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# Health foods and foods with health claims in Japan

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**Abstract**

The terms 'nutraceuticals' and 'dietary or food supplements' are not very popular in Japan as compared to most of other countries. However, the concept of 'functional foods', which benefits the structure and function of the human body, is known as a result of research studies initiated on the health benefits of foods in 1984. The Ministry of Education organized a national research and development project to evaluate the functionalities of various foods. Researchers from diverse scientific fields succeeded to define new functions of food, successfully incorporating the previously recognized functions of nutrition, sensory/satisfaction and physiological effects of ingredients in foods. Some of the food manufacturers and distributors unfortunately capitalized on such food functionalities to promote 'health foods' by claiming drug-like effects and violating laws. In 1991, the Ministry of Health and Welfare (MHW) now as the Ministry of Health, Labor and Welfare (MHLW) introduced a 'foods for specified health uses' (FOSHU) system, for the control of such exaggerated and misleading claims. The other reason for such enforcement is due to an increase in the population of elderly people and lifestyle-related diseases that include obesity, diabetes mellitus, high blood pressure, cerebro- and cardiovascular diseases and cancer. In 2001, a new regulatory system, 'foods with health claims' (FHC) with a 'foods with nutrient function claims' (FNFC) system and newly established FOSHU was introduced. In addition, MHLW has changed the existing FOSHU, FNFC and other systems in 2005. Such changes include the new subsystems of FOSHU such as (1) standardized FOSHU, (2) qualified FOSHU and (3) disease risk reduction claims for FOSHU. In the present chapter, two guidelines that require good manufacturing practice (GMP) and self-investigative systems for ensuring the safety of raw materials used for products in the dosage forms such as capsules, tablets, etc. have been discussed. Furthermore, issues related to positioning and definition of supplements are also discussed in the light of the enhancement of understanding the beneficial roles that supplements may play for human health in Japan.


*Keywords:* Health food; Foods for specified health uses (FOSHU); Foods with nutrient function claims (FNFC); GMP; Safety; Supplements

## 1. Introduction

Japanese have long history and recognition in eating healthy nutritious foods. Procurement of food in the past had been very much limited by the geographical location of the country. The presence of the four distinct seasons in Japan helped develop the unique Japanese food eating custom and created a novel Japanese food culture. Furthermore, the availability of agricultural crops, such as soybean, mushroom, rice, wheat, tea and marine products including seaweed, algae, bonito, bream enriched the food resources to the Japanese traditional diet. Fermentation know-how also played a pivotal role to constitute Japanese traditional foods, such as natto (fermented soybean with *Bacillus subtilis natto*), miso (soybean

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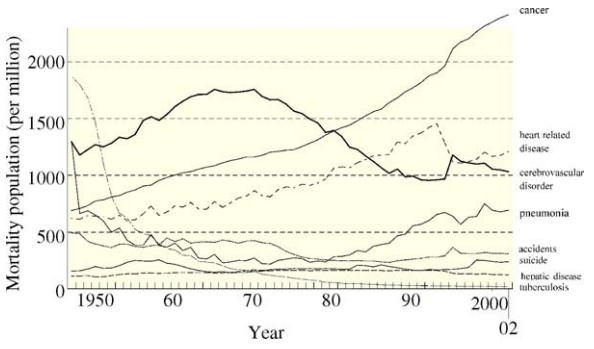



Fig. 1. Changes in mortality population according to causes in Japan (*source*: The MHLW, Minister's Secretariat Statistics and Information Department, 2004. Vital Statistics. p. 296).

paste), sake, katsuobushi (fermented bonito), which is utilized primarily for the preservation of food.

After the World War II, changes in food eating customs along with lifestyle changes brought in the so-called 'westernization', including the consumption of a wide diversity of foods, were significantly noted in the rapidly growing Japanese economy. The changes eventually caused the necessity for positioning the foods not only for function as nutrition, but also for sensory/satisfaction and health. From the viewpoint of nutrition and sensory/satisfaction, foods based on meats, eggs, milk, butter, etc. of animal origins, processed foods, and so-called 'fast foods' and 'instant foods' with artificial food additives have predominated and become popular in the modern Japanese diet, in particular, the diet among younger generations.

Japan has been known as a country of healthy longevity in the world; however, lifestyle changes and related diseases such as obesity, diabetes mellitus, high blood pressure, cerebrovascular and cardiovascular diseases, and cancer have remarkably increased, which is attributable not only to the 'westernization' of the food, but also stress, drinking and smoking habits and lack of exercise. Moreover, the increase in the lifestyle-related diseases has strongly affected the mortality of Japanese people. In fact, mortality caused by cancer and vascular diseases continues to increase, while cancer is the dominant or the number one cause of death in Japan (Fig. 1). According to Sugimura (2002), a dietary factor is one of the main causes of cancers, suggesting that the aforementioned 'westernization' might have some negative influence on the balance of nutritional food intake of Japanese people.

In the 1980s Japanese people began to realize the importance of maintaining and improving their health with a gradual increase in the occurrence of lifestyle-related diseases and the Government also started to pay more attention to the aging population. Concurrently, intensive studies were performed on the physiological effects of various foods and their constituents for so-called 'the tertiary function of foods' as described by Arai (1996). In brief, the tertiary function of foods is directly involved in the modulation of the human physiological systems such as the immune, endocrine, nerve, circulatory as well as digestive systems, while the primary and secondary functions are related to nutrition and sensory satisfaction, respectively.

In 1984 the term 'functional foods' was first assigned in the project initiated by the Ministry of Education (presently as The Ministry of Education, Culture, Sports, Science and Technology), thus crediting Japan for the creation of the term 'functional foods'. The concept of 'functional foods' attracted the 'health foods' industry and health-conscious consumers. The Government, however, prohibited the use of the term 'functional' because of its implication as a drug-like effect. As a result, the term 'health foods' was widely used and recognized by consumers and even became part of their diets, replacing the term 'functional foods'. The concept of the 'functional foods' was ultimately integrated into the 'foods for specified health uses' (FOSHU) system.

In this paper, we describe how 'health foods' is positioned related to regulations and how it was distinguished from FOSHU under a new regulatory system enacted in April 1991. This paper also attempts to interpret recent regulatory movements on 'health foods' and 'foods with health claims' (FHC) such as FOSHU and 'foods with nutrient function claims' (FNFC) and to discuss consumer and regulatory concerns regarding 'health foods' from various aspects, including safety.

## 2. Brief history of regulatory control of 'health foods'

In 1984, the Ministry of Education conducted studies on functional foods which was initially led by the Special Study Group on the Systematic Analysis and Development of Food Function. This project was focused on investigating the benefits of functional foods in controlling the physiological function of a living body (Arai, 1996).

The well-known examples of the studies adopted in the projects were the elucidations of the influences of food ingredients on the functions of hormones, neural systems, biophylaxis systems, and so forth. The results from these studies supported by the Ministry of Education were reflected in the newly introduced regulatory system of functional foods by the Ministry of Health and

Welfare (MHW) in 1991 as the FOSHU system (Hosoya, 1998).

In 1996, the American Chamber of Commerce of Japan (ACCJ) requested the deregulation of dietary supplement system in Japan, to remove an important trade barrier of dietary supplements between the United States and Japan. The regulatory system of dietary supplements that are generally called as 'health foods' in Japan was unique and rigid to the products imported from overseas countries. Dosage forms orally taken as drugs such as small round tablet and capsule were prohibited to distribute as supplements under the regulation. The petition was accepted by the Government and then the deregulation was discussed in the special investigative committee on dietary supplements for succeeding 4 years. Based on the conclusion of the committee, the Ministry of Health, Labor and Welfare (MHLW) decided to frame a new regulatory system of 'health foods' called FHC and enforced the new system in April 2001. The new system of 'health foods' integrated the novel FOSHU and another new category, FNFC. Prior to 2001, in the FOSHU only the form of conventional foods had been permitted, but not forms such as tablets or capsules.

The progressive introduction of the regulatory system of 'health foods' was taking place; however, 'health foods' that were not regulated by the new system grew and occupied the largest segment of the 'health foods' market, accounting for about 65% of total market in Japan. The MHLW decided to reconsider the regulatory system of 'health foods' with the request of the Liberal Democratic Party, in 2003. As a result of the discussion from the special investigation committee for the reconsideration, the FOSHU system was relaxed by proposing subcategories such as the qualified FOSHU and standardized FOSHU systems to the existing FOSHU. Furthermore, the disease risk reduction claims were allowed to make for FOSHU products containing specified nutrients concurrently. Two ingredients, calcium and folic acid, are presently allowed for the disease risk reduction claims.

## 3. Current regulatory system for 'health foods'

It must be emphasized that there is no category or no term for supplements (irrespective of terms dietary or food) according to the regulatory or legal understanding, in Japan. While foods having dosage forms or shapes such as tablets or capsules are included in the category of 'health foods', discrimination between conventional food and supplement is not legally accepted. Even in the FOSHU system, most of the products are in the form of conventional foods, whereas FOSHU products in tablets or capsules are seldom found. The above mentioned situation may often make it difficult to comprehend the Japanese regulatory system of 'health foods' for food industry in foreign countries.

### *3.1. Regulations for 'health foods' by the Pharmaceutical Affairs Law*

The positioning of 'drug' and 'food' or 'non-drug' is shown in Fig. 2, according to the Pharmaceutical Affairs Law. 'Health foods', FHC (FOSHU and FNFC) and others belong to the 'non-drug' category. The FHC is

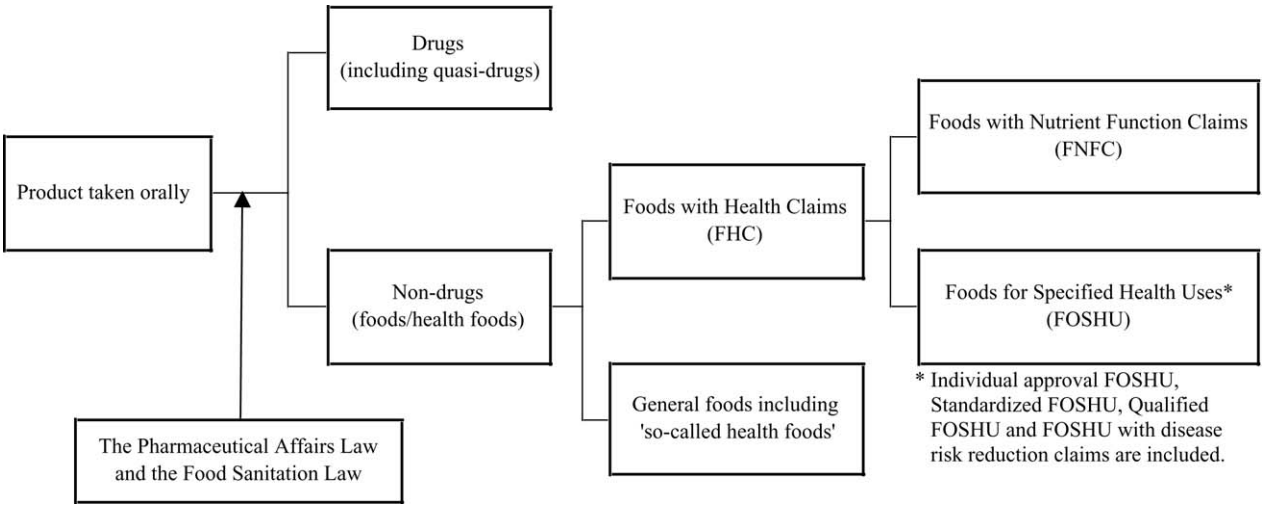



Fig. 2. Positioning and classification of 'drug' and 'non-drug' including 'so-called health foods' and FHC (FOSHU and FNFC).

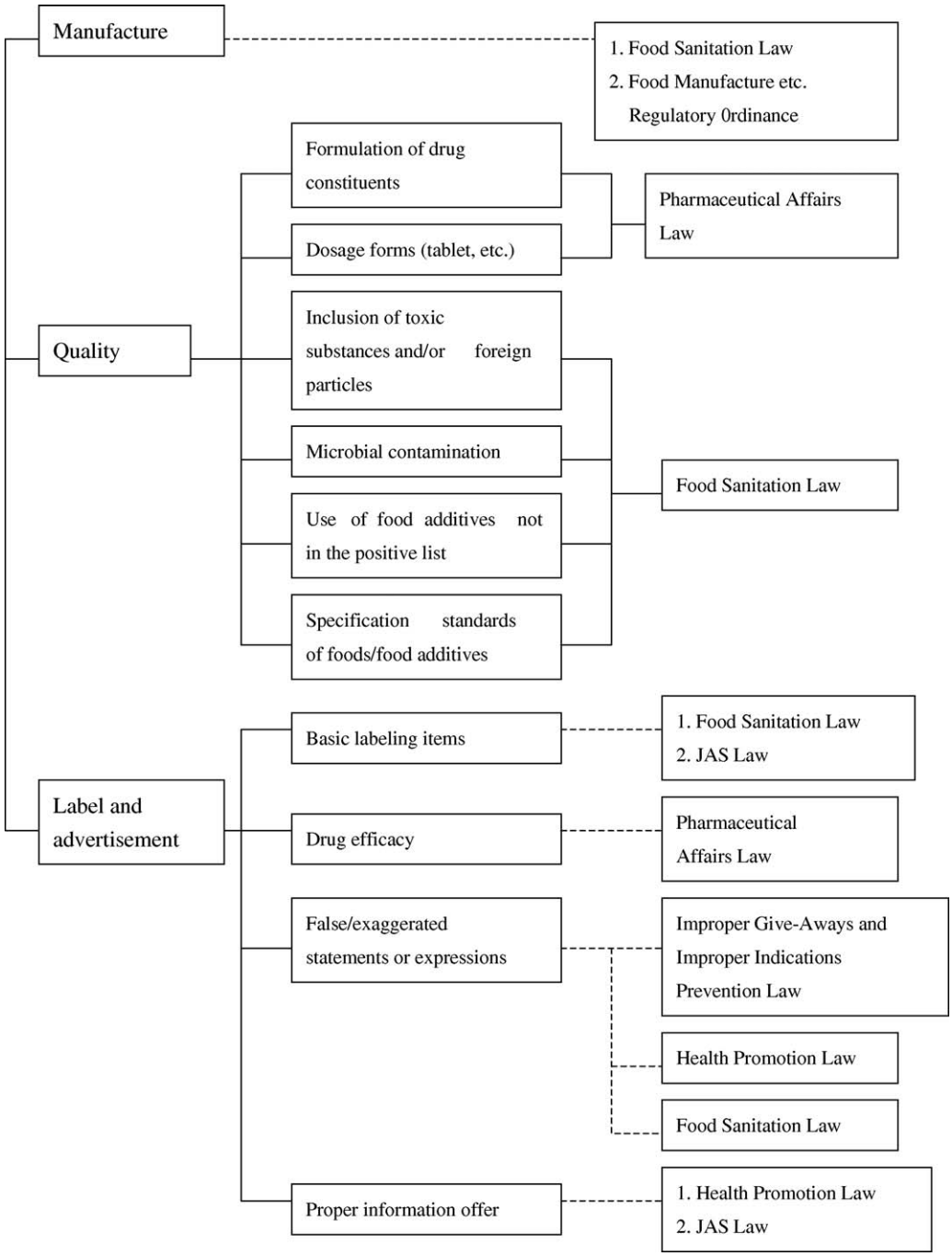
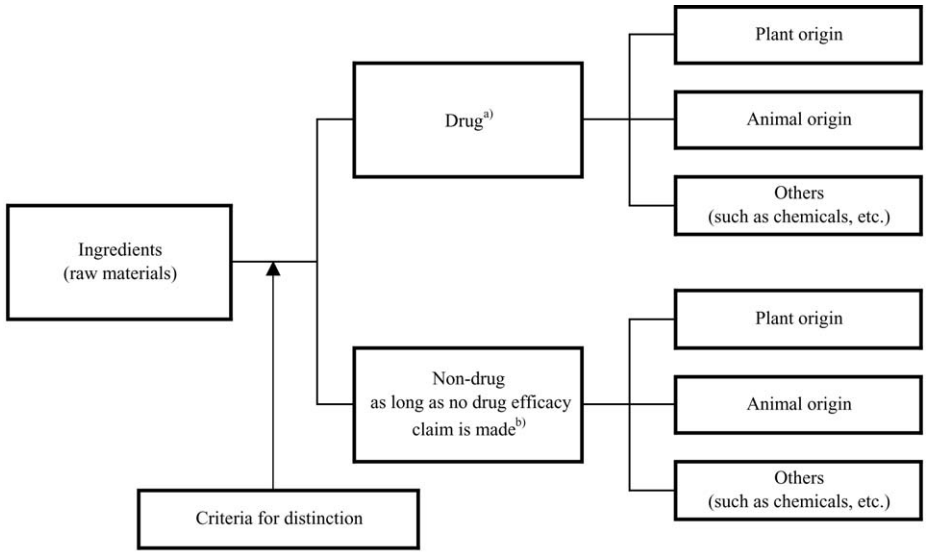



Fig. 3. Regulations for 'health foods' as products (*source*: Tokyo Metropolitan Health Bureau and Tokyo Metropolitan Life Culture Bureau, 2005. Health Food Handling Manual, fourth ed. Yakuji-Nipposha, Tokyo, p. 6 (in Japanese)).

regulated based on the Health Promotion Law, whereas 'health foods' are not controlled by any specific law or specific regulatory system, but regulated by diverse laws (Fig. 3). Each law regulates 'so-called health foods' in terms of manufacturing, quality, labeling, advertising, etc.

According to the Food Sanitation Law, any substance ingested orally is defined either as 'drug' or 'non-drug' (Fig. 2). 'Drug' is strictly specified by the Pharmaceutical Affairs Law according to (1) items recognized in the *Japanese Pharmacopoeia*, (2) items (other than quasi-drugs) that are intended for use in the diagnosis, cure or




Note: [a)] List of ingredients (raw materials) used as exclusively as drugs.
[b)] List of ingredeints (raw materials) used as materials not judged as drugs ('non-drugs') as long as no drug efficacy claim is made.

Fig. 4. Distinction between 'drug' and 'non-drug'.

prevention of disease in man and animal, and which are not equipment or instruments, and (3) items (other than quasi-drugs and cosmetics) that are intended to affect the structure or functions of the body of man or animal.

Based on the Pharmaceutical Affairs Law, two lists are issued by the MHLW for identifying 'drug' and 'non-drug'. Such lists are (1) list of ingredients (raw materials) used exclusively as drugs (drug list) and (2) list of ingredients (raw materials) used as materials not judged as drugs (non-drugs), as long as no drug efficacy claim is made (non-drug list).

These lists are further classified into three subcategories as (1) substances originating from plants, (2) substances originating from animals and (3) other substances such as chemicals, minerals, and others, which are synthesized or highly purified substances obtained from living organisms (Fig. 4). Thus, the substances listed as 'non-drug' may mostly be used as foods and 'health foods', but the substances included in the third subcategory (e.g. chemicals) are basically required to be approved as food additives (e.g. coloring agents).

When substances or raw materials that once allowed in the non-drug list are processed further to obtain specific ingredient(s) originally contained in the initial substances obtained by means of extraction with solvents excluding water and ethanol (and probably carbon dioxide using for supercritical fluid extraction method), the ingredient(s) obtained will be reinvestigated in the light of the criteria described below to determine if it should be included in the drug list. Hence, the solvents excluding water and ethanol are forbidden in the manufacturing process of preparing such ingredient(s).

The criteria for distinguishing substances to be included in the drug list that are established by the MHLW are briefly summarized as follows:

(1) The substances actually used exclusively as drugs (e.g. antipyretic, analgesic, anti-inflammatory agents, hormones, antibiotics and digestive enzymes).
(2) The substances such as those of plant or animal origin (including extracts) and synthetic chemicals as poisons or powerful drugs (e.g. highly toxic alkaloids or toxic proteins), narcotic, psychotropic drug or stimulant having drug-like action and substances that can be designated as drugs from the standpoint of public health. However, substances that are generally used for eating or drinking and considered as foods are excluded.
(3) Furthermore, vitamins, minerals and 23 amino acids including 4-hydroxyproline and hydroxylysine are excluded from the drug category.

To apply for a new ingredient (raw material) not in the above mentioned two lists for distinction and that

Table 1
Documentations and evaluations for new ingredients (raw materials)

| | | |
|---|---|---|
| 1 | General name and family | |
| 2 | Latin name | |
| 3 | Site of use | |
| 4 | Active components or contents | |
| 5 | Toxicological data | $LD_{50}$ (p.o., etc.) (mg/kg) |
| | | Other chronic toxicological data: Yes, No |
| 6 | Narcotic, psychotropic drug or stimulant drug-like action | Yes, No |
| 7 | Examples of approvals as a drug | Yes, No |
| | (1) Previous examples of approvals as a drug in Japan or overseas | If Yes: country<br>Efficacy statement |
| | (2) Traditional or historical use as a drug | Yes, No |
| 8 | Eating custom in Japan | Product form: eat raw·cooked |
| 9 | Eating custom in overseas | Yes, No<br>If Yes: country<br>Product form: eat raw·supplements |
| 10 | Refer to herbs, animals or ingredients in the non-drug list and drug list | |

*Note*: (1) List of such ingredients shall be periodically published (once a year). (2) It will be insufficient if the eating custom is limited to supplements.

intended to be categorized as 'non-drug', manufacturers or importers may request its evaluation by submitting data and documents to the Compliance and Narcotics Division, Pharmaceutical and Medical Safety Bureau, the MHLW. The data required for investigation include scientific names of the ingredients (raw materials), site of use, pharmacological and/or physiological actions, any narcotic, psychotropic drug or stimulant drug-like action, any previous examples of approval as a drug in Japan or overseas and eating customs (Table 1). Historical uses as edible materials and eating customs play a key role for the evaluation. Data and information submitted are reviewed by designated pharmaceutical and medical authorities of the MHLW.

Furthermore, reclassifying ingredient(s) in the drug list to the non-drug list is also possible. The petition of the reclassification of ingredient(s) is accepted by the division of the MHLW and allowed after being reviewed by designated pharmaceutical and medical authorities.

Three prominent ingredients have been reclassified from the category of 'drug' as an example of the relaxation. The first one is coenzyme $Q_{10}$ approved in March 2001, and the others are L-carnitine and its organic salts in November 2002, and α-lipoic acid (thioctic acid) in March 2004. It is apparent that some discrepancy arises in the daily doses (Table 2). The issue concerning the daily dose as a 'health food' product that exceeds the

Table 2
Example of reclassifying from 'drug' to 'food' ('non-drug')

| Substance (reclassified date as food) | Drug | Food[a] |
|---|---|---|
| Coenzyme $Q_{10}$ (March 2001) | *Dosage*: 30 mg/day p.o.<br>*Indication*: mild or moderate congestive cardiac failure | Generally 100–200 mg/day |
| L-Carnitine (November 2002) | *Dosage*: 30–60 mg/kg/day p.o. (as levocarnitine chloride)<br>*Indication*: L-carnitine deficiency in patients with propionic acidemia or methyl malonic acidemia | Generally not more than 20 mg/kg/day[b] or 1000 mg/day[c] |
| α-Lipoic acid (thioctic acid) (March 2004) | *Dosage*: 10–25 mg/kg/day i.v., i.m., s.c.<br>*Indication*: (1) supplementation of thioctic acid when highly needed (by hard physical labor); (2) Leigh syndrome; (3) poisoning deafness, noise-induced deafness | Generally 100–200 mg/day |

[a] *Note*: No upper limit has been decided by the MHLW.
[b] Maximum dose determined by the U.S. These daily doses are suggested by the MHLW as the maximum doses in Japan.
[c] Maximum dose determined by Switzerland. These daily doses are suggested by the MHLW as the maximum doses in Japan.

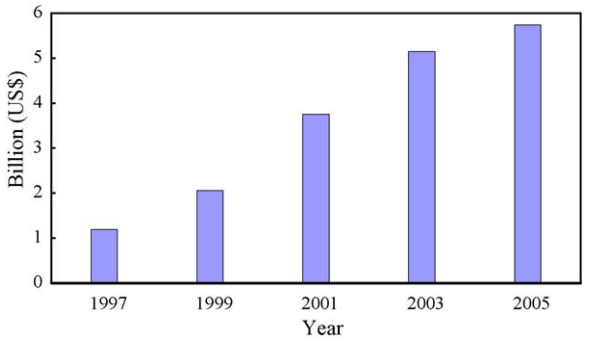



Fig. 5. The changes in retail-sales based market size of FOSHU products in Japan (*source*: personal communication from the Health Industry News, CMP Japan Co. Ltd.).

dose as a drug is now under dispute in the Food Safety Commission of the Cabinet Office.

### *3.2. Regulation for 'health foods' by the Health Promotion Law*

#### *3.2.1. Enlarging 'health food' and FOSHU market*

With the introduction of the FHC system in 2001, drugs and foods were categorized according to the laws of food–drug classification (Fig. 2). Since then, the market size of FOSHU rapidly increased and was about US$ 3.8 billion in 2001. It has reached about US$ 5.7 billion in 2005 (Fig. 5). In spite of the drastic increase in FOSHU products in the market, 'so-called health food' products still represent the largest market share.

#### *3.2.2. Implications of defining 'health foods'*

According to the proposed definition of 'health foods' by the MHLW, the category of 'health foods' is the sum of two categories, that is, FHC and 'so-called health foods' as follows:

'health foods' = FHC + 'so-called health foods'

Although the proposed definition remained ambiguous because the term 'health foods' has been used by consumers and 'health foods' industry with the implication of the foods that are good for health, 'so-called health foods' comprises a wide range of food products including products in tablets, capsules or other various dosage forms. Moreover, 'so-called health foods' products unlike FHC often are without scientific results to support efficacy. Consequently, for inadequate safety data there is risk of overdose resulting in adverse reactions in this category.

#### *3.2.3. Necessity of regulation for 'health foods'*

In April 2003, the MHLW held a new special investigative committee on the revision of the regulatory system for 'so-called health foods' with the request of the Liberal Democratic Party. After discussing in the committee for more than 1 year, the MHLW announced the implementations of new systems onto the previous frame of the FOSHU system. The objective of adding the new frame of FOSHU is primarily to ease regulations on 'so-called health foods' and to offer better opportunities to food industry [FOSHU under the new categories such as 'qualified FOSHU' and 'standardized FOSHU' (Table 3)].

FOSHU is a subcategory of FHC, and FNFC belongs to the other subcategory of FHC. The product of the former category is individually approved by the MHLW on the basis of the conclusion from deliberations in the Pharmaceutical Affairs and Food Sanitation Council of the MHLW, while FNFC is a new system under the regulations on 'health foods' restricted to the specified nutrients which nutritional function claims are firmly established on the basis of scientific evidence in 2001.

## 4. FHC

Conventional foods such as yogurt, cooking oil and lactic acid drink were originally in the FOSHU category, but dosage forms such as tablets or capsules had not been approved. In 2001, criteria for FOSHU were integrated into the FHC system and then revised to make capsules, tablets or other dosage forms commonly as supplements usable. Consequently, health benefits are permissible to claim on the labels of the products. The domain of claims are limited to the contents (1) indicating the benefits for maintaining or improving healthy condition that are clearly observed and measured (e.g. to help maintain the blood pressure in normal), (2) indicating that the food product aids to maintain or improve healthy physical condition or tissue functions (e.g. to help maintain the bowel motion) and (3) indicating that the food product improves temporarily the physical condition according to subjective symptoms, provided that it will not provide continuous or long-term effects and the one in expectation notices such effects (e.g. appropriate to the one who feels tiredness).

### *4.1. Approval system for FOSHU*

The FOSHU is allowed for the structure and function claims on the human body with the approval of the Minister of the MHLW. To obtain approvals as for FOSHU products, identification of the decisive

Table 3
Revision of FHC in February 2005

| | FHC | | |
|---|---|---|---|
| | FNFC | FOSHU | |
| Type of system | Standardized | Individual approval FOSHU<br>Standardized FOSHU | Qualified FOSHU |
| Functional component(s) | Nutrients (12 vitamins and 5 minerals) | Nutrients and other food ingredients | Nutrients and other food ingredients |
| Claims | Nutrient function claims (structure and function claims) | Specified health claims (structure and function claims)<br>Disease risk reduction claims | Specified health claims (structure and function claims) |
| Ranking of scientific evidences | A | A,B | C |

*Note*: Ranking of scientific evidences is defined as follows—(A) evidences are both medically and nutritionally established from the scientific point of view; (B) evidences are confirmed at the level previously required for the approval of existing FOSHU; (C) evidences are not established but the efficacy is suggested.

ingredient (currently single component) and elucidation of the action mechanism of the ingredient are essential. When a FOSHU product is designed, it must be accompanied with rationale how the product makes contributions to the improvement of the Japanese diet life and also the maintenance of good health by ingesting the product. With this background fully explained, the core part of the FOSHU application should include (1) needs of consumers satisfied by the launch of the product, (2) objective of developing the product, (3) scientific evidence concerning the product, that demonstrates the ingredient, with effectiveness, safety and quality, and (4) clarification on the benefits of the finished product as a FOSHU product.

Effectiveness or efficacy is substantiated by elucidating the mechanism of activity, establishing the dosage level, performing tests by using animal and human subjects and employing appropriate statistical analyses. Safety is confirmed by demonstrating the historical diet uses in Japan and foreign countries, conducting toxicity tests that include acute, subacute, chronic toxicities and mutagenecity. It must also be clinically proven by administering an overdose, usually three- to five-fold of the established dosage level. Reproductive toxicity, carcinogenicity or teratogenicity studies may be required depending on the results of the toxicity studies or if an applied product contains a new decisive ingredient which was previously not found in the list of the approved FOSHU products. Physicochemical properties as well as the stability of the decisive ingredient and the product formulated must be assessed in terms of quality.

All toxicity tests should be performed under good laboratory practice (GLP) conditions, whereas clinical studies must be approved by a committee on ethics in consideration of the protection of human rights in accordance with the spirit of the Helsinki Declaration. Furthermore, the clinical studies should be randomized placebo-controlled, double blind trials, and the results must show statistical significance against the control at the *P*-value less than 0.05. The subjects for the clinical trial should be healthy subjects or subjects who are in the borderline between health and illness. The data of clinical study are crucial for determining the approval as a FOSHU product.

Accurate determination of an active constituent is essential as a part of the approval process. The manufacturing procedure of a FOSHU product is also required. Labeling, shelf-life, formulation, dosage, nutritional information, precautions, etc. of the intended product for FOSHU should be clearly stated.

### 4.2. Number of FOSHU products

More than 569 products have been approved as FOSHU as of December 9, 2005. In Table 4, decisive or functional ingredients of FOSHU products are listed according to the categories of health claims. About 45% of FOSHU products claim ‘maintaining gastrointestinal condition’. Oligosaccharides, Lactobacillus, Bifidobacterium and dietary fibers are major ingredients for the activities in this category. The category for gastrointestinal condition was followed by about 21% of those with health claims, that the product is ‘good for those concerning about high serum cholesterol/triglycerides’. Various products included in this category are soy proteins, peptides, dietary fibers, diacylglycerol and plant sterol/stanol.

Table 4
FOSHU products (569 products approved as of December 9, 2005)

| Target | Specified health claims | No. of products (%) | Main decisive ingredients |
|---|---|---|---|
| Intestinal condition | Maintain intestinal condition by improving balance of enterobacterium and/or promoting regular bowel movement.<br>Improve bowel movement by improving balance of enterobacterium. | 254 (44.6) | Oligosaccharides, Lactobacillus, Bifidobacterium, Psyllium husk, indigestible dextrin, wheat bran, low molecular sodium alginate, partially hydrolyzed guar gum |
| Cholesterol/triglycerides | Good for those concerning about serum cholesterol and/or triglycerides.<br>Good for those having relatively high serum cholesterol and/or triglycerides.<br>Good for those concerning about body fat. | 117 (20.6) | Soy protein, chitosan, low molecular sodium alginate, peptides, diacylglycerol, plant sterol/stanol (esters), green tea catechin, middle chain fatty acid, DHA, EPA, degradation products of globin protein, Psyllium husk |
| Blood sugar | Good for those concerning about blood glucose level. | 71 (12.5) | Indigestible dextrin, L-arabinose, wheat albumin |
| Blood pressure | Good for those having relatively high blood pressure. | 64 (11.2) | GABA, peptides |
| Teeth | Maintain teeth strong and healthy. | 34 (6.0) | Xylitol, polyols, tea polyphenols, CPP-ACP |
| Bone | Help maintain calcium in bones.<br>Make bone strong by efficient calcium absorption. | 26 (4.6) | Soy isoflavone |
| Iron supply | Good for those who are susceptible to be anemic. | 3 (0.5) | Heme iron |
| Total | | 569 (100) | |

### 4.3. Qualified FOSHU and standardized FOSHU

With the recent innovation of FHC system, the qualified and the standardized FOSHU systems were introduced to relax the frame of the FHC, making it easier for applicants to obtain approvals for distributing the FOSHU products in the marketplace. At the same time, the 'disease risk reduction claims' were added to the present Individual Approval FOSHU, reflecting the Codex decision. The schematic illustration of the new FHC system is exhibited in Table 3, whereas differences between the existing FOSHU and qualified FOSHU systems are shown in Table 5. The major differences are (1) requirement for elucidating the mechanism of a decisive ingredient and (2) employment of the *P*-value for statistical analysis. The elucidation of the mechanism in the action of the decisive ingredient is not always required for the qualified FOSHU. For the statistical analysis of the clinical studies, significant difference against the control may be accepted with *P*-value less than 0.1 and the randomized controlled study is not essential for the qualified FOSHU products. The other data and documents are necessary for the approvals of the qualified FOSHU products in accordance with the existing FOSHU system.

Enforcement of the standardized FOSHU system permitted functional ingredients to make existing health claims, such as, 'maintaining good gastro-intestinal conditions'. Such functional ingredients include (1) indigestible dextrin (3–8 g/day), (2) polydextrose (7–8 g/day), (3) xylooligosaccharide (1–3 g/day), (4) fructooligosaccharide (3–8 g/day), (5) soybean oligosaccharide (2–6 g/day), (6) isomaltooligosaccharide (10 g/day), (7) lacto-

Table 5
Differences in criteria between the existing and qualified FOSHUs

| Clinical study | | Randomized controlled trial (RCT) | | Non-randomized controlled trial |
|---|---|---|---|---|
| | | $P < 0.05$ | $0.05 < P < 0.10$ | |
| Mechanism of action | Clear | Existed FOSHU | Qualified FOSHU | Qualified FOSHU |
| | Unclear | Qualified FOSHU | Qualified FOSHU | – |

*Note*: Control, placebo; subjects, healthy subjects; compliance with Helsinki Declaration.

fructooligosaccharide (2–8 g/day), (8) galactooligosaccharide (2–5 g/day) and (9) partially hydrolyzed guar gum (5–12 g/day). More than 100 food products containing above mentioned ingredients were approved as FOSHU products from 1991 and possess sufficient scientific evidence to support the claims. Furthermore, clinical studies for evaluating the safety are always not required for approval.

### 4.4. FOSHU and the Japanese traditional diets

Some of the FOSHU products were based on food materials used the Japanese traditional diet. For example, natto of fermented soybean is an approved FOSHU product which contains Vitamin $K_2$ (menaquinone-7) that helps absorb calcium into the bone (Yamaguchi et al., 1999). Soybean is a traditionally inherent crop and a source for fermentation to yield miso, soy sauce and natto. Soybean isoflavone was shown to be effective against the improvement of mineral absorption (Fujikura et al., 2003). Soy protein is a decisive ingredient proven to control the serum cholesterol level (Ishikawa et al., 2002). 'Katsuobushi' or fermented bonito is another Japanese traditional food, which contains peptides demonstrated to lower blood pressure (Fujita et al., 2001), and therefore have the health claim 'good for those having relatively high blood pressure'. Tea polyphenols is another decisive ingredient, which helps to maintain strong and healthy teeth (Sakanaka et al., 1992). It is expected that additional claims for FHC will be adopted as FOSHU products based on the Japanese traditional diets.

### 4.5. FOSHU and botanicals

A few botanical products which have been approved as FOSHU products, are the leaves of guava (*Psidium guajava* L.), which contains polyphenols as the decisive ingredient, claiming 'good for those concerning about blood glucose level' and green tea (*Camellia sinensis* L.) catechin for claiming as 'good for those concerning about body fat'. Another botanical species approved for FOSHU are the leaves of *Eucommia ulmoides* Oliv., which contain geniposide and claim that it can help reduce the blood pressure. The above mentioned FOSHU products are examples of various tea products. It is expected that FOSHU products based on botanicals listed in 'non-drug' or which has been evaluated for safety and effectiveness will become more available to the consumers for maximizing the FOSHU system.

A possible candidate is the extract of the dried fruit rind of *Garcinia cambogia* (family Guttiferae) which contains (−)-hydroxycitric acid (HCA) that possesses an inhibiting effect on ATP-citrate lyase. Furthermore, HCA has been sufficiently studied for its safety, mechanism and efficacy, to help reduce the serum lipid level, satisfying a health claim of FOSHU (Watson et al., 1969; Watson and Lowenstein, 1970; Sullivan et al., 1972, 1977; Rao and Sakariah, 1988; Bagchi et al., 2002; Hayamizu et al., 2003; Soni et al., 2004).

### 4.6. Disease risk reduction claims

According to the Codex committee under WHO/FAO, the MHLW introduced the disease risk reduction claims to the existing FOSHU system. The disease risk reduction claims are currently limited to two ingredients, calcium and folic acid, specifying the minimum and maximum limits of daily intake.

#### 4.6.1. Calcium

Daily intake of calcium from the FOSHU products should be included between 300 and 700 mg. Labeling includes (1) the product contains adequate calcium and (2) intake of a proper amount of calcium contained in healthy meals with appropriate exercise may support healthy bones of young women and reduce the risk of osteoporosis when aged.

#### 4.6.2. Folic acid

Daily intake of folic acid from the FOSHU products should be included between 400 and 1000 μg. Labeling includes (1) the product contains adequate folic acid and (2) healthy meals containing an appropriate amount of folic acid may support healthy fetal development in pregnant women to bear healthy baby by reducing the risk of neural tube defect, such as spondyloschisis.

### 4.7. FNFC

FNFC is the category of 'health foods' which permit the use of functional claims for nutrients according to their fundamental and decisive scientific evidence. It was enforced by the MHLW and authorized by the Minister of the MHLW. The claims are standardized according to the conclusion derived by the authorities of the MHLW. To make claims for FNFC, the minimum and maximum daily intakes of an individual nutrient are determined as the standard of daily dosage by the MHLW. The disclaimers are also required to be described on the label depending on individual ingredient. FNFC category was enforced from April 1, 2001, in which 12 vitamins, β-carotene and 5 minerals have been adopted with an individual nutrient function claim. The FNFC permitted

Table 6
Vitamins and minerals permitted and not permitted as FNFC

| | | |
|---|---|---|
| Permitted (17) | 12 Vitamins | A (and β-carotene), $B_1$, $B_2$, $B_6$, $B_{12}$, pantothenic acid, biotin, nicotinic acid/nicotinamide, folic acid, C, D, E |
| | 5 Minerals | Iron, calcium, copper, zinc, magnesium |
| Not permitted (8) | No deficiency in Japan | Vitamin K, phosphorus, potassium |
| | Data not available for the calculation of nutritional parameters based on the national nutritional survey | Iodine, manganese, selenium, chromium, molybdenum |

*Note*: Claims are determined by the MHLW for individual nutrient based on the Significant Scientific Agreement Disclaimer that is required for description.

Table 7
Standards of daily dosage of FNFC (revised in July 2005)

| | Vitamins | | | |
|---|---|---|---|---|
| | Niacin (mg) | Pantothenic acid (mg) | Biotin[a] (μg) | Vitamin A[b] |
| Maximum limit | 60 | 30 | 500 | 600 μg (2000 IU) |
| Minimum limit | 3.3 | 1.65 | 14 | 135 μg (450 IU) |

| | Vitamins | | | |
|---|---|---|---|---|
| | Vitamin $B_1$ (mg) | Vitamin $B_2$ (mg) | Vitamin $B_6$ (mg) | Vitamin $B_{12}$ (μg) |
| Maximum limit | 25 | 12 | 10 | 60 |
| Minimum limit | 0.3 | 0.33 | 0.3 | 0.6 |

| | Vitamins | | | |
|---|---|---|---|---|
| | Vitamin C (mg) | Vitamin D | Vitamin E (mg) | Folic acid (μg) |
| Maximum limit | 1000 | 5.0 μg (200 IU) | 150 | 200 |
| Minimum limit | 24 | 1.50 μg (60 IU) | 2.4 | 60 |

[a] *Note*: Biotin is permitted only for FHC.
[b] β-Carotene as the precursor of Vitamin A can be approved as the FNFC of Vitamin A source. In that case the maximum limit is set at 7200 μg the minimum limit is set at 1620 μg.

Table 8
Standards of daily dosage of FNFC (revised in July 2005)

| | Minerals | |
|---|---|---|
| | Calcium (mg) | Iron (mg) |
| Maximum limit | 600 | 10 |
| Minimum limit | 210 | 2.25 |

| | Minerals | | |
|---|---|---|---|
| | Zinc[a] | Copper[a] | Magnesium[a] |
| Maximum limit | 15 mg (UL[b] minus maximum amount of intake from conventional foods) | 6 mg (UL minus maximum amount of intake from conventional foods) | 300 mg (calculated by modifying the UL set by the U.S. comparing the weight difference of the average American and Japanese) |
| Minimum limit | 2.10 mg (30% of NRV)[c] | 0.18 mg (30% of NRV) | 75 mg (30% of NRV) |

[a] *Note*: Zinc, copper and magnesium were added in 2004.
[b] UL, tolerable upper intake level.
[c] NRV, nutrient reference value.

Table 9
Nutrient function claims of vitamins

| Vitamin | Nutrient function claims |
|---|---|
| Niacin | Niacin is a helpful nutrient for the healthy maintenance of the skin and mucosa. |
| Pantothenic acid | Pantothenic acid is a helpful nutrient for the healthy maintenance of the skin and mucosa. |
| Biotin | Biotin is a helpful nutrient for the healthy maintenance of the skin and mucosa. |
| Vitamin A[a] | Vitamin A is a helpful nutrient for the maintenance of eyesight at night. Vitamin A is a helpful nutrient for the healthy maintenance of the skin and mucosa. |
| Vitamin $B_1$ | Vitamin $B_1$ is a helpful nutrient for producing energy from carbohydrate and the healthy maintenance of the skin and mucosa. |
| Vitamin $B_2$ | Vitamin $B_2$ is a helpful nutrient for the healthy maintenance of the skin and mucosa. |
| Vitamin $B_6$ | Vitamin $B_6$ is a helpful nutrient for producing energy from protein and the health maintenance of the skin and mucosa. |
| Vitamin $B_{12}$ | Vitamin $B_{12}$ is a helpful nutrient for the formation of the red cell. |
| Vitamin C | Vitamin C is a helpful nutrient for the healthy maintenance of the skin and mucosa, and with the process of anti-oxidation. |
| Vitamin D | Vitamin D is nutrient for speeding up the absorption of calcium in the bowel and helping the formation of the bones. |
| Vitamin E | Vitamin E is nutrient for preventing the internal lipid from oxidizing by the process of anti-oxidation and helping the health maintenance of the cell. |
| Folic acid | Folic acid is a helpful nutrient for the formation of the red cell. Folic acid is nutrient for contributing to the health growth of the embryo. |

[a] *Note*: β-Carotene as the precursor of Vitamin A can be approved as the FNFC of Vitamin A source. In that case the maximum limit is set at 3600 μg, the minimum limit is set at 1080 μg.

Table 10
Nutrient function claims of minerals

| Mineral | Nutrient function claims |
|---|---|
| Calcium | Calcium is a necessary nutrient for the formation of the bones and teeth. |
| Iron | Iron is a necessary nutrient for the genesis of the red cell. |
| Zinc | Zinc is a necessary nutrient for keeping the normal condition of degustation.<br>Zinc is a helpful nutrient for the healthy maintenance of the skin and mucosa.<br>Zinc is a necessary nutrient for maintaining the normal vital activity participating in the metabolism of proteins and nucleic acids. |
| Copper | Copper is a helpful nutrient for the formation of the red cell.<br>Copper is a necessary nutrient for the normalization of the function of various endogenous enzymes, for helping the formation of the bones. |
| Magnesium | Magnesium is a necessary nutrient for the formation of the bones and teeth.<br>Magnesium is a necessary nutrient for the normalization of the function of various endogenous enzymes, for helping the energy generation and for the normalization of the blood circulation. |

and non-permitted list of vitamins and minerals are listed in Table 6. Specified dosage levels of the vitamins and minerals of FNFC and the claims allowed are listed in Tables 7–10. The labels of FNFC contain statements, such as 'intake of excessive quantities of this product does not heal the illness or improve health' and 'follow the dosage as directed.' Furthermore, it is stated as, 'this product has not investigated individually by the Minister of the MHLW unlike FOSHU.'

## 5. General foods and safety concern

'So-called health foods' which are included in the category of the general foods are shown in Fig. 2. Tablets, capsules and others generally employed in the category of supplements are included in the categories of FNFC and 'so-called health foods' in Japan. Most of the herbal or botanical products are seen in the 'so-called health foods' category. Only statements on the nutritional content are accepted on the labels of products in the general food category, but any functional claim is prohibited. As previously mentioned, 'so-called health foods' are regulated by various and separate laws (Fig. 3), which are not included in the framework of the specific laws. Most of 'health foods' products in the form of tablets or capsules included in the category of 'so-called health foods' have possibilities of risks of overdoses, resulting in adverse reactions, due to the presence of highly concentrated ingredients from original materials. In fact, some accidental events such as the liver disorders have occurred in the past, which were thought to be relevant to the intake of 'so-called health foods' products. This situation inevitably requires an efficient countermeasure to prevent such accidents and adverse events.

In 2005, the MHLW announced two guidelines to ensure safety and to guarantee the quality of 'health foods' products in the form of tablets, capsules and related forms are (1) good manufacturing practice (GMP) guideline, and (2) guideline for the

self-investigation of safety of raw materials included in these 'health foods' products.

### 5.1. GMP guideline for 'health foods' products

GMP guideline that has been established by the MHLW for the 'health foods' follow the same GMP guidelines applicable for drugs. Japanese Government strongly recommends the GMP guidelines in the product manufacturing lines for the 'health foods'. The guideline requires that GMP is not only for finished products, but also for raw materials. For imported raw materials and finished products, the guideline requires to gurantee qualities equivalent to those manufactured in Japan.

Recently, two organizations, the Japan Health and Nutrition Food Association (JHNFA) and the Japanese Institute for Health Food Standards (JIHFS), have established their own GMP regulatory systems and introduced a certifying system for manufacturing facilities. The latter, JIHFS is going to qualify the products manufactured in the facility certified by the GMP auditing by affixing with a GMP certification mark on the product.

### 5.2. Guidelines for self-investigation on the safety of raw materials

Raw materials used for manufacturing 'health foods' are required to be investigated voluntarily in accordance with the safety guidelines established by the MHLW. Tablets, capsules, powder or liquid are subjected to a safety 'self-investigation' of its raw materials, particularly, when raw materials are processed by using the methods of extraction, fractionation, purification and chemical reaction. Raw material manufacturers as well as the distributors of finished products are required to evaluate the safety on the basis of the self-investigation system of raw materials.

The self-investigation of the safety of materials is accomplished according to the following steps established by the MHLW as a model system:

Step 1. To identify all raw materials in a finished product.
Step 2. To define raw materials according to the drug or non-drug list.
Step 3. To confirm the identity of an individual raw material by employing reasonable techniques such as profile and DNA analyses and morphologic characterization or to confirm if cultivation of raw material is carried out under voluntary good agricultural practice (GAP) system, etc.
Step 4. To confirm if it is equivalent to the existing materials used as ingredients in the conventional foods generally distributed.
Step 5. To study/research everything available regarding safety, toxicology, epidemiology and efficacy on the raw materials obtained from the public databases including Chemical Abstract, PubMed and RTECS.
Step 6. To identify undesirable substances e.g. alkaloids, toxins, hormones, and neurotropic, carcinogenic, teratogenic, genotoxic and other toxic substances and also substances having related chemical structures to those of the aforementioned undesirable substances from the published papers. If sufficient information regarding the above mentioned substances are not available, then the raw materials should be analyzed to confirm if undesirable substances are contained.
Step 7. To perform toxicity studies such as 90 days repeated subchronic toxicity study and in vitro genotoxic studies that are required.
Step 8. To conclude by certifying the absence of impurities such as heavy metals and microorganisms still be required and the manufacturing process desirably be controlled under a proper GMP system.

## 6. Labeling for 'health foods' products

'Health foods' including FHC and 'so-called health foods' are characterized as (1) basic nature of the ingredients (raw materials) (2) functional statements on labeling, (3) directions and dosage and (4) dosage forms. The basic nature of ingredients are indispensable for defining 'health foods' under the aforementioned regulatory systems, but the other criteria (see Section 6.1) are also important to define the criteria of 'health foods'. For example, accurate statements on the label of a 'health foods' product are essential for preventing any confusion and misinterpretation on the product by consumers.

### 6.1. Labeling and laws

Labeling is essentially ruled by the Pharmaceutical Affairs Law, while functional and efficacy claims are prohibited in principle for 'health foods' except FHC. The functional efficacy claims or indications are interpreted as drugs. The claim, however, with expression such as to maintain or promote health condition of a non-sick individual is acceptable for 'health foods'. Examples of claims include (1) for prevention or treatment

of disease, (2) for promotion or improvement of general physical condition and (3) 'hints' for drug efficacy are violation of the Pharmaceutical Affairs Law. Such 'hints' for drug efficacy includes (a) product naming or promotional statements or phrases, (b) description of ingredient, (c) description of manufacturing process, (d) description of origin or history and (e) reference to articles from newspapers and magazines or quotations from interviewing medical doctors or scientists.

### 6.2. Use directions for 'health foods' products

Directions for the use of 'health foods' products must not be stated in a similar format used by drugs. The following examples include (1) before meals, after meals or during meals, (2) two to three times daily, (3) one to two tablets per dose, twice a day, (4) adult three to six tablets a day—adjust according to condition (5) one to two tablets before and after meals and (6) one to two capsules before bedtime.

### 6.3. Dosage forms of 'health foods' products

Dosage forms or shapes such as tablet, capsule, etc. used for 'health foods' products have been deregulated, although several specific delivery forms used in drugs are still forbidden. The examples of delivery forms are ampoules, sublingual tablets, the product absorbed via mucous membranes and spray type product into oral cavity. On the other hand, the forms allowed for food uses include hard gelatin capsule, soft gelatin capsule (e.g. softgel), tablet, powder, liquid or granule.

## 7. Discussion

Japan is one of a few countries in the world to achieve a large health food market. Following the United States, Japan as a country possesses the second largest health foods market in the world, which is almost equivalent to the EU market. In fact, the market of 'health foods' without FOSHU has reached to about US$ 11.7 billion in 2005 (Fig. 6). The FOSHU market represents about 30% of the total 'health foods' market (Fig. 5). The growth of the 'health foods' market has remarkably accelerated since 2001, which was presumably reflected by the deregulations that the Japanese Government implemented (Fig. 6). On the other hand, the systems that the Government developed for 'health foods' differ from the systems in Europe, the United States and also various Asian countries. The most notable difference is that the positioning of supplements which was not legally defined as a system.

As the systems of FHC and 'so-called health foods' are recognized in Japan, the framework is classified and determined by the approval of labeling of functional claims of 'health foods'. Furthermore, both FOSHU and FNFC are allowed for specific functional claims that are approved by the Minister of the MHLW and recognized as an exceptional case of the Pharmaceutical Affairs Law. While 'so-called health foods' is solely positioned as general foods and is distributed in the marketplace, the products are under the strict control of the Pharmaceutical Affairs Law and are prohibited from making any functional claims on the labels.

Thus, 'health foods' is classified into FHC and 'so-called health foods' by the approval of functional claim. That is, supplementation of the ingredients which are occasionally lacked in conventional foods or of which physiological and nutritional functions are not expected from general foods is efficiently fulfilled by employing a dosage form such as tablet or capsule. The maximization of using such dosage form, the needed ingredients become available regularly, quantitatively and continuously for the health benefits of consumers. Unfortunately, the concept or system that distinguishes 'health foods' by 'dosage form' is completely absent in the regulatory system in Japan.

In major foreign countries, it has been attempting or is under progress to establish a system for supplement, while some countries have already completed the system. The establishment of such system will accomplish pivotal roles in respect to evidence based efficacy, safety and quality assurance that supplement requires. On the other hand, the advanced approval system for FHC, FOSHU in particular, is present in Japan; however, the law that specifically regulates 'so-called health foods' is totally absent. Thus, the regulations are dependent on various laws. Because of the non-specific regulatory system for the category of 'so-called health foods', the products under the category are not allowed to make any efficacy statements on the labels, but they are required to handle the issues of safety and quality comprehensively. Furthermore, 'health foods' industry is forced to market 'so-called health foods' products with no mentioning of the functions of active ingredients in the products, since functional statements are prohibited in this category. In addition, concerns being raised under such circumstance are that the majority of products in tablet and capsule forms are distributed as 'so-called health foods' products, but are seldom sold as in FOSHU products. Since 'so-called health foods' differs from FOSHU due to the rigorous approval systems, 'so-called health foods' products that satisfy the legal requirements based on voluntary judgments may be freely

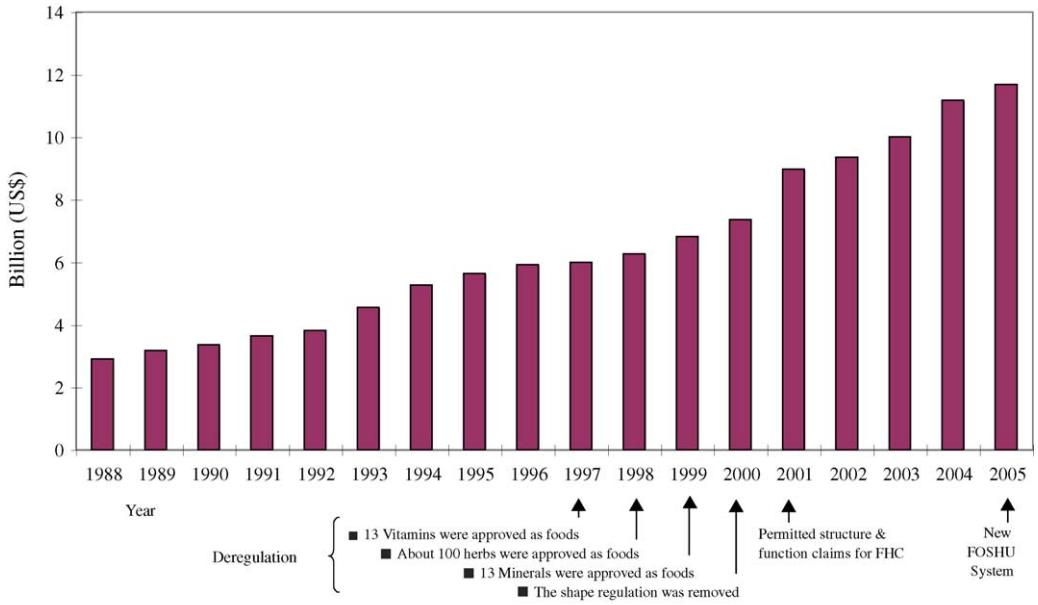



Fig. 6. The changes in retail-sales based market size of 'health foods' without FOSHU in Japan (*source*: personal communication from the Health Industry News, CMP Japan Co. Ltd.).

available without any registrations or approvals from the Government.

With the distribution of 'health foods' products in the forms of tablets and capsules, specifically in 'so-called health foods', overdosing is a major risk that causes crucial problems such as adverse reactions. In addition, exaggerated and false advertising, contamination with toxic substances and drug interactions are possibly found in the 'so-called health foods' products as legal and often social problems. The serious health hazards as social problems related to 'health foods' products that occurred among Japanese consumers have been caused by 'so-called health food' products. Those problematic situation is suggestive to require the establishment of the exclusive law for regulating supplements more in the comprehensive manner as observed in many overseas countries.

While those circumstances may never be allowed, the MHLW has shown a strong concern and presented countermeasures. Paying much attention to 'health foods' products in tablets or capsules, the MHLW has recently introduced two guidelines for the management of the manufacturing process with respect to GMP and the self-investigation of the safety of raw materials for 'health foods' industry, requiring industries who are responsible for assuring the safety and quality to resolve aggressively the issues: the two guidelines are controlled under the Food Sanitation Law which defines the responsibilities of manufacturers.

GMP as a standard for managing the manufacturing process is demanded not only for finished products, but also for raw materials and further for imported raw materials and finished products. The two guidelines are considered to be a unique and important guideline from the global point of view. Also, in the guideline assuring the safety of raw materials the way to assure the safety is like 'decision tree', which scheme is highly sophisticated. Furthermore, as it is perceived in the total framework of safety, the two guidelines that are to have close relationship may be well-advanced as viewed internationally.

As explained earlier in this paper the absence of a regulatory system for supplement implies that the system is not accepted in Japan even though the significance of supplement has been well-recognized globally. On the other hand, the Government has begun to pay attention on the important issue of the products with tablets, capsules, etc. Also, it is well understood the importance and necessity of the supplement products to be dealt and managed with an independent legal system.

Although the Japanese Government has presently promoted to systemize 'health foods' from an independent standpoint apart from the global movement of dietary supplements, we ought to think that the establishment of an exclusive regulatory system for supplement is indispensable in the light of international sharing of information and data for efficacy and safety, global harmonization of the methodology for

quality management and also promotion of international trade.

It is important to recognize that Japan is required to show an aggressive position toward the establishment of the regulatory system for supplements to enhance understandings of roles that supplement plays in the midst of the global harmonization, resolving various health concerns such as securing of health and reducing disease risks, as well as improving welfare of all mankind. The roles that Japan plays are significant as proven in developing the concept of the functionalities of foods and presently proposing the new guidelines for safety and quality management by employing an advanced methods.

The newly introduced system added the qualified and standardized FOSHUs. These 'deregulations' are intended to resolve various issues, including the decrease in the number of illegal labeling, advertising and products with poor quality by bringing 'health foods' products under the FOSHU system. Since regulatory systems for 'health foods' in Japan have become rather complex compared with the systems in other countries, the MHLW strongly recommends the necessity of consumer education concerning roles that 'health foods' products play and fostering supplement advisers, in view of safety and efficacy.

As mentioned above, the MHLW is concerned about consumer's overdosing of 'health foods' products on the market and recommending 'health foods' companies to perform a series of safety tests on their products to secure the consumer's good health. However, from the viewpoint of the 'health foods' industry, small to medium-sized companies might suffer for carrying heavy cost burden for conducting safety and relevant tests to ensure the safety of the products, as well as introducing the GMP regulating system. As a result, some of the companies may have to withdraw from the 'health foods' market, while large food or pharmaceutical companies will have opportunities to dominate the market. In fact, most of the FOSHU products approved are of the major companies with good research and development.

To make small to medium-sized companies viable in the market, the Government and their related organizations or even universities support them financially, as well as technically, for example, as grants-in-aid or technically allowing to use their laboratories to perform tests required to ensure safety and substantiate efficacies of their products. The other possibility is to establish Contract Research Organization (CRO) to support those companies to help obtaining safety and efficacy data on the 'health foods' products at low costs. As a result, the proposed systems might promote switching 'health foods' on the market into FOSHU or the qualified FOSHU. Japanese Government is aiming at possibly reducing consumer complaints and the incidence of regulatory violation.

Finally, assisting such research activities may create new categories of FHC, thereby leading to the further growth of the FHC market. Japanese Government may consider the 'health foods' products that have been on the market for some time with no adverse effects reported to consumer groups or to the Government and substantial volume of the products being sold as proofs of safety, thereby exempting the products from some of the safety tests using animals or involving humans, if not all.

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