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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