation and innovation has been accumulated with a focus on environmental regulations, which are social regulations. Regulations could affect firms' technology and product development activities by bring compliance costs and incentives for compliance, which could promotively or restrictively affect innovation. Firms would gain competitive advantage by complying with regulations by extending their knowledge, adopting technologies, and developing technologies, processes, and products. Conversely, regulatory conformance costs may induce more efficient R&D because they discourage firms from investing in R&D.

Therefore, regulations are expected to influence knowledge convergence and technology convergence through firms' knowledge and technology search activities, thereby triggering innovation. It is significant in convergence theory to elucidate the effects of regulation, which is one of the powerful driving forces of convergence. However, there is a lack of research on the phenomenon of regulation affecting supply-side convergence through firms' R&D activities. While the impact of regulation on innovation is being discussed, understanding the supply-side convergence caused by regulation as a starting point, especially through firms' R&D activities, would be an academic issue in innovation science.

The direction and strength of the impact of regulation on innovation has been discussed to relate to numerous factors on the regulatory and firm side. Therefore, the relationship between regulation and innovation has not yet been elucidated in a unified manner. Combined with the theory of convergence, the theory of regulation adds a new perspective and a broader view of the relativity between the industry targeted by regulation and neighboring industries. The combination of regulatory theory and convergence theory would be a research challenge that needs to be solved in order to reach a unified and general understanding of the relationship between regulation and innovation.

Despite the importance of social regulation and the high expectations for innovation in the healthcare sector, there is a lack of research on the relationship between regulation and innovation, making it an important subject of academic research. Case studies on the relationship between regulation, firm behavior, and innovation in this area could provide useful material for theory building.

Functional Foods in Convergence and Regulatory Theory

Functional foods industry has been formed by the industry convergence of the pharmaceutical and food industries. Convergence has occurred from both supply and demand sides, introducing scientific knowledge and technology from the pharmaceutical

industry, introducing marketing knowledge from the food industry [30]. Few convergence studies in the functional food industry have discussed the impact of regulation at the firm or product level.

The regulation of functional foods forms a regulatory system with a set of regulations on quality, safety, function, etc. The institutional design of these sets of regulations has been the subject of descriptive comparative studies in terms of international regulatory harmonization. On the other hand, the utility and action of regulations on consumers and companies has been only discussed regarding individual regulations, and comprehensive discussions has been lacking. This study reviewed functional food regulations, categorizing and conceptualizing them into regulations for consumer protection from risks and regulations for product benefits. The nature of regulation in functional foods has been discussed from the perspective of both consumer protection and the competitive environment for companies in the market, based on the characteristics of the product as a general consumer product with high information asymmetry.

The characteristics of functional foods, similar to pharmaceuticals, require consumer protection through regulation because of the potential for market failures that pose risks to consumers in terms of quality and safety [81]. Appropriate and regulated health claim labeling is needed to ensure that consumers are aware of the health benefits of a product when choosing a product [84], [91], [92]. As health claims can increase the values of products, appropriate rules would be beneficial for the company. In addition, companies can promote technology and product development by competing in a regulated environment [80].

Too strong regulations may pose the cost of compliance to companies and constrain corporate behavior, leading to regulatory failures that impede industry development [85], [86]. Conversely, if the regulation is too weak, a market failure may occur in which products of poor quality or improper labeling are introduced, to the detriment of consumers and ultimately to the detriment of firms [80]. Few studies have comprehensively discussed the impact of these systems of benefit-side and risk-side regulation on firm behavior, convergence, and innovation.

In order to discuss the relationship between regulations and firms from the perspective of convergence theory, and to obtain implications for designing regulations that are compatible with innovation, it would be a suitable case study to observe changes in the Japanese supplement industry as a result of regulatory changes. In this study, empirically and quantitatively analyses were conducted about the impact of regulations on firm behavior using data of companies and products. By focusing on observations of company behavior in response to regulations for functional foods in Japan, the impact of regulations on firm behavior and industry convergence would be clarified. Comprehensively discussion regarding the impact of these systems of benefit-side and risk-side regulation on firm behavior, convergence, and innovation, would be expected to provide contributions in regulatory science and convergence theory.

1.3 Overview of Functional Food in Japan

This section provides an overview of the functional food industry and regulations in Japan. As this study focused on dietary supplements as stated in 1.1.2, their industry was focused on in following section. For regulations, the overall functional food system including dietary supplement were outlined.

1.3.1 Overview of the Dietary Supplement Industry

This section argues the dietary supplement industry and its regulatory status and evolution.

Industry Structure

As mentioned above section, the Japanese dietary supplement market is characterized by the fact that the majority of products are outside the FHC system. In Japan, 73% of supplement final product manufacturers utilize contract manufacturing companies [97]. A typical value chain for dietary supplements consists raw material manufacturers that handle functional ingredients, contract manufacturing companies that produce products, and final product manufacturers that sell the dietary supplement, as shown in Figure 1-5. While the market size of supplement final products is approximately 1 trillion yen, the market size of contract manufacturing is approximately 290 billion yen, and more than 300 OEM companies are operating [98][99].

The history and business domains of dietary supplement contract manufacturing companies vary. Besides companies specializing in contract manufacturing, there are case of dietary supplement and pharmaceutical raw material manufacturers engaging in contract manufacturing, and tablet and capsule manufacturing equipment and packaging material manufacturers that have expanded their business into contract manufacturing [98]. Some OEM companies sell final products on their own. Companies that have other business areas besides dietary supplements would have an ability other than manufacturing dietary supplements. Those abilities may affect the introduction of Good Manufacturing Practice (GMP), the topic of this study. This point will be addressed again in the hypotheses discussed below.

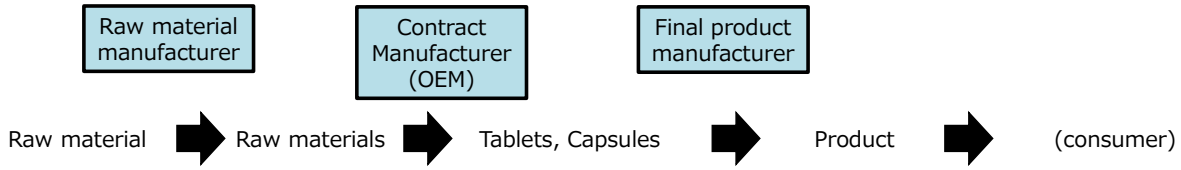

Figure 1-5 Dietary supplement value chain (Source: Prepared by the author)

Manufacturing Process

A typical manufacturing process for the four dosage forms, excluding beverages, was shown in Figure 1-6. In the case of tablets, firstly, raw materials, excipients, oils, etc. are mixed, then tablets are produced by granulation and tableting, and finally products are packaged. Soft capsules are manufactured by continuously forming an oval sphere between two sheets of gelatin while sealing in oil in which the ingredients are dissolved or suspended. They require specialized equipment, and know-how is needed to set the manufacturing conditions.

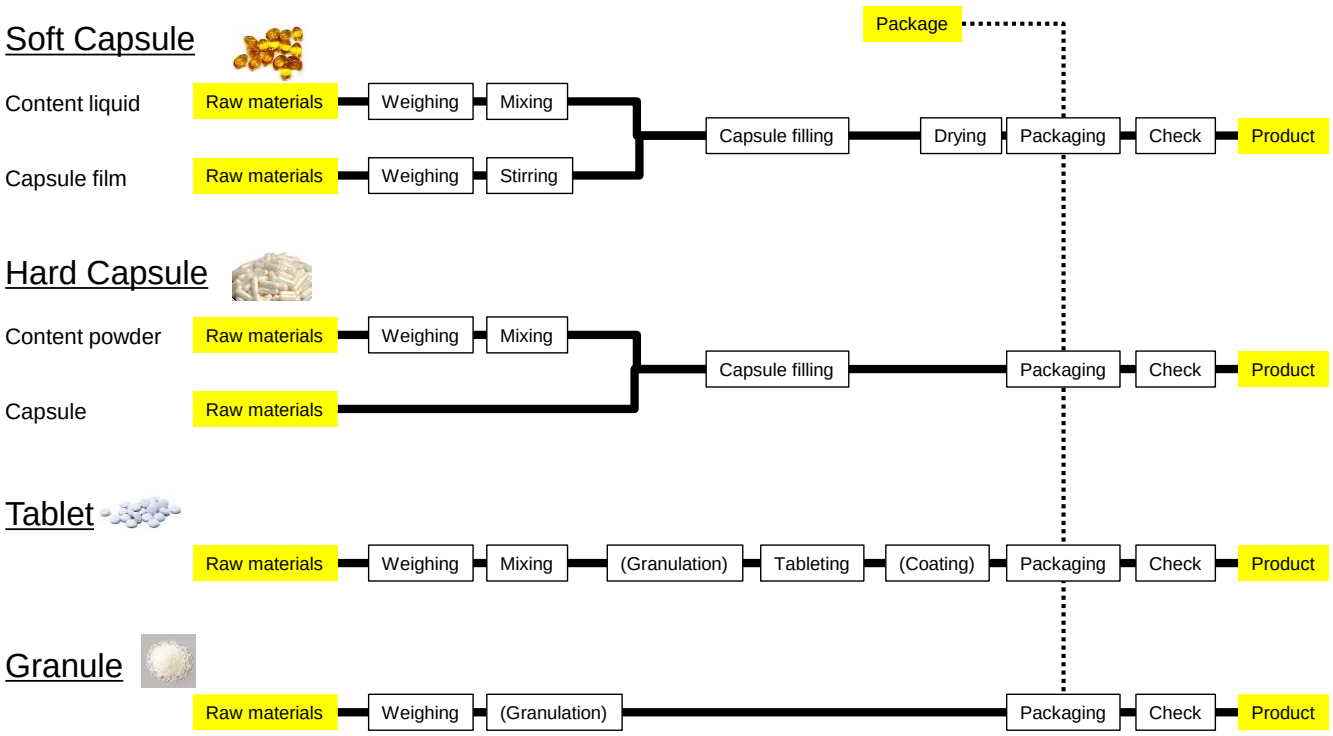

Figure 1-6 Standard manufacturing processes of dietary supplements

1.3.2 Regulatory system of Food with Health Claims

The system of Foods with Health Claims (FHC) can be delineated into three categories, as shown in Figure 1-7.

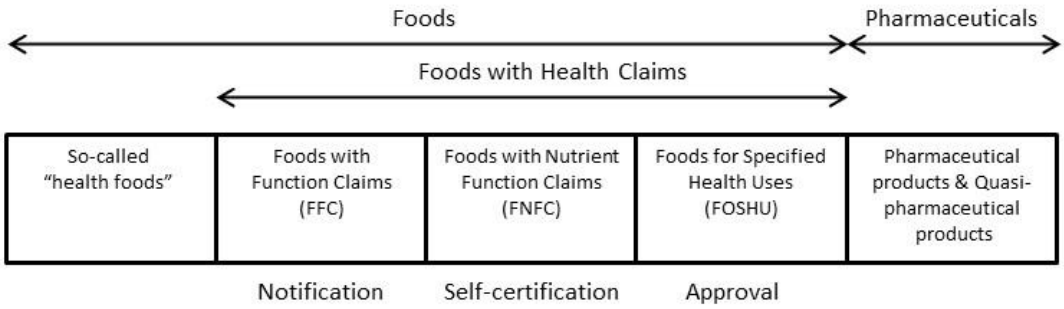

Figure 1-7 Categories ranging from food to pharmaceuticals containing Foods with Health Claims.

Foods for Specified Health Uses (FOSHU)

Foods for Specified Health Uses (FOSHU) is a licensing system that came into effect in 1991 and covers all processed foods. In principle, scientific evidence is required for each individual product, and various functional claims can be made by obtaining permission after examination by the government [15]. In the case of FOSHU, the initial examination was on an individual basis, but later the standardized criteria type was introduced. FOSHU requires that each individual product be examined for food

efficacy and safety, and that permission for labeling be obtained from the Commissioner of the Consumer Affairs Agency. Therefore, although FOSHU has the advantage of being able to show labeling approved by the Director-General of the Consumer Affairs Agency, it requires enormous cost and time to acquire scientific evidence of efficacy and safety, making it difficult for small and medium-sized enterprises to enter the market.

Foods with Nutrient Function Claims (FNFC)

Foods with Nutrient Function Claims are a self-certification system that came into effect in 2001, which allows for labeling in a standardized format without the need for procedures as long as the product contains designated ingredients such as vitamins and minerals, but the content of the labeling is limited [15]. Foods with nutrient function claims have the advantage that they can be labeled on food products without notification as long as the content of nutrients conforms to the standard values. However, the labeling is limited to the specific nutrients and their functions specified in the standard specifications.

Food with Function Claims (FFC)

As a recent regulatory movement, a unique Food with Function Claims (FFC) system was launched in Japan in 2015. This system was introduced with the policy intention to use functional food and dietary supplements for health promotion and disease prevention as well as for control of medical expenses. FFC are foods submitted to the Secretary-General of the Consumer Affairs Agency (CAA) as products whose labels bear function claims based on scientific evidence, which is the responsibility of food business operators [15]. Before the launch of the system, making function claims on food labels was only allowed for government-approved FOSHU and self-certified FNFC that complied with the specifications and standards designated by the government.

In the current FFC system, the government does not evaluate the safety and effectiveness of function claims. Food business operators submit an appropriate function claim based on scientific evidence for which they are responsible. Scientific evidence for function claims must be obtained through a clinical trial or systematic review of the literature. To propose function claims under the FFC system, it is required to submit a premarket notification and to label the package in accordance with the Food Labeling Standards pursuant to the Food Labeling Act as well as the "Guidelines for Notification of Foods with Function Claims" [21]. This system provides more information about functional food products to consumers and helps especially small companies develop functional foods[15], [100]–[102]. The FFC system has been accelerating new entrants and the further growth of the market.

The basic concept of the Food with Function Claims system is "labeling system not misleading to consumers and promoting consumer's voluntary and reasonable product choices", based on "ensuring safety", "establishing requirements for scientific evidence to make function claims", and "providing consumers with information through proper labeling" [103]. As with FOSHU, it has the advantage that specific functionalities can be expressed in easy-to-understand terms, helping consumers to select products. The content of information submitted under Food with Functional Claims is the responsibility of the business entity submitting the notification, and careful judgment must be made as to the appropriateness of the content. Since the submitting documents are published on the website of the Consumer Affairs Agency [104], it helps reduce the asymmetry of information between consumers and business operators.

For the company who are notifiers, it will be possible to promote their products in the field of functionality, which has never been done before, as long as appropriate scientific evidence is obtained and the requirements of the system are met. If the required information is notified to the Commissioner of the Consumer Affairs Agency at least 60 days prior to the sale, the notifier can label the functionality on the container or packaging of the food product on their own responsibility. The required information includes "the contents of the labeling," "basic information on food-related business operators such as names and contact information," "information on the basis of safety and functionality," "information on production, manufacturing and quality control," and "information collection system for health damage. If the information is verified by the Consumer Affairs Agency and meets the requirements for notification, a notification number is issued and the notification information is published in the Foods with Functional Claims System Notification Database of the Consumer Affairs Agency [104].

The documents that need to be prepared as the scientific basis for the functionality to be labeled are one of the following two types. The first is peer-reviewed literature showing the results of clinical trials using the final product; the second is a systematic review of research papers on the final product or the functionally involved ingredients [21]. When multiple functionalities are to be labeled in a single food, it is possible to submit a notification combining these types of scientific evidence as appropriate, as long as each functionality corresponds to each scientific evidence. When using systematic reviews for functional ingredients, it is sufficient if the equivalence of the functional ingredients in the adopted literature and the functional ingredients in the final product can be reasonably explained. Thus, businesses do not need to conduct their own clinical trials, and the same research review can be used for a variety of products. This has the effect of lowering the research and development costs for businesses required to obtain scientific evidence. Since there is no approval process like FOSHU, the cost of the commercialization process can be significantly lowered. It is expected that not only existing food-related businesses but also new food-related businesses will enter the market, and the policy aim is to promote the Japanese economy through the expansion of the food market. [15], [100].

On the other hand, FFC also has the aspect of tightening regulations on quality control. The notification guidelines for FFC [21] stated that “for processed foods in the form of dietary supplements, manufacturing process control based on GMP is highly desirable”. That means CAA effectively made GMP mandatory for dietary supplements under FFC system.

Situation after the introduction of the FFC system

FFC system has changed the market environment and the industry has been undergoing rapid change. The status of new product applications and notifications were shown in Figure 1-8. Since the start of the FFC system in 2015, several hundred FFC products have been submitted annually. On the other hand, for FOSHU, where about 50 products were approved annually at that time, the number of approvals has decreased significantly to about half since 2017. A shift from the FOSHU system to the FFC system has occurred. As of 2023, the number of items has reached 6,000 for FFC [104], while FOSHU has about 1,000 [105].

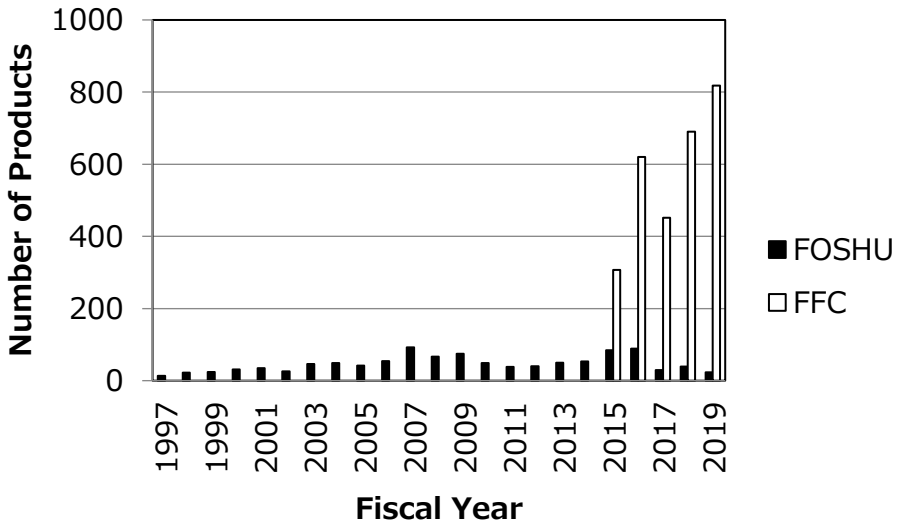

Figure 1-8 Number of yearly approved FOSHU products and yearly notified FFC products

These statistics were derived from the CAA's database of FFC [104] and FOSHU [105].

1.3.3 Historical Transition of the regulatory systems in Japan

Complexity of regulatory systems in Japan

Although the systems for functional foods vary from country to country, the Japanese system is particularly complex and unique, with its multi-line route of FOSHU and FFC [17], [71].

Table 1-4 shows the Japanese system for dietary supplements (pharmaceutical-like shape) and pharmaceuticals. Comparing dietary supplements and pharmaceutical regulations in terms of quality, safety, and efficacy (functionality), dietary supplements incorporate regulations based on the pharmaceutical concept, such as GMP and clinical trials. Among four categories in dietary supplements, contents and levels of regulations are different each other. This implies that, from the firm's perspective, the compliance cost of regulations and the product differentiation that provides incentives to comply with regulations would differ by category. A complexity of the system would provide firms with options on how to respond to regulations.

Table 1-4 Comparison among dietary supplements (so-called health food and under FHC system) and Pharmaceuticals.

Category	The so-called health food	Foods with Health Claims (FHC)			Pharmaceutical
		Foods with Function Claims (FFC)		Food for Specified Health Use (FOSHU)	
Administrative process	No	Notification		Approval	Approval
Basis of efficacy or functionality	Not allowed to label about functions	Systematic review (SR) of functional components (literature of clinical trial)	Product Clinical Trials	Product Clinical Trials (Large-scale)	non-clinical studies, Clinical Trials (3 phases)
Basis of safety	Not required (eating experience assuming safety)	Acceptable by food experience (If the basis of dietary experience is insufficient, it will be based on clinical trials, etc.)		Clinical Trials	non-clinical studies, Clinical Trials
Quality Control Regulations	Not mandatory (voluntary GMP)	GMP is practically mandatory (Described in the Guidelines for FFC)		Not mandatory (voluntary GMP)	GMP is mandatory (high level)
Development cost	Extremely low	Low	Middle	High	Extremely high
Product differentiation (Incentive to adopt regulation)	Extremely low Difficult to differentiate products technically	Low It is possible to develop similar products with the same ingredients	Middle Uniqueness is ensured by intellectual property rights, etc. Application patents, formulation patents, etc.	High In addition to securing with intellectual property rights, the cost of administrative processes is a barrier.	Extremely high Secured by ingredient patents, formulation patents, etc.

Note: Foods with Nutrient Function Claims (FNFC) were omitted in the table, because this system only allows to label their functions in case of specific nutrients specified in the standard specifications.

Path dependency of the system from historical transition

As shown at appendix, the complexity of the Japanese system is attributed to the path dependency of the system, which has been repeatedly expanded and modified. The following is a brief historical transition in the regulation of dietary supplements. When dietary supplements first appeared on the market, there were no regulations governing them. There was a subsequent period when dietary supplements in pharmaceutical form were banned. FOSHU initially covered only foods in ordinary form, and later expanded the scope to dietary supplements. In recent years, regulatory reforms of introduction of FFC system have added to the complexity of the FHC system. The regulatory transition of functional foods in Japan could be viewed in terms of both the benefit side and the risk side, which is the perspective presented in the literature review. Table 1-5 shows the changes in regulations related to benefit side (health claims) and risk side (safety or quality control). Health claims began with FOSHU program, but at that time, dietary supplement forms were not approved as FOSHU, and dietary supplement labeling was not approved until 2001. Compared to FOSHU, FFC can be labeled at a lower cost, and regulations on the benefit side have been eased. On the other hand, for quality control, the introduction of GMPs has been promoted since around 2005, and in 2015, GMPs for FFC dietary supplements were effectively made mandatory. At that time, in its notification guidelines for FFC [21], the Consumer Affairs Agency requested for manufacturer to manufacture dietary supplements under Good Manufacturing Practice (GMP), that means, made effectively GMP mandatory for dietary supplements under FFC system. Thus, risk-side regulations

have been strengthened in the FFC. FFC system could be regarded as a set of deregulations on the benefit side and tightening of regulations on the risk side.

Table 1-5 Changes of regulations of dietary supplements on risk side and benefit-side

Step	Event	Related regulation	Risk-side	Benefit-side
1	Rise of the functional food market in 1960s.	-	-	-
2-1	Dietary supplement with pharmaceutical-like shape was prohibited.	"46 Notice" (1971)	Tightening	
2-2	Relaxation of shape restrictions. Must be labeled "food."	Revision of "46 Notice" (1987)	Deregulation	
3	Dietary supplements were not allowed in FOSHU.	Foods with Health Claims (1991)		Unchanged
4	Dietary supplement with pharmaceutical-like shape was allowed.	Revision of "46 Notice" (1997~2000)	Deregulation	
5-1	Dietary supplements as FOSHU were allowed.	Revision of the Health Claims Food System (2001)		Deregulation
5-2	Introducing voluntary GMP for dietary supplement products.	GMP certification (2005)	Tightening	
6	GMP became practically mandatory for dietary supplements. Cost for health claim decreased by SR / certification system.	FFC system (2015).	Tightening	Deregulation

Note: Step numbers correspond to Figure A-1; Refer to Appendix 1, explaining a historical transition of regulations on functional food in Japan.

1.4 Objective and Theoretical framework

1.4.1 Research Objective

The purpose of this study is to clarify the effects of regulations in the industry convergence process by analyzing the responses of companies to the system in the Japanese functional food industry, mainly from the perspective of the path dependency of the companies. Furthermore, this study aims to make recommendations on how the system should be designed to create a market conducive to health promotion.

Regulations for functional foods in Japan have been in transition and have affected the market environment and the competitive environment for companies. FFC regulations have been a set of stricter regulations on the risk side and deregulation on the benefit side. This study observed how this regulatory shift has affected industrial structure, firm behavior and products from a convergence perspective. The risk-side regulatory tightening was aimed at protecting consumers from risk. For companies, compliance costs would increase, including capital investment, human resource training, and other costs to comply with regulations to ensure quality and safety. On the other hand, there should be incentives to comply with regulations, which would

be assumed that the competitive advantage would be enhanced through improved product value, internal company effects, and external market-side effects, etc., according to previous studies. In addition, when complying with regulations, firms would move to lower compliance costs as much as possible. Firms would decide whether to comply with or avoid regulations in the balance between compliance costs and incentives.

Deregulation on the benefit side would lower the cost of regulatory compliance to provide information to consumers, such as the cost and time required for R&D and administrative procedures. Regulatory conformity would provide companies with a competitive advantage, such as increased product value and quality through labelling health claims. This would give firms an incentive to comply with regulations because FFC health claims are more flexible than FOSHU and can increase the appeal of a product to the same or higher level as FOSHU. Furthermore, regulatory compliance costs would be lower under the SR route, which utilizes external knowledge without cost and time of clinical trials. In that case, regulatory compliance would occur even with smaller compliance incentives because of the lower compliance costs. Conversely, if the compliance incentive was high, a company could invest in R&D with high compliance costs.

While companies have to pay costs to comply with the regulations, the benefits gained from compliance provide an incentive for companies to comply with the regulations. It was assumed that companies would decide the appropriateness of regulatory compliance in terms of cost-effectiveness, based on the costs of regulatory compliance and the incentives for regulatory compliance. This "efficiency related to regulatory compliance" would be considered as a latent variable influencing regulatory compliance as shown in Figure 1-9. While companies would comply with the regulation under high efficiency condition, they would avoid to comply with the regulation under low efficiency condition.

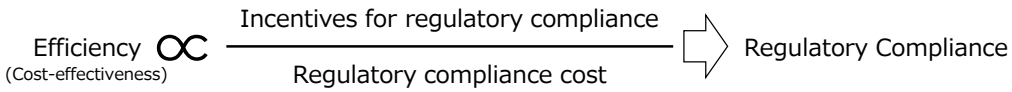

Figure 1-9 Balance of regulatory compliance costs and incentives

Balance of regulatory compliance costs and regulatory compliance incentives would depend on the attributes of the firm and its position within and outside the industry. As each firm acts to take advantage of external environmental changes in the form of regulatory change as an opportunity, the industry structure would change and products would be affected. In this case, the R&D activities of firms are expected to promote supply-side convergence of knowledge and technology.
Therefore, the following research questions were set.

Main Research Question

How have regulatory reforms in Japan's functional food changed the costs of compliance and the incentives to comply regulations for companies, and how have they affected the industrial structure, companies, and products?

Research Question 1

How did tighter regulations on risk side change the incentives to comply regulations for companies, and how did companies respond to reduce the costs of compliance?

Research Question 2

How did deregulation on the benefit side change the costs of compliance and the incentives to comply regulations for companies in and outside the industry, and how did companies respond and take advantage of the opportunity?

1.4.2 Theoretical framework

Figure 1-10 shows research framework for this study. This study empirically observed the effects of regulatory transitions on the industry, corporate behavior, and products, and discussed the impact of regulations on innovation from the perspective of their relativity with neighboring industries by using the Japanese functional food industry as a case study. The unique situation in the Japanese health food market, where two systems of FOSHU and FFC coexist, was suitable for examining the impact of regulatory change on corporate behavior. This study was positioned at the theoretical crossroads between industrial theory, concerning with knowledge and technology integration and industry creation, and regulatory science, concerning with the relationship between regulation and innovation. It will provide knowledge that deepens the debate on the duality of regulation (inhibiting and promoting) on innovation in the healthcare domain.

This study is expected to provide both key academic and practical insights. The novelty of this study would be that it builds on existing research on industry convergence, focusing on the influence of adjacent industries (regulation, knowledge and technology, and firms) and examining the dynamic relationship between regulation and firm behavior through quantitative analysis of firm attributes and product characteristics. The expected academic contribution would be an improved understanding of the behavioral processes and market formation of each layer of actors in the health food industry. Practical contributions would include recommendations for how the functional food domain should be institutionalized for the implementation of high-quality products and services, and for the strategies that should be adopted by companies in the functional food industry.

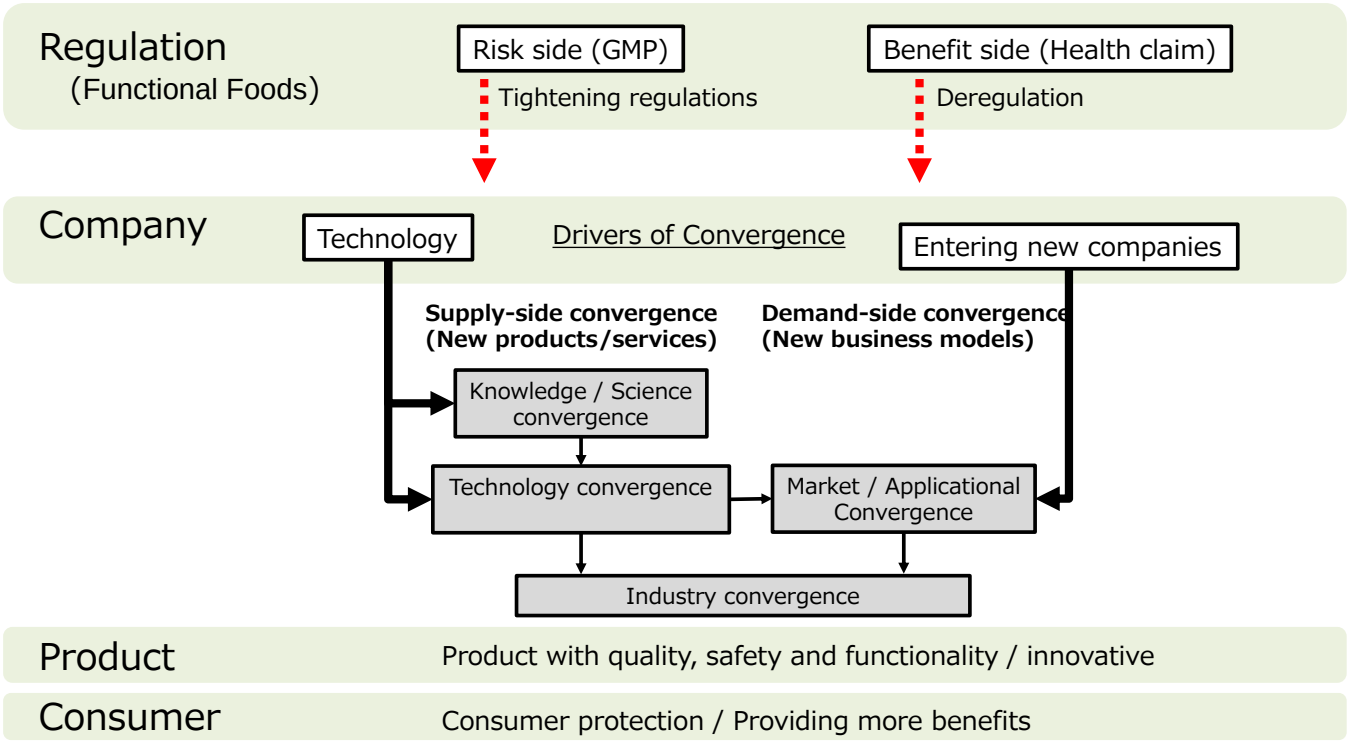

Figure 1-10 Research framework for this study.

1.5 Chapter structure

This study focused on GMP, which is a risk-side regulation on quality and safety and targets OEMs, and FFC's functionality labeling, which is a benefit-side regulation on functionality and targets end-product manufacturers. Under the FFC system, GMP is practically mandatory, and the two are related. Table 1-6 shows the outline of two studies. In Chapter 2 (study 1), GMP, influenced by regulations in the pharmaceutical sector was analyzed. The behavior of companies (OEMs) in response to GMP regulations, which are voluntary, was discussed based on the path dependency of the companies. In Chapter 3 (study 2), health claims with the FFC system, set up in 2015, was analyzed. The behavior of firms (end-product manufacturers) in response to the regulatory change from FOSHU was discussed. Finally, the overall discussion the impact of the regulation on firm behavior in the Japanese dietary supplement market was conducted.

Table 1-6 Outline of two studies.

	Study 1: Risk side	Study 2: Benefit side
Chapter	Chapter 2 GMP	Chapter 3 Health claim
Regulatory Objectives	Quality and the safety ensured by quality	Functionality (efficacy in pharmaceuticals)
Target companies	OEM	Final Product Manufacturer

2 Effect of risk side regulation (GMP) on OEM companies

2.1 Introduction

A dietary supplement is a food shaped as a soft capsule, hard capsule, tablet, granule, or liquid that differs from regular food and contains functional physiological ingredients. It is expected to contribute to promoting health and preventing disease in aging societies, and considered a way of self-medication with the potential to reduce the public health burden. The market for dietary supplements has expanded steadily in accordance with expectations and increased food technology innovation [23]–[25]. The dietary supplement industry is open to various business entities: pharmaceutical and food companies, small and medium-sized enterprises (SMEs), start-up companies that use novel functional ingredients and/or local specialty foods, new entrants from other industries, and original equipment manufacturers (OEMs).

In Japan, the size of the dietary supplement market has been growing and currently totals USD 8 billion (Figure 2-1), and the industrial ecosystem has developed based on the transdisciplinary environment described above. Notably, more than 70% of dietary supplement manufacturers outsource their manufacturing process to OEMs.

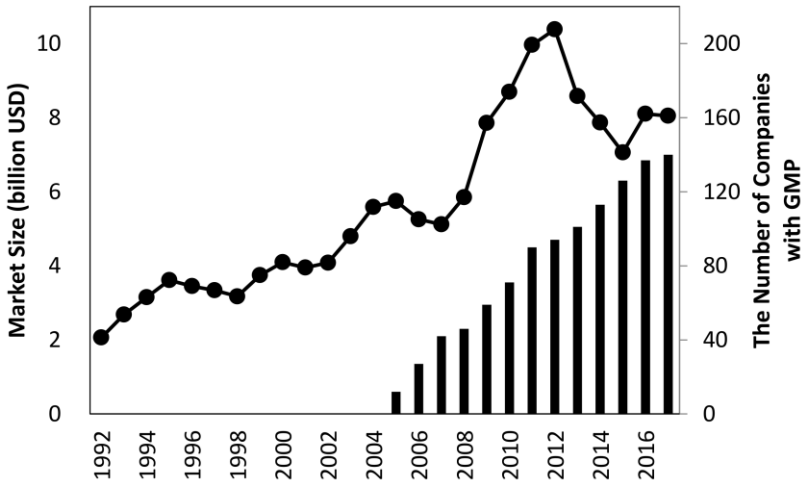

Figure 2-1 Historical transition of the market size of dietary supplements and number of GMP-licensed manufacturers.

The line shows the market size of dietary supplements, and bars show number of GMP-licensed manufacturers for dietary supplements in Japan. Data on the market size was obtained from commercially available sources [43]. Data on the number of companies was collected from GMP certification organizations (the Japan Health and Nutrition Food Association (JHNFA) and Japanese Institute for Health Food Standards (JIHFS)).

As a recent regulatory movement, a unique FFC system was launched in Japan in 2015. This system was introduced with the policy intention to use functional food and dietary supplements for health promotion and disease prevention as well as for control of medical expenses. FFC are foods submitted to the Secretary-General of the Consumer Affairs Agency (CAA) as products whose labels bear function claims based on scientific evidence, which is the responsibility of food business operators.[103] Before the launch of the system, making function claims on food labels was only allowed for government-

approved FOSHU and self-certified FNFC that complied with the specifications and standards designated by the government. The system of FHC can be delineated into three categories.

In the current FFC system, the government does not evaluate the safety and effectiveness of function claims. Food business operators submit an appropriate function claim based on scientific evidence for which they are responsible. Scientific evidence for function claims must be obtained through a clinical trial or systematic review of the literature. To propose function claims under the FFC system, it is required to submit a premarket notification and to label the package in accordance with the Food Labeling Standards pursuant to the Food Labeling Act as well as the "Guidelines for Notification of Foods with Function Claims" [21]. This system provides more information about functional food products to consumers and helps especially small companies develop functional foods [100]–[102]. The FFC system has been accelerating new entrants and the further growth of the market.

Alongside the growth of the market and industry, quality issues such as inappropriate manufacturing process management and insufficient ingredient amounts emerged [81]. According to the Food and Drug Administration (FDA) report about dietary supplements in 2013, 6307 adverse event reports from 2008 to 2011 resulted in serious outcomes—unspecified important medical events of a serious nature (53%), hospitalization (29%), serious injuries or illnesses (20%), resulted in a life-threatening condition (8%), and death (2%) [82]. In Japan, the Ministry of Health, Labor, and Welfare (MHLW) drew attention to quality issues by presenting examples of health hazards caused by health foods [83]. The factors that affect the quality of the product are the quality of the raw materials themselves, the addition of multiple materials, and impurities. Since raw materials are not standardized, purity and ingredient amounts vary from manufacturer to manufacturer. In the case of natural plant extract ingredients, in addition to the fact that the ingredients contained are often not specified, the ingredients contained in the product vary depending on where it is grown and when it is harvested. The National Institute of Health and Nutrition disseminates information on safety and health damage for health foods through their website [106].

It is problematic that consumers can hardly determine whether a product is sufficiently qualified when purchasing it, since all products have a similar shape and appearance, for example, tablets or capsules. Therefore, quality assurance standards were developed and implemented to reduce this asymmetry of information between manufacturers and consumers. For example, in the pharmaceutical industry, good manufacturing practice (GMP) was adopted as a means of quality assurance and control. This regulatory standard ensures the compliance of pharmaceutical manufacturers with defined manufacturing and packaging procedures.

The present study aims to explore the effect of the key characteristics of a company on the adoption of and compliance with GMP for dietary supplements, with a focus on the effect of expertise in the pharmaceutical industry. This study also explores how to successfully implement GMP to further innovate dietary supplements by identifying factors that influence the adoption (or rejection) of GMP. Furthermore, the required organizational capability needed for implementation is discussed. This chapter provides a literature review and hypotheses in section 2.2, a methodology of this study in section 2.3, results in section 2.4, discussion in section 2.5 and conclusions in section 2.6.

2.2 Literature review and hypotheses

2.2.1 Literature review

Several studies have reported that the implementation of GMP by a company effectively induces profound behavioral changes in the organization and individuals, and furthermore, enhances the level of awareness knowledge and awareness of the significance of product quality and safety [87]. GMP is used to manage an appropriate operation under a manufacturing process in accordance with defined standards to ensure that quality control is properly implemented. Quality risks such as misidentification or mislabeling of ingredients, adulterations, substitutions, and contaminations in the production process can be decreased through the GMP system, ultimately decreasing the number of consumer complaints [74]. In addition, the implementation of GMP reportedly improves the working environment and promotes employee motivation and productivity [75].

In the pharmaceutical industry, GMP has been advocated as a standardized regulatory system for the manufacturing process of dietary supplements, as in the pharmaceutical industry [24], [75]. Some countries including the United States as the largest market for dietary supplements have already adopted GMP as a regulatory requirement for product qualification [24], [72], [73]. However, in Japan, GMP for dietary supplements is still voluntary. In Japan, two organizations certify the GMP for dietary supplements, namely JANFA and JIHFS. However, since 2005, only around 150 Japanese OEM companies (half of all OEM companies) have adopted GMP (Figure 1). The GMP system is not mandated, because dietary supplements are not legally defined in Japan [107].

Several studies revealed the significance of implementing standards for quality control in the manufacturing process, such as pursuing operational excellence in improving product quality and productivity, and educational contributions to employees. Others are external effects such as building healthy relationships with customers and the positive effects of product marketing [88]–[90]. Reportedly, the size of an enterprise affects the adoption of quality control standards. Notably, small-sized companies with relatively undifferentiated product lines tend to be motivated to adopt a quality control standard for differentiation purposes in the competitive marketplace and as a requirement by customers with relatively large buying power [90].

As a negative impact, additional costs for quality assurance including human resource development or hiring and investment for GMP-complying facilities and equipment are obstacles to the introduction of GMP [85], [86]. Therefore, larger enterprises tend to more proactively introduce quality standards, because of a relatively lower cost burden than small and mid-sized enterprises [108].

2.2.2 Hypotheses

As discussed, prior studies revealed the existence of external and internal factors that affect the adoption and implementation of quality control standards. In the business of contracted manufacturing organizations (CMOs) for dietary supplements, the cost burden and organizational capability are considered key internal factors that affect the adoption and implementation of GMP for dietary supplements. Specifically, the introduction and maintenance of GMP-complying manufacturing facilities and equipment for inspection are key elements of direct costs, and building organizational capabilities such as improving operations

and employees' education may increase indirect costs. These additional costs are considered relatively lighter for larger enterprises in terms of the economy of scale, resulting in the smoother adoption of GMP.

Hypothesis 1: The adoption rate of GMP for dietary supplements is correlated with the size of the CMO.

Regarding CMOs in the pharmaceutical sector, their organizational capability to manufacture pharmaceutical products may contribute to dietary supplements, since they operate GMP-level manufacturing processes and quality controls that are mandatory for pharmaceutical products. Their policy, expertise, and human resources could contribute to improving the level of manufacturing process and quality control in the dietary supplement sector, promoting the more proactive adoption of GMP for dietary supplements.

In contrast, as the path-dependency theory points out, non-pharmaceutical manufacturing companies such as food manufacturers have a lower awareness and absorptive capability to adopt GMP for dietary supplements, i.e., they may need to spend additional time and cost to acquire and nurture their organizational capability [109]. Based on these considerations, we hypothesize that barriers to adopting GMP may differ between pharmaceutical and food manufacturers.

Hypothesis 2: The adoption rate of GMP for dietary supplements is higher among manufacturers of pharmaceutical products than among food product manufacturers.

Customer relationships are considered key external factors in the adoption of GMP. Manufacturing under the GMP system standardizes and guarantees a certain level of product quality and reduces the level of uncertainty on the customer side. It is also expected to reduce transaction costs between a CMO as an OEM and their clients as end-product manufacturers. Furthermore, in an environment wherein information between OEMs and their clients is asymmetrical, acquiring GMP provides to clients a certificate of quality control in manufacturing, which may contribute to building credibility. In other words, GMP as a certification has a signaling effect that eliminates asymmetrical information and strengthens the relationship between two manufacturers.

In the present study, considering difficulties in measuring the level of a specific customer relationship, number of product categories that the CMO can manufacture was employed as a proxy for the strength of the customer relationship. Typical categories of dietary supplements are soft capsule, hard capsule, tablet, granule, and liquid. CMOs capable of manufacturing various forms of dietary supplements are considered to sufficiently meet its customers' requirements. Therefore, number of categories of manufactured dietary supplements at a CMO was set as a surrogate variable for the strength of the customer relationship.

Hypothesis 3: The adoption rate of GMP for dietary supplements is correlated with number of product categories a contract manufacturing enterprise can manufacture.

2.3 Materials and Methods

Data was collected for 90 OEMs in the Japanese dietary supplement industry in 2016 [98] ([110]. We considered the possession of one or more of four types of licenses related to marketing or manufacturing for pharmaceutical or quasi-pharmaceutical products as a surrogate variable for the manufacturing capability of pharmaceutical products. We also considered the possession of 1 or more of 22 types of licenses related to manufacturing processed food as a surrogate variable for the manufacturing capability of food products. The manufacturing licenses were shown in Table 2-1.

The shape of the dietary supplement was classified into five categories (i.e., soft capsule, hard capsule, tablet, granule, and liquid). The number of product categories ranged from 0 (with only a packaging process) to five (with manufacturing processes for all categories mentioned). Statistical analyses were performed using R statistical software (version 3.4.1).

Motivations and driving forces to introduce GMP and utilities for GMP were complementary and qualitatively examined by interviews. Interviews for two GMP certification organizations and an OEM company were conducted as shown in Table 2-2 Summary of interviews. Details of interviews were shown in Appendix 2.

Table 2-1 Manufacturing license based on the Food Sanitation Act, manufacturing license based on the Pharmaceuticals and Medical Devices Act, manufacturing and sales license

Confectionery manufacturing
Sweet bean pastes manufacturing
Ice cream manufacturing
Dairy manufacturing
Meat products manufacturing
Fish batter products manufacturing
Food freezing or refrigeration
Soft drink manufacturing
Lactic acid bacteria beverages manufacturing
Ice and snow manufacturing
Edible oils and fats manufacturing
Margarine or shortening manufacturing
Miso manufacturing
Soy sauce manufacturing
Sourced manufacturing
Alcoholic beverage manufacturing
Tofu manufacturing
Natto manufacturing
Noodle manufacturing
Sozai Manufacturing
Canned or bottled foods Manufacturing
Additive manufacturing

Pharmaceutical manufacturing
Pharmaceutical manufacturing and sales
Quasi-drug manufacturing
Quasi-drugs manufacturing and sales

Table 2-2 Summary of interviews

	Subject of interview	**Asked topics**
GMP certification organizations	(1) Japan Health and Nutrition Food Association (JHNFA) (2) Japanese Institute for Health Food Standards (JIHFS)	1. The past and current situation for GMP certification 2. Reason of GMP development as a third-party certification 3. Issues for quality improvement 4. Motivation of companies to introduce GMP
OEM company	(3) Large OEM company X	・ The company's manufacturing system ・ Management of pharmaceuticals and dietary supplements ・ Impact from an in-house pharmaceutical manufacturing sector during an introduction of GMP ・ Effects and Impacts of Introducing GMP for Dietary Supplements

2.4 Results

2.4.1 Descriptive statistics

Table 2-3 provides the descriptive statistics of the sample data. The standard deviations for revenue and number of employees were relatively large, suggesting a considerable difference in the size of these CMOs.

Table 2-3 Descriptive statistics of the samples.

Variables	Mean	Standard deviation	Maximum value	Minimum value
Compliance of GMP	0.51	0.50	1	0
Revenue (billion yen)	5.99	19.13	170.46	0.04
Number of employees	160.9	291.4	1837	3
License for manufacturing pharmaceutical products	0.27	0.44	1	0
License for manufacturing food products	0.51	0.50	1	0
Number of product categories	1.81	1.41	5	0

2.4.2 Effect of company size

Figure 2-2 Revenue and number of employees of CMOs for dietary supplements with and without GMP in Japan. compares the revenues and number of employees of CMOs with and without GMP (n=46 and 44, respectively). To test hypothesis 1, the Mann-Whitney U test was employed to compare the revenue and number of employees of companies that do or do not comply with GMP for dietary supplements. The test revealed that companies with GMP have significantly more revenue and a larger number of employees than those without it (p<0.01 and 0.01, respectively). This supports hypothesis 1.

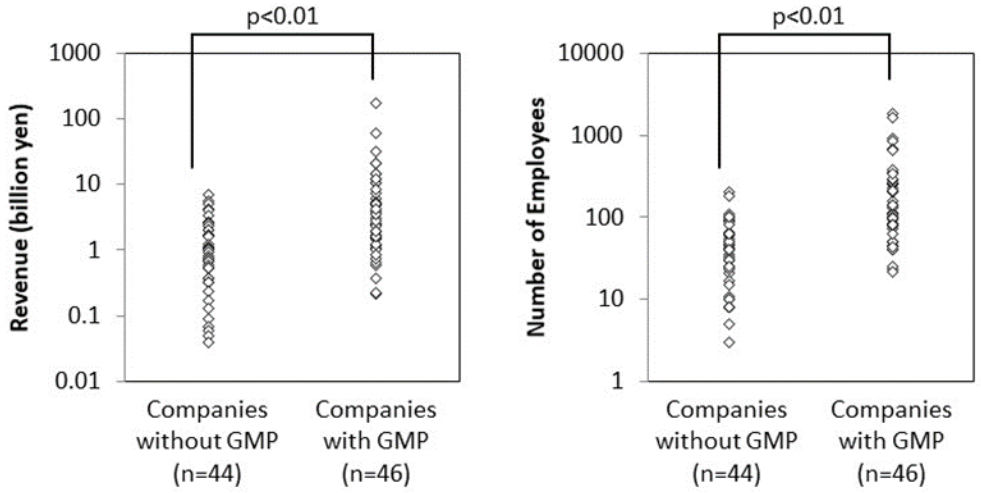

Figure 2-2 Revenue and number of employees of CMOs for dietary supplements with and without GMP in Japan.

2.4.3 Effect of business domains

To test hypothesis 2, the samples were divided into four subgroups based on the possession of license(s) for both manufacturing food and pharmaceutical products (subgroup A), only for food (B), only for pharmaceutical (C), or neither (D) (Table 2-4 and Figure 2-3). Fisher's exact test revealed that the adoption rates of GMP varied across these subgroups ($p < 0.01$). Furthermore, we examined the difference between Subgroup A (both food and pharmaceutical products) and D (neither) using a t-test (Holm method). The results in Figure 2-3 show that companies with a license for manufacturing pharmaceutical products tend to have a significantly higher adoption rate of GMP for dietary supplements. These results support hypothesis 2.

Table 2-4 Comparison of the adoption rate of GMP by business domains.

Subgroup	**Business domains**		**Number of companies**		**Adoption rate**
	Pharmaceutical	**Food**	**Without GMP**	**With GMP**	**of GMP**
A	✓	✓	3	13	81%
B		✓	18	12	40%
C	✓		1	7	88%
D			22	14	39%

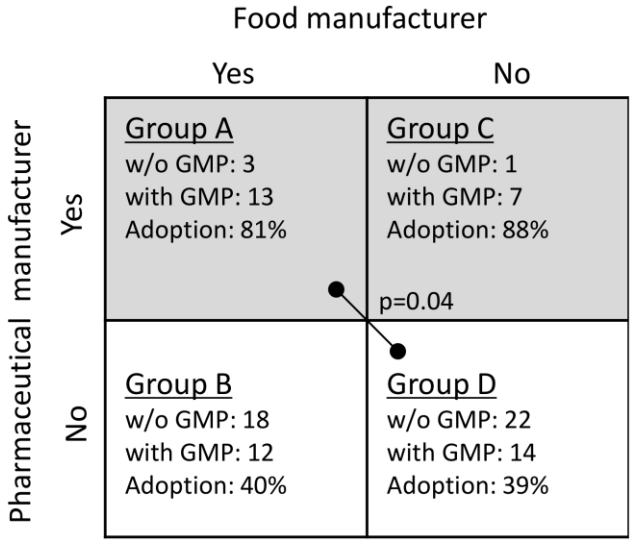

Figure 2-3 Summary of adoption rates of GMP for dietary supplements for possession of license(s) for manufacturing food and/or pharmaceutical products.

2.4.4 Effect of number of product categories

To test hypothesis 3 regarding the effect of the number of product categories, the company samples were divided into six subgroups according to the number of categories of manufactured dietary supplement products, ranging from G-0 (no product, i.e., only packaging process) to G-5 (five categories, i.e., soft capsule, hard capsule, tablet, granule, and liquid). Table 2-5 shows the results of the comparisons of these subgroups. Fisher's exact test revealed that the adoption rates of GMP for dietary supplements varied across subgroups ($p<0.00001$). Then, the differences were further examined between subgroups G-0 and

G-3, G-0 and G-4, G-1 and G-3, and G-1 and G-4 using a t-test (Holm method). Figure 2-4 indicates that the adoption rates of GMP for dietary supplements were significantly correlated with number of product categories manufactured by the companies (r^2= 0.952). This supports hypothesis 3.

Table 2-5 Comparison of the adoption rate of GMP by number of product categories.

Subgroup	Number of product categories	Number of companies		Adoption rate of GMP
		Without GMP	With GMP	
G-0	0	14	4	22%
G-1	1	18	7	28%
G-2	2	9	11	55%
G-3	3	3	11	79%
G-4	4	0	9	100%
G-5	5	0	4	100%

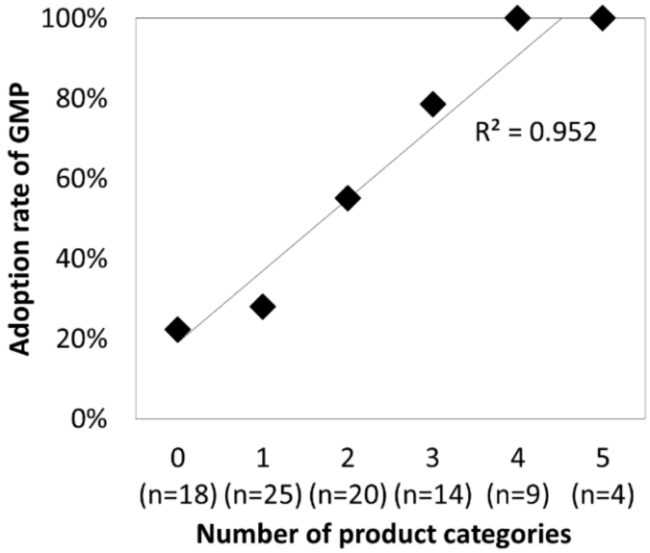

Figure 2-4 Relationship between number of product categories and adoption rate of GMP.

2.4.5 Binomial logistic regression analysis

Based on the abovementioned results, a binomial logistic regression analysis of the adoption rate of GMP for dietary supplements was conducted. Table 2-6 shows the correlation coefficients of selected variables: revenue size, possession of a license for manufacturing pharmaceutical products, and number of categories of manufactured dietary supplement products. Considering multicollinearity caused by the high correlation between revenue and number of employees (correlation coefficient = 0.82), a model including revenues without the number of employees was run based on the lower value of Akaike's Information Criterion (AIC).

Table 2-6 Correlation coefficients.

Variable	GMP	Revenue	No. of Employees	Pharm. dummy	Food dummy
Revenue	0.231 *				
Number of employees	0.374 **	0.824 **			
Pharmaceutical manufacturer dummy	0.389 **	-0.002	0.098		
Food manufacturer dummy	0.066	-0.112	-0.096	0.188	
Number of product categories	0.546 **	0.121	0.317 **	0.169	0.121

*: $p < 0.05$; **: $p < 0.01$.

Table 2-7 provides the results of a binominal regression analysis of the adoption rate of GMP for dietary supplements with four independent variables. The odds ratio for revenue size was 1.04 (95% confidence interval 1.01 to 1.09, $p = 0.019$); for the pharmaceuticals dummy, 13.7 (95% confidence interval 2.85 to 90.8, $p = 0.003$); and for number of product categories, 3.93 (95% confidence interval 2.14 to 8.61, $p = 0.00009$). This model confirms the three hypotheses of the study and provides a consolidated view of the contribution of these factors to the adoption of GMP for dietary supplements.

Table 2-7 Binomial logistic regression analysis.

			95% confidence interval			
Variables	**Coefficient**	**Odds ratio**	**Lower**	**Upper**	**p-value**	
Constant	-3.86	0.021	0.0025	0.106	0.00004	***
Revenue size	0.04	1.04	1.01	1.09	0.019	*
Pharmaceutical manufacturer dummy	2.62	13.7	2.85	90.8	0.003	**
Food manufacturer dummy	-0.13	0.88	0.24	3.10	0.84	
Number of product categories	1.37	3.93	2.14	8.61	0.00009	***

*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

2.4.6 Interview Results

The interviews with OEMs regarding their motivation to implement GMP and the benefits of GMP implementation was summarized as followed. Details of the interviews are shown in the Appendix.

According to the GMP certification organizations, OEMs were motivated to implement GMP for internal corporate benefits, such as improved quality, and for market-side benefits, such as responding to customer requests, sales appeal, and responding to overseas exports. From the interviews with OEMs, the external effect of GMP certification in terms of appeal to customers was mentioned. Since third-party certification is useful in promoting the high quality of manufacturing of dietary supplements, cases

in which GMP certification was obtained were identified. The company's dietary supplement manufacturing division and pharmaceutical manufacturing division are separated from each other. With the exception of some shared facilities, the facilities for manufacturing dietary supplements and those for manufacturing pharmaceuticals are different. This is to avoid contamination of pharmaceuticals and dietary supplements. On the other hand, some of the employees involved in pharmaceutical manufacturing were also involved in supplement manufacturing, confirming the commonality of human resources.

2.5 Discussion

2.5.1 Significance, effectiveness, and issues of GMP

The results obtained in this study suggested that the size of the company in terms of revenue or number of employees, license for manufacturing pharmaceutical products, and number of categories of manufactured dietary supplements contributed to the adoption of GMP for dietary supplements. From a historical viewpoint, the dietary supplement industry emerged through the convergence of the food and pharmaceutical industries, and was nurtured by these two streams of industrial and organizational capabilities. The present study found that pharmaceutical capability influences defining a quality level for manufacturing dietary supplements, accompanied by expertise in manufacturing a wide range of dietary supplement products.

Qualitative research through interviews with GMP certification organizations and OEMs suggested that endogenous factors of pharmaceutical manufacturing capacity and factors of business side of marketing utility and necessity influence the adoption of GMP by OEMs. Companies that manufacture both pharmaceuticals and dietary supplements have facilities with a high level of control in pharmaceutical manufacturing under GMP. Although these pharmaceutical facilities were rarely utilized directly in dietary supplement production, employees were shared between pharmaceutical and dietary supplement manufacturing. Shared human resources is a direct influence of the transfer of quality and manufacturing control knowledge in pharmaceutical manufacturing to dietary supplement manufacturing.

The logistic regression analysis, which evaluated the contribution of factors to GMP adoption in an integrated manner, yielded significant positive coefficients for three variables: revenue, pharmaceutical manufacturer dummies, and the number of product categories. Among these variables, pharmaceutical manufacturer dummies and the number of product categories had relatively large odds ratios. This suggested that pharmaceutical manufacturing capacity and the relationship with customers had a particularly strong influence on GMP implementation. It appeared that customer relationships acted as a strong incentive for regulatory compliance, and that ownership of pharmaceutical manufacturing capacity significantly lowered the cost of regulatory compliance. Firms with pharmaceutical manufacturing capacity appeared to lower the cost of regulatory compliance by sharing human resources and transferring knowledge and technology.

In addition, although the number of product categories (the number of compatible dosage forms) was set as a proxy variable for the strength of the relationship with the client company and was positioned as an incentive factor for regulatory compliance in this study, this may also positively correlate with the cost of compliance with GMPs. Dietary supplement manufacturing processes included common processes (e.g., weighting, mixing and packaging) regardless of formulation type, as well as processes that varied by formulation type (Figure 1-6). Therefore, if differences in productivity by equipment were ignored, it could be inferred that the greater the number of product categories, the greater the number of GMP-compliant facilities and

the greater the compliance costs. In other words, the number of product categories could relate to both a driver (the strength of the relationship with the client company) and a deterrent (compliance costs) to GMP implementation. The fact that the odds ratio of the number of product categories was much higher than 1 in the present results would suggest that the strength of the relationship with the client company was a very significant incentive to promote GMP implementation.

2.5.2 Impact of industry convergence

In the industry convergence model, multiple convergence steps (knowledge convergence, technology convergence, applicational convergence, and industry convergence) were proposed as a route to industry convergence [30]. Applicational convergence was pointed out as being influenced by the institution and customer needs. The results of this research suggested that, under the application of quality standards such as GMP, it is relatively easy to integrate the pharmaceutical industry into the food industry, whereas it is not so for the food industry into the pharmaceutical industry, i.e., potential asymmetric process/dynamics of the industry convergence, which is expected to provide practical implications to revisiting regulatory conditions in Japan.

2.5.3 Implications for institutional design

Since the introduction of GMP is voluntary in Japan, companies are not uniformly affected by the institution. In the paragraph below, we discuss the reason why Japan's GMP system is voluntary in comparison with the United States case. In the United States, GMP for pharmaceuticals was formalized in 1962 [74]. Until 1994, dietary supplements were treated in the same way as regular foods. Since 1994, dietary supplements are regulated under the Dietary Supplement Health Education Act (DSHEA). Dietary supplements are defined as foods with a shape that was processed for consumption, such as a capsule or tablet. In 2007, the cGMPs for dietary supplements were published by the Food and Drug Administration (FDA). The GMP-based product qualification is mandatory for all firms that manufacture, package, label, or hold dietary supplements in the United States [71], [75], [76]. While statements of functional claims can be displayed on the packaging or labels according to the DSHEA, the manufacturing process is controlled by the GMP.

On the other hand, Japan introduced a legislative framework for FFC in 2015. This system spans food and dietary supplements. However, dietary supplements under this system account for a small part of the Japanese dietary supplement market. In Japan, many dietary supplements are excluded from the system, and no legal system exists to comprehensively regulate dietary supplements. The relationship between dietary supplements and related legal systems is shown in Figure 2-5. Complex Japanese institutions are attributed to the historical path-dependency of a repeatedly revised system. It is difficult to redesign the Japanese legislative framework and legally define dietary supplements, because of the historical path-dependence of the system for dietary supplements and the market structure, which is dominated by dietary supplements outside the system, as mentioned. These factors developed a voluntary system without GMP being mandated in Japan.

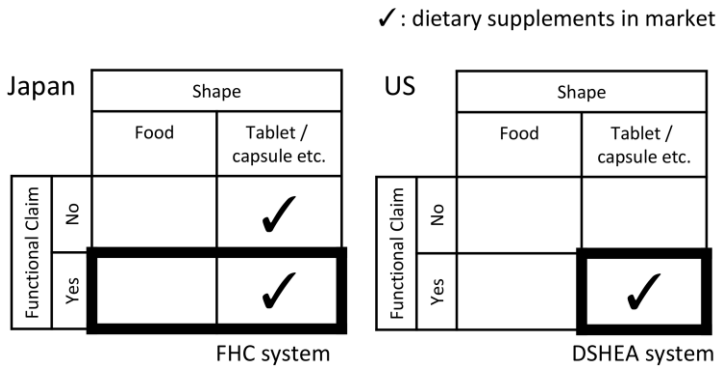

Figure 2-5 Comparison of legislative frameworks of functional foods in Japan and the United States. FHC and DSHEA stand for Foods with Health Claim and Dietary Supplement Health Education Act, respectively.

In Japan, the introduction of GMP was discussed since the 2000s. In 2005, MHLW required that the industry work on ensuring the safety of dietary supplements. MHLW published the "GMP guidelines", specifying the GMP management process from the acceptance of raw materials to packaging and shipment of final products. In response, two organizations (JANFA and JIHFS) implemented voluntary GMP certifications. In 2008, a third party-certification system related to GMP was proposed in a report by the MHLW on the safety assurance of "Health Food". Thereafter, the Health Food Certification Council was founded in 2009, and JANFA and JIHFS were designated as third party-certification organizations in 2014. Under the FFC system in 2015, GMP for dietary supplements was further promoted. According to the guidelines for notification for FFC by the CAA [21], it is strongly recommended that dietary supplements as FFC are manufactured at plants with GMP certification. Because one of the goals of FFC is safety assurance, manufacturers are required to ensure an appropriate manufacturing process. As the market for FFC is expanding, the GMP adoption rate will increase further.

According to the results of this study, food-based SMEs and companies with fewer products have lower rates of GMP adoption. Since these companies tend to deal with dietary supplements as a means of promoting regional economy and innovation, mitigating such trade-offs could be a key point of discussion to make the regulation more effective. Large-scale pharmaceutical manufacturers have the capability of pharmaceuticals. However, in Japan, because the preventive approach is not built into the healthcare system, few large-scale pharmaceutical companies deal with dietary supplements. In an effort to achieve disease prevention and health promotion endorsed by the central and local governments, the design and construction of an industrial/social system that integrates prevention and treatment would be effective to join more pharmaceutical companies.

2.5.4 Limitation

As for the limitations of the present study, it employed cross-sectional data of 90 CMOs in Japan. As such, it was limited to a specific period and/or regional context. To obtain a deeper understanding of the adoption process of GMP for dietary supplements, it is necessary to conduct a time course observation and analysis of these cases. In addition, some dietary supplement manufacturers keep the manufacturing process inside their own facilities and highly comply with GMP. Factors

regarding the adoption of GMP in these companies would differ from those regarding the CMOs examined in this study. Further studies are needed in the future to address these points.

2.6 Conclusions

The present study focused on key success factors related to the adoption and implementation of GMP for dietary supplements in Japan. As a result of the empirical observations of 90 CMOs that are OEM manufacturers of dietary supplements, three factors were identified as affecting the adoption of GMP: company size, manufacturing capability of pharmaceutical products, and number of categories of manufactured dietary supplements. Among those, expertise in manufacturing pharmaceutical products seemed to be the most influential for the dissemination and implementation of quality standards in the regional dietary supplement industry. These results and suggestions are expected to form a theoretical base for policy makers and regulatory authorities to reconsider the current regulatory framework and need for international harmonization, and to provide a cue for practitioners in industry on how to improve their capability to manufacture dietary supplements.

3 Effect of benefit side regulation (Health claims) on final products manufacturing companies

3.1 Introduction

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 [1]. 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 [11]. Thus, regulation has either positive or negative aspects for innovation depending on the characteristics of the business or the technology [6], [111]. 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 [11]. With the lowering or removing of barriers to competition, deregulation often stimulates the market entry of new competitors with alternative technologies or business models [37]. For example, regulatory reforms implemented by the United States Food and Drug Administration (FDA) have driven the growth of FDA-approved mobile medical apps [6]. This suggests that regulatory health-care reform—when properly implemented—can stimulate innovation in technology and the delivery of health care.

While understanding and utilizing the optimal regulation is important promote innovation in a regulatory environment, there is few previous research discussing how regulatory in the health-care sector, especially functional foods sector can stimulate innovation in technology as we mention in following section. Although Japan has a large functional foods market of USD 20 billion per year, there is a lack of previous research describing the industrial structure and products properties in details in Japanese functional foods industry under the regulatory system. This paper is the first study to examine empirically and quantitatively the impact of transition of the regulatory of Japanese functional foods since 2015 to the dietary supplements industry, manufacturing companies, and their products. The study focuses on the change of the Japanese regulatory system of foods with health claims (FHC) as an opportunity to observe the influence of the regulation to the innovation, and aims to obtain insights into the relationship between innovation and regulation.

3.2 Literature review and hypotheses

The Japanese functional foods sector has been steadily growing and the current market volume is USD 20 billion per year. The Japanese regulatory system for foods with health claims (FHC) includes foods for specified health uses (FOSHU), foods with nutrient function claims (FNFC), and the newest category of foods with function claims (FFC). The FNFC category is a self-certified system and the labeling mainly addresses conventional nutrients such as vitamins and minerals. The FOSHU and FFC systems are systems for labeling the health claims of food ingredients beyond these conventional nutrients.

FOSHU includes foods approved by the Japan's Consumer Affairs Agency (CAA) and include manufactures' labeling of food nutrients, based on safety and efficacy evaluations supported by clinical trials [112]. Initiated in 1991, the FOSHU system

allowed the labeling of foods to help consumers take a proactive approach to their health care. The FOSHU market has grown to over JPY 600 billion, accounting for approximately one-third of the Japanese health food market. However, the disadvantages of the FOSHU system include high costs and risks for manufacturers in the process of developing and bringing a product to market, with costly R&D and clinical trials, and lengthy approval time [112].

The FFC system includes functional foods with information supporting the safety and effectiveness of the product submitted to, but not individually pre-approved by, the Secretary General of the CAA prior to product marketing. Thus, although the labeling of these foods' function claims is based on scientific evidence, accuracy is the responsibility of food business operators [16], [102], [113]–[115]. Introduced in 2015, the less rigid FFC system was intended to stimulate the health food market through deregulation, and make 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.

From the viewpoint of the health food industry, deregulation was intended to reduce companies' costs and risks of product development [100], [112]. 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 [71], [100], [102]. 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 a lot of 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 [100].

There are two ways for companies to evaluate the functionality of a product. One is by a systematic review (SR) of scholarly papers about clinical trials (CTs) of product ingredients, and the other is by a CT of the product itself (Figure 3-1)[113]. An SR allows the use of external knowledge to evaluate product claims instead of conducting CT by manufacturing companies themselves, and FFC products evaluated using the SR route may be developed at a lower cost than those evaluated using the CT route [100], [114]. However, if a number of similar FFC products based on the same SR are introduced to the market by multiple companies, companies following the SR route for the evaluation of their FFC products may find it difficult to establish a competitive advantage. In contrast, FFC products evaluated using the CT route are more costly than those evaluated using the SR route, because the CTs for those products evaluated through the SR route are basically conducted in-house.

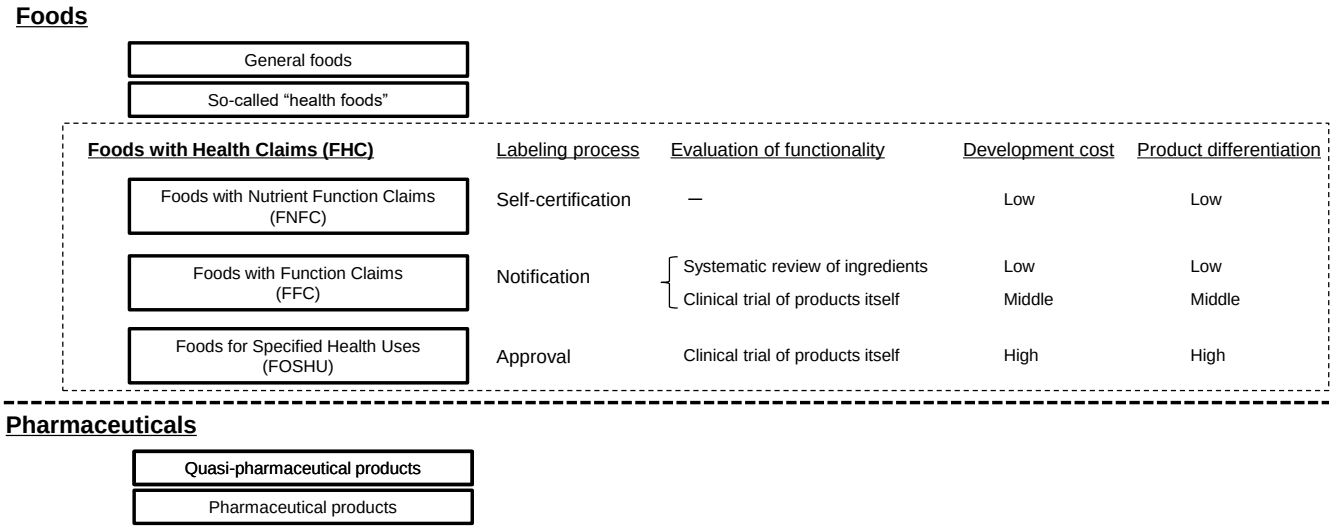

Figure 3-1 Food with health claims (FHC) system in Japan.

In this study, we empirically explored how the regulatory environment affected the innovation process in Japan during the transition of the regulatory approval process for functional foods. Specifically, legislation for FHC expanded from only allowing function claims on food labels for FOSHU and FNFC to including a new type of FHC, the less stringent regime for FFC. In particular, we examined the positive impact of the regulatory transition on industry and firm performance. We posit that the study of the Japanese FFC system is relevant to the discussion of the achievement of optimal regulation in the health-care sector, the issues of innovation promotion and inhibition in a regulatory environment, and how regulatory health-care reform—when properly implemented—can stimulate innovation in technology and the delivery of health care. We consider the timeframe for observation, seven years after the launch of the FFC system in 2015, sufficient to observe companies' adaptation strategies for deregulation and their consequences.

We examined the influence of Japan's FFC system on companies in the dietary supplement industry. One of the policy intentions for the introduction of the FFC system was to facilitate companies' ability to develop and bring functional foods to the market, and to stimulate the health food industry by lowering the costs and risks of product development. This study set forth the following hypothesis:

H_1: The introduction of the FFC system has led to the market entry of a diverse range of companies.

In the FFC system, a variety of health claims emerged, including those that had not previously existed in the FOSHU system and a combination of multi-health claims. Some FFC products label multi-health claims relating to several functions such as sleep and mental stress, gut condition and obesity, and joints and muscle. As a result, companies were able to develop FFC products with novel value, and the system provided companies new competitive opportunities. This study set forth the following hypothesis:

H_2: Companies that use the FFC system perform better than companies that do not use the FFC system.

The FFC system has two ways to evaluate the functionality of functional product. The SR route enables manufactures to develop FFC products at a low cost, efficiently, and rapidly by using external knowledge through SRs. The CT route enables manufactures to develop new, differentiated FFC products using in-house CTs. Based on these considerations, we hypothesized that the way of assessing product functionality (i.e., internal or external company test type) influenced functional product sales. As one of the constitutive factors, we analyzed the approaches to assessing product functionality and product characteristics. The in-house testing type refers to an approach in which the company conducts its own CTs to substantiate the evidence of its product claims (i.e., the CT route), whereas the external testing type is based on an approach in which the company uses the existing evidence base documented by previous studies (i.e., the SR route). This study set forth the following hypothesis:

H_3: Products evaluated by in-house testing have a higher market value than those evaluated by external testing.

To verify H_1, we analyzed the size and attributes of companies that provided the CAA notification of their FFC evidence (Analysis 1). To verify H_2, we analyzed the sales and growth rate of the supplement business with and without the use of the FFC system (Analysis 2). To verify H_3, we analyzed the product attributes and sales of FFC products (Analysis 3).

3.3 Materials and methods

3.3.1 Analysis 1: Sales and properties of companies submitting foods with function claims (FFC)

Data were collected for 169 companies in the Japanese dietary supplement industry in 2019 [104], [110]. The variables included:

- Corporate revenue;
- Main business of the company (pharmaceutical, food, retail, functional materials, supplement OEM, and other categories);
- Whether or not the company had a track record of handling FOSHU (food, beverages, or supplements) [105].

3.3.2 Analysis 2: Performance and product characteristics of top companies

First, the top 30 dietary supplement manufacturers were identified by aggregating product sales in an industry information data book [43]. Sales of these companies' dietary supplements totaled JPY 590.7 billion per year, covering 61% of the Japanese dietary supplement market. Next, the dataset of 27 companies (excluding three companies that could not obtain sales data in 2015) was created by composing (a) the CAA's database of FFC [104], and (b) relevant market research data [43]. The dataset was selected from the top 30 companies in the dietary supplement market (sales of dietary supplements business) in 2020. Due to data source limitations, time-series data for these firms could not be obtained. Instead of panel data, the CAGR (compound annual growth rate) between 2015 and 2020 for the 27 companies for which 2015 sales data were available, was calculated by using the following formula:

$$CAGR = (\text{Sales in 2020} / \text{Sales in 2015})^{0.2} - 1$$

By using the CAGR based on 2015, the year in which the FFC program started, as an indicator, the impact of the FFC regulations on the performance of the companies was aimed to observe. Of the Top 30 companies in 2020, a dataset of 27 companies was prepared, excluding 3 companies for which data for 2015 was not available.

For the 15 companies selling FFC products, four variables (based on the FFC product data set described in Analysis 3 showing their FFC product properties) were added. The variables included:

- Sales of dietary supplement in 2015 (when the FFC system started) and 2020;
- FOSHU dummy (if the company sells FOSHU, whether food, beverages, or dietary supplements, the dummy is 1) [105];
- Indices of the properties of FFC products of each company (sales weighted by average number of product materials; sales weighted by average number of product functions; sales by weighted new function rate; and sales weighted by in-house CT rate).

3.3.3 Analysis 3: Product attributes and sales of foods with function claims (FFC)

The product data set for 74 FFC products (sold by 15 companies) was created by composing (a) the CAA's database of FFC [104], and (b) market research data[43]. These 74 FFC products consisted of those, for which sales [43] could be identified among the FFC products [104] that were submitted from 4/1/2015, when the system started, to 3/31/2022. The product variables included:

- Sales figures
- Product properties, including the number of functional materials; the number of functions; whether the function is new or not; the number of papers on which the functionality is based; and the year of publication of the paper;
- CT implementation body (in-house trial type [in-house CT] or external trial type [External SR]), returning to product CTs and SR papers to check whether they were in-house CTs or external SRs, and categorized products into the following two categories: In-house test type: Products for which clinical trials are being conducted in-house; External test type: Products that have not undergone clinical trials in-house;
- Release year (in addition to the year of notification of FFC, if the same product was marketed as a health food before that, we included the year of its release).

Statistical analyses were performed using R statistical software (version 3.4.1, R Foundation, 2017).

3.4 Results

3.4.1 Revenue and properties of companies submitting FFC

Table 3-1 provides the descriptive statistics of the 169 companies submitting dietary supplement-type FFC products, comparing the revenue of the companies using both FOSHU and FFC system (i.e., the existing companies) and that of companies entering the new FFC system (i.e., the newly entering companies). The Wilcoxon rank sum test was employed to compare the revenue. The test revealed that the existing companies have significantly more revenue ($p < 0.01$). The 121 entering companies that newly entered the FFC claim system were outnumbered by the 48 existing companies who had FOSHU (either food, beverage, or dietary supplements).

The corporate characteristics of entering companies differed from those of existing ones. Although the existing company group consisted of 22 food companies (46%) and 11 pharmaceutical companies (23%), accounting for two-thirds of the total, the entering company group consisted of 17 food companies (14%) and six pharmaceuticals companies (5%). Conversely, in the entering company group, retailers (68 companies, 56%) and raw material manufacturers (14 companies, 12%) were more than those in the existing company group.

Table 3-1 Number of companies by attribute and corporate revenue.

Number of Companies							Revenue (100 million yen)				
	Pharm.	Food	Retail	Material	OEM	Other	Minimum	Maximum	Mean	S.D.	
Existing Company (n=48)	11 (23%)	22 (46%)	9 (19%)	2 (4%)	2 (4%)	2 (4%)	5	14894	2495	3485	p= 0.000
Entering Company (n=121)	6 (5%)	17 (14%)	68 (56%)	14 (12%)	7 (6%)	9 (7%)	0.2	19154	700	2376	

Note: The existing companies group consists of those that use both the FOSHU and FFC systems. The entering companies group consists of those entering the new FFC system. The six categories are representative of the main business domain of each company: pharmaceuticals, food, retail, functional materials, supplement OEM, and other. Revenue is corporate revenue of the manufacturing company (refer to Section 3).

Table 3-2 shows the revenue of retail companies and that of non-retail companies in the entering group. The Wilcoxon rank sum test between them revealed that revenue of retail companies is significantly less than that of non-retail ($p < 0.01$).

Table 3-2 Corporate revenue of retailers and other than retailers among entering company group.

Variables	Retail Company (n=68)		Other than Retail (n=53)		p-value
	Mean	S.D.	Mean	S.D.	
Revenue (100 million yen)	368	1481	1126	3123	0.00

Note: Wilcoxon rank sum test was applied. Revenue is the corporate revenue of the manufacturing company (refer to Section 3).

Among the 169 companies, no companies submitted all FFC products via only the CT route; 132 companies (78%; SR only companies) had only SR FFC products, and 37 companies (22%; SR & CT companies) had both CT FFC products and SR FFC products. The number of SR FFC products was 652, which accounted for 89% of the total of 731 FFC products. Table 3-3 shows the results of the comparison between the SR group and the SR & CT company group. The Wilcoxon's rank sum test revealed that the former group companies had lower revenue than the latter. This suggests that small companies, in particular, used the SR route.

Table 3-3 Corporate revenue of 169 companies by notification route.

Variables	SR only (n=132)		SR & CT (n=37)		p-value
	Mean	S.D.	Mean	S.D.	
Revenue (100 million yen)	1123	2732	1520	3233	0.01

Note: Wilcoxon rank sum test was applied. SR=systematic review; CT=clinical trial. Revenue is the corporate revenue of the manufacturing company (refer to Section 3).

In summary, under the FFC system, many small-scale companies, especially retailers, have entered the market of dietary supplements with health claims, showing the diversity of companies in the market. This supports H_1.

3.4.2. Sales and growth rate of the dietary supplement business with and without the use of FFC

Figure 3-2 shows the details of the top 27 dietary supplement companies. Table 3-4 shows the dietary supplement sales and the compound annual growth rate (CAGR) for 12 companies without FFC product (non-FFC company) and 15 companies with FFC products (FFC company). Wilcoxon's rank sum test shown that the CAGR of FFC companies was larger than that of non-FFC company ($p = 0.01$). This suggests that the use of the FFC system is linked to corporate growth. Therefore, H_2 was supported. The 15 companies that used the FFC system were divided into existing companies (n=8) and entering companies (n=7). None of the intergroup comparisons between these two groups showed significant differences (Data not shown). In the following analysis, the analysis was performed without distinguishing between the existing companies and the entering ones.

ID	FFC	Existing Company	Sales	CAGR	Sales Rate of FFC	Properties of FFC products (Sales Weighted Average)					
						No. of FFC	in-house CT rate	Ave. No. of Ingredients	Weighted Ave. No. of Materials	Weighted Ave. No. of Functions	New Function Adopsion Rate
1			83.3	4.2%	35%	3	100%	3.4	3.1	1.3	100%
2	✓	✓	45.8	1.5%	15%	10	0%	1.5	1.1	1.3	87%
3			44.6	-2.7%	0%						
4	✓		43.1	9.1%	58%	16	66%	3.2	2.7	2.3	59%
5			37.5	1.4%	0%						
6	✓	✓	23.6	4.2%	6%	1	100%	3.0	3.0	1.0	0%
7	✓		22.7	-6.7%	0%						
8	✓		22.2	16.7%	14%	12	59%	1.3	1.0	1.6	48%
9			21.9	1.1%	0%						
10	✓	✓	17.3	12.9%	12%	4	35%	1.9	1.5	1.0	61%
11	✓		15.7	9.9%	51%	3	93%	2.0	1.9	1.0	100%
12			15.7	2.5%	0%						
13	✓	✓	15.2	4.5%	56%	2	58%	1.0	4.3	1.0	100%
14	✓		14.8	0.0%	0%	1	0%	1.0	1.0	1.0	0%
15	✓	✓	13.7	-10.4%	4%	2	26%	1.0	1.0	1.0	100%
16	✓	✓	12.6	-1.0%	4%	7	0%	1.2	1.0	1.0	30%
17			11.9	3.7%	0%						
18	✓		11.2	-4.0%	87%	2	100%	1.0	1.0	1.0	100%
19			11.0	-3.3%	0%						
20	✓	✓	9.6	9.1%	40%	5	16%	1.0	1.0	1.3	26%
21			9.2	-9.4%	0%						
22	✓		8.9	34.3%	100%	5	98%	4.0	4.0	3.1	94%
23			8.7	-6.7%	0%						
24			7.8	-4.1%	0%						
25	✓	✓	7.6	0.3%	85%	1	100%	1.0	1.0	1.0	100%
26			7.5	4.4%	0%						
27			7.2	-6.2%	0%						

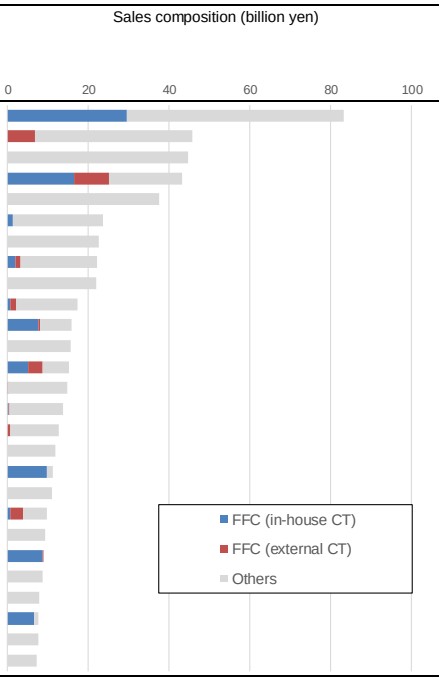

Figure 3-2 Details of the top 27 dietary supplements companies

Table 3-4 Sales and CAGR of 12 companies without food with function claims (FFC) and 15 companies with FFC.

Variables	non-FFC (n=12)		FFC (n=15)		p-value
	Mean	S.D.	Mean	S.D.	
Sales (100 million yen)	171.4	119.2	229.8	195.3	0.24
CAGR	-0.022	0.045	0.061	0.100	0.01

Note: Wilcoxon rank sum test was applied. FFC means foods with function claims. Sales are those of dietary supplement in 2015 (refer to section 3. Materials and Methods). CAGR (compound annual growth rates) was calculated from sales in 2015 and 2020.

3.4.3. Product properties and sales of FFC

Table 3-5 shows the classification of 74 FFC products. Among them, 12 products were shown its functionality by product CT, 57 products were submitted via the ingredient SR route, and five products demonstrated functionalities by a combination of product CTs and ingredient SRs. These were classified into in-house study types and external study types according to the entity conducting the clinical study. Among the 12 “product CTs type” products, two products were classified as "External CT" because those CTSs were conducted by raw material manufacturers rather than by FFC product manufacturers. That is, from the perspective of FFC product manufacturers, these products have been developed particularly efficiently by using external product clinical tests and formulations. Among the 57 ingredient SR type products, 10 products were categorized as in-house CTs, because their systematic review included article(s) reporting CTs conducted by the FFC product manufacturers themselves. As a result, 74 FFC products were divided into 25 in-house test products and 49 external test products. Figure 3-3 shows a detailed list of the 74 FFC products.

	in-house CT (n=25)	External CT (n=49)
Product CT (n=12)	10	2
Ingredient SR (n=57)	10	47
Hybrid (n=5)	5	

Table 3-5 Notification routes for foods with function claims (FFC) and the number of products by clinical trial implementation body (n = 74).

Note: SR=systematic review; CT=clinical trial.

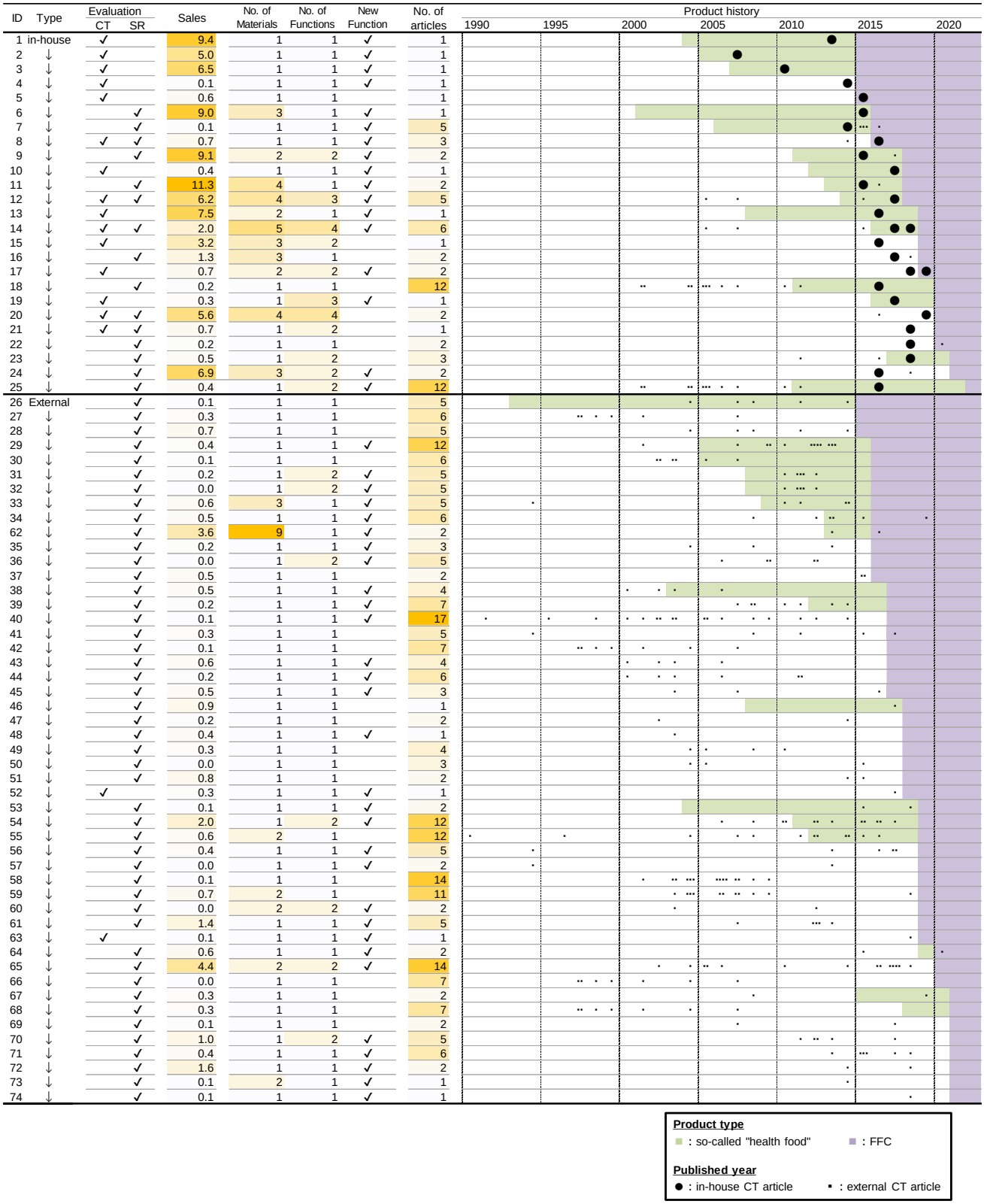

Figure 3-3 List of products (n = 74).

In terms of the number of products, 25 were in-house test type and 49 were external test type. Latter products were the products developed by utilizing existing research (external knowledge) to improve R&D efficiency. As shown in Table 3-5, there were 10 products that were notified through the "Ingredient SR" route even though they were tested in-house. In some cases, the results of in-house studies were used as SR to develop new products, while in other cases, the efficacy of the products was firmly demonstrated by combining them with existing external studies. In addition, there were two products that were notified under the "product clinical trial" route, although they were external studies. These were products that were developed in a particularly efficient manner, utilizing "product clinical trials" conducted by raw material manufacturers and OEMs as they were, and also utilizing external research for the development of formula.

Twelve of products with in-house trials were those upgraded by health claim from existing products that had be sold without health claims. Six of these products were commercialized as FFC based on clinical trials conducted prior to the start of the FFC system. Efficient product development was achieved by diverting the company's own products and evidence. The number of cases where products were commercialized after clinical trials were conducted after the start of the FFC system has been increasing since 2017.

Table 3-6 shows the comparison of sales, number of CT papers, year of publication, number of materials, number of functions between in-house test type products (n = 25) and external test type products (n = 49). Table 3-7 shows the correlation coefficients between indicators for 74 FFC products. Table 3-8 shows the results of multiple regression analysis of sales with four independent variables (number of materials, number of functions, new function as a dummy variable, and in-house as the dummy variable).

In the external trial type, the average number of papers used for efficacy evaluation was 5.1 papers, published from the 1980s to the 2010s (the median year was 2010). In the in-house trial type, the average number of papers was 2.8, and the median year of publication was 2015. The Wilcoxon's rank sum test revealed that the external trial type evaluated their efficacy by more papers published over a longer period. The external CT type utilized the accumulation of research (i.e. clinical trials on ingredients) from a long period of time in the past by external parties such as academia or raw material manufacturers. This is a form of "knowledge spillover" in convergence theory.

The correlation coefficients in Table 3-7 reveals that number of materials, number of functions and in-house CT dummy are correlated with each other (correlation coefficients: 0.25 to 0.39, $p < 0.05$). Because the maximum of all correlation coefficients is $r = 0.54$ (between Sales and in-house CT dummy, $p < 0.01$), showing loose positive relationships, there is little concern about multicollinearity. Multiple regression analysis of sales including all variables was run.

The results of multiple regression analysis showed that the coefficient for the in-house CT dummy was 26.8 (95% confidence interval (CI) [15.9, 37.6], $p = 0.00001$). This result revealed that the in-house test type had higher sales than the external CT type. The coefficient for number of materials was 7.6 (95% CI [3.5, 11.7], $p = 0.0004$). The coefficient for new functions dummy was 10.2 (95% CI [0.4, 20.1], $p = 0.04$). This model confirms that in-house CT, large volume of materials and new functions could increase sales of FFC products. Thus, H_3 was supported. In-house test-type products combine functional materials, conduct CTs, create knowledge in-house, and differentiate themselves as multi-functional products, resulting in high sales.

Table 3-6 Inter-group testing between in-house and external test types (sales, number of clinical trials [CT] papers, year of publication, number of materials, number of functions).

Variables	in-house CT (n=25)		External CT (n=49)		p-value
	Mean	S.D.	Mean	S.D.	
Sales (100 million yen)	3.5	3.7	0.5	0.8	0.00002
Number of Articles about CT	2.8	3.0	5.1	3.8	0.001
Published Year (Median)	2014.9	3.9	2009.7	5.5	0.00007
Number of Materials	2.0	1.3	1.3	1.2	0.002
Number of Functions	1.7	0.9	1.1	0.4	0.002

Note: Wilcoxon rank sum test was applied. CT=clinical trial. Refer to Section 3 for explanations of the variables.

Table 3-7 Correlation coefficients between indicators for 74 foods with function claims (FFC) products.

	Sales		Number of Materials		Number of Functions		New Functions	in-house CT dummy
Sales	1							
Number of Materials	0.46	**	1					
Number of Functions	0.22		0.37	**	1			
New Functions	0.25	*	0.12		0.12		1	
in-house CT dummy	0.54	**	0.25	*	0.39	**	0.07	1

Note: p-values of correlation analysis are shown by * and ** (*: $p<0.05$; **: $p<0.01$). CT=clinical trial.

Table 3-8 Multiple regression analysis of product sales.

Variables	Coefficient t	Std. Error	95% Confidence Interval		t value	p-value
			Lower	Upper		
Constant	-5.2	6.0	-17.1	6.7	-0.9	0.39
Number of Materials	7.6	2.1	3.5	11.7	3.7	0.0004
Number of Functions	-4.9	4.1	-13.0	3.2	-1.2	0.23
New Functions	10.2	4.9	0.4	20.1	2.1	0.04
in-house CT dummy	26.8	5.4	15.9	37.6	4.9	0.00001

Note: CT=clinical trial.

3.4.4. Properties of company developing in-house CT type FFC products

In Analysis 3, it was found that in-house CT products achieved high sales by combining functional materials, conducting CT, creating knowledge in-house, and differentiating themselves as highly functional products. In this section, a further analysis focusing on the strategies and actions of companies developing in-house CT type FFC products was conducted. Table 3-9 shows properties for FFC companies (n=15) and characteristics of their products. Some of the manufacturers whose main business was supplements were privately held firms, whose exact firm sales were not published. For the larger firms, supplement business sales were less than 10% of total firm sales. Table 3-10 shows descriptive statistics of the properties for FFC companies (n=15) and characteristics of their products.

Table 3-11 shows the correlation coefficients between indicators for the 15 companies that have introduced FFC system. Strong correlation confirmed between total sales of dietary supplements, sales of FFC, and sales of in-house FFC (R = 0.72 to 0.95). Hereafter, three variables were noted: (a) sales composition rate of FFC products, (b) in-house CT Rate, and (c) average sales per FFC products. (a) sales composition rate of FFC products was ranged from 0.3% to 100%. That meant depend on the FFC company, the utilization of the FFC system differed widely. (b) in-house CT Rate correlated to (a) FFC rate (R=0.66, p=0.007). (c) average sales per product correlated to (a) FFC rate (R=0.51, p=0.050) and (b) in-house CT rate (R=0.66, p=0.008). In other words, these results suggested that companies utilizing the FFC system actively (higher sales ratio of FFC) tended to conduct in-house clinical test to develop large sales products. Conversely, among the FFC companies, those that only partially utilized the FFC system may be pursuing a strategy of leveraging outside knowledge to create a series lineup of FFC products with relatively small-sales by smaller compliance cost.

Assuming (a) sales composition rate of FFC products as degree of compliance for the FFC regulation, (b) in-house CT rate as degree of R&D activity as additional efforts for compliance, and (c) average sales per FFC product as return from compliance for the regulation, this results suggested that when firms seek to strongly comply with FFC regulations, they seek to differentiate their products and increase their competitive advantage by developing products with in-house trials as an additional innovation investment as shown in Figure 3-4. These differentiations enabled the company to achieve higher sales of its products. The sales allowed the company to recoup higher compliance costs of aggressive R&D investments due to in-house clinical trials. Companies would conduct in-house clinical trials with the aim of developing differentiated, appealing, and high-value products within regulation. R&D activities, which was presented by in-house clinical trial rates as a proxy variable, could be viewed as a company's effort to comply more strongly with regulations to take advantage of the regulatory environment.

In-house clinical trial rates were not associated with revenue and CAGR (R=0.13 and 0.29, respectively) shown in Table 3-11. Results that in-house clinical trial rates were not associated with company performance suggested that there was no significant superiority by comparing between external utilization type strategy and in-house development type strategy.

Table 3-9 Properties for FFC companies (n=15) and characteristics of their products.

				1	2	3	4	5	6	7	8	9	10	11
ID	Maim bussiness of company	Company sales	Exsisting (FOSHU)	Total sales of dietary supplements	Sales of FFC	Sales of in-house CT FFC	Number of FFC	(a) Sales Composition Rate of FFC	(b) in-house CT rate	(c) Average Sales per FFC product	CAGR of total salse of dietary supplements	Weighted Average Number of Materials	Weighted Average Number of Functions	Weighted Average New Function Adopsion Rate
1	Beverage	2970	0	83.3	29.4	29.4	3	35%	100%	9.8	4.2%	3.1	1.3	100%
2	Dietary supplements	ND	1	45.8	6.8	0.0	10	15%	0%	0.7	1.5%	1.1	1.3	87%
4	Dietary supplements	104	0	43.1	25.1	16.5	16	58%	66%	1.6	9.1%	2.7	2.3	59%
6	Food	1062	1	23.6	1.3	1.3	1	6%	100%	1.3	4.2%	3.0	1.0	0%
8	Beverage	2511	0	22.2	3.2	1.9	12	14%	59%	0.3	16.7%	1.0	1.6	48%
10	Pharmaceutical	1738	1	17.3	2.1	0.7	4	12%	35%	0.5	12.9%	1.5	1.0	61%
11	Dietary supplements	ND	0	15.7	8.1	7.5	3	51%	93%	2.7	9.9%	1.9	1.0	100%
13	Food	1359	1	15.2	8.6	5.0	2	56%	58%	4.3	4.5%	4.3	1.0	100%
14	Dietary supplements	ND	0	14.8	0.1	0.0	1	0%	0%	0.1	0.0%	1.0	1.0	0%
15	Dietary supplements	ND	1	13.7	0.5	0.1	2	4%	26%	0.3	-10.4%	1.0	1.0	100%
16	Pharmaceutical	166	1	12.6	0.6	0.0	7	4%	0%	0.1	-1.0%	1.0	1.0	30%
18	Dietary supplements	ND	0	11.2	9.8	9.8	2	87%	100%	4.9	-4.0%	1.0	1.0	100%
20	Pharmaceutical	301	1	9.6	3.8	0.6	5	40%	16%	0.8	9.1%	1.0	1.3	26%
22	Chamical	2859	0	8.9	8.9	8.7	5	100%	98%	1.8	34.3%	4.0	3.1	94%
25	Chamical	390	1	7.6	6.5	6.5	1	85%	100%	6.5	0.3%	1.0	1.0	100%

Note: Variables were summarized from Figure 3-2. ND: no data. Sales figure units: billion yen

Table 3-10 Descriptive statistics of the properties for FFC companies (n=15) and characteristics of their products.

		1	2	3	4	5	6	7	8	9	10	11
	Company sales	Total sales of dietary supplements	Sales of FFC	Sales of in-house CT FFC	Number of FFC	(a) Sales Composition Rate of FFC	(b) in-house CT rate	(c) Average Sales per FFC product	CAGR of total salse of dietary supplements	Weighted Average Number of Materials	Weighted Average Number of Functions	Weighted Average New Function Adopsion Rate
	(n=10)	(n=15)	(n=15)	(n=15)	(n=15)	(n=15)	(n=15)	(n=15)	(n=15)	(n=15)	(n=15)	(n=15)
Min.	104	7.6	0.1	0.0	1.0	0.3%	0.0%	0.1	-10.4%	1.0	1.0	0.0%
Max.	2970	83.3	29.4	29.4	16.0	100.0%	100.0%	9.8	34.3%	4.3	3.1	100.0%
Med.	1211	15.2	6.5	1.9	3.0	35.3%	59.2%	1.3	4.2%	1.1	1.0	87.4%
Mean	1346	23.0	7.6	5.9	4.9	37.9%	56.7%	2.4	6.1%	1.9	1.3	67.1%
S.D.	1071	19.5	8.4	7.8	4.3	32.6%	39.4%	2.7	10.0%	1.2	0.6	36.7%

Sales figure units: billion yen

Table 3-11 Correlation coefficients between indicators for 15 companies using FFC system.

	Variables	1 Total sales of dietary supplements	2 Sales of FFC	3 Sales of in-house CT FFC	4 Number of FFC	5 (a) Sales Composition Rate of FFC	6 (b) in-house CT rate	7 (c) Average Sales per FFC product	8 CAGR of total salse of dietary supplements	9 Weighted Average Number of Materials	10 Weighted Average Number of Functions	11 Weighted Average New Function Adopsion Rate
1	Total sales of dietary supplements	1										
2	Sales of FFC	0.77 **	1									
3	Sales of in-house CT FFC	0.72 **	0.95 **	1								
4	Number of FFC	0.30	0.32	0.10	1							
5	(a) Sales Composition Rate of FFC	-0.17	0.41	0.44	-0.06	1						
6	(b) in-house CT rate	0.13	0.47 †	0.60 *	-0.23	0.66 **	1					
7	(c) Average Sales per FFC product	0.48 †	0.67 **	0.79 **	-0.34	0.51 †	0.66 **	1				
8	CAGR of total salse of dietary supplements	-0.06	0.13	0.12	0.31	0.38	0.29	-0.12	1			
9	Weighted Average Number of Materials	0.25	0.46 †	0.45 †	-0.06	0.37	0.49 †	0.33	0.48 †	1		
10	Weighted Average Number of Functions	0.10	0.38	0.31	0.50 †	0.48 †	0.25	-0.09	0.78 **	0.48 †	1	
11	Weighted Average New Function Adopsion Rate	0.16	0.41	0.43	-0.09	0.59 *	0.42	0.56 *	0.01	0.22	0.13	1

Note: p-values of correlation analysis are shown by †, *, and ** (†: p<0.1; *: p<0.05; **: p<0.01). CT=clinical trial.

Figure 3-4 Relationship among (a) sales composition rate of FFC products, (b) in-house CT rate, and (c) average sales per FFC products.

3.4.5. Strategies of companies with FFC products

As above section revealed, the correlation between the sales composition rate of FFC and the in-house CT rate suggests that when firms strongly seek to comply with FFC regulations, they seek to differentiate their products and increase their competitive advantage by developing products through in-house clinical trials as an innovation investment. To gain further insight into the characteristics of firm behavior, it was attempted to observe a developmental focus on the regulatory compliance and innovation behavior of individual firms shown in Table 3-9.

Company #1 is a subsidiary of a major food and beverage manufacturing group with sales exceeding 2 trillion yen [116]. The sales composition rate of FFC was 35%, which was closed to the average of all 15 companies at 38%. The three FFC products included in this study were all in-house CT type and all had acquired new functional claims such as joint care and brain

health. In response to FFC regulations, the company complied with regulations, invested in innovation, and their products were differentiated and competitive. It was presumed that a small number of large products with competitive advantages were being developed. Conversely, the remaining products are marketed as "so-called health foods" and avoid regulation.

Company #2 and #4 are companies with cosmetics and dietary supplements as their business lines. Their channels are both mail-order and retail. The corporate strategies of #2 and #4 are quite different as following. Company #2 declared that they would provide variety of products at low prices as corporate policy [117]. The sales composition rate of FFC was 15% and the in-house CT rate is 0%. Due to its low-cost strategy, their R&D investment was estimated to be at a low level and the company was basically reluctant to respond to FFC regulations with compliance costs. It was presumed that their strategy was to concentrate on products that can obtain new functions (the new function adoption rate was 87%), utilize SR, which is external knowledge, partially complied with regulations with low compliance costs, and efficiently gain competitive advantage. In contrast, company #4 announced that they would utilize FFC actively as the corporate strategy [118]. The number of FFC products covered in this study was 16 products, the largest number among the 15 firms. Both the sales composition rate of FFC and the in-house CT rate are higher than those of #2. It was presumed that they aimed to comply with FFC regulations actively, invested in innovation, and were differentiated to obtain competitive advantages.

Company #6 is a major dairy, confectionery, and pharmaceutical manufacturer [119], [120]. The company's main dietetic supplement is a sports-oriented protein, primarily whey protein derived from milk. Under the FFC system, basic nutrients such as protein are out of scope, so most products of the company are not FFC with low sales composition rate of FFC at 6%. Due to promotions using athletes, their protein products are sold as large brands in retail channels. On the other hand, the company conducts its own testing of amino acid-based ingredients and markets them as in-house CT type FFC dietary supplements for sports. In addition, it should be notable that in the company's pharmaceutical business, based on synergies between the group's pharmaceutical and food businesses, the company also sells dietary supplements to the medical institution channel.

Company #8 is a beverage and food manufacturer and #10 is a pharmaceutical and nutritional food manufacturer. Both companies have sold series brands of dietary supplement such as vitamins, minerals, herbs, etc., respectively, primarily through the store channel. These "traditional" dietary supplement lineups have stayed the two companies' FFC sales composition at around 10%. Company #8 has also developed products based on the seeds of research on lactic acid bacteria and fermented milk ingredients at a lactic acid bacteria beverage manufacturer it acquired in 2012. This in-house CT type FFC products provide functions of mental health or blood pressure, increasing the in-house CT ratio to 59%.

Company #11, #14, #15, and #18 are all dietary supplement manufacturers specializing in mail-order sales [121]–[124]. While #11 and #18 have high FFC rates (51% and 87%, respectively) and high in-house CT rates (93% and 100%, respectively), #14 and #15 had quite low FFC rates (0.3% and 4%, respectively) and low in-house CT rates (0% and 26%, respectively). One common feature of #11 and #18 is that their main products are both joint care dietary supplements, which they market as in-house CT type FFC. Joint care is a new health claim that did not exist in the FOSHU, and the granting of a health claim can strongly differentiate a product. This may be the reason behind offering FFC products through in-house CT with R&D investment.

Company #13 is a seasoning and food product manufacturer [125]. They have been researching and manufacturing amino acids for many years. The dietary supplements consist of non-FFC products taken in sports scene and FFC products for

health purposes, with FFC rate of 56%. The former non-FFC products have been branded by appealing the diversity of amino acid formulas and using athletes in their promotions. The latter products are also made by amino acids, with health claims such as "sleep improvement" and "muscle function maintenance", which were not included in FOSHU, based on their research.
Company #16 and #20 are pharmaceutical manufacturers that deal in OTC medicine and daily necessities [126], [127]. They have a series of brands with a large lineup of dietary supplement products, and their sales composition rate of FFC are 4% and 40%, respectively.

Company #22 and #25 are chemical manufacturers, entering the dietary supplement market in the 2000s under a diversification strategy [128], [129]. Both companies have sold in-house CT type FFC dietary supplements based on their original R&D, resulting in high FFC rate (100% and 85%, respectively) and high in-house CT rates (98% and 100%, respectively). These main dietary supplements are both FFC with new functions regarding weight loss that FOSHU does not have.

Table 3-12 summarized companies' behavior for FFC regulation as described above, and Figure 3-5 shows 15 companies' (a) Sale composition rate of FFC and (b) in-house CT Rate. It can be inferred that the sales composition rate of FFC and the in-house CT rate would be affected by competitive strategies, product lineup, brand strength, products area in efficacy, technology seeds, etc. Thus, it is suggested that these factors would meditate the corporate decision-making regarding degree of compliance for the regulation and R&D investments as additional efforts for compliance.

Table 3-12 Companies' behavior for FFC regulation

Company ID	Companies' behavior for FFC regulation
#1	Innovation investments develop a small number of large FFC products. The remaining products are marketed as "so-called health foods" to avoid regulations.
#2	Corporate policy: "Offer a variety of products at low prices"; reluctant to comply with FFC regulations (concentrating on new functional products by utilizing SR).
#4	Corporate policy: "Proactively utilize FFC"; proactively comply with FFC regulations and differentiate through investment in innovation.
#6	Main focus is on branded sports proteins (non-compliant with regulations). Some FFC products for sports are sold through in-house CTs.
#8, #10	Has "traditional" supplement brands such as vitamins, minerals, herbs, etc., and is less FFC compliant.
#11, #18	Strongly compliant with regulations and investing in innovation to secure competitive advantage with new functional "joint care" supplements.
#13	Leveraged seeds to market amino acids for sports (non-compliant with regulations) and health function amino acids (FFC compliant).
#14, #15	Low compliance with FFC regulations
#16, #20	Low FFC compliance with many brands of supplements.
#22, #25	Entered the market before the FFC regulation, strongly compliant with the FFC regulation, and developed product with new features related to "weight loss" through its own CT.

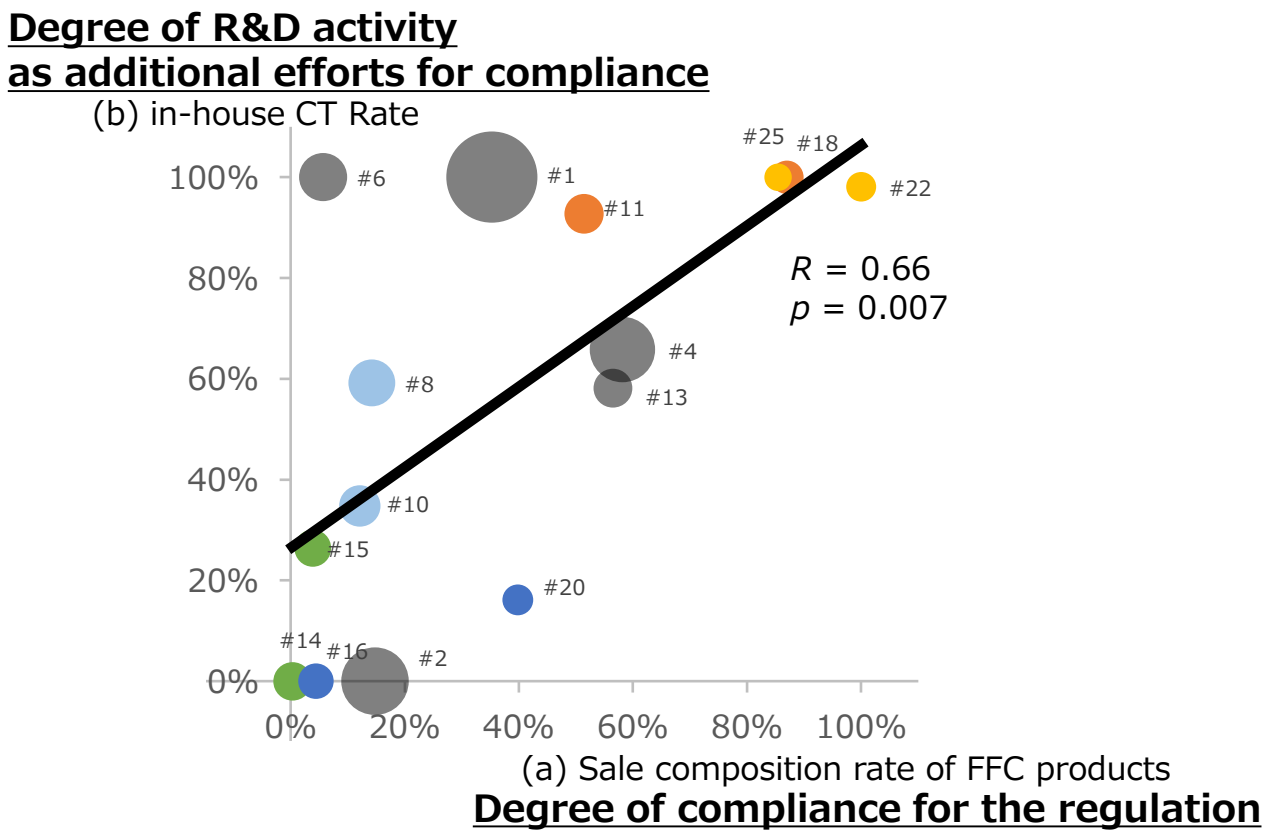

Figure 3-5 Scattering plots of 15 companies' (a) Sale composition rate of FFC and (b) in-house CT Rate.

Note: The circle size indicates sales. The circle colors are as same as those in Table 3-12. Label numbers are company IDs.

3.5 Discussion

3.5.1 Benefit from Health claims (Benefit-side regulation)

This study discussed the benefit-side regulation, the health claim regulation, based on end-product manufacturers' compliance with the FFC regulation. In this section, the design of this study with respect to the interpretation and setting of the benefits derived from the FFC regulation was examined. Figure 3-6 organized the benefits derived from FFC regulations based on the summarization in the research review (Figure 1-4). The proxy variables in each analysis also shown. The beneficiaries can be categorized into consumers, existing companies, and entering companies.

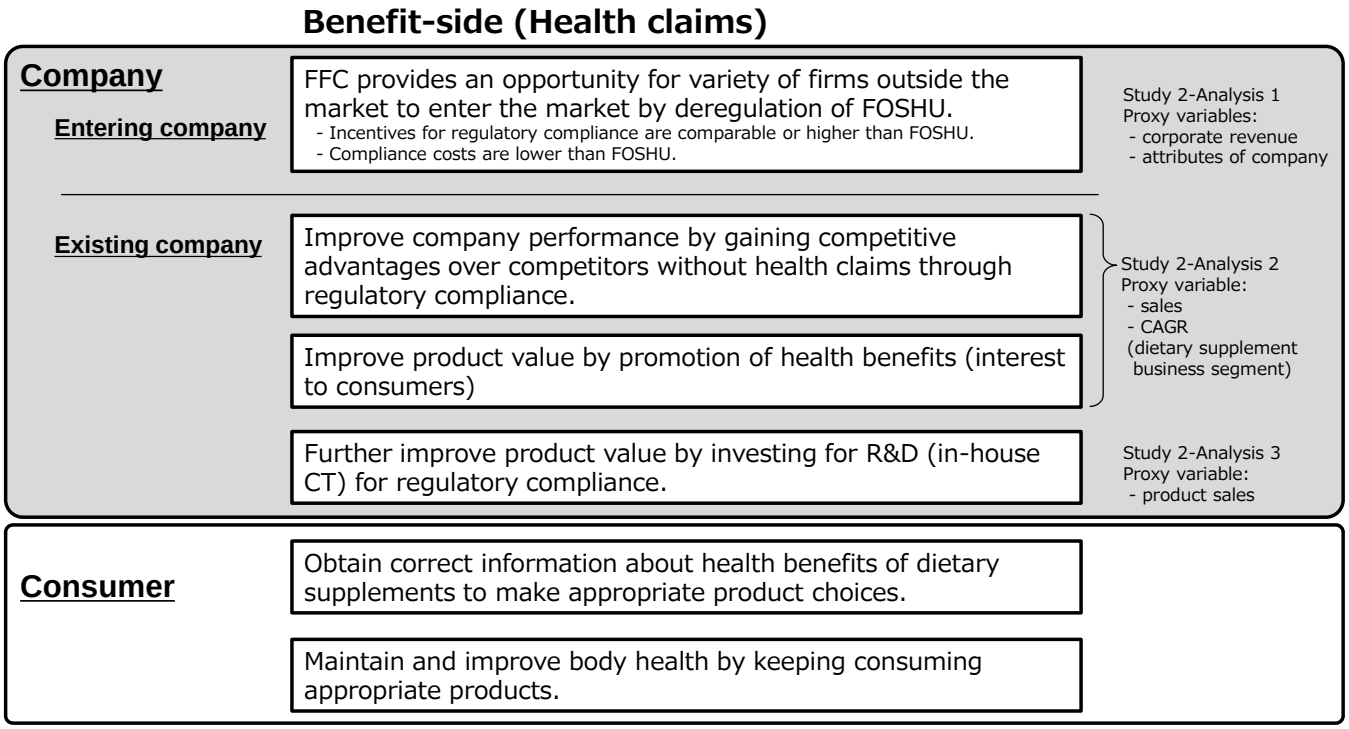

Figure 3-6 the benefits derived from FFC regulations and proxy variables in each analysis.

Entering companies

FFC regulation was a deregulation of FOSHU in the FHC regulation; firms that had not taken advantage of the FHC system were offered the opportunity to enter the market from this deregulation. Analysis 1 showed that new entrants differed from established firms in terms of firm size (sales) and firm core business. This indicated that the FFC program provided benefits to a group of firms that had not benefited from the program prior to its inception. Based on the hypothesis of increased firm diversity, this analysis used total firm sales to compare firm size and showed that the new entrants were smaller firms. The design of this

study using total sales, a representative size indicator that characterizes firms, was considered appropriate. However, the new entrant firms include firms that sold dietary supplements as "so-called health foods" before the FFC system and firms that did not sell any dietary supplements before the FFC program. Firms that newly entered the "dietary supplement market" as a result of the FFC deregulation were not analyzed separately. This is a limitation of this study due to the limitations of the data set used.

Existing company

The top firms in the dietary supplement industry (27 firms in this study) had been selling supplements prior to the start of the FFC program. These dietary supplements were mostly "so-called health foods," and the FFC system offered these top firms the option of either developing and marketing dietary supplements that conformed to the FFC regulations or bypassing the FFC regulations and continuing to market traditional "so-called health food" dietary supplements. The FFC regime could provide two benefits to companies that pursue the former strategy. That is, the benefits that health claims confer value on individual products [84], [91], [92] and the benefits that compliance with the regulation confers competitive advantage to the firm as a whole [12], [55].

In Analysis 2, sales and growth rates of supplement businesses between firms that took the option to comply with FFC regulations (FFC company) and those that took the option not to comply (to avoid) were compared. FFC firms had higher growth rates than non-FFC firms, even though there was no difference in business size. These results suggested that FFC provided the above benefits to firms. However, the effects of increased product value and the effects of increased overall firm competitive advantage were not analyzed separately.

To measure the benefits gained by the firms, the growth rate of sales of the dietary supplement business was used as a proxy variable due to the constraints of externally observable indicators. Firm growth could be also affected by various factors such as firm strategy, promotions, prices, and channels. The benefits derived from regulation could explain a part of firm growth. A limitation of this study was the use of sales growth rate as a proxy variable for benefits, under the ideal assumption that the function of firm growth on the benefits derived from regulation could be the same across the firms under study.

The study was designed to analyze the top firms in the dietary supplement market based on the objective of examining the impact of FFC regulatory compliance, so sales from the dietary supplement business were used instead of overall firm sales. The 27 companies included both companies whose main business is the dietary supplement business, and companies with overall sales of more than 1 trillion yen. In other words, the share of the dietary supplement business within a company had a wide range among the target 27 companies. The share of dietary supplements business within a company may influence strategic decisions to comply with or avoid regulations.

Larger firms typically have larger R&D resources, which may result in relatively smaller compliance costs (especially R&D costs) due to economies of scale and scope. In this case, the firm would be more likely to choose to comply with regulations. Conversely, if a large firm has a competitive advantage resulting from another business (e.g., a strong corporate brand, a dominant channel, etc.), the incentive for competitive advantage from regulatory compliance in the supplement business may be relatively small. In this case, they would be less likely to choose regulatory compliance. In addition, larger firms may be prevented from developing and implementing agile strategies in the dietary supplement business under the corporate strategy

of the entire company. In this case, regulatory compliance actions would be delayed and, consequently, benefits would be harder to obtain.

The FFC system has a multi-line notification route for clinical trials and SR. Analysis 3 showed that FFC products in in-house clinical trials have higher sales. Based on the assumptions in Analysis 2 above, it was assumed that FFC products with higher sales would provide firms with benefits from regulatory compliance. In other words, the FFC regulation with double track routes provided additional benefits to existing firms that were compliant with the FFC regulation and invested in R&D for their own clinical trials. Furthermore, the more compliant firms were more likely to invest in R&D for their own CT trials.

Consumers

This study did not evaluate the benefits that the FFC system provided to consumers as out of scope. Since health claims increase consumers' willingness to purchase products [84], [91], [92] and enable them to make appropriate product choices, the FFC system may have increased benefits to consumers as well, but this study did not quantitatively evaluate these benefits. In contrast to Analysis 3, which evaluated benefits to firms by using products sales as an indicator, it may be possible to evaluate benefits to consumers by using the unit prices of products. Prices of products could be newly surveyed and set as a proxy indicator, to conduct a similar multiple regression analysis, using the factors used in Analysis 3 as explanatory variables. This future developmental study would show another aspect of effects of the FFC regulation over innovation.

Furthermore, dietary supplement products compliant with the FFC regulations, which have some evidences of effectiveness on the human body, would provide consumers with the benefit of maintaining or improving their health when taken for an appropriate duration and in appropriate amounts. The "value of health" to which these benefits correspond has difficulty to measure and a lot of discussion [130]. The amount of money converted as a reduction in health care costs is both practical and academic topics from a policy and health economic perspective [65], [68], and it is expected to the development of long-term, large-scale observational cohort studies or social experiments in the future.

3.5.2 Assessment of the FFC System

Functional foods are developed through a long and highly uncertain process, which includes gathering knowledge about diseases and nutrition, obtaining evidence, and responding to regulations [41]. The FFC system, which consists of notifications by a SR of ingredients or clinical trial for individual products, is a deregulation to FOSHU system, whose products are admitted based on clinical trial evidence. This deregulation has led to an increase in the number of companies entering the system, especially small retailers. This is expected to consequently lead to the provision of products that better meet consumer needs, allowing consumers to proactively manage their healthcare.

The FFC system provides a variety of product development strategies for manufacturing companies. In notification using SR, the company supplemented its own research and development resources with accumulated external knowledge to commercialize their product efficiently. From an industry perspective, collaboration with the academia and government could reduce companies' R&D costs and risks [131]. It is posited that the creation and systematization of knowledge by the public sector will be useful. Some companies launched differentiated and competitive FFC products to realize their corporate growth by adapting to the new FFC system. As it is not easy for follower companies to use the evidence of clinical trials conducted by leading companies on their unique formulations, the latter can increase the competitiveness of their products with their

uniqueness and differentiation. These R&D activities are expected to lead to market introduction and popularization of new products, which in turn can lead to innovation.

The FFC system is a case of a regulatory system (re)design that promotes innovation by adjusting and optimizing the level of regulation. To promote health, mitigate lifestyle-related chronic diseases, and reduce healthcare costs, non-medical products and services that allow consumers to proactively manage their health care are required. This suggests the possibility of creating innovation through deregulation and open innovation using a different approach from that of the medical industry, which typically makes significant investments for R&D.

However, there are also some concerns about the current FFC system. Some health benefits are unsuitable for functional claim, which limits product development under the FFC system. Some studies indicate that SR used in FFC is unreliable [113], [114]. In addition, the combination of multiple ingredients has a possibility of unexpected effects in terms of safety due to the interaction of the ingredients. To further the research on the functions and effects of ingredients, future scholars, practitioners, and policymakers should engage in transdisciplinary R&D.

3.5.3 Prospects for Japanese and International Functional Food System

The number of FFC products continues to grow steadily; however, there are also systemic distortions of functional foods as a whole. In particular, there are a considerable number of companies that produce so-called "health foods" without using the FHC system. The FFC system has facilitated company entry but utilization is solely left to the company's discretion, and loopholes remain, particularly for those that are prone to opportunistic behavior. It should also be noted that these is an overlap of FOSHU and FFC in the current regulation system. The FFC system allows companies to label health claims that are similar to those used for FOSHU (and even those not available for FOSHU) at a lower cost. FFC with similar health claims as FOSHU may confuse consumers and would be a threat to companies selling FOSHU. The complexity of the Japanese functional food regulation shown in Figure 1 is attributed to a repeatedly revised and expanded system [27]. Redesigning the Japanese regulation framework would be difficult because of the historical path-dependency of the system even though reorganization of the regulation system (such as repositioning FOSHU) would be desirable.

Looking at another case, in the U.S., which is the largest market for supplements, the Dietary Supplement Health and Education Act (DSHEA) allowed dietary supplements to label functional claims in 1994 [24], [27]. Since then, the dietary supplement market in the U.S. has expanded significantly. Labels related to functionality increase consumer willingness to purchase and stimulate the market. However, the DSHEA, applicable only to dietary supplements, does not allow clinical trials on individual products. Hence, some of the sales factors revealed in this study, such as in-house clinical trials, would not be applicable to the U.S. market.

FFC is a unique system containing a double track of notification by SR of ingredients or clinical trial for individual products, leading to reduced administrative costs and promotion of product development competition among companies. It is possible that, in regulatory systems other than that of Japan as well, system revisions that allow notification by product clinical trials would bring market expansion through industrial revitalization and the new product development. Regulations for functional foods vary from country to country. In addition to the U.S., according to Singapore's regulations, which require

notification, clinical trials for individual products are not permitted; However, regulations in some countries such as South Korea and Taiwan require approval for individual products [71].

Conversely, the Japanese system is not sufficiently harmonized internationally. Compared to other systems, the Japanese system has some unique practices such as voluntary good manufacturing practice for quality control [27], [71]. The lack of global regulatory harmonization could bar foreign companies from entering the Japanese market; it could also reduce product variety, limiting Japanese consumers' access to and choice of products including those from overseas. Moreover, Japanese companies incur additional costs to comply with foreign regulations when exporting their products overseas.5.3. Limitations and future perspectives

3.6 Limitation

This study has several limitations due to the data set. It employed cross-sectional data of 74 FFC products from 15 companies in Japan. As such, it was limited to a specific period or regional context. To obtain deeper insights into the relationship between innovation and regulation in the functional foods market, future scholars should conduct a time–course observation and analysis of these cases.

The year of notification of FFC products may influence a company's decision to comply with the regulation. As time passes since the inception of regulation, the uncertainty of the benefits derived from regulatory compliance would decrease. Therefore, incentives for regulatory compliance may also change, potentially affecting the decision to comply with the regulation. In this study, given the sample size of the data, an analysis that included the year of notification as a factor was not conducted. The possible existence of time dependence is a limitation of this study.

In addition, the present study's analysis was conducted by using externally observable indicators, but firm performance could be measured not only by sales and sales growth, but also by profit margins, stock prices, and so on. Firm sales are affected by various factors such as corporate strategy, marketing strategies about promotions, prices, and channels, of which regulatory influences are only a part. Product sales are influenced by many kinds of factors such as type of functionalities, brand image, product price, product channel, or promotions. Further studies are needed to address these points. The use of sales as a performance evaluation method is a limitation of this study due to data limitations.

It is undeniable that reverse causality can also be inferred especially in hypothesis 2 of this study. In other words, it is possible that higher performance may have high financial capacity, result in complying to FFC regulation. To verify this point, it is necessary to confirm the causal relationship by comparing the firm's performance with its performance prior to the start of the FFC regulation or by confirming strategic decisions made within the firm. This point is a research limitation.

3.7 Conclusion

In this study, we empirically explored how the regulatory environment affected the innovation process in Japan during the transition of the regulatory approval process for functional foods. The Japanese FFC system allowed the entry of several companies, mainly small retailers, into the Japanese FHC market. This deregulation contributed to an increase in the diverse range of companies entering the market and broadening its base. The relatively high compound annual growth rates of companies utilizing the FFC system suggest that this scheme also contributed to the growth of the companies.

Under FFC with notification system, it is difficult to achieve product competitiveness by adapting to regulations, compared to the situation under FOSHU's approval system. The FFC system's double-track notification routes diversify corporate strategic options and make companies compete based on their respective strategies. Small companies tend to use SR, a set of external knowledge, to reduce development costs. To increase product value in the market, it is necessary to strengthen the required efforts, including the development of multiple-materials formula and the in-house testing process. The FFC system, which is unique to Japan, promotes competition among diverse companies by encouraging them to develop competitive products to expand the market. However, the Japanese functional foods system has become complex and does not harmonize with the other international regulatory systems.

Finally, we propose two suggestions for the Japanese functional foods system. The system, including FOSHU and so-called health foods, should be totally reorganized. International regulatory harmonization should be promoted to improve consumer ac-accessibility. We expect that these findings on the relationship between regulation and innovation will provide useful implications for scholars, practitioners, and policymakers for its optimization in the dietary supplements market.

4. Discussion and Conclusions

In this chapter, first, the FFC system is comprehensively discussed, and the effectiveness of FFC regulations on industry convergence and innovation is examined. Next, conclusions are drawn in response to research questions. Then, academic and practical implications are presented. Finally, the significance, limitations, and future prospects of this study are presented.

4.1 Summary of key findings

This section synthesizes Study 1 in Chapter 2 and Study 2 in Chapter 3 to provide a comprehensive discussion and findings on the effectiveness of FFC regulations on industry convergence and innovation. First, the two studies are evaluated and the relationship between the two regulations on the risk side and the benefit side is summarized. Based on the impact of each regulation on the industry, the impact of the comprehensive FFC system on convergence is summarized. In addition, the effectiveness of the FFC system on innovation will be discussed in terms of its impact on firm behavior. Furthermore, beyond the scope of the quantitative analysis conducted in this study, a developmental discussion is given to firm behavior, industry formation, and opportunities for new entrants. Finally, the significance of this study is emphasized through comparisons with foreign regulations.

4.1.1. Assessment of risk- and benefit-side cases

The Study 1 in Chapter 2 focused on GMP, one of the risk-side regulations for quality and safety. The present study focused on key success factors related to the adoption and implementation of GMP for dietary supplements in Japan. As a result of the empirical observations of 90 CMOs that are OEM manufacturers of dietary supplements, three factors were identified as affecting the adoption of GMP: company size, manufacturing capability of pharmaceutical products, and the number of categories of manufactured dietary supplements. The interviews suggested that GMPs appeal to client firms and have a signaling effect. Adoption of GMPs was found to be facilitated by pharmaceutical manufacturing competence, in addition to firm size and relationship with the customer, the end-product manufacturer, but not in relation to food manufacturing competence. In other words, it is clear that compliance with GMP, a manufacturing standard for quality, was influenced by pharmaceuticals in adjacent sectors, and that this influence was asymmetric, coming from the side with stronger regulations.

The study 2 of Chapter 3 focused on the FFC system, the 2015 regulatory reform of the FFC system, which is a benefit-side regulation regarding the labeling of functionalities. FFC was a deregulation from FOSHU. Corporate behavior in response to regulatory change was discussed based on corporate pathways. In this study, it was empirically explored how the regulatory environment affected the innovation process in Japan during the transition of the regulatory approval process for functional foods. The Japanese FFC system allowed the entry of several companies, mainly small retailers, into the Japanese FHC market. The external clinical test type FFC products utilized the accumulation of research (i.e. clinical trials on ingredients) from a long period of time in the past by external parties such as academia or raw material manufacturers. This deregulation contributed to an increase in the diverse range of companies entering the market and broadening its base. The relatively high compound annual growth rates of companies utilizing the FFC system suggest that this scheme also contributed to the growth of the companies.

Under FFC with its notification system, it is difficult to achieve product competitiveness by adapting to regulations, compared to the situation under FOSHU's approval system. The FFC system's double-track notification routes diversify corporate

strategic options and make companies compete based on their respective strategies. Small companies tend to use SR, based on external knowledge, to reduce development costs. To increase product value in the market, it is necessary to strengthen the required efforts, including the development of multiple-materials formulas and in-house testing processes. The FFC system, which is unique to Japan, promotes competition among diverse companies by encouraging them to develop competitive products to expand the market.

4.1.2. Relationship between risk-side and benefit-side regulations

As shown in Chapter 1, FFC system could be regarded as a set of deregulations on the benefit side and tightening of regulations on the risk side. GMPs for FFC dietary supplements were effectively made mandatory by recommending to manufacture products in GMP-controlled factories in FFC guidelines [21]. That means that risk-side regulations have been strengthened in the FFC. On the other hand, due to its certification process, FFC can allow to label health claims at a lower cost compared to FOSHU. That means that benefit-side regulation has been eased. Firms that utilize FFC have increased sales and introduced new products. For end-product companies, FFC is introduced as an incentive for corporate growth with functional claims that are accepted by consumers.

For OEMs whose customers are manufacturers of finished products, the structure of the system is such that there is a motivation to introduce GMP because the introduction of GMP will lead to business expansion and strengthen relationships with manufacturers of finished products, amid the trend for customer companies to utilize the functional food labeling system. Figure 4-1 illustrates this structure. The bundling GMP with FFC has strengthened the incentive for OEMs to adopt GMP to strengthen their relationships with customer companies that adopt FFC. The introduction of GMP in combination with the introduction of the FFC System will further promote GMP, which is a regulation on quality control.

The FFC system has coordinated both risk-side and benefit-side regulations as levers, balancing the level of regulation throughout the system. The relationships between firms would promote to increase compliance with regulations structurally. As a result, consumers would be protected and benefit, and companies (both OEMs and end-product manufacturers) would create economic value.

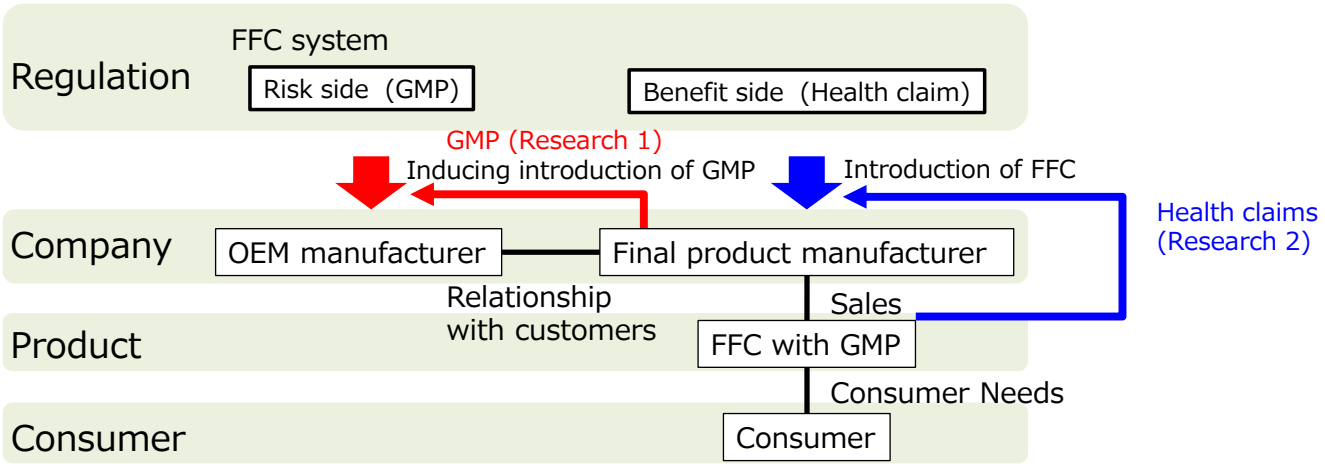

Figure 4-1 Relationship between GMP and health claim of FFC

4.1.3. Impact of risk- and benefit-side regulations to the industry

It was revealed that some companies brought knowledge and technology from outside the functional food domain when complying with GMP and FFC regulations. Figure 4-2 shows this process, where changes of regulation affected companies. In Figure 4-2, red lines indicated impacts of GMP, and blue lines indicated impacts of FFC. In GMP, some companies have utilized in-house capabilities in pharmaceutical manufacturing. The similarity of regulations in the pharmaceutical domain regarding GMP has facilitated the transfer of knowledge and technology, to promote quality improvement. This process was indicated as (i) in Figure 4-2.

External knowledge from academia and materials companies was introduced especially in systematic review (SR) indicated as (ii) in Figure 4-2. The simplicity of process by SR has promoted the entry of new small companies and retailers, indicated as (iii). Retail firms are thought to bring marketing knowledge and skills [30], and alliances with OEMs to manufacture products would promote industry convergence. In addition, existing firms have developed and launched differentiated products in the new competitive environment (indicated as (iv)). Among company behaviors shown in Figure 4-2, "Introduction of external knowledge and technology" was related to supply-side convergence, and "new companies entering" was related to demand-side convergence [37], [38]. In next section, Impacts on Industry convergence from regulations would be discussed.

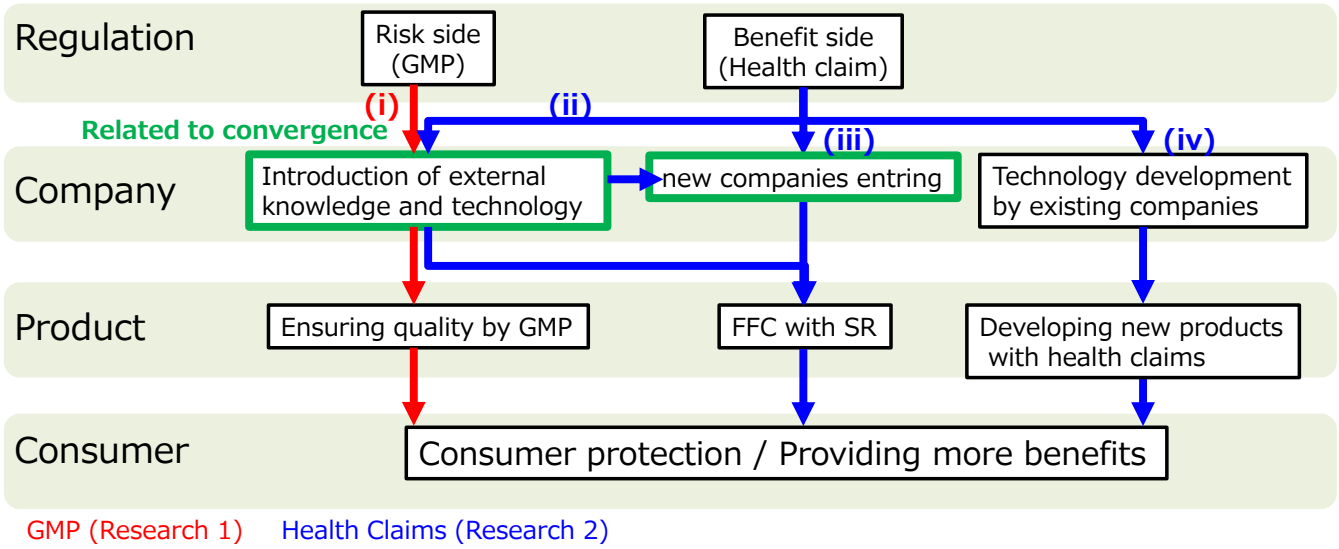

Figure 4-2 Impacts from regulations on company behavior

4.1.4. Impact of regulations on Industry convergence

The result of the regulatory transition from FOSHU to FFC, which caused creating new markets and the entry of new firms, would be one example of deregulation as a driving force for market convergence [37] as shown by green lines in Figure 4-3. Furthermore, the FFC system has encouraged spillover of pharmaceutical knowledge and introduction of technology for quality control in GMP (Study 1) and spillover of outside knowledge for product development by SR (Study 2). These results suggested that regulations in functional food not only affect market convergence on the demand side, but also induce firm behavior in response to

regulations, inducing knowledge convergence and technology convergence from the supply side. It was suggested that there would be a route, shown by red lines in Figure 4-3.

In the functional food area, much has been discussed about the convergence of the pharmaceutical and food industry domains in horizontal direction. In this study 1, knowledge and technology convergence from pharmaceutical to food were occurred inside OEM company horizontally due to compliance for regulation. Meanwhile, the entry of retailers due to deregulation, demonstrated in this study 2, is a demand side convergence in vertical direction along a supply chain. One of novelties of this study is integrated discussion of regulation-driven convergence that regulation would affect convergence in different side and different directions simultaneously; on the supply side in horizontal and on the demand side in vertical. The former convergence in OEM case was from single interview of a firm has not been demonstrated sufficiently. This point was one of limitations of the study.

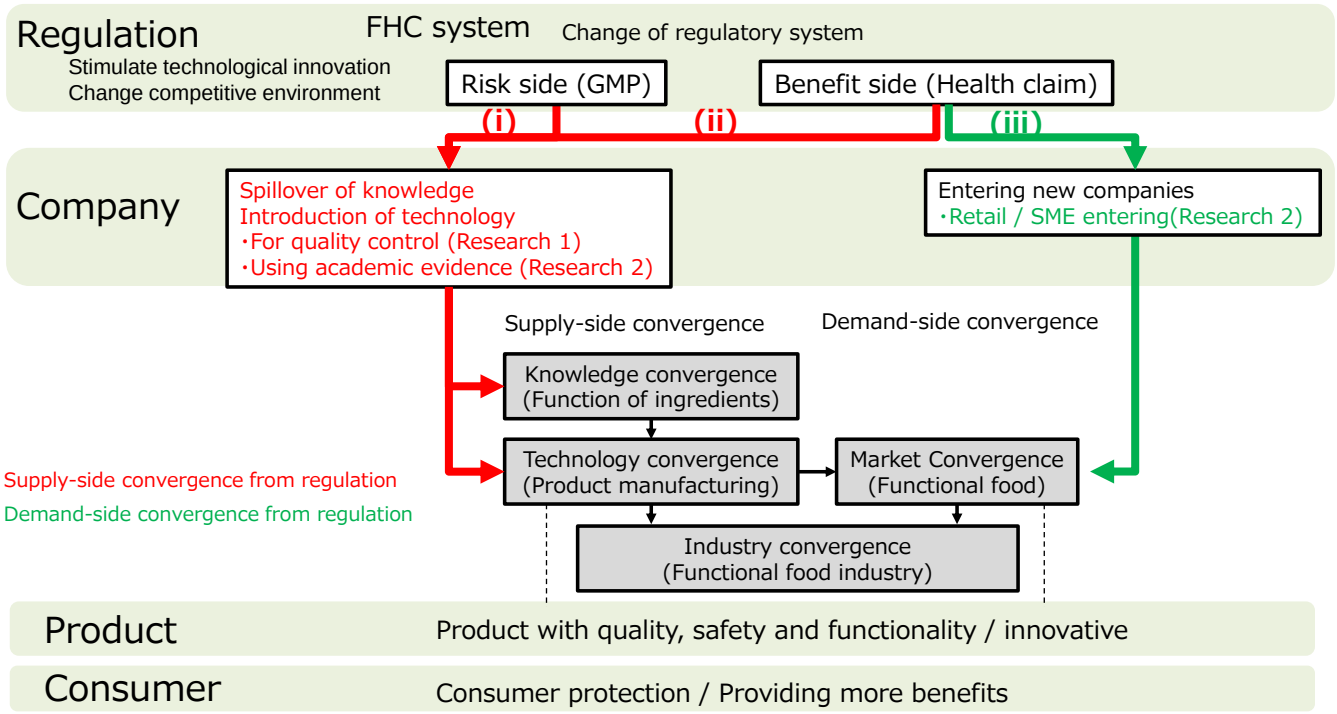

Figure 4-3 Impact of regulations on industry convergence

4.1.5. The Aims of Japan's Functional Food Regulations and Their Effectiveness on Innovation

This section examined the impact of the FFC regulations on business behavior and innovation, based on the review of the regulatory studies (Figure 1-3). The purpose of the FFC was to both protect consumers and revitalize the industry, which led to the deregulation of the FFC and the tightening of regulations on quality standards. As revealed in research 2, the FFC allowed firms outside the system, especially the SR route, the opportunity to take advantage of the FFC and gain a competitive advantage by conforming to FFC regulations, thereby improving firms' performance. It also diversified the market and expanded the market.

In addition, due to the double track notification route, firms that conformed particularly strongly to the regulations were given incentives to acquire more appealing health claims through R&D investments to further increase their competitive advantage. This induced innovation behavior among firms, and the ingenuity of firms led to the provision of innovative products with various health claims.

In subsequent parts, the FFC system is evaluated according to the three aspects of regulatory innovation (stringency, flexibility and information) presented by Stewart [64] as introduced in literature review in this thesis. Regulatory stringency is the degree of compliance burden. The lower the stringency, the more innovation is encouraged [64]. In terms of regulatory stringency, the FFC, which was a notification system under the responsibility of the operators, was less stringent than the FOSHU, which requires clinical trials and is licensed by the implementing authority.

Flexibility is measured by the number of pathways available for regulatory compliance. Health claims can be devised in function, ingredients, and wording to meet consumer needs, and there are many pathways for compliance. Companies can label a variety of health claims as long as they are within the scope of "health maintenance and promotion" and are based on scientific evidence. There are many options for ingredients to support the same functional claim. There is room for companies to devise health claim text that conveys the benefits in a way that is clear and attractive to consumers. Furthermore, the FFC notification procedure has two routes, SR and clinical trials, with more options for companies to choose from compared to FOSHU. Under the notification system, the FFC regulation regulates the methodology and process for labeling. FFC has more flexibility than FOSHU. Regulations with high flexibility increase incentives for regulatory compliance and are positive for innovation [11], [64]; the high degree of flexibility of FFC regulations gives firms room for ingenuity, and the potential for competitive advantage provides incentives for regulatory compliance.

The health claims regulation was intended to ensure adequate information to consumers in order to reduce asymmetry in consumer health information. In previous studies of safety regulations and other regulations, it was pointed out that, regulations that reduce information asymmetry was the provision of information to consumers through regulatory compliance serves as proof of product quality and provides incentives for firms to comply with regulations [64]. Moreover, health claims do not merely reduce information asymmetry between firms and consumers, but they present specific and direct consumer health benefit information. The adequacy of the information is ensured by regulation. Companies can take advantage of the highly flexible health claims regulations to gain additional competitive advantage by more aggressively seeking to make their products more acceptable and to provide differentiated information. As a result, products with new features were offered to consumers, along with information showing specific benefits. New and unique products with new functional features not found in FOSHU, offer new types of value to consumers that were not previously available. This corporate strategy could be considered a type of blue ocean strategy [132], a non-competitive strategy to create new markets.

The study showed that firms that were more compliant with FFC regulations would more likely to invest in R&D and market products with new function in multiple materials. The fact that highly flexible regulations to offer benefit information provide firms with strong regulatory compliance incentives to pursue the development of innovative products with additional R&D efforts, even at the expense of additional compliance costs, extends concepts of flexibility and information of regulation on innovation in prior research and provides new insights. The concept of benefit-side regulation (providing benefit information to consumer) provided a new viewpoint to the study of the relationship between regulation and innovation. Furthermore, as GMP

of risk-side regulation were bundled together, the whole system of FFC regulation had an impact not only on final product manufacturers but also on OEM companies on the upstream side.

The complex functional food regulatory framework including FFC and FOSHU shown in

Table 1-4, give firms many strategic options. While the complexity of the regulatory system due to pass-dependency may lead to cumbersome and inefficient administrative procedures, there may be an aspect in which innovation is generated as a result of each company choosing a strategic option suitable for the company. This is a noteworthy example of how innovation, including competition among firms and the creation of new markets by firms, is being realized within the constraints of regulations with complexity and flexibility.

As far as investigated, this phenomenon seems to have achieved a level of effect that exceeds the degree of "industrial revitalization" that was envisioned when the FFC regulations were designed. However, the exact intentions and assumptions of the institutional design need to be confirmed through interviews with policy makers. This is a limitation of this study.

This study has a novelty in that it focused on the Japanese functional food regulatory system, in which multiple regulations are permanently set for the same industry and market, and empirically and quantitatively analyzed the differences in firm behavior and their effectiveness on innovation by comparing and observing firms inside and outside the regulatory system, discussing their decision-making patterns to comply with or avoid regulations.

4.1.6. Behaviors of companies with other attributes, industry formation and entry opportunities due to regulatory changes

The impact of the FFC regulations on convergence and innovation would not be limited to the range of OEMs and end-product manufacturers covered by this study. The higher percentage of Material companies in the Entering group than in the Existing group in the firm characteristics in Table 3-1 suggested that this regulatory change provided also opportunities for Material manufacturers. Material manufacturers have a typical business model of exploring new materials and ingredients and selling them to OEMs and end-product manufacturers. They have been promoting their ingredients to OEMs and end-product manufacturers based on the efficacy evidence of their ingredients, demonstrated through in-vitro, in-vivo, or clinical studies. The FFC system has provided an opportunity for material manufacturers to develop FFC products and obtain health claims. For example, in the area of brain cognitive function, as much as 18 different ingredients were used in FFC products between 2016 and 2020 (source: author's survey using the FFC database). In some cases, material manufacturers were the first to launch FFC products with their materials, and university scholars developed FFC products based on their research. It was assumed that in some cases FFC products were actually marketed to end consumers, while in others they were promoted as prototype products to end-product manufacturers. In either case, FFC regulatory compliance gave the material manufacturer a competitive advantage over competing material manufacturers. Academia, which explores and researches the functions of new food ingredients and components, gained business opportunities by leveraging Material's assets, forming alliances with companies, and starting businesses as start-ups.

Fresh foods are also allowed to be granted functional claims by FFC system. Of all FFCs, several percent were fresh foods, and a wide variety of fresh foods were notified, including fruits, vegetables, seafood, eggs, meat, and many others, increasing the value of food ingredients [133]. The FFC regulation provided a way to differentiate in a different direction than the traditional differentiation strategies of branding and pursuing quality. By adding new value to local specialties, increasing their competitive advantage, and marketing them nationwide, the FFC also promoted developing local businesses and fostering regional industry. For local businesses lacking academic knowledge, public research institutes provided SR for functional

ingredients and supported the commercialization of FFC products [133]. The FFC system provided business creation opportunities for local governments, agricultural and fishery organizations, and others with the seeds of local specialty products. Under the FFC, some new technologies are required to ensure the content of functional ingredients in fresh foods. For example, the need to develop production and cultivation management techniques to reduce variation, as well as inspection techniques and equipment for agricultural products [133], would provide opportunities for academia and companies involved in these areas. Convergence of knowledge and technology with different fields may be occurring.

The distribution of fresh foods and general processed food products with function claims would promote the implementation of the FFC system into society. In order to further promote the social implementation of the FFC system, two directions would need to coexist as shown in Figure 4-4. One is keeping to create innovative and highly functional FFC products to increase products diversity, driving the market. This could be promoted due to FFC's regulatory aspects of high flexibility, reduction of information asymmetry, and Concrete and direct presentation of health benefits for consumers as discussed previous section. And the other is that more consumers consume FFC on a daily basis to expand the market base. Aspect of deregulation over FOSHU would give business opportunities diverse companies to enter the market, resulting in making consumer access a variety of FFC much easily. The double-track notification route for clinical trials and SR of FFC systems is consistent with each of these two directions.

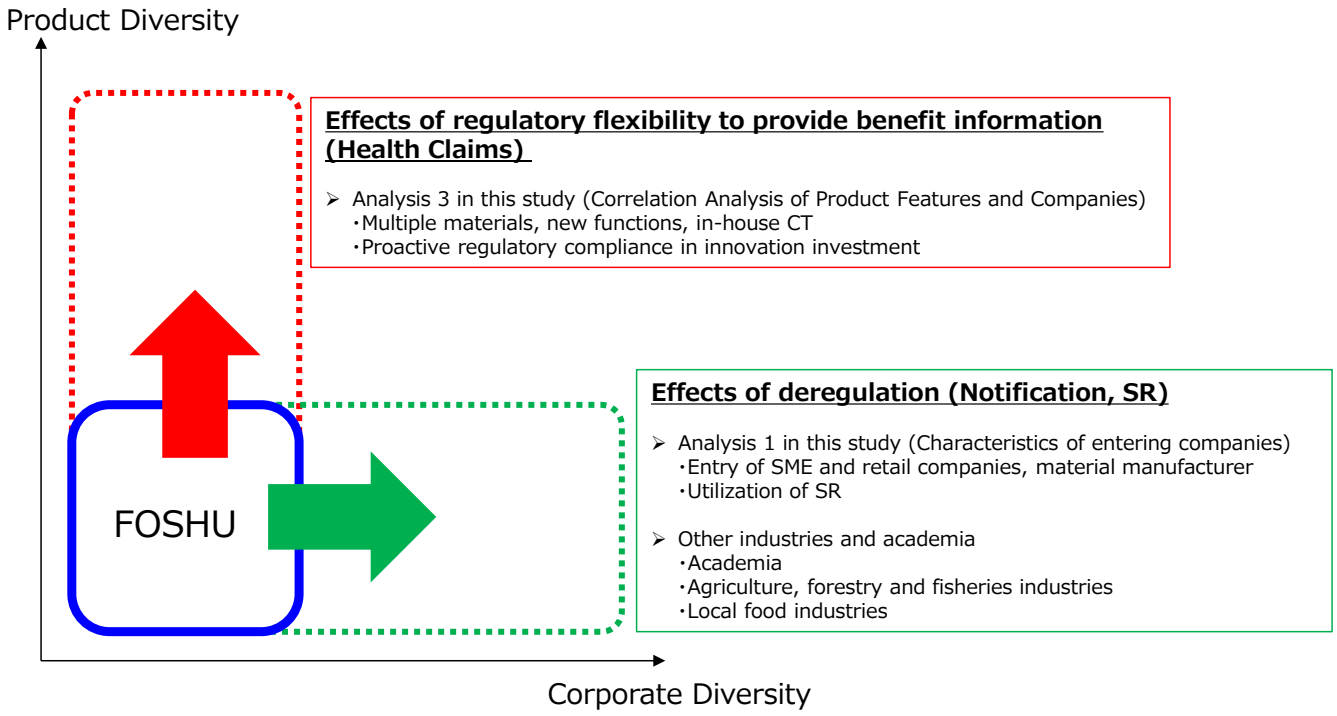

Figure 4-4 Two aspects of FFC regulation and effects of products and companies, resulting in promotion of the social implementation of the FFC system.

The FFC system has also affected industries related to clinical trials because it requires evidence of clinical trials on ingredients or products. Clinical trials using food samples increased in terms of registrations to the University hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) [134], [135]. FFC health claims are highly flexible, and FFC products have been launched using outcome measures that have not been used in FOSHU (e.g., electroencephalography, sleep status, walking speed, immune markers, etc.) as evidence. In the future, new biological sensing and testing technologies could be applied to evidence for FFC products by allowing new outcome measures. In addition, due to the nature of dietary supplements, whose effects are manifested through ingestion over a long period of time, clinical trials require data acquisition using methods that are less burdensome on subjects. There is a need for methods that are equally accurate and more convenient for existing biomedical measurements such as blood markers and CT measurements, etc. The FFC system may provide opportunities for companies and academia with these technologies and induce innovation through convergence of knowledge and technology.

In the field of environmental regulation, there have been reported cases in which regulations have indirectly promoted innovation not only among the targeted end-product manufacturers, but also among raw material manufacturers with whom they have business relationships on supply chain [63]. This study 1 suggested that FFC regulations for final product manufacturers would indirectly promote compliance with GMP regulations by OEMs with their business relationships on supply chain. In addition, there would be also a spillover effect to companies with related technologies and complementary products and services as mentioned above. Thus, regulations would not only directly affect the target industries, companies, and products described in the normative definition in them, but also indirectly affect related industries and companies in the industrial ecosystem formed under various relationships among companies as illustrated in Figure 4-5.

For example, the expansion of the contract research organization (CRO) industry after the start of the FFC system [134] suggests that raw material manufacturers, academia, and companies adopting FFC regulatory compliance strategies in their own clinical trials are outsourcing to contract research organizations (CROs) in order to reduce costs and utilize know-how. Through clinical trials and the acquisition of evidence, collaborated relationships between companies and physicians or researchers in academics may also be strengthening. As a topic for future research, it would be necessary for a discussion of the spillover effects of regulation on peripheral industries and industrial ecosystems via inter-firm and firm-academia relationships. Specifically, a bibliometric analysis of the authors of articles on clinical trials or the actors listed in the registry of to the University hospital Medical Information Network Clinical Trials Registry (UMIN-CTR)[135] would make it possible to visualize the impact of regulations on the industrial ecosystem and examine spillover effects. This kind of research would be useful for further generalized understanding of relationship between regulation and innovation.

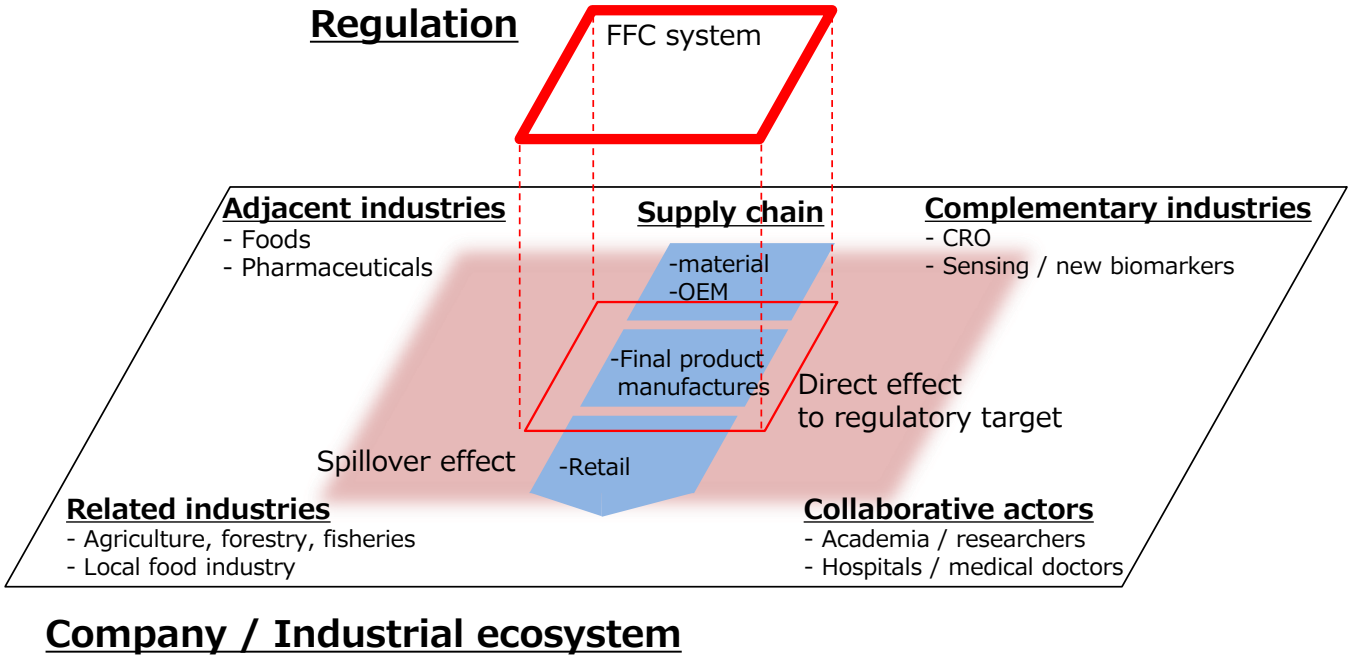

Figure 4-5 Impacts of regulation on industry ecosystem

4.1.7. Background and intent of the FFC regulatory design

Was the impact of the FFC regulations on the industry, as described above, intended when the regulations were designed? This section describes the background and history of the creation of the FFC regulations and considers the intent of the regulatory design.

In 2013, the Council for Regulatory Reform and the Japan Revitalization Strategy, which aim to contribute to national growth and development, stabilization and improvement of people's lives, and revitalization of economic activities, identified development of a system to enable functional labeling of general health foods as one of the issues and started discussions on regulatory reform in the functional food field [136]–[138]. As an issue of the existing regulation, the FOSHU system, it was pointed out that the high cost of regulatory compliance was a barrier to entry for small and medium-sized enterprises. The high cost was due to the fact that clinical trials on safety and efficacy were required for each food product, and that the approval process was time-consuming and costly. In the regulatory reform, it was decided that the labeling system for dietary supplements in the U.S. would be used as a reference, with the aim of utilizing the know-how of the private sector by having companies evaluate the scientific basis for the labeling and then label the function of the product themselves [136].

During 2013-2014, the “Study Group on a New Functional Labeling System for Foods” met eight times to discuss the direction of the new system in terms of ensuring safety, scientific grounds, labeling, and the government’s involvement [138]. The study group consisted of academics in the fields of food science and pharmacology, physicians, consumer groups, media, and industry associations related to health foods. Through these discussions, the new system also reflected the opinions of the industry [137]. The Food Labeling Law was subsequently revised and the FFC system was established in 2015.

The impetus for the FFC regulation was a top-down industrial policy, and the intent of the regulatory reforms was to increase the diversity of companies through deregulation and the utilization of their know-how. During the regulatory design phase, the intentions of firms were also reflected in the regulations through industry associations. It was possible that firms’ strategic intentions from the regulatory design stage existed behind the strong regulatory compliance and innovation activities being made by existing firms. It is a subject for future study to examine the interaction between regulations and firms by means of referring minutes of the study group and interviewing.

4.1.8. Comparison with regulations in other countries

As indicated in the introduction, supplement regulations vary from country to country, and international harmonization has not been achieved. Table 4-1 shows the administrative process, whether or not a GMP system is required, and whether or not it can be used as evidence in clinical trials. Japan's supplement regulations were unique in that they included multi-track health claim regulations (FFC, FOSHU, so-called health food) and voluntary GMP.

In the United States, the largest market, a comprehensive supplement regulation law (Dietary Supplements Health Education Act; DSHEA) was established, providing for labeling and GMP compliance. Under strong regulations, the supplement industry has grown while ensuring consumer safety. In Japan, there are no comprehensive regulations regarding dietary supplements, such as labeling regulations or mandatory GMP. GMP is a voluntary regulation, and whether or not to comply with labeling regulations depend on each companies' strategy. The FFC, on the other hand, was designed with reference to the U.S. DSHEA with the policy intent of promoting self-medication. Under the FFC with effectively mandatory GMP and attractive labeling system for companies and consumers, it is expected to approach the U.S. structure as the FFC market grows. Unlike the U.S., the FFC focuses on a voluntary system and uses relationships and incentives among firms to enforce quality regulations that impose regulatory compliance costs. This is a case with both practical and academic implications. Figure 4-6 shows comparison of legislative frameworks of functional foods in Japan and US.

However, with this institutional design, it is expected that it will be difficult for all supplements to come under the system in the future. There is a difference in product attributes and market needs between US and Japan. While U.S. supplements are dominated by so-called "nutrients" such as vitamins and minerals [139], Japanese dietary supplements are dominated by natural ingredients with functionality as shown in Figure 4-7. Many natural ingredient supplements have been promoted as "so-called health foods" based on the name recognition and healthy image of the ingredients, without promoting their functions for long time [43].

Some of these ingredients have yet to be fully elucidated and their functions have yet to be fully clarified academically. Demonstrating their functions in clinical trials likely to take time and cost. This is also because some functions, such as anti-aging

functions, are technically difficult to make into FFC because they are difficult to use as evaluation indices in clinical trials, although consumer needs are high.

Table 4-1 Comparison with systems in other countries

	EU	US	Korea	Taiwan	China	Singapore	Japan
Registration / Approval System (Business Item)	Yes	No	Yes	Yes	Yes	No	In parallel
GMP system by country	Yes	Yes	Yes	Yes	Yes	No	No
Clinical trials of individual products	For new ingredient	No	Depends	Depends	New Ingredient	No	Depends

Japan

		Shape	
		Obviously Food	Tablet / capsule etc.
Food		✓	
Functional Food	Without Health Claim	✓	☆
	with Health Claim	✓	★
Pharmaceutical			✓

US

		Shape	
		Obviously Food	Tablet / capsule etc.
Food		✓	
Functional Food	Without Health Claim	✓	
	with Health Claim	✓	★
Pharmaceutical			✓

Note: check mark (✓) shows exsistance of products.
Note: filled star mark (★) shows dietary supplements with GMP.
Note: hollowed star mark (☆) shows dietary supplements without GMP.
Note: red bold line indicates the boundary of FFC system in Japan.
Note: brue bold line indicates the boundary of DSHEA system in US.

Figure 4-6 Comparison of legislative frameworks of functional foods in Japan and the United States.

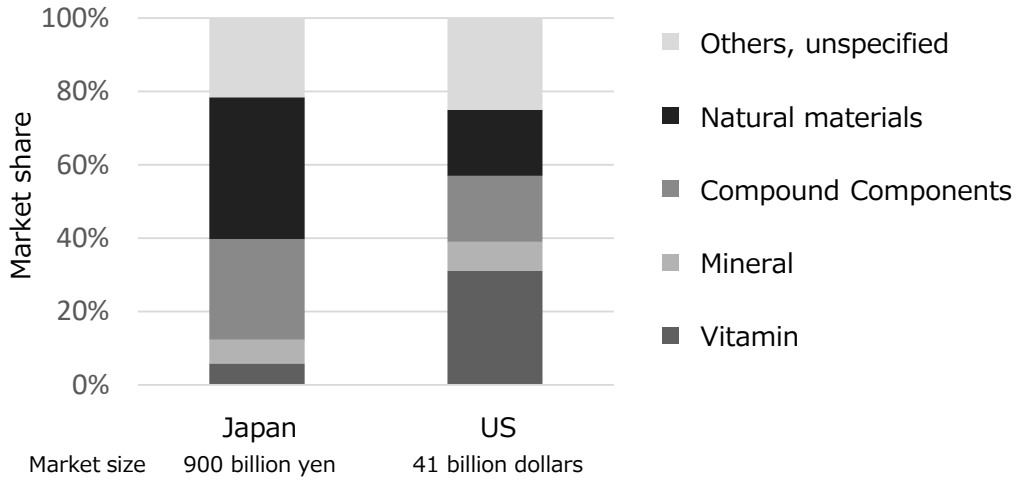

Figure 4-7 Market Share by Ingredient Type in Japan and the U.S.

Note: Prepared by the author from [43], [139]

4.2 Conclusions for research questions

In this section, the above results and discussion were summarized and conclusions to the research questions were stated below.

Main Research Question

How have regulatory reforms in Japan's functional food changed the costs of compliance and the incentives to comply regulations for companies, and how have they affected the industrial structure, companies, and products?

The FFC system was a regulatory change that combined risk-side regulatory tightening with benefit-side deregulation. In the former, a structure was formed in which OEMs introduced GMP regulations based on their relationships with end-product manufacturers. The latter provided business opportunities for end-product manufacturers, leading to the entry of new firms and the introduction of new products. The assurance of product quality through tighter regulation on the risk side and the enhancement of product value through deregulation on the benefit side realized benefits for consumers and profits for companies.

Research Question 1

How did tighter regulations on risk side change the incentives to comply regulations for companies, and how did companies respond to reduce the costs of compliance?

GMP regulations similar to those in the pharmaceutical sector were tightened, and OEMs needed to comply with the regulations due to their relationships with their customers. To suppress compliance costs, knowledge of pharmaceutical manufacturing was introduced and knowledge and technology convergence was promoted.

Research Question 2

How did deregulation on the benefit side change the costs of compliance and the incentives to comply regulations for companies in and outside the industry, and how did companies respond and take advantage of the opportunity?

Deregulation has allowed firms to enter the market. Market convergence has progressed with the entry of small and medium size and distribution firms. With the use of SR, knowledge from outside academia and other sources was introduced to firms. Top-ranking firms took advantage of the opportunities created by regulation to develop new products, increase sales, and provide benefits to consumers.

In this study, the following factors were assumed to influence the decision of regulatory compliance. In study 1 for GMP, while compliance cost would be establishment and maintenance of GMP management system (human-resources, equipment), incentive for compliance would be customer relationship (e.g., increased FFC contracting opportunities and signaling of quality). Presence of pharmaceutical knowledge would lower compliance costs. In study 2 for health claim, while compliance cost would be administrative procedure costs (e.g., notification) and R&D costs (for clinical trials), incentive for compliance would be product value enhancement through health claims and competitive advantage by differentiation. It was assumed that companies would decide the appropriateness of regulatory compliance in terms of cost-effectiveness, based on the costs of regulatory compliance and the incentives for regulatory compliance. This "efficiency related to regulatory compliance" would be considered as a latent variable influencing regulatory compliance as shown in Figure 1-9. The change in Japan's functional food system was an example of both consumer protection and innovation through regulation.

4.3 Theoretical implications

4.3.1 Perspectives of relativity to adjacent industries

The ability of firms to confront the new demands faced by convergence were affected by firm path dependency [50]. The finding that the transfer of pharmaceutical manufacturing knowledge and technology has occurred in OEMs with pharmaceutical manufacturing indicated that regulatory-driven knowledge and technology convergence would be also affected by path dependency.

In knowledge convergence, it was pointed that an erosion of boundary defining and separating industry-specific knowledge has occurred [32]. Hacklin (2009) noted that knowledge boundary erosion was often an autonomous and contingent effect [32].

In the case of functional foods, GMP regulations for functional foods have been influenced by GMP regulations on the adjacent pharmaceuticals and have been partly similar to them. So to speak, an erosion of boundaries has also occurred in regulation. This has resulted in an erosion of the boundary of knowledge, as knowledge of pharmaceuticals is half-forcibly linked to knowledge of functional foods, and companies have been incentivized to utilize this knowledge. Correspondingly, quality control knowledge and technology have been transferred from the pharmaceutical side. Regulatory design has intentionally caused convergence on the supply side.

The health care industry lies between the medical domain with a high level of regulation and the non-medical domain with a relatively low level of regulation. As shown in Figure 4-8, in designing regulations in the health care industry, there will be a need to consider relative levels and similarities of the regulations to those of adjacent industries. As shown in

Table 1-4, in addition to GMP, several regulatory concepts of functional food were similar to those of pharmaceuticals. These each regulation could be utilized as multiple levers to adjust relative levels and similarities of whole regulatory system in functional food. Similarities of the regulations to those of adjacent industries would induce industry convergence as firms respond to regulations, such as knowledge spillovers, firm entry from outside. Relative gaps of regulatory levels between medical sector and healthcare sector would affect firm behavior.

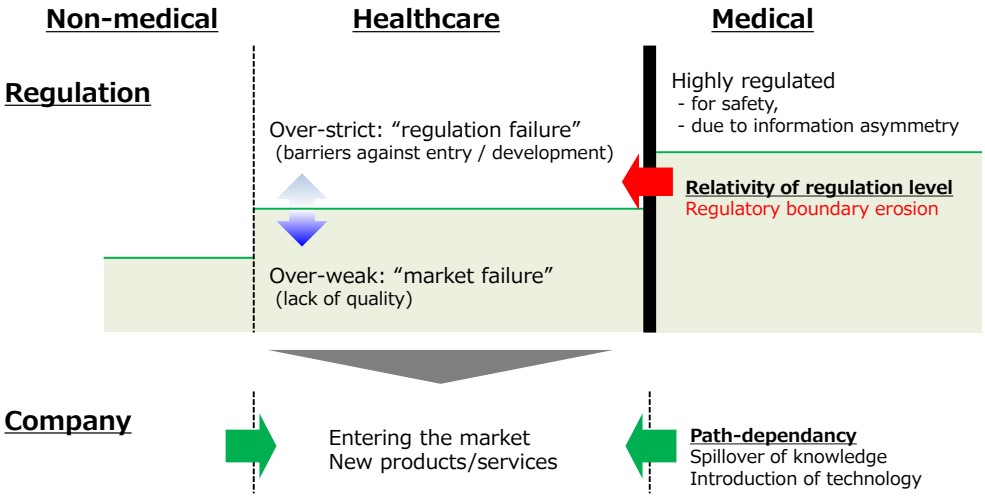

Figure 4-8 Relative to the regulation of the medical domain and the regulation of the health care domain

4.3.2. Framework of convergence in healthcare sector considering regulatory implications

In summary, it was noted that in designing the system, it was important to take into account the behavior of the firms that would be affected by the regulations. Generalizing the findings of this study shown in Figure 4-3, and adding the perspective of relativity stated in a previous section, Figure 4-9 proposed a convergence framework based on the corporate behavior induced by regulations as a starting point.

It was important that multiple regulatory levers, such as risk-side and benefit-side, were moved in sets, taking into account the relativity of regulatory levels with adjacent areas. In the Japan's functional foods case, risk-side regulation of GMP was strengthened while benefit-side regulation of health claims was relaxed to adjust overall system. Regulations influenced corporate behavior while being controlled by relationships among firms and path dependency from adjacent industry. As a result, firms have brought in knowledge and technology from outside to comply with regulations and act profitably under inter-firm relationships. In the Japan's functional foods case, FFC were introduced to final product manufacturer, GMP were introduced to OEMs, and as a result, the FHC system became more pervasive, leading to market convergence.

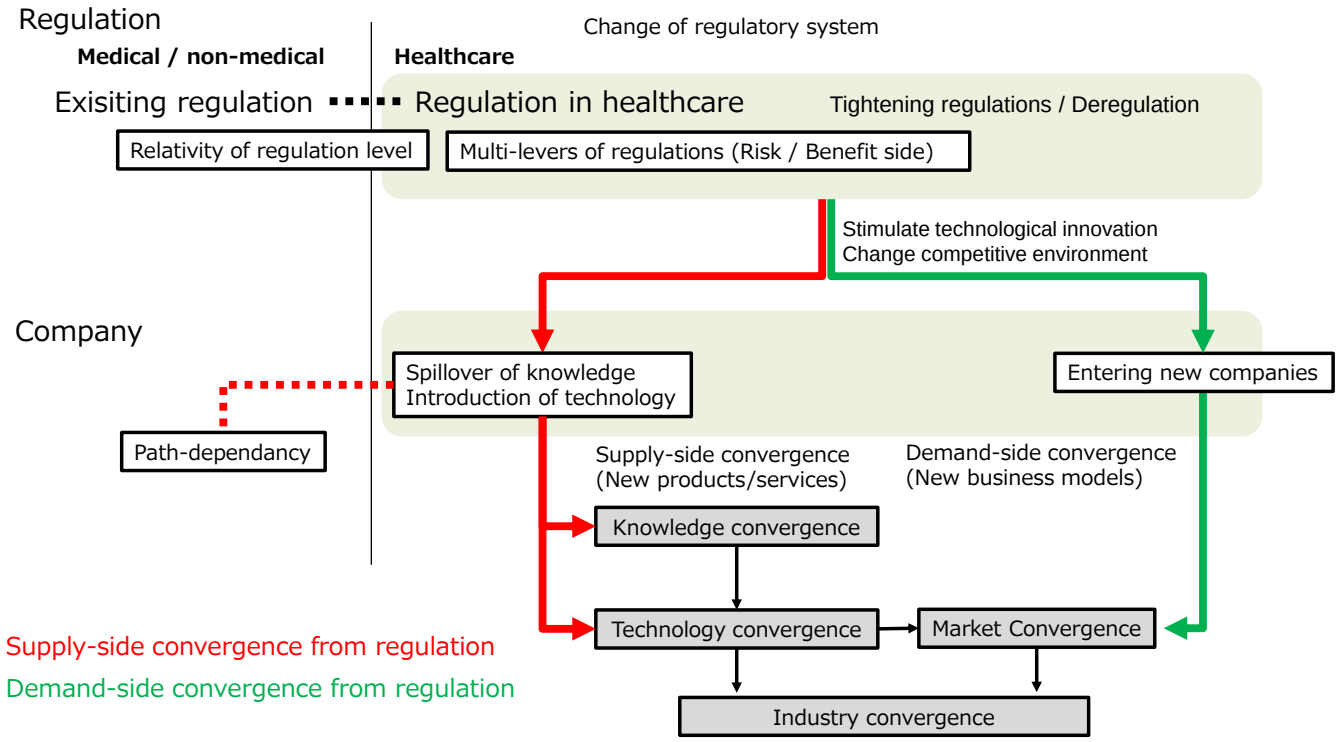

Figure 4-9 Framework of convergence in healthcare sector considering regulatory implications

As mentioned in Introduction 1.1.1, the healthcare domain, existing at the boundary between medical and non-medical domains, has been expected innovation, but has not yet created regulatory framework properly. Appropriate institutional design is important to achieve consumer protection while allowing companies to innovate in free competition and promoting the healthy development of the industry. This area includes products and services such as health devices, measuring instruments (digital health), fitness, and aesthetics, in addition to functional foods, as shown in Figure 1-1. From the viewpoints of company behaver, examples exist of medical equipment manufacturers entering the health care equipment market, hospitals entering the rehabilitation and fitness industries, and IT companies entering clinical testing market. In the regulatory side, in health care industries other than functional foods, regulations have also been formed in the form of certifications and guidelines by industry associations, aim to ensure safety and reliability. Health care products, such as health equipment [140] and bedding [141], and health care services, such as fitness [142] and esthetic treatments [143], are certified based on management systems and evidence. Certified products and stores providing services can label the certification mark. These marks would bring signaling effects.

This FFC case study was generalized to develop a framework to analyze regulation and firm behavior for innovation in an emerging industry and peripheral sectors in Figure 4-10. Specifically, three schematic models were abstracted and conceptualized to propose as a flamework: the supply-side and demand-side convergence of the FFC regulation origin (Figure 4-9), the spillover effects of the regulation on the industrial ecosystem (Figure 4-5), and relativity of regulations between the adjacent pharmaceutical and food area (Figure 4-8). In Figure 4-10, analyzing relationship between regulations (1) and innovation

in an emerging industry, it is important to consider company behaver (2) in the industry, as well as, companies (3) and regulations (4) in existing industries in peripheral segments. Product value enhancement by existing companies (2) in compliance with regulations may involve supply-side convergence from surrounding industries. Peripheral firms (3) exist in an ecosystem consisting of various relationships. Some firms would enter the emerging industry, while others would receive spillover effects from the activities of firms in the emerging industry. Regulatory system in emerging industries (1), affecting these corporate activities, would be well analyzed in consideration of their relativity to regulations (4) in peripheral existing industries.

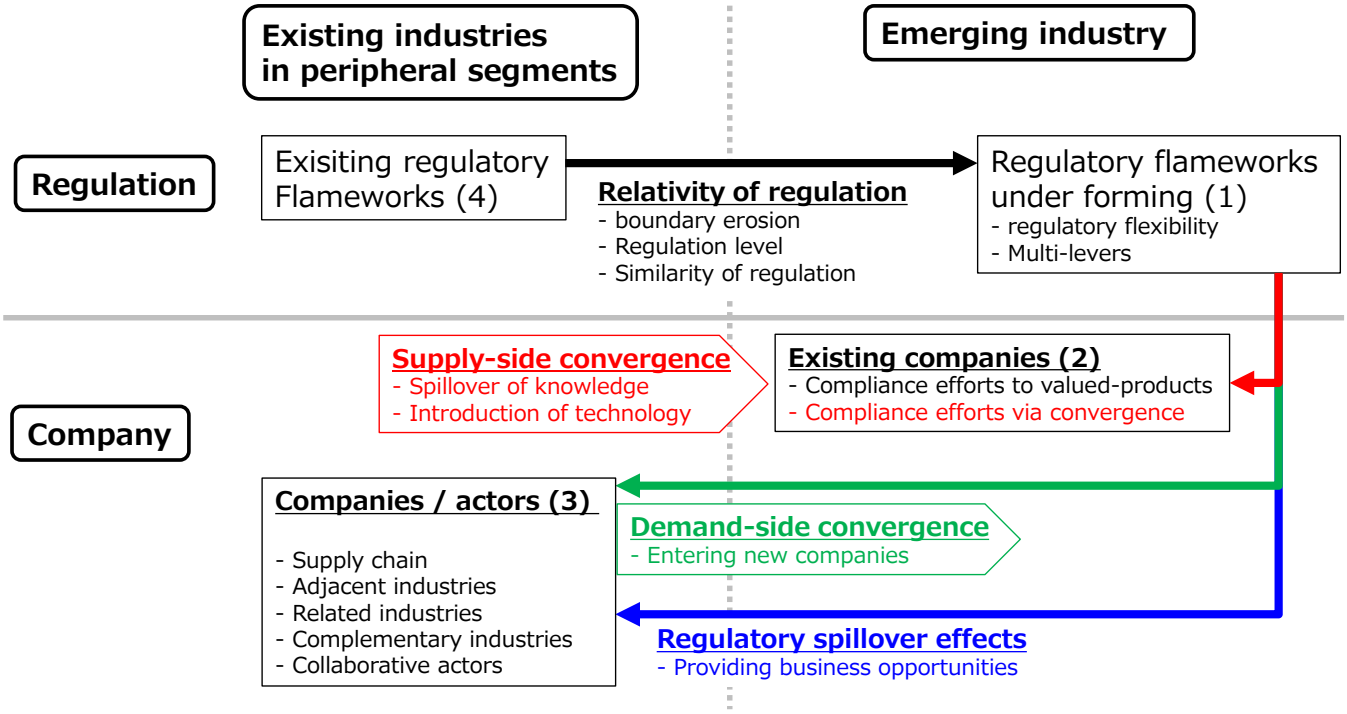

Figure 4-10 Framework for regulation and firm behavior for innovation in an emerging industry and peripheral segments.

4.4. Practical implications

4.4.1. Practical implications for policy-makers and administrators

This study will provide practical implications for policy and administrative personnel that binding and enforceable regulations are not the only solution, but that FFC is effective with practical and realistic solutions based on path dependency and corporate behavior.

The Japanese functional food market was originally created from the state of existence of "so-called health foods," with a series of systems created in a retrospective manner. While it is possible in principle to achieve harmonization by establishing binding and enforceable regulations, its path-dependency make it difficult to regulate through mandatory legislation in practice. It is also undesirable in terms of the expectation of innovation in a free market and under competition among firms. In this study, we found that regulation has led to the formation of actual markets through the movement of firms and the introduction of technologies and products. This is a case study on regulatory design for innovation under market principles while ensuring safety and consumer protection in the peripheral area of healthcare, represented by functional foods.

The healthcare industry has been forming between medical sector and non-medical sector, where innovation is expected. The healthcare domain is an area where business activities and products precede regulations. Regulation has been an important issue from a policy perspective, and trial and error has carried out as in the case of METI's gray-zone elimination system in Japan [140]. In light of this case in which companies' ingenuity and competition within regulations and rules bring benefits to both companies and consumers, it is important that not only binding companies by normative regulations but also creating an environment in which companies benefit from regulations. Because this domain is a boundary area between the heavily regulated medical domain and the weakly regulated non-medical domain, the flexibility of designing regulations is rather wide. The design of regulations that give companies a choice of strategies, taking into account the situation of companies already in existence would be suitable, rather than establishing laws and regulations that are highly coercive and inflexible. The FFC offers suggestions for institutional design here. This case study suggested that the regulation with flexibility and incentive would lead innovation through diversity of companies of entry and through actively compliance by R&D investment, and create a market where a variety of products can be distributed and consumers can make choices according to their needs. Specifically, by using relationships among firms to optimize the risk-benefit balance, and by designing institutions with a perspective of relativity to adjacent pharmaceutical and food regulations, it may be possible to create economic value and benefit consumers through firm behavior in response to regulations.

The flamework proposed in Figure 4-10 would be also utilized at regulatory design in an emerging industry. In designing regulations for an emerging industry (1), it is important to consider existing companies in the industry (2), companies (3) and regulations (4) in existing industries in peripheral segments and, with the objectives of consumer protection and industry development (innovation). Product value enhancement by existing companies (2) in compliance with regulations may involve supply-side convergence from surrounding industries. Peripheral firms (3) exist in an ecosystem consisting of various relationships. Some firms would enter the emerging industry, while others would receive spillover effects from the activities of firms in the emerging industry. In order to stimulate these corporate activities in a healthy manner, it would be desirable to design regulations for emerging industries (1) in consideration of their relativity to regulations in peripheral existing industries (4). New industries would emerge through the industrial convergence process, blurring the boundaries of existing industries. It is hoped that, coevolving with industrial convergence, regulations would be designed with deep consideration of existing industry regulations and industry conditions, so that the sound development of emerging industries and consumer protection will be compatible, and innovation will be promoted.

4.4.2. Practical implications for innovators and business practitioners

This study will provide practical implications for innovators and business practitioners in the fields of food, nutrition, and physiology, regarding the effectiveness of introducing knowledge and technology from different disciplines. The perspective of industry convergence will provide useful suggestions for future functional food research and development strategies.

The following is a discussion from the viewpoint of convergence on the characteristics of functional foods with high sales: complex formulation with multiple ingredients, implementation of clinical trials, and new functions. Complex formulation with multiple ingredients is a feature that differs from typical low-molecular-weight drugs, which often contain a single ingredient. While utilizing the knowledge and techniques of formulation science and formulation technology cultivated in the

pharmaceutical field, there would be room for further technological development and knowledge accumulation in the application of complex formulations with multiple ingredients. There may be potential for technological development and innovation through the introduction of knowledge and technology from different fields, such as chemical engineering, for example. In terms of the effects of multiple ingredients of compound system, the knowledge of herbal medicine or foods including variety of ingredients may be useful.

In order to obtain new evidence through in-house clinical trials, it would be a powerful strategy to design and conduct clinical trials based on the knowledge gained from clinical trials of pharmaceuticals. Although there are no pharmaceutical companies in the top 15, several pharmaceutical companies have been new entrants into the functional food market, and it is expected that they may develop innovative functional food products in the future by utilizing their pharmaceutical development capabilities. In many cases, clinical trials for functional foods are outsourced to CROs, and it is expected that alliances with CROs that have conducted numerous clinical trials and accumulated knowledge can be strengthened to take advantage of their capabilities.

Due to the revision of food and pharmaceutical categories, some of the ingredients, such as coenzyme Q10 and carnitine, which used to be pharmaceutical ingredients have been permitted to be used in foods and have become common ingredients in dietary supplements in Japan [141], [142]. Changes in regulations regarding ingredients introducing into the food domain may promote convergence of knowledge and technology, and lead to the development of foods with functional claims using these ingredients.

4.4.3. Proposed strategic framework for corporates and FFC products

It has been argued that there were two main types of differentiation strategies for firms: vertical differentiation and horizontal differentiation [51], [143]. Firms would differentiate vertically until the market has reached saturation. Firms then horizontally differentiate themselves from other industries and integrate product functions to expand the boundaries of the market. The trend toward multifunctional products with integrated product features would be also consistent with consumer preference for one-stop shopping.

Figure 4-11 illustrates a two-dimensional matrix plotting the sales-weighted average number of features versus each company's in-house clinical trial rate (both original data were shown in Table 3-9), as well as a schematic diagram of the development process of FFC. The horizontal axis of this plot, the sales-weighted average number of functions, indicated the degree of multifunctionality of each company. Firms would horizontally differentiate themselves by broadening the needs they address by making their products multifunctional. The vertical axis of this plot, the in-house clinical trial rate, indicated the degree of in-house development by each firm. Firms would vertically differentiate by conducting their own clinical trials, pursuing new functions, etc. This plot was proposed as a matrix to visualize company strategies.

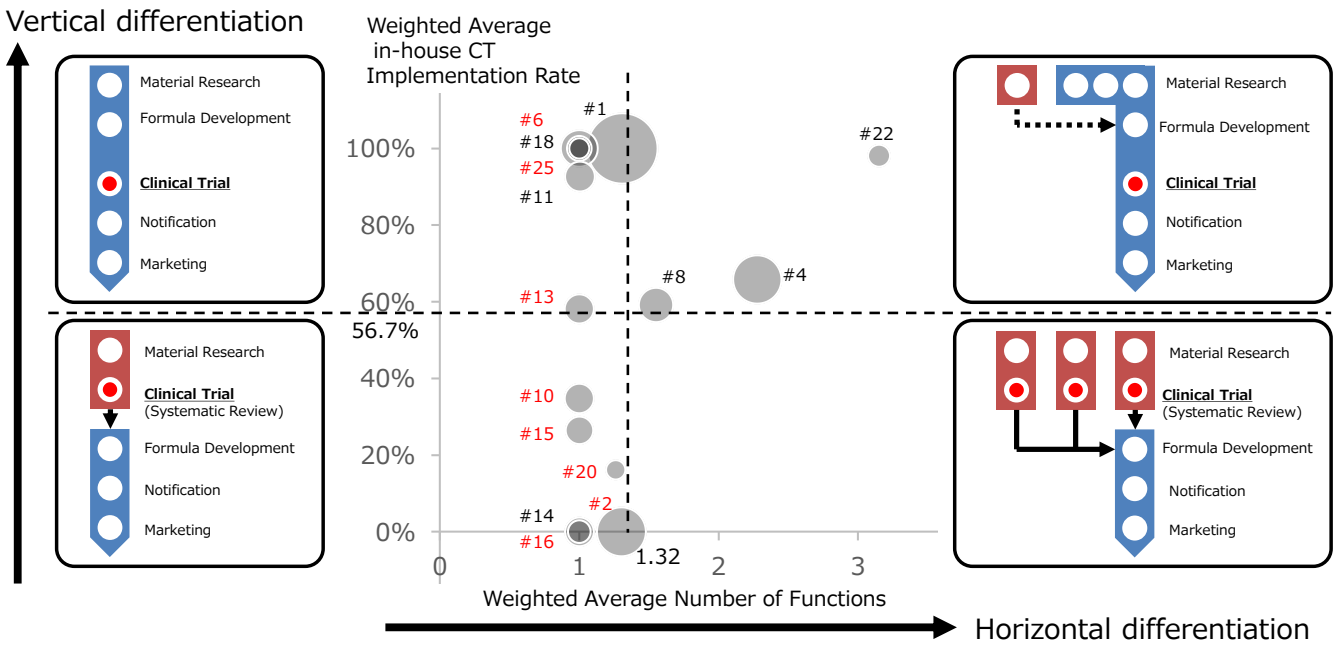

Figure 4-11 Strategic framework for corporates to develop FFC products

This matrix consists of the four quadrants, bounded by the average of the 15 companies' sales-weighted average number of functions (1.32) and the average of the 15 companies' in-house clinical trial rate (56.7%). Outside the matrix represents a schematic diagram of the development process for each quadrant. Each plot represents the average number of functions vs. in-house clinical trial rate for top 15 firms utilizing FFC. The circle size indicates sales. Label numbers are company IDs (sales rank). Firms in red are those with FOSHU; Each schematic diagram in the box delivers a typical development process of FFC where blue and red bands indicate in-house and external processes, respectively.

- The upper left schematic shown a vertical process, conducting research on a single ingredient, designing a formulation, conducting clinical trials in-house, and submitting the product as FFC. This commercialization process was similar to the FOSHU commercialization process. Six companies were classified in the upper left quadrant. These companies may conduct their own clinical trials, focus on products with a small number of ingredients and functions, and have a conventional product strategy similar to that of FOSHU products. Three existing companies that had been using FHC since FOSHU were included.
- The schematic diagram on the lower left shown the commercialization process based on external knowledge such as ingredient SR. Typically, the commercialization process consisted of clinical trials conducted externally, while the design of the formulation, the notification of the functional food, and the commercialization of the product conducted in-house. Six companies were classified in the lower left quadrant. These firms may adopt a product strategy to efficiently develop modular products by using SR for a single ingredient and leveraging external knowledge. Five existing companies were included.

The two schematic diagrams on the right side shown the process of developing products combining multiple functions. Since the number of functions correlated with the number of materials, a typical development process was designing a formulation that combines materials to increase the number of functions.

- The schematic diagram on the upper right shown the commercialization process of designing formulations combining ingredients and conducting clinical trials in-house. In some cases, basic research on the efficacy of the ingredients would be conducted in-house, while in other cases, the company would utilize ingredients with known efficacy properties. This quadrant was classified with three companies. These firms are likely to design products with unique formulations by combining ingredients, conduct clinical trials, and differentiate their products by offering multiple functionalities in a combined product. No existing companies were included in this area.
- The lower right quadrant does not have real cases. However, the schematic diagram on the lower right illustrated the commercialization process, combining ingredients for which efficacy findings existed and conducting the formulation design and subsequent processes in-house. This strategy may have some advantages, such as relying on outside parties for the highly-uncertainly basic research step of ingredients and the costly clinical trial step may reduce investment in R&D. On the other hand, it may have some disadvantages, such as the difficulty of obtaining intellectual properties because merely combination of existing ingredients has little patentable inventiveness. So, under this strategy, companies are expected to find it difficult to maintain a sustainable competitive advantage. It is considered necessary to secure competitive advantage through various strategic options such as branding, promotion, and pricing.

There was no statistically significant difference in CAGR or sales for each of these corporate strategies (Data not shown). In the future, a detailed observation of the differences in commercialization strategies among firms and a comparative analysis of firms' responses to FFC regulatory changes would help to clarify the impact of regulations on firm behavior and its mechanisms.

4.5. Academic Significance of this Study

Promoting Understanding of Convergence Starting from Regulations

In Study 1, the findings demonstrated the role of regulations in inducing knowledge convergence and technology convergence. Specifically, firms utilized internal pharmaceutical knowledge and technology to reduce compliance costs imposed by regulations. The similarity between risk-side regulations for dietary supplements and those of the adjacent pharmaceutical industry led to the interconnection of dietary supplement knowledge and pharmaceutical knowledge, facilitating knowledge convergence and technology convergence.

Study 2 further explored the impact of benefit-side regulations on firms, revealing diverse patterns of impact among different firms. Deregulation, by reducing compliance costs and promoting market convergence through the entry of external firms, as well as knowledge convergence through knowledge spillovers in product development, facilitated market dynamics. Integration of the two studies presented a mechanism in Study 1 whereby firms' compliance incentives were strengthened through their relationships with end-product manufacturers, thus promoting regulatory compliance. This integration enabled us to model a process wherein regulatory changes affect firms' compliance costs and incentives, consequently triggering knowledge

and technology convergence on the supply side. The phenomenon and process presented in this study contribute significantly to the academic understanding of the impact of regulations on convergence.

Promoting Understanding of the Impact of Regulation on Firm Behavior and Innovation in the Healthcare Domain

Furthermore, Study 2 highlighted that the diverse regulatory compliance options provided by regulatory bodies allowed firms to differentiate themselves and gain a competitive advantage through innovation investments, despite the associated higher compliance costs. This observation indicated that certain firms were willing to incur increased costs, invest in innovation, and developed competitive products to achieve superior performance, demonstrating the emergence of innovation in this domain. The considerable regulatory flexibility in health claims has incentivized individual firms to pursue customer acceptance through ingenuity and regulatory compliance, thus fostering innovation and gaining a competitive edge.

Although innovation is expected in the healthcare sector and regulatory design plays a crucial role, research on the relationship between regulation and innovation in this domain remains scarce. This study's findings serve as a valuable case study, shedding light on the interplay between regulation and innovation, particularly through firm behavior, a key driver of innovative activities. Consequently, this study contributes significantly to our understanding of the impact of social regulation on innovation in the healthcare sector, providing a foundation for theory development regarding the relationship between regulation and innovation.

4.6. Limitations and Future Perspectives

This study focused on Japan, one of the largest functional food markets in the world, but considering that the functional food market is expanding globally, it is necessary to make observations in other regions as well, and to compare the characteristics and environment in each country. Further research and analysis should be needed to improve prevention outcomes and cost-effectiveness, which is the aim of functional foods.

The perspective of consumers outside the scope of this study would be an important issue. As consumers needs for functional foods varying prevention, nutritional intake, and treatment [91], [144], which would perceive functional foods as products positioned between pharmaceuticals and foods. In convergence theory, one of the driving forces for demand-side convergence is consumer needs, besides regulation, which was focused in this study. As consumer needs affect especially market convergence, examining the impact from two domains from the consumer's perspective is a topic for future study.

Studies on marketing of functional foods revealed that health claims increase willingness to purchase. As the characteristics of FFC with large sales (in-house testing, numerous ingredients, and novelty functional claims), as this study revealed, could affect purchase intention, how consumers perceive them would be an issue for future study.

Whether similar events occur in other health care industries and whether they can be generalized would be also issues for future study. From the viewpoints of company behaver, examples exist of medical equipment manufacturers entering the health care equipment market, hospitals entering the rehabilitation and fitness industries, and IT companies entering clinical testing market. In the regulatory side, in health care industries other than functional foods, regulations have also been formed in the form of certifications and guidelines by industry associations, aim to ensure safety and reliability. Health care products, such as health equipment [145] and bedding [146], and health care services, such as fitness [147] and esthetic treatments [148], are certified based on management systems and evidence. Certified products and stores providing services can label the certification mark. These marks would bring signaling effects.

All of these are boundary industries affected from both the highly regulated medical sector and non-medical sector in the free market. Conducting empirical research on these issues from the perspective of regulatory science and convergence research would help the appropriate design of regulations in the healthcare domain existing medical periphery. Additionally, an appropriate design of regulations would be expected to protect consumers while encouraging innovation through free competition among companies, thereby contributing to the improvement of consumers' health, and at the same time, curbing healthcare costs.

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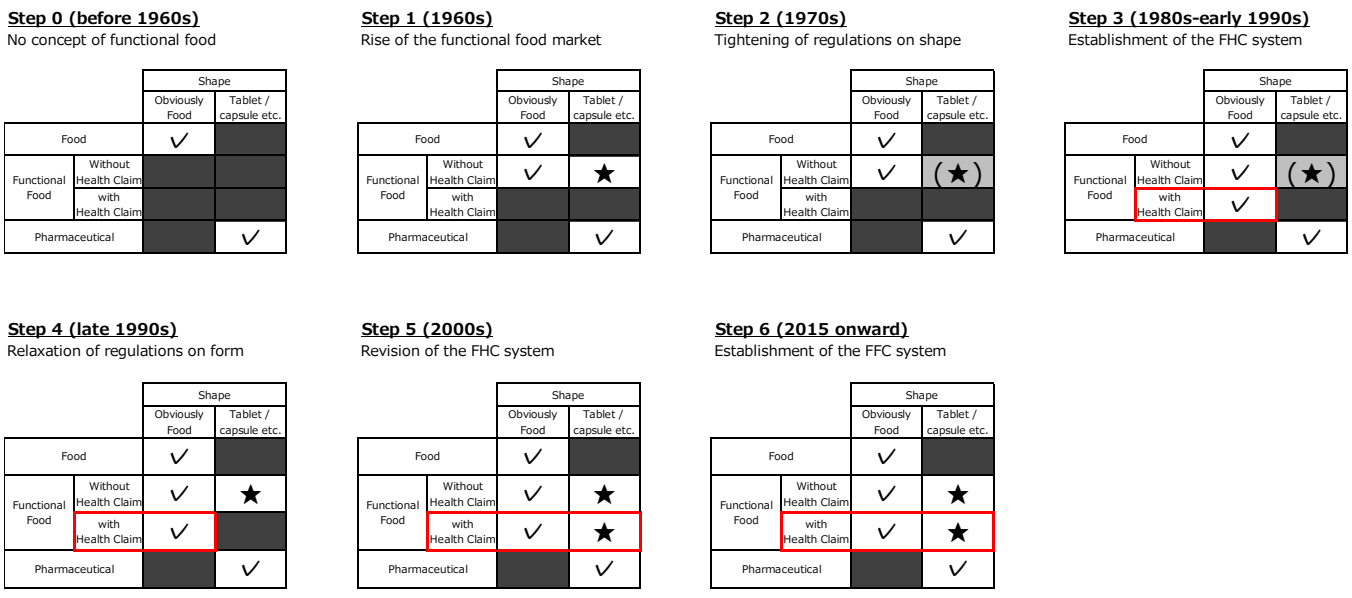
APPENDIX

APPENDIX 1 Transition in the Japan's Functional Food System

APPENDIX 1.1 Regulatory system

This section presented a detailed history of Japan's regulatory system for functional foods. The system has undergone a historical transition. Figure A-1 shows a matrix of a relationship between products and the corresponding scope of regulations in terms of shape and functional claims. The regulatory system has been repeatedly expanded and modified. It indicated that a complexity of the system was due to a historical path dependency. The following is a brief historical transition in the regulation of dietary supplements. When dietary supplements first appeared on the market, there were no regulations governing them. There was a subsequent period when dietary supplements in pharmaceutical form were banned. Foods for Specified Health Uses (FOSHU) initially covered only foods in ordinary form, and later expanded the scope to dietary supplements. In recent years, regulatory reforms of introduction of FFC system have added to the complexity of the FHC system.



Note: check mark (✓) shows exsistance of products.
Note: star mark (★) shows dietary supplements.
Note: red bold line indicates the boundary of FHC system.

Figure A-0-1 Transition in the Japan's Functional Food System

Step 0 (before 1960): No concept of functional food

Legally, food has no function in preventing or treating disease, and this is the clear boundary between food and pharmaceuticals. Before the advent of dietary supplements, food in the form of tablets or capsules did not exist in the first place. In the 1960s, products in the form of tablets or capsules were only pharmaceuticals.

Step 1 (1960s): Rise of the functional food market

In the 1960s, the health boom arrived in Japan and the concept of "health food" emerged. But no rule for health food brought a state of anarchy and health hazards.[149].

Step 2 (1970s): Tightening of regulations on form

In 1971, the Pharmaceutical Affairs Bureau of the Ministry of Health and Welfare issued the "Standards on the Scope of Drugs" (so-called "46 Notice", named after 46th year of Showa), which notified prefectural governors to strengthen the crackdown on food products in pharmaceutical-like form, such as tablets or capsules, as falling under unapproved unlicensed drugs [150]. In other words, "dietary supplements" became treated as a violation of the Pharmaceutical Affairs Law. In reality, however, "dietary supplements" existed in a gray area. For example, supplements were sold in the form of triangular or other special-shaped tablets instead of round tablets, which were considered to be a pharmaceutical shape.

Step 3 (1980s-early 1990s): Development of research on food functionality and establishment of the Food with Health Claims System (Food for Special Health Uses: FOSHU)

In the 1980s, research on the functional properties of foods began to progress. In Japan, the "Systematic Analysis and Development of Functional Foods" (1984) by the Ministry of Education, Culture, Sports, Science and Technology, and the "Functional Food Study Group" (1988-1990) by the Consumer Health Bureau of the Ministry of Health and Welfare were conducted. Based on the results of food functionality research, the concept of functionality of food was established as a legal system in 1991 with the establishment of the FOSHU system. However, only obvious food forms were allowed for FOSHU. FOSHU system was recognized as a pioneering system and was featured in Nature, leading to the creation of a 600 billion yen market by 2005 [151].

Step 4 (late 1990s): Relaxation of regulations on form

In the late 0190s, there was a request for deregulation from the U.S. in response to the so-called "46 Notice" regulation on dietary supplements [152]. The U.S. government and the American Chamber of Commerce in Japan raised the issue and brought to the Cabinet Office's "Market Opening Issues Complaint Handling System" in 1996. The ban on vitamins, herbs, and mineral supplements was lifted among 1997-1999.

In the Report of Office of Trade and investment Ombudsman (OTO), it was decided to review the scope of pharmaceutical products with regard to vitamins and other substances. Subsequently, the "46 Notice" was amended and the restrictions on the shape of tablets or capsules were removed in 2000 [153]。

Step 5 (2000s): Revision of the Food with Health Claims System

In 2001, the Food with Health Claims system was revised, allowing tablets and capsules in FOSHU, and creating new category of Food with Nutrient Function Claims. Under this self-certification system, foods or Tablets and capsules containing certain vitamins, minerals, and other nutrients in certain content levels, can be labeled as food with nutrient function claims [153]

GMP has been discussed toward its introduction in Japan began in the 2000s, after introduced in the U.S. since the DSHEA in 1994.

In 2005, the Ministry of Health, Labor, and Welfare of Japan issued "GMP Guidelines" requiring the industry to work to ensure the safety of dietary supplements.

The guidelines provided GMP management guidelines from the receipt of raw materials to the packaging and shipment of the final product. In response, two organizations in the industry began voluntary GMP certification. In 2014, the Health Food Certification Council designated two organizations working on certification since 2005 as certification bodies.

Step 6 (2015 onward): Establishment of the Food with Function Claims (FFC) System

As part of the health and medical care strategy by the Abe administration, a policy to utilize health foods and dietary supplements was discussed for the purpose of health promotion, disease prevention and medical cost containment. And a new system of FFC was introduced in 2015 [43] [44]. The system design for functional claims was based on the DSHEA in the U.S., but did not include the concept of form regulation. The system spans both obvious food forms and dietary supplement forms such as tablets and capsules.

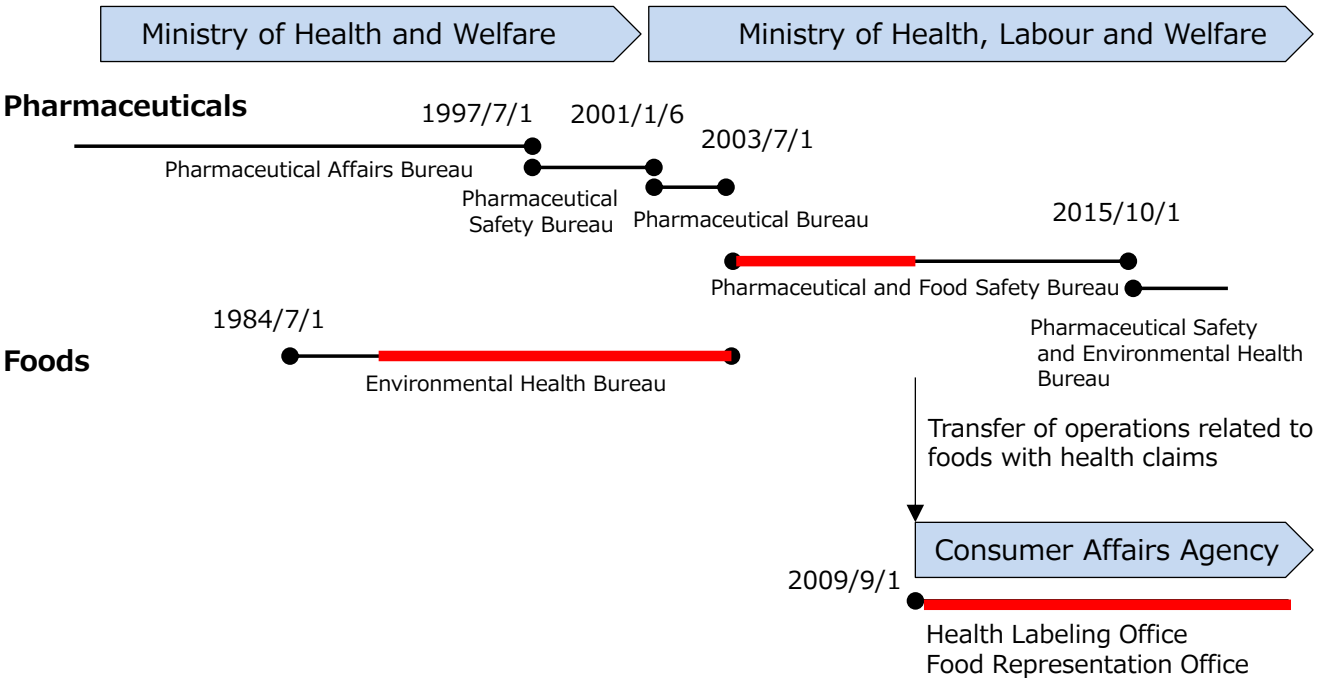
APPENDIX 1.2. Competent authority for foods with health claims

While the system has changed, the government agency with jurisdiction over food with health claims has changed, too. At this time, the Consumer Affairs Agency is in charge, but prior to 2009, the Ministry of Health, Labor, and Welfare was in charge.

Figure A-2 shows the transition of the departments in charge of functional foods since 1980s. Health food and the Food with Health Claims was under the jurisdiction of the Environmental Health Bureau of the MHLW, which was a different department from the Pharmaceutical Affairs Bureau, which had jurisdiction over pharmaceutical.

The departments in charge of pharmaceuticals and health foods were separated until 2003, when the Pharmaceutical and Food Safety Bureau was established and both pharmaceuticals and the Food with Health Claims were placed under the jurisdiction of this bureau.

In 2009, jurisdiction of the Food with Health Claims system was transferred to the Consumer Affairs Agency. The Food Labeling Planning Division promotes system design and dissemination, and the Labeling Measures Division issues guidance and action orders based on the Act against Unjustifiable Premiums and Misleading Representations and the Health Promotion Act.



* Red lines: Department in charge of the food system with health claims

Figure A-0-2 Transition of departments related to the health food system

(Source: Prepared by the author based on publicly available information)

APPENDIX 2 Interviews

As stated in Chapter 2, motivations and driving force to introduce GMP and effects for GMP were complementary and qualitatively examined by interviews. Interviews for two GMP certification organizations and an OEM company were conducted as shown in Table A-1 (Table 2-2 restated).

Table A-1 summary of interviews (Table 2-2 restated)

	Subject of interview	**Asked topics**
GMP certification organizations	(1) Japan Health and Nutrition Food Association (JHNFA) (2) Japanese Institute for Health Food Standards (JIHFS)	1. The past and current situation for GMP certification 2. Reason of GMP development as a third-party certification 3. Issues for quality improvement 4. Motivation of companies to introduce GMP
OEM company	(3) Large OEM company X	1. The company's manufacturing system 2. Management of pharmaceuticals and dietary supplements 3. Impact from an in-house pharmaceutical manufacturing sector during an introduction of GMP 4. Effects and Impacts of Introducing GMP for Dietary Supplements

Interview transcript

(1) Japan Health and Nutrition Food Association (JHNFA)

Interviewee	Three members relating to GMP
Date and Time	2017/8/17 14:00 - 15:00
Place	JHNFA office (Ichigaya, Tokyo)

1. The past and current situation for GMP certification

Has the situation (national and industry) for GMP certification changed between when certification started and now?

Answer

The association had been preparing before the 2005 Ministry of Health, Labor and Welfare notification, but the notification raised awareness.

At that time, even though the notice was issued, it was a 100% private sector initiative. One major turning point was the subsequent MHLW study group that proposed a third-party certification system supported by the government, and the establishment of the Council for Health Food Certification System in 2014. It is significant that the system has taken on a public character from being entirely private.

In 2015, GMP was recommended for functional foods in the form of tablets and capsules, which is a boosting factor, or rather, the social and public environment is moving in the direction of promoting GMP. Even if it is not a functional food, the consigner may demand the introduction of GMP to the consignee.

Awareness of GMP is low among consumers, but awareness of the need for GMP is growing among industry players.

In a 2016 survey of member companies, 58% of companies with manufacturing facilities have GMP-certified plants, and 71% self-report that they have controls (including voluntary ones) in place with GMP.

12 years have passed, and it is permeating right through the country.

2. Reason of GMP development as a third-party certification

Why did GMP develop as a third-party certification?

Answer

The sequence of events is that an official definition of dietary supplements is needed before GMP is mandated, and then GMP is mandated for dietary supplements.

Discussion of a legal definition of dietary supplements has not progressed for more than a decade because only a few in the industry want it, and many do not want it as a whole. The reason is that they want to label functionality but do not want to be regulated.

Because they can get by with the way they sell their products without labeling their functions, many companies are more comfortable with being less than FOSHU or FFC and more than food products, and prefer to keep their somewhat delicate positioning as it is.

I don't think there is such a sense of urgency on the part of the government to define dietary supplements and mandate GMP, even if this is the right thing to do, for the safety of health food products. There are occasional cases of obviously criminal behavior, such as contamination with pharmaceutical ingredients, but that is dealt with on a case-by-case basis.

There are many manufacturers who are serious about their products, and there are not so many examples of unexpected problems causing health problems or serious issues, so the government does not feel an imminent need to do so.

If functional foods become more widespread, there will be a move to make them mandatory, including the category, but at the moment there are still only 1,000 functional items, and although sales are increasing, some of them are cannibalizing conventional food products. If 70% of all health foods are labeled as functional, it may become mandatory, but I do not think this will happen very quickly. The composition of FFC and FOSHU, and the rest of the market will probably remain the same.

3. Issues for quality improvement

What are the issues for quality improvement?

Answer

It would be good if GMP-level management could be voluntarily implemented without GMP certification, but I am aware that not doing so should not be allowed.
Small factories and other companies that do not understand GMP should raise their level.

4. Motivation of companies to introduce GMP

What motivates companies to introduce GMP?

Answer

Some companies introduce GMP to raise the level of their production so as not to manufacture defective products. Others implement GMP because they are required to do so by their contract manufacturers. Others introduce GMP as a sales tool to increase contract manufacturing.
Even if a company utilizes GMP as a marketing tool, GMP will improve the company's level of quality control, and the company believes that the purpose of GMP will be achieved.
Some large companies that manufacture pharmaceuticals are of the opinion that GMP for health foods is unnecessary because their companies can handle their own pharmaceutical GMP.

(2) Japanese Institute for Health Food Standards (JIHFS)

Interviewee	Hideko Ikeda, President of the Board of Directors
Date and Time	2017/7/18 10:00 - 11:00
Place	JIHFS office (Hongo, Tokyo)

1. The past and current situation for GMP certification

Has the situation (national and industry) for GMP certification changed between when certification started and now?

Answer

GMP is strongly desired for processed foods in capsule/tablet form among functional foods. I think the awareness of the government and industry regarding the need for GMP has changed.
The GMP guidelines issued by the Ministry of Health, Labor and Welfare cover capsules and tablets, as well as liquids and powders, but some companies that produce liquid products feel that liquid products are not covered. It's the functional labeling that indicates that the liquid form is also a dietary supplement.
GMP for product factories is becoming more widespread; there are about 300 OEM companies in Japan, and about 200 companies with two organizations have certified factories.
Awareness of GMP is changing, for example, consumer groups are calling for it to become mandatory.

2. Reason of GMP development as a third-party certification

Why did GMP develop as a third-party certification?

Answer

There are calls for making it mandatory, but there is no legal system to support making it mandatory. In order to make it mandatory, it is necessary to know what kind of food and what it covers.
In Europe and the U.S., it is assumed that a food has a function, and dietary supplements can be defined by dosage form (tablets, capsules) and functional claims can be made. However, since safety differs between pharmaceutical-like products such as tablets and capsules and other products, the approach to ensuring safety also differs, and the concept is that tablets and capsules require GMP. In Europe, the U.S., Korea, and ASEAN, the concept of shape regulation is clearly defined from the perspective of ensuring safety and quality.
On the other hand, in Japan, the concept of shape regulation is not divided according to shape, but according to whether or not the function is indicated. This is a completely different approach than in Europe and the United States. Since dietary supplements are not legally defined, the system is voluntary.

3. Issues for quality improvement

What are the issues for quality improvement?

Answer

Spreading GMP to in-house factories that are not OEMs.
The postponement of the TPP has eliminated the influx of imported health foods, but various products are coming in without tariffs. Can imported health foods be subject to the same quality control as domestic products?
There is GMP for raw materials, but it is not yet widely used. 70% of raw materials are imported from overseas, and import trading companies do not invest much resources in quality, and are satisfied as long as quality assurance data is attached at the time of importation. There is no international framework for raw material GMP yet, but Europe and the U.S. are ahead of the

pack; GMP guidelines require not only product manufacturing, but also raw materials, but this is difficult to understand.

4. Motivation of companies to introduce GMP

What motivates companies to introduce GMP?

Answer

If the company expects to export its products to foreign countries, it will have an incentive to introduce GMP.

Since GMP is mandatory in many foreign countries, some companies consider it an anachronism if they do not obtain GMP in Japan.

Conversely, possible reasons for not obtaining GMP are as follows. Large companies may be able to sell their products without GMP; obtaining GMP certification is costly but does not differentiate them.

They do not want outsiders in their factories, which may be another reason.

(3) Large OEM company X

Interviewee	General Manager of Research and Development Division Manager of Quality Assurance Division
Date and Time	2017/12/4 13:00 - 14:00
Place	Company X Head Office (Shizuoka Prefecture)

The company's manufacturing system

1. The company's manufacturing system

What are the organization, personnel, and facilities related to manufacturing and quality control in the pharmaceutical contract manufacturing division and the dietary supplement contract manufacturing division?

Answer

Facilities

In the same building of the plant, the changing rooms and corridors are common, but the manufacturing facilities have separate work rooms. The administration requires strict measures to prevent mixing and contamination when pharmaceutical products and food products are produced in the same facilities and workrooms. Specifically, (1) pharmaceuticals and foods cannot be produced at the same time in the same workroom, and (2) it must be confirmed that no pharmaceutical or food ingredients remain when switching from foods to pharmaceuticals, or vise versa. In our case, the food area has a large number of lines per workroom, which may result in unused lines when producing pharmaceutical products.

Organization

We have separate organizations for pharmaceuticals and dietary supplements. For dietary supplements, there is a general manager, a manufacturing manager, and a quality manager, each with the necessary managers, etc. under them. In the case of pharmaceuticals, the system is more rigorous, and in addition to the manufacturing manager, there are many other managers necessary for manufacturing control, such as a shipping judge, etc.

Human resources (managers)

In reality, this is handled by the same person working concurrently. The workload is not large enough to assign a different person, and the duties are close enough. When both are done in one factory, it has to be done that way.

Human resources (employees)

At the several factories, some of the employees involved in dietary supplement production are trained and allowed to be involved in pharmaceutical production, rather than being exclusively involved in pharmaceutical production. Since the volume of pharmaceutical production is not so large, we are operating in such a way. The training is not specifically about the concept of pharmaceutical GMP, but rather about the training necessary for manufacturing the pharmaceuticals, such as reading product standards, procedures necessary for work, and precautions in work, to supplement the education that is not sufficiently provided by simply being involved in health food production.

2. Management of pharmaceuticals and dietary supplements

Q. Do you think it is better to have a separate person to manage pharmaceuticals and dietary supplements, or do you think it is better to have a dual role?

Answer

We think it is preferable from a practical standpoint to have them serve concurrently. The basic base for both pharmaceuticals and health foods is GMP, so the concept is the same, and the only difference is what is being handled. In the first place, the concept of health food GMP comes from pharmaceuticals.

There are some positions that are missing from health food GMP. The GMP does not include a person in charge of responding to abnormal situations or handling complaints, and the general manager is in charge, but I have a feeling that this may be too strict when actually operating the system. I suppose a small-scale company can operate with this level of organization without requiring a lot of manpower, but if the scale of production is large and the number of items is large like our company, it will not be able to operate.

However, if it become stricter, small companies will not be able to obtain GMP. The JHNFA has been trying to raise the level of dietary supplements and to spread GMP as much as possible. However, the reality is that there are contract manufacturing companies with 10 or 20 employees, and for small companies, even the current regulation is too strict.

Q. You mean that you have a higher level of control than required by health food GMP?

Answer

We have a high level of control because we have to deal with exports. cGMP, the US certification, has been certified at two plants. Depending on the level of requirements of the consignor, there are cases where the GMP level is not sufficient. There are cases in which ISO and other standards are required, and we are doing things according to our way of thinking. We are dealing with major food manufacturers and pharmaceutical manufacturers, so we need to raise our level of quality.

There are three types of GMP, including pharmaceutical GMP, health food GMP, and cGMP, and we are in the process of organizing the total quality assurance system horizontally. The concept is the same, and the requirements are roughly the same, but the level of requirements are different.

3. Impact from an in-house pharmaceutical manufacturing sector during an introduction of GMP

Q. In introducing GMP, was there any impact on the manufacturing of pharmaceuticals?

Answer

We had been manufacturing dietary supplements, but our subsidiary, obtained a license to manufacture pharmaceuticals and started contract manufacturing of pharmaceuticals. Since there is no manufacturing license for dietary supplements in capsule or tablet form, we had to appeal to the outside world that we have a pharmaceutical manufacturing license and have a good understanding of GMP and have good quality control and manufacturing management in dietary supplements. Therefore, when the health food GMP certification system started in 2005, we immediately applied for and obtained certification.

We consider our infrastructure and management to be at a level closer to that of pharmaceuticals. It could be said that we are a bit over-specified, but this is not a bad thing, and we believe that it has supported our quality. On the other hand, it may cost us more than other companies that have not gone this far.

Currently, the ratio of dietary supplements to pharmaceuticals is about 8 to 2.

4. Effects and Impacts of Introducing GMP for Dietary Supplements

Q. What are the effects of GMP?

Answer

It is sufficient PR for customers. Customers know what kind of certification is available in most cases, so it helps us clear the first barrier in the selection criteria at the customer's site.

Q. Are there any internal benefits?

Answer

We keep all the raw material acceptance tests and manufacturing records required by GMP, so if something goes wrong, we can tell our clients the facts. We are doing exactly what we are supposed to do, such as managing hygiene and the daily health of our employees. Monthly in-house training has been done since the company's inception, including in the sales department, and this has been done since before the introduction of GMP.

Rather than a tangible effect, the fact that we do it tightly gives our customers a sense of security. We had been doing pharmaceutical GMP even before the introduction of GMP for health foods, and there is no indication that anything has changed just because we took GMP later. If anything, it helped establish our status in the health food industry.

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