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Functional Food Center's vision on functional food definition and science in comparison to FDA's health claim authorization and Japan's Foods for Specified Health Uses

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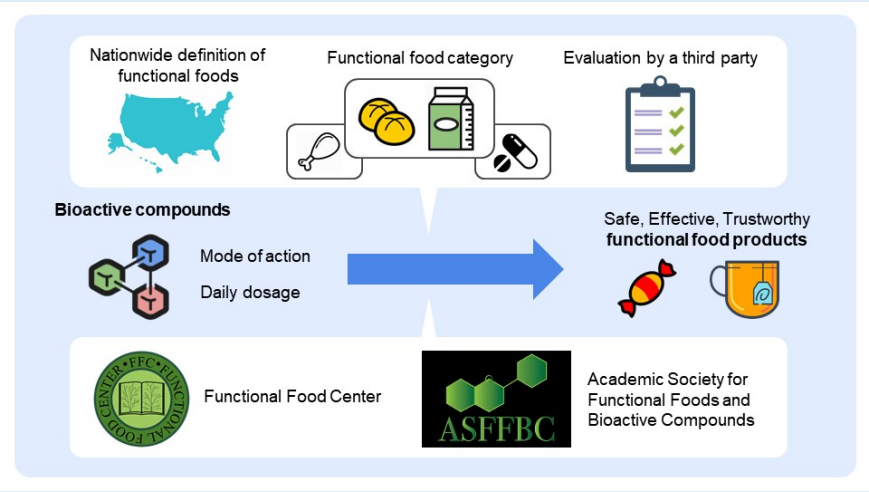
ABSTRACT



The aging population and skyrocketing medical costs are an urgent problem in some countries, which necessitates the prevention of diseases and postponement of disease progression with non-medical means. Functional foods are those that exhibit beneficial effects on human health and play a vital role in supporting part of normal diets. In order to produce functional foods with safe and effective active compounds, it is necessary to define functional foods and to identify the bioactive compounds, the mode(s) of action, and the proper daily dosage. Furthermore, functional foods should undergo a neutral evaluation by an independent organization to ensure only safe and effective products will be released to the market. Japan's Foods for Specified Health Uses (FOSHU) approval system will be described in this review as an example in which individual functional foods are evaluated with numerous criteria by a governmental agency. Whilst the Food and Drug Administration (FDA)

evaluates and authorizes health claim petitions, a definition of functional foods and a distinct functional food category are lacking in the U.S.. The Functional Food Center **(**FFC) has been supporting functional food scientists worldwide through research and the publishing of numerous educational materials on functional foods. Thus, the FFC and the Academic Society for Functional Foods and Bioactive Compounds (ASFFBC) can and are willing to help the FDA and other governmental agencies establish the category of functional foods and the field of functional food science, which needs to be highly collaborative and multidisciplinary. This review will also describe the current health claim authorization by the FDA and the FFC's vision on the definition of functional foods, bioactive compounds, and the establishment of functional food science that will eventually contribute to human health and well-being in the US and across the globe.

Keywords: functional food definition, functional foods, FOSHU, bioactive compounds, functional food science, health claim, foods for specified health uses

INTRODUCTION

In most developed countries, the average life expectancy is over 80 years, and medical expenses are steadily increasing to support the aging population [1]. Therefore, it is becoming more important to improve and maintain health through lifestyle without the need of medication. Certain food components are reported to have beneficial effects on human health, and numerous food products are on the market with claims to improve health or decrease disease risks. In order to provide food products that are effective and trustworthy, some countries appoint a government agency to be in charge of the evaluation and approval of relationships between food and health. In the United States, the Food and Drug Administration (FDA) evaluates petitions to approve health claims, which regard the relationships between food or food components and a particular disease [2]. In Japan, the Consumer Affairs Agency (CAA), is in charge of regulating health claims on foods. This review compares the evaluation and approval systems used by both the FDA in the United States and the CAA in Japan, and describes the vision of the Functional Food Center in the definition and scientific development of functional foods.

Foods for Specified Health Uses (FOSHU) in Japan:

Foods for Specified Health Uses (FOSHU) refer to foods with a claim that identifies the product is suited for specified health uses, and is evaluated and approved by the CAA. "Specific health uses" refer to the maintenance or promotion of health; for example, gastrointestinal health or lipid absorption [3]. FOSHU is a part of Foods with Health Claims regulations, which enable health claim labeling on foods that meet specific requirements by the government. Under the FOSHU approval system, the CAA evaluates documentation submitted by applicants to determine if candidate products meet the FOSHU criteria. Five subcategories exist for FOSHU foods, depending on the type of products, the type of the active ingredients, and the strength of scientific evidence (Table 1).

Table 1. Subcategories of FOSHU

Subcategories of FOSHU	Applicable compounds	Process
Regular	Applicable to any active ingredient.	Goes through the full evaluation process for efficacy, safety, quality control etc.
Standardized	Only applicable to certain dietary fibers for which an adequate amount of scientific evidence exists regarding their efficacy.	Must be in accordance with the upper and lower limits for daily dosage and health claim wording pre-determined by the government.
Risk-reduction	Only applicable to calcium (with osteoporosis) and folate (neural tube defect).	Goes through the full evaluation process for efficacy, safety, quality control etc. A meta-analysis is required to show the effectiveness in disease risk reduction.
Reauthorized	Changes in flavors or names only. Applicable to products already approved for FOSHU.	The stability and quality control methods will be reviewed.
Qualified	Applicable to any active ingredient with suggestive evidence and/or unknown mechanism.	Goes through the full evaluation process for efficacy, safety, quality control etc. A randomized controlled trial with significant differences at α=0.10, or a non-randomized controlled trial with significant differences at α=0.05 is necessary. The labeling must state that "the evidence has not necessarily been established" and "'possibly' exert the health benefit".

Unlike any other foods, FOSHU approved products have a unique logo on them. The logos have texts that translate to "Approved by Consumers Affairs Agency" and "Food for Specified Health Uses". All FOSHU approved products, except qualified FOSHU, can have a standard logo on them (Figure 1A), while qualified FOSHU must have the qualified logo, which has the wording "Qualified" across (Figure 1B) [4]. The presence of the logo distinguishes FOSHU approved products from other foods and influences consumers' purchasing decisions [5]. The information on each FOSHU product is available on the Information System on Safety and Effectiveness for Health Foods (https://hfnet.nibiohn.go.jp, in Japanese), where the public can access a photo of each product, the manufacturer's contact information, the description of the active ingredient, and references to scientific articles that show the efficacy and safety of the product.

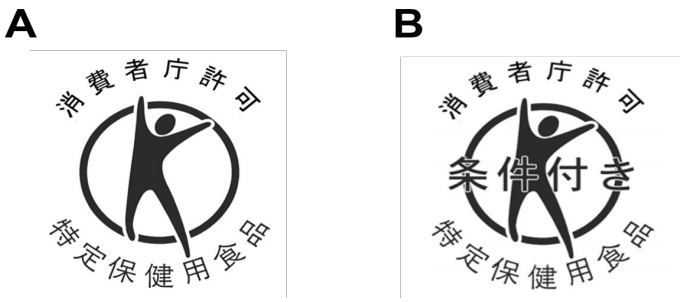


Figure 1. The FOSHU logos [4]. A: The standard logo for regular, standardized, risk-reduction, and reauthorized FOSHU products. B: The qualified logo for qualified FOSHU.

From October 1997 to April 2020, 1,072 products produced by 153 companies were approved as one of the five FOSHU categories [6]. Of the 153 companies, the majority of them have 1-10 approved products, and very few companies have more than 10 FOSHU approved products (Figure 2). This is most likely due to the time-consuming and expensive process of obtaining FOSHU approval, which involves *in vivo* and *in vitro* experiments, clinical trials, and preparing elaborate application materials.

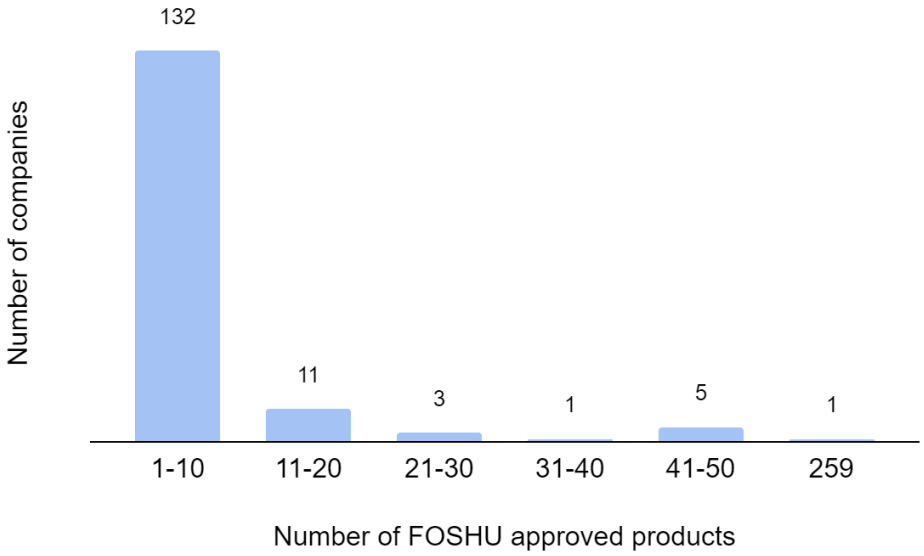


Figure 2. The distribution of companies by the number of FOSHU approved products.

The number of regular FOSHU products approved each year has slowly decreased over the past 20 years; however, in the last decade, 10-20 products have been constantly approved ([6], Figure 3). It is noteworthy that a substantial number of reauthorized FOSHU are approved each year, which pertains to changes in flavor or product names. The numbers of standardized and risk-reduction FOSHU are fluctuating over time and account for relatively a small number of total products. For these types of FOSHU, the applicable active ingredients are limited; therefore, the variety of products that contain those compounds may also be limited. There has been only one qualified FOSHU thus far which was approved in 2016 [7].

The number of FOSHU approval may further decline because of the introduction of the Foods with Function Claims labeling system in 2015. The readers

are referred to other resources such as the CAA (2015), [8] and Iwatani and Yamamoto (2019), [9], for a detailed description, but it is in essence a system that allows health claims on foods without the government's evaluation and approval, instead using the manufacturer's evaluation and relevant information disclosure on the active ingredients in their products on the CAA website (https://www.fld.caa.go.jp/caaks/cssc01/, in Japanese). Foods with Function Claims are distinct from FOSHU, and do not have the FOSHU logo on them.

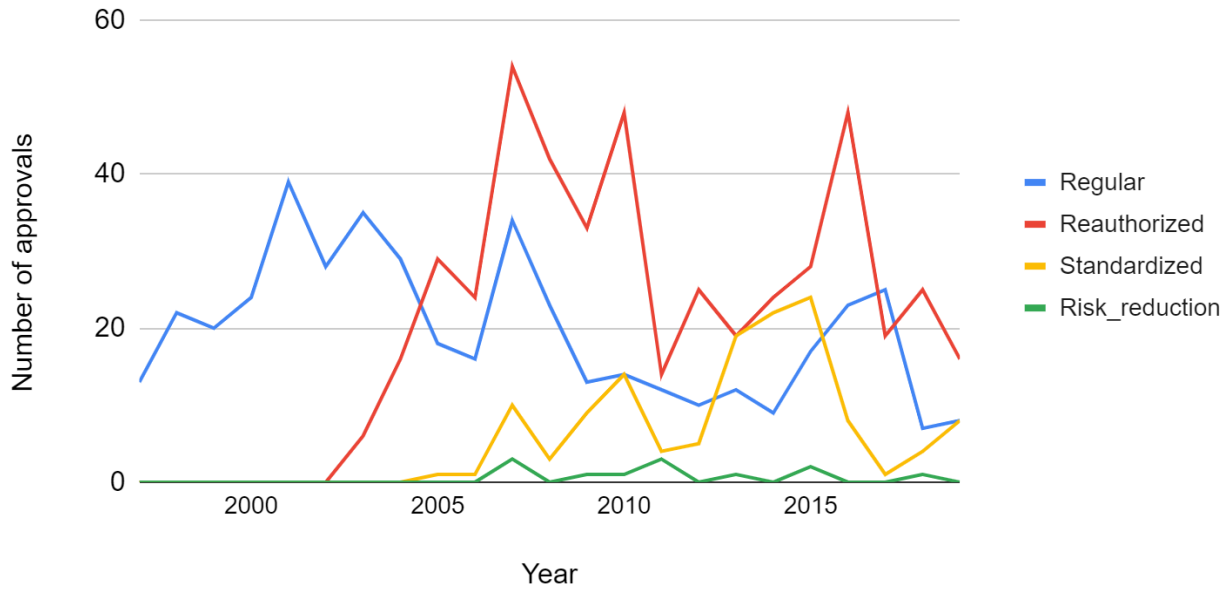


Figure 3. The number of approved products by FOSHU type (1997-2019).

Numerous documents are required to apply for a FOSHU approval, and the documents are to be evaluated by the CAA and other organizations. Required application materials are described in detail by Yamada et al. (2008), [10], which states that the agency in charge of FOSHU is the Ministry of Health, Labor, and Welfare (MHLW), however, at the time of this manuscript preparation, CAA governs FOSHU.

Brief descriptions of required documents to be submitted to CAA are as follows [11]:

1. Documents that scientifically prove the efficacy of the active ingredient to be evaluated, including *in vitro* and *in vivo* tests that describe the mode of action and the *in vivo* kinetics, and human trial results that prove the efficacy of the product containing the active ingredient.

Instructions for the design of human trials are given in detail by the CAA, and trials that fail to meet the standard may disqualify the product as FOSHU. For example, the trial must be a double-blind, randomized controlled study; if a trial is not randomized, the product can only be approved as a qualified FOSHU. In addition, the dosage to be tested needs to be determined in a preliminary trial to determine the optimum dosage. The number of subjects must be sufficient to detect significant differences between the control and the exposure

groups, and the computation of the required number of subjects must be reported in their experimental plan, which is a separate document. The intervention period must be at least 12 weeks unless it is established that the effect can be measured in less than 12 weeks and there is no attenuation effect. Qualified FOSHU can be granted if the human trial is a randomized trial with significant differences between the control group and the exposure group at α=0.10, or if the trial is a non-randomized trial with significant differences at α=0.05. The criteria of scientific evidence for regular and qualified FOSHU approval is shown in Table 2. For a risk-reduction FOSHU application, a meta-analysis must be done to prove that the active ingredient has an established risk-reduction effect on a specific disease. The efficacy trials and meta-analyses must have been accepted in a peer-reviewed journal.

2. Documents that prove the safety of the product containing the active ingredient.

In vitro and *in vivo* trials using animals must be conducted to determine the safe consumption quantity of the active ingredient unless there has been a sufficiently long history of its consumption. A safety trial with humans must also be conducted with excess quantities of the active ingredient, at least 3 times of the daily dosage for 4 weeks, and for a long term, at least for 12 weeks. A summary of literature about allergies caused by the active ingredient must also be submitted. Similarly to the efficacy trial, an experimental plan is required detailing the statistical analysis methods and how missing data and outliers will be handled. The health conditions of subjects in the safety trials must be monitored by blood and urine tests and it is required that a medical doctor be seen every 4 weeks.

3. Documents on the stability of the active ingredients and the food product being evaluated.

Chronological changes in the quantity of the active ingredient must be monitored to determine the best-before date of the product. The stability tests should be conducted under various storage and handling conditions that can be expected.

4. Documents describing the biochemical, chemical, and physical characteristics of the active ingredient and the analytical methods for them.

5. Quantification methods and results for the active ingredient.

The quantification must be done with at least 3 random samples from different manufacturing dates or production lots.

6. The quality control methods implemented at the production facility of the product, including the ingredient and final product specifications and the equipment present at the production facility.

As described above, the CAA evaluates and ensures that the active ingredient in the food product is safe, effective and that the intended quantity of that ingredient will be consumed. With all the requirements deemed satisfactory, an approval will be given to the product manufactured by the applicant, and the manufacturer can use the FOSHU logo and the approved health claims on the product label accompanied by other required information.

Table 2. The approval criteria of regular and qualified FOSHU in relation to the mechanism and the characteristics of the human intervention study of active ingredients [4]. English translation by one of the authors (Sadohara, R).

	Randomized controlled trial		Non-randomized controlled trial and p-value < 0.05	Intervention with no control group and p-value < 0.05
	p-value < 0.05	p-value < 0.10		
Mechanism known	Regular FOSHU	Qualified FOSHU	Qualified FOSHU	No approval
Mechanism unknown	Qualified FOSHU	Qualified FOSHU	No approval	No approval

One of the noteworthy characteristics of the FOSHU system is that the active ingredient and its mode of action in FOSHU-approved products must be known. Required documentation is all based on the identification and characterization of the active ingredient. If the mechanism of health benefit is not discovered after an investigation, the product has a chance to be approved as a qualified FOSHU (Table 2), but requires additional statements on the FOSHU logo and the label stating that the scientific evidence for the active ingredient has not been established. Furthermore, it is required that the efficacy trial for a qualified FOSHU must be randomized and controlled (Table 2; [11]). There has been only one qualified approval granted to date.

As expected from the volume of required documents, the approval process of FOSHU is complicated and time-consuming. It is further complicated by involving six parties: an applicant, the CAA, the Consumers Commission, the Food Safety Commission, the MHLW, and the National Institute of Biomedical Innovation, Health, and Nutrition (NIBIHN) (Figure 4; [12]). The application materials are submitted to the CAA along with a sample product from an applicant. The CAA then requests evaluation on the product to the Consumers Commission, the Food Safety Commission, and MHLW. The Consumers Commission and the Food Safety Commission are Japanese organizations that assess the effectiveness and the safety of products, respectively, and are independent from the CAA or the MHLW [13], [14]. The MHLW ensures that the labeling does not give a wrong impression to consumers, for example, by equating food products to medicine. Additional documentations may be requested to the applicant for clarification by either organization. While their product is being evaluated, the applicant requests analysis to the NIBIHN or a registered testing organization. The NIBIHN validates the analytical method described by the applicant and the concentration of the active ingredient in the product being evaluated. The analysis results validated by a third party, such as NIBIHN, ensures that the specific active ingredient is contained in the specific food product. These analysis results are submitted to the CAA. With all the evaluation satisfactory, the CAA grants a FOSHU approval to the product; therefore, it is a product-specific process. Required documentations and the processes are described in detail by Yamada et al. (2008), [10], which states that the MHLW is the competent authority, but the CAA has been the competent authority since 2009. According to the CAA guideline for the industry, it usually takes 5 months from application submission to a regular FOSHU approval; however, in practice, the process is expected to take up to a year because of requests for additional documentation [15].

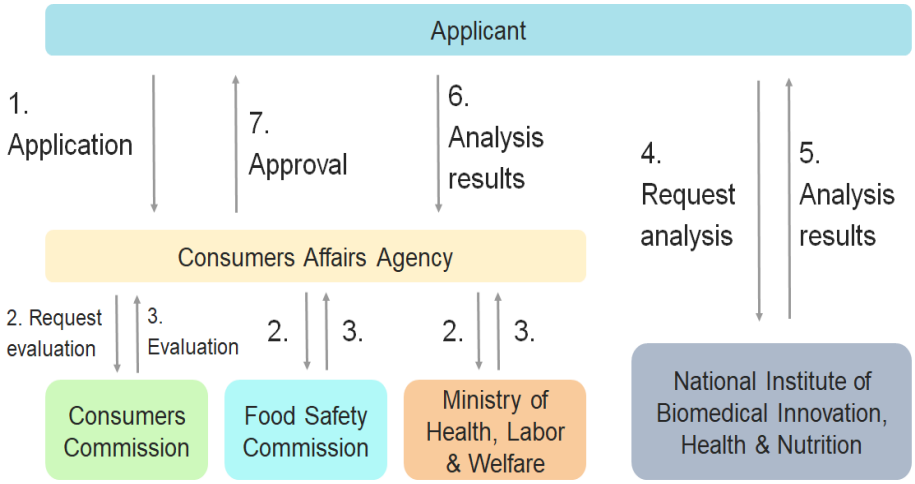


Figure 4. The FOSHU application process [12]. English translation by one of the authors (Sadohara, R).

The information that must appear on FOSHU-approved product labels is also specified in detail by the CAA (Table 3). First, general information such as the product name, category, manufacturer's information, ingredients, a best before date, and the energy and nutrition facts must be shown. In addition, information on the active ingredient including appropriate daily dosage, consumption and storage instructions, and warnings must also be shown. The approved health claims must accompany a statement that emphasizes the importance of a well-balanced healthy diet made from various ingredients. The health claim must not mention specific disease names (e.g. high blood pressure, cardiovascular events) because the intention of the FOSHU labeling is to maintain or improve health not to cure a disease. FOSHU products must not be confused with medicine, and FOSHU labels must not include statements that can mislead consumers to believe that the products have medicine-like effects.

Table 3. Label requirements on FOSHU-approved products [4]

"Food for Specified Health Uses"	Product name
Food category to which the product belongs	Ingredients
Best before date	Net weight
Appropriate daily dosage (e.g. 2 packages per day)	Energy and nutrition facts
Consumption instruction (e.g. dissolve in water.)	Warnings (e.g. an excessive intake at one time may produce laxative effects.)
Cooking or storage instructions	Manufacturers' name and address
Approved health claim. For a qualified FOSHU, it must state that "the evidence has not necessarily been established" and "'possibly' suited for the specified health use".	
"Maintain a good and well-balanced diet with a staple food, a main dish, and a side dish."	
The proportion of the daily dosage of the active compound in the total standard daily value if the active compound is a nutrient of which daily value is specified by the government.	

FOSHU product manufacturers must fulfill requirements and responsibilities after they obtain a FOSHU approval. They must constantly search for new information on the safety and efficacy of the active ingredients in their products after their products are approved. Manufacturers must inform the CAA within 30 days if they find information that disproves or casts a doubt on the safety, effectiveness, or the quantity of the active ingredient in their products. Moreover, manufacturers must collect, record, and maintain complaints by consumers about their FOSHU-approved products and how they were handled. Manufacturers must inform the CAA if their products are recalled or significant health problems are reported [11]. Those requirements are to ensure FOSHU-products are safe, effective, and manufactured with appropriate quality control procedures as described in the application.

Because of the high standard for evaluation and Japanese people's trust in the government, FOSHU products are regarded as trustworthy and effective by Japanese consumers [16]. Another consumer survey reported that almost 90% of consumers know about FOSHU products and 48% have purchased a FOSHU product in 2008 [17]. Conversely, the amount of required experiments and clinical trials can be a financial burden for small businesses, making it hard for them to have multiple FOSHU-approved products. One solution for that is the Foods with Function Claims labeling system, which started in 2015 [8]. Under that system, food manufacturers can either conduct a clinical trial to test the effectiveness of their product (or the active ingredient in it) or a literature review on the effectiveness if there is already a solid body of evidence [8]. As mentioned earlier in this review, the function of this system is that the CAA does not evaluate individual products as with FOSHU; instead, food manufacturers evaluate the strength of evidence and upload all information on a dedicated page on CAA's website (https://www.fld.caa.go.jp/caaks/cssc01/, In Japanese) so that consumers can view it. This system is an attempt of the CAA to strike a balance between maintaining the high standard of functional foods, and enabling small firms to have a health claim on their products. With this self-report system, it is important to monitor the quality and neutrality of literature reviews conducted by the food manufacturers themselves, such as the quality of systematic reviews submitted, which have much room for improvement [18]. Therefore, the practical way of ensuring high quality of functional foods on the market is to have them evaluated by a third party organization, like CAA at the moment.

Health claims regulated by the Food and Drug Administration in the US: The definition of "functional foods" and the regulatory landscape for them differs from the FOSHU approval system in Japan, with some similarities. Health claims in the U.S. are statements that characterize the relationship between a substance and a disease and are evaluated and authorized by the Food and Drug Administration [19]. A "substance" is defined as food or a food component; therefore, the active ingredient may not be identified if a food product has an authorized health claim instead of a component, a compound identified at the molecular level. Unlike Japan's FOSHU regulations, health claims authorized by the FDA can mention a disease or a health condition and state that the food with the approved health claim may decrease risk of a particular disease. Similar to Japan's the CAA in the FOSHU system, a health claim authorization starts with a petition submitted to the FDA. All complete petitions are prioritized according to several factors including the strength of evidence,

the impact of the authorization of a petition on public health, and whether the subject of the claim has been reviewed by the FDA for safety. In addition, if the subject of the claim is deemed adequately characterized, it is likely to be prioritized because the characterization of the substance will enable the evaluation of relevant studies [19]. The FDA evaluates "the totality of the publicly available evidence" supporting the subject of health claims and determines if there is "significant scientific agreement" among qualified experts in the field [19]. Authorized health claims can be shown on either conventional foods or dietary supplements provided that they comply with other applicable labeling regulations.

To assess the totality of scientific evidence for proposed health claims, the FDA utilizes an evidence-based review system by which the agency systematically collects scientific evidence and other data, selects them according to predetermined criteria, and assesses the quality of evidence of the selected scientific literature [19]. The FDA primarily focuses on scientific articles on clinical intervention or observational studies involving human subjects. The methods by which the FDA collects an evaluation of scientific evidence on a proposed health claim involves multiple steps. First, studies with no drawn conclusion on the relationship between the substance and the disease of the pertaining health claim will be excluded. Second, the methodological quality of studies will be evaluated. Finally, the strength of evidence supporting the health claim will be evaluated, considering numerous factors such as study design and type, methodological quality, the relevance to the U.S. population or specified target groups, whether studies supporting the proposed health claim have been replicated, and the overall consistency of the body of evidence.

The daily intake of the substance to achieve a claimed health effect must also be specified if the daily value of the substance has been established. If there is no daily value for the substance of a health claim, the FDA determines the daily intake of the substance when there is sufficient evidence to do so. As such, if there is not sufficient evidence to determine a daily value for the substance, the FDA is unable to set a daily value for the substance of the health claim.

"Qualified health claims" refer to health claims in which the scientific evidence for the claim is credible to a varying degree, but not strong enough to meet the "significant scientific agreement" standard necessary for authorization [20]. For those health claims, instead of progressing to authorization, the FDA issues a letter of enforcement discretion that includes a specific disclaimer and qualifying language stating that the evidence supporting the claim is limited. The exact wording depends on the strength of the scientific evidence. This is to communicate the qualifying nature of products with qualified health claims and to prevent misleading consumers. In the case that the FDA determines that there is no or very little scientific basis for a proposed claim, it may not allow the use of disclaimer or a qualifying language in order to prevent consumer deception.

Table 4 lists authorized health claims by FDA as of September 10, 2020 [21]. Multiple substances are approved for cancer and risk of coronary heart disease. Calcium and folate, which are approved as risk-reduction FOSHU in Japan, are also included in

authorized claims in the U.S. In order to properly show authorized health claims on food labels, manufacturers must meet various requirements regarding the food containing the substance and claims to be placed on the label. The readers are referred to a comprehensive food labeling guide issued by the FDA in multiple languages to ensure they meet the health claim labeling requirements [2].

Table 4. Authorized health claims (a relationship between substance and a disease/health condition) by FDA as of September 10, 2020 [21].

Substance	Disease/health condition
Calcium, Vitamin D	Osteoporosis
Dietary lipids (fat)	Cancer
Fiber-containing grain products, fruits and vegetables	Cancer
Fruits and vegetables	Cancer
Dietary non-cariogenic carbohydrate sweeteners	Dental caries
Folic acid	Neural tube defects
Sodium	Hypertension
Fruits, vegetables and grain products that contain fiber, particularly soluble fiber	Risk of coronary heart disease
Soluble fiber from certain foods	Risk of coronary heart disease
Soy protein	Risk of coronary heart disease
Stenols/steols	Risk of coronary heart disease
Dietary saturated fat	Cholesterol and risk of coronary heart disease

Table 5 lists some of the differences between the FOSHU approval system in Japan and the health claim authorization system in the U.S.. The causal compound does not need to be identified at the molecular level in the U.S.. For example, an authorized health claim for the relationship between fruits, vegetables, and cancer, states that it has not reached a consensus on whether some nutrients have potentially protective effects against cancer or if other non-nutrients present in vegetables and fruits play a role [22].

Table 5. Difference between health claims in the US and FOSHU in Japan.

Parameters	FOSHU in Japan	Health claims in the US
Causal compound/food	An active ingredient is characterized chemically, biologically, and physically. The mechanism must also be known (except qualified FOSHU; see **Table 2**).	A substance that is the subject of a claim is a food or a food component; therefore, the active ingredient or the mode of action does not need to be known.
Product or claim based	Product-based: an approval is given to each product	Claim-based: authorization is given to each food/disease relationship
Source of literature	An applicant submits scientific evidence on the efficacy, safety, and other requirements.	FDA collects literature on a specific substance-disease relationship and evaluates if there is significant scientific agreement.
"Qualified" claims	Qualified FOSHU approvals are given to claims that meet the specific requirements for qualified FOSHU but fall short of regular FOSHU standard.	FDA does not "approve" qualified health claims but issues a letter of enforcement discretion that describes how the proposed food/disease relationship must be expressed according to the strength of evidence.

Functional Food Center's vision on functional food definition and development: The Functional Food Center (FFC) has been an independent organization to facilitate communication and collaboration among functional food scientists both in academia and the industry. For more than 25 years, the FFC has been promoting research and development of functional foods worldwide by publishing peer-reviewed journals, creating educational materials, and organizing international conferences. We have a large network of scientists, Academic Society for Functional Foods and Bioactive Compounds (ASFFBC, https://www.functionalfoodscenter.net/ASFFBC.html) with the aim of raising global awareness of functional foods. The FFC has published reviews to call for improvement of the current situation of functional foods in the U.S.. Interestingly, the term "functional food" is not defined by the FDA, while well-known organizations, such as the National Academy of Sciences Food and Nutrition Board and the Institute of Food Technologists, hold their own definitions of 'functional foods' [23]. Without support from a governmental agency and a formal definition, parties with various interests can misrepresent the meaning of functional foods, leading to public confusion and distrust of functional foods [23]. Given that properly evaluated and manufactured functional foods can, and do, exert scientifically proven health benefits to consumers, it is a loss of opportunity for both food manufacturers and consumers if the lack of definition and discrete guidelines by the government hinders the development of functional food science.

The FFC has proposed and improved its working definition over the past decade, to achieve the current definition, which states that functional foods are "natural or processed foods that contain

biologically-active compounds; which, in defined, effective, non-toxic amounts, provide a clinically proven and documented health benefit utilizing specific biomarkers, for improving general health, for the prevention, management and treatment of chronic and viral disease or its symptoms," reflecting the recent suggestive evidence that functional foods could provide immunoprotective effects against viral infections [24]. This current definition reflects FFC's vision that functional foods should be researched and developed based on scientific evidence on the effectiveness of their bioactive compounds. The definition of bioactive compounds in functional foods has been proposed by Martirosyan and Pisarski (2018), [25], as follows: "primary and secondary metabolites of nutritive and non-nutritive natural components generating health benefits by preventing or managing chronic disease or its symptoms." We believe that biologically active compounds must be characterized, and the mechanism of action be identified because detailed knowledge on the active compounds is essential to determine its non-toxic, proper dosage and to evaluate the safety of the functional foods containing the bioactive ingredient.

Scientifically appropriate approaches and methodology are necessary to determine the efficacy and safety of bioactive compounds and foods containing them, and Japan's FOSHU system can serve as a model to build a framework to develop functional foods that meet high standards of safety and efficacy. A formal functional food science is still in its emerging state, and the FFC recently has proposed a comprehensive process for functional food research and development [26]. Briefly, functional food science should start from identifying a food that may help improve human health, followed by obtaining knowledge on the bioactive compound and its mechanism of exerting its health benefit. Based on its mechanism, a biomarker can be identified, which will be used to measure the effectiveness of the compound. By using the biomarker, a proper dosage of the bioactive compound can be determined first with *in vitro* and animal tests followed by clinical human trials. New functional food products can be developed with a label that has consumption instructions and the shelf life to ensure the quantity and the quality of the bioactive compound remains as designed at the time of consumption. After the product is released, epidemiological studies should be conducted to evaluate the performance of the product and its impact on public health [26]. The authors emphasized the importance of epidemiological studies because they are helpful in evaluating the effectiveness and consistency of the health benefits of the functional foods consumed by the general public. Epidemiological studies will also be helpful in refining the research and development process of functional foods by identifying the potential gap between the effectiveness detected in controlled clinical trials and in uncontrolled consumption behaviors by consumers. This "evaluation after release" phase will also help build trust for functional foods among the public [26]. Standardizing the methodology is the first step to ensure that resulting food products are safe and provide the health benefit as they are intended to.

Table 6. Comparison of the Ideal functional food products (FFP) by FOSHU and FFC

Ideal Process and Development of FFP	**FOSHU**	**FFC**
Contains causal compounds	Active ingredients with established mechanism, characteristics, and stability	Similar in concept to bioactive compounds
Required establishment of bioactive mechanism	Yes	Yes
Establishment of dosage and non-toxic quantities of the bioactive compound	Yes	Yes
Possibility of FF with or without proven bioactive compounds	The active ingredient(s) must be identified and be measurable	It is absolutely necessary to find out bioactive compound(s) and ratio of compounds if there more than one bioactive compound responsible for a health benefit
Contains definition of bioactive compounds	The word equivalent to "bioactive compound" is not officially defined, but contextually it is obvious that the Japanese word "active ingredients" refers to the causal compound that provides health benefits	Yes, and FFC suggested [27]
Necessary definition of functional foods for governmental agencies, manufacturers, and consumers	The equivalent of "Functional Foods" is "Foods with Health Claims", which includes FOSHU	Yes, and FFC suggested [27]
Conditions and disease identified by FFP to reduce the risk or mitigate disease	1. Special health condition 2. Maintenance of health 3. Cannot mention disease names (with exception of risk reduction: FOHSU is not medicine)	1. General health 2. Chronic diseases 3. Reduce the risk of viral diseases
Evaluation of new delivery vehicle with each new FFP	Yes, the effectiveness is tested on the final product basis, and each product will be evaluated by CAA under the FOSHU regulation.	Yes, necessary evaluate all steps since new product is a new environment and bioactive compounds mechanism and activity might be changed
Ideal intervention	12 weeks of randomized controlled trials (or less if justifiable)	90-120 days of randomized controlled trials

Measurement of the outcome	Use an indicator that is appropriate for the purpose and widely considered clinically and nutritionally meaningful	Find the biomarker that can be tested via that mechanism or pathway, which indicates effectiveness of the bioactive compound
***In vitro*, *in vivo*, and clinical studies necessary for approval as FF product**	Yes	Yes Perform in *vitro, vivo*, clinical human trials with strict compliance standards, utilizing biomarkers, to confirm dosage and efficacy
Requirement of specialized label	Yes, special FOSHU label is needed with mandatory items to inform consumers (see Table 3)	Special label with intake/consumption Guidelines/recommendations as well as shelf life for the food product with bioactive compound(s)
Requirement of epidemiological studies necessary or not to finalize FF product)	Companies must collect new scientific knowledge on the active ingredient and report severe health problems caused by the product or information contradictory to the evidence of the product	Epidemiological studies needed to confirm the effects in an uncontrolled consumption settings. Perform long-term epidemiological studies to ensure efficacy, safety, and consistency or predictability. Making changes in label about the duration of consumption as well as possible warnings/possible side effects after epidemiological studies.
Government approval of FFP	Yes, a FOSHU approval is given after evaluation of a product by CAA. However, Foods with Function Claim are not evaluated or approved by CAA, and therefore they are not FOSHU.	Yes, government should approve and take responsibility with the manufacturing company for each FFP
Beneficiaries of the FF product	1. Manufacturers, 2. government and 3. consumers	1. Scientist(s) who come up with formulation and tested in different steps, 2. manufacturers, 3. government and 4. consumers

CONCLUSIONS:

In this review, the FOSHU approval system in Japan, health claim authorization in the U.S. by the FDA, and FFC's vision on the development of functional food science have been discussed. Under Japan's FOSHU labeling, the CAA, a government body, evaluates individual products to permit the use of a FOSHU logo and health claim on the products.

The FDA evaluates health claim petitions, which refers to the relationship between a food or food component and a disease, and authorizes them in accordance with significant scientific agreement.

Currently, the FDA does not have a special category for functional food products, nor do they evaluate whether a food is a functional food or not. We urge the governmental agencies to create a distinct category of functional foods to distinguish them from other general foods with no legitimate health claims. Under that category, functional foods can be classified further based on the target of the functionality, which will help consumers identify functional foods that suit their needs [27].

Considering the historic role that the FFC have played in functional food science, we request that the FFC's Functional Food definition and the processes of functional food science be considered and evaluated to be used as a guideline by the FDA. We also propose that bioactive compounds in functional foods should be determined in order to produce functional food products that are effective as advertised and are trusted by the public. It is possible to take advantage of both Japan's FOSHU and the FDA's health claim authorization systems to build a comprehensive, interdisciplinary framework for functional food development. The FFC and ASFFBC could support the FDA or other governmental agencies along the way by using our 25-year experience in the field. A rigorous scientific testing followed by a third-party evaluation will be building blocks of functional foods that contribute to human health worldwide.

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Abbreviations: ASFFBC: Academic Society for Functional Foods and Bioactive Compounds; CAA: Consumer Affairs Agency; FDA: Food and Drug Administration; FFC: Functional Food Center; FFP: functional food products; FOSHU: Foods for Specified Health Uses; NIBIHN: the National Institute of Biomedical Innovation, Health, and Nutrition; MHLW: the Ministry of Health, Labor and Welfare.

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