



Comparing the FDA's process for health claim submission and the FFC's guidelines for regulating functional foods

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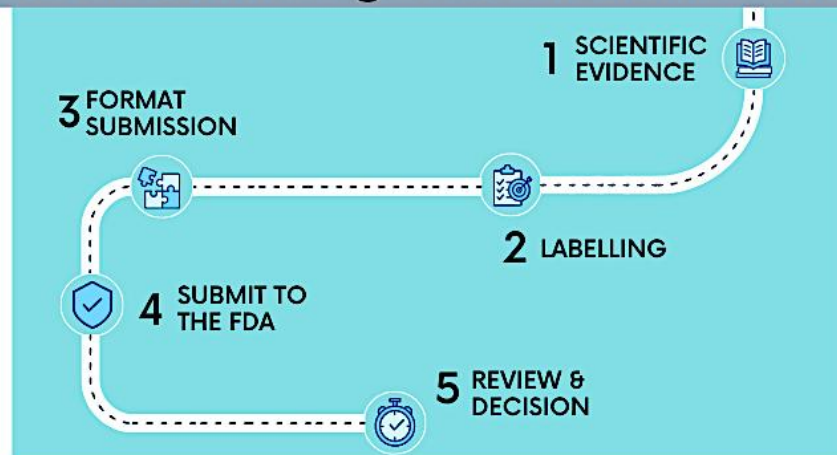
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ABSTRACT

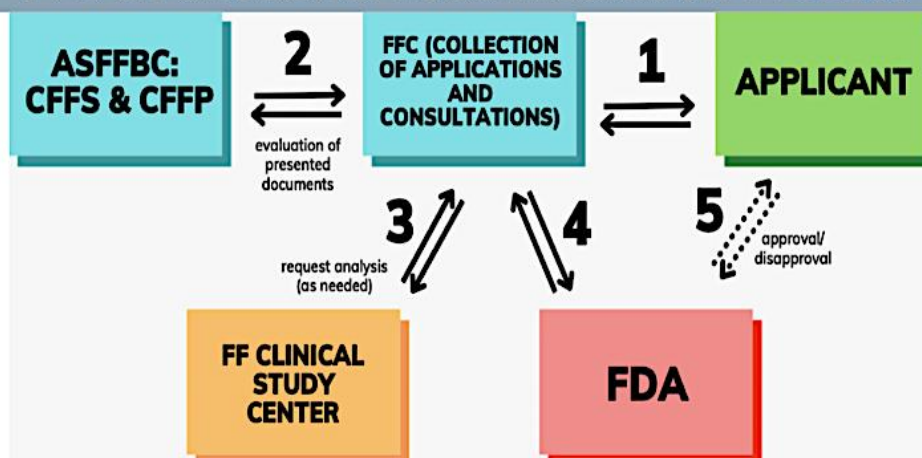
Health claims are essential for providing accurate information about the relationship between nutrients and health outcomes to consumers. They facilitate informed decision-making and support individuals in making healthy dietary choices. The U.S. Food and Drug Administration (FDA) regulates health claims to guide consumers in maintaining healthy dietary practices. Health claims on food labels help consumers understand the potential health benefits associated with specific products and make informed choices aligned with their health goals. These claims also promote transparency and trust in the food industry by providing evidence-based information. The process of submitting a health claim to the FDA involves complying with regulatory requirements and providing robust scientific evidence. Scientific evidence plays a crucial role in substantiating health claims and should be based on well-designed clinical trials, epidemiological studies, and mechanistic research. Adhering to FDA labeling requirements ensures the accurate and informative presentation of health claims on food labels. The Functional Food Center (FFC) is working on theoretical aspects of creating ideal functional food (FF) products as well as how these products should be identified with special FF labels. While the FDA focuses on evaluating health claims, the FFC emphasizes the safe and effective use of functional foods. Understanding the FDA's evaluation process and the FFC's guidelines is crucial for researchers, food manufacturers, and policymakers to navigate the regulatory landscape and promote informed consumer choices. Compliance with regulatory guidelines, adherence to scientific standards, and clear communication of health claims contribute to a more informed and health-conscious society.

Keywords: Health claims, health outcomes, regulatory requirements, functional foods, health benefits

Process of Submitting a Health Claim to the FDA



FFC's Functional Food Mediation Process



Graphical abstract: FDA's Health claims and FFC's functional foods mediation process

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INTRODUCTION

Health claims play a crucial role in providing consumers with accurate and meaningful information about the relationship between nutrients and health outcomes. These claims are essential for promoting informed decision-making and assisting individuals in making healthy dietary choices. According to the U.S. Food and Drug Administration (FDA), health claims serve the purpose of guiding consumers toward maintaining

healthy dietary practices [1]. The presence of health claims on food labels helps consumers better understand the potential health benefits associated with specific products, such as reducing the risk of certain diseases or improving overall well-being. Consumers can make more informed choices aligned with their health goals through health claims. Additionally, health claims facilitate transparency and trust in the food industry by promoting evidence-based information [2]. By adhering to

regulatory guidelines and scientific evidence, health claims contribute to a more informed and health-conscious society.

Functional foods (FFs) hold great promise in managing chronic diseases and improving public health while reducing healthcare costs. However, to ensure the safety and efficacy of functional food products (FFPs) in the market, it is crucial to establish a comprehensive definition and regulatory framework [3,4]. The Functional Food Center (FFC) proposes a definition for FFs as "natural or processed foods that contain bioactive compounds, which, in defined, effective, non-toxic amounts, provide a clinically proven and documented health benefit utilizing specific biomarkers, to promote optimal health and reduce the risk of chronic/viral diseases and manage their symptoms" [18]. The FFC has proposed a comprehensive 17-step process to define functional foods, ensuring clarity and precision in their categorization. This process includes identifying the food item, evaluating its intended health benefits and active compounds, conducting scientific reviews, ensuring safety, setting dosage guidelines, conducting biomarker assessments and clinical trials, and considering cost-effectiveness and regulatory compliance. The FFC also emphasizes post-market monitoring, data collection, stakeholder engagement, and educational programs to promote global standards for functional foods [18,22]. FFC aims to establish regulations, educate the public, and create standards for evaluating and labeling functional food products [5]. Defining a functional food by FFC standards can be compared to the approval of a health claim by the FDA.

The development of functional foods, driven by advancements in health, nutrition, and food processing sciences, has opened new possibilities for promoting overall well-being and managing specific health conditions through daily dietary choices. However, despite the scientific foundation supporting their

benefits, many foods with proposed health benefits struggle to gain market acceptance. One key challenge lies in effectively communicating the health claims of these products and successfully marketing them to consumers. The strategic positioning of food products on a health platform varies across different categories, formats, and claims, with varying degrees of freedom for food companies. While legal and scientific requirements restrict the content and communication format of health claims, companies still face decisions regarding the specific health claims to focus on, the food product through which the benefit is delivered, and how the health claim is communicated [6].

The process of writing a health claim by the FDA involves a comprehensive regulatory framework established under the Nutrition Labeling and Education Act (NLEA) [23]. The FDA Modernization Act of 1997 (FDAMA) introduced provisions allowing the use of health claims based on authoritative statements, expanding the sources for supporting claims. Before FDAMA, FDA regulations were required for any health claim. Notifications for claims based on authoritative statements should be submitted to the FDA, and compliance will be assessed within 120 days. Claims must be based on current, published authoritative statements from federal scientific bodies like the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC). These statements must pertain to the nutrient-disease relationship, be published by the scientific body, currently in effect, and not be made by an individual employee. Health claims must comply with regulations, be accurate representations, and not exceed disqualifying nutrient amounts. While nutrient content claims for dietary supplements are allowed, health claims are currently not permitted, though the FDA intends to propose their allowance. This regulatory process ensures that health claims are supported by credible scientific

evidence and promotes accurate and informative labeling for consumers [7,8]

Interested individuals can petition the FDA by submitting an original copy of the petition, along with necessary translations if applicable. The petition should include pertinent information and references to supporting documents. Compliance with laboratory and clinical study requirements should be stated. The petition's content and attachments should follow specific guidelines, including preliminary requirements, a summary of scientific data, analytical data, model health claims, and relevant attachments. The petitioner should sign a statement of balanced submission. The FDA will notify the petitioner within specific timeframes, and a final rule will be published within 270 days of the proposal or extensions may be granted. All information is subject to public disclosure, except for certain confidential details [9].

PROCESS OVERVIEW

Preparation: Preparing a submission for a health claim to the FDA involves navigating the regulatory requirements established by key legislation such as NLEA and FDAMA. The NLEA introduced mandatory nutrition labeling and placed restrictions on food label claims related to nutrient levels and health benefits. The FDA's authority to authorize health claims is guided by the significant scientific agreement (SSA) standard, which sets a rigorous scientific evidence threshold [10]

Under the FDAMA, an alternative pathway was introduced, allowing U.S. government scientific bodies other than the FDA to determine the presence of SSA for a substance-disease relationship. This expansion led to the inclusion of qualified health claims (QHC), which require a qualifying statement indicating the level of evidence supporting the claim. To address this evolving landscape, the FDA developed an evidence-based

ranking system to assess the level of evidence substantiating a health claim [9,10].

When preparing a submission for a health claim, it is essential to ensure compliance with the established regulations and provide robust supporting evidence based on scientific standards [40,41]. The submission should accurately describe the relationship between the substance and the targeted disease or health-related condition, including any relevant qualifying statements or evidence-based rankings [9]. By diligently adhering to these guidelines, the petitioner can facilitate the FDA's evaluation process and enhance the chances of successful authorization.

Submitting a health claim to the FDA for food products involves understanding the four recognized types of health claims: nutrient content claims, authorized health claims, qualified health claims, and structure/function claims [38]. Nutrient content claims characterize nutrient levels in a food product, while authorized health claims establish a relationship between a substance and a disease or health condition. Qualified health claims require less scientific support but must be accompanied by a disclaimer. Structure/function claims describe the effect on the body without referencing a disease. Although functional foods lack a specific regulatory category, their claims are regulated under existing food and drug regulations [11]

Scientific Evidence: When preparing a submission for a health claim to the U.S. Food and Drug Administration (FDA), it is essential to gather various types of scientific information to support the claim [42]. This includes conducting a thorough literature review to identify relevant studies, research articles, clinical trials, and other sources of scientific evidence that establish the relationship between the substance and the targeted disease or health-related condition [11]. The FDA

primarily relies on well-designed clinical trials, epidemiological studies, mechanistic studies, and other rigorous scientific research to evaluate the validity and strength of the proposed health claim, see Image 1. Clinical trials involving human subjects are particularly important for establishing causality and demonstrating the direct impact of the food or nutrient on the claimed health benefit. Epidemiological studies provide valuable

population-based evidence, while mechanistic studies elucidate the underlying biological mechanisms. Additionally, the FDA may consider expert opinions and authoritative statements from reputable scientific organizations [12]. Researchers must ensure that the evidence they submit meets the FDA's criteria for reliability, relevance, and scientific rigor.

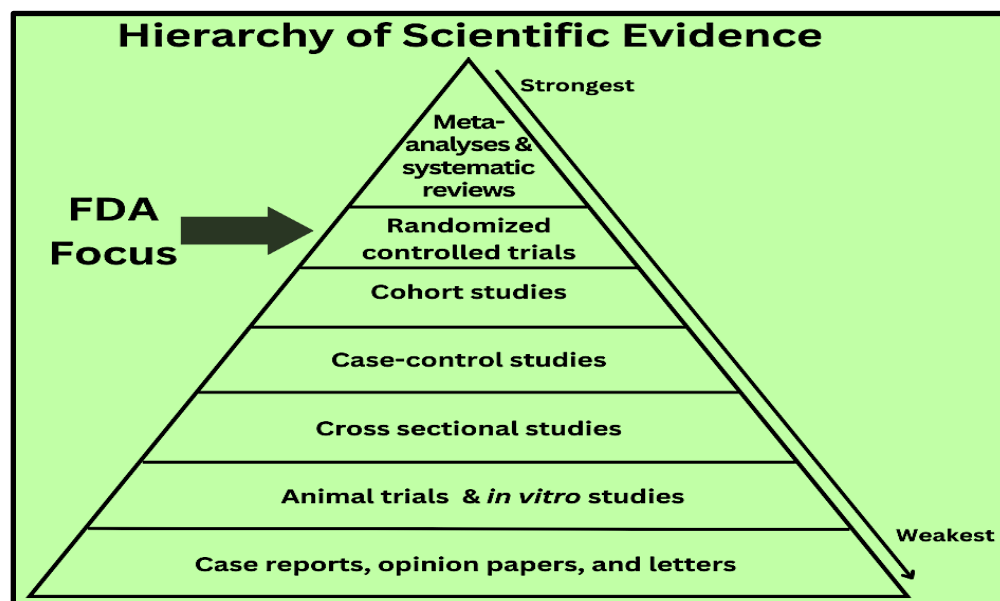


Image 1: Hierarchy of scientific evidence and FDA's evidence focus.

To ensure the credibility and validity of scientific information, it is important to rely on authoritative sources. These may include peer-reviewed scientific journals, publications from reputable research institutions, and reports from federal scientific bodies such as the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) [12]. Information from these sources undergoes rigorous review processes, ensuring that the studies are conducted using sound methodologies and meet high scientific standards.

The FDA places significant emphasis on the quality and reliability of the scientific evidence supporting a health claim. Studies that are well-designed, with

appropriate sample sizes, randomized control trials, and placebo-controlled studies, carry more weight and credibility [13]. Additionally, studies published in reputable journals with a strong impact factor are generally considered more reliable due to their rigorous peer-review process and adherence to scientific standards.

In contrast, anecdotal evidence, personal testimonials, or studies with small sample sizes and limited statistical significance hold less weight in the evaluation process. The FDA seeks scientific information that demonstrates consistency, reproducibility, and robustness of the findings to establish a solid scientific basis for the health claim. When preparing a submission,

it is important to accurately cite the scientific information used, providing proper references to allow the FDA to verify the sources. This helps demonstrate the credibility and validity of the supporting evidence, increasing the likelihood of the health claim being authorized by the FDA [11].

Labeling Requirements: When submitting a health claim to the U.S. Food and Drug Administration (FDA), it is crucial to comply with the labeling requirements established by FDA regulations. These requirements ensure that the health claim information is accurately conveyed to consumers, allowing them to make informed decisions about the food or dietary supplement [9]. The FDA's regulations are guided by the significant scientific agreement (SSA) standard, which sets a high threshold for scientific evidence. It is important to accurately represent the scientific evidence supporting the relationship between the substance and the health condition [12].

According to a guidance document by the FDA, all label or labeling statements about the substance-disease relationship must be based on the conclusions outlined

in the regulations authorized by the FDA [7]. This ensures that the health claim is grounded in sound scientific evidence. Additionally, the FDA's regulations require that the health claim is limited to describing the value that ingestion or reduced ingestion of the substance, as part of a total dietary pattern, may have on a particular disease or health-related condition. The claim should not overstate or exaggerate the benefits and must be complete, truthful, and not misleading [14].

By FDA guidelines, the health claim should be presented clearly and understandably, using appropriate language and format [7,12]. This helps consumers comprehend the information provided and understand its relative significance in the context of a total daily diet. Furthermore, the health claim should be placed in a location where all the required information appears in one place without other intervening material, with the option to include a reference statement on the principal display panel that directs consumers to additional information about the relationship between the substance and the health condition [12], see Image 2 and Image 3.

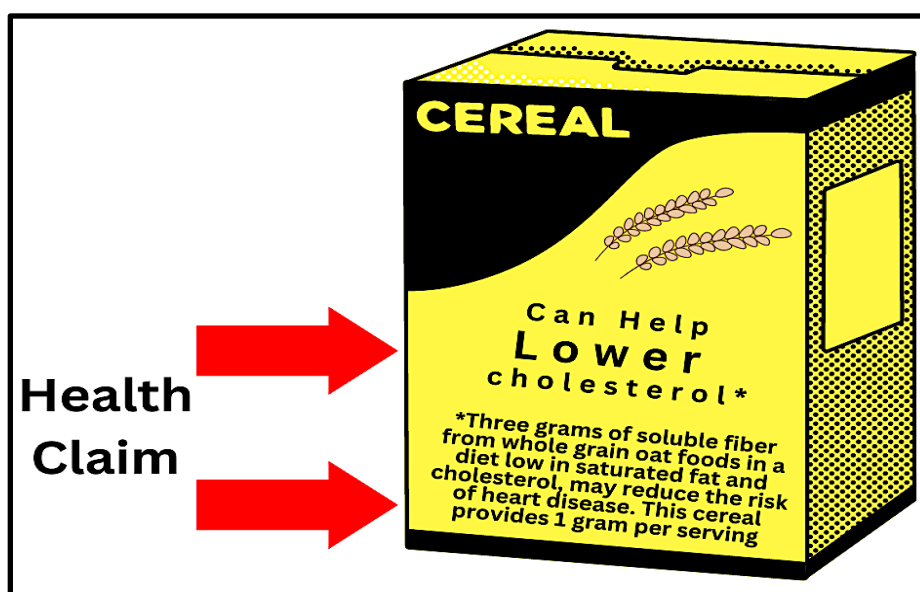


Image 2: Example of an appropriately labeled health claim.

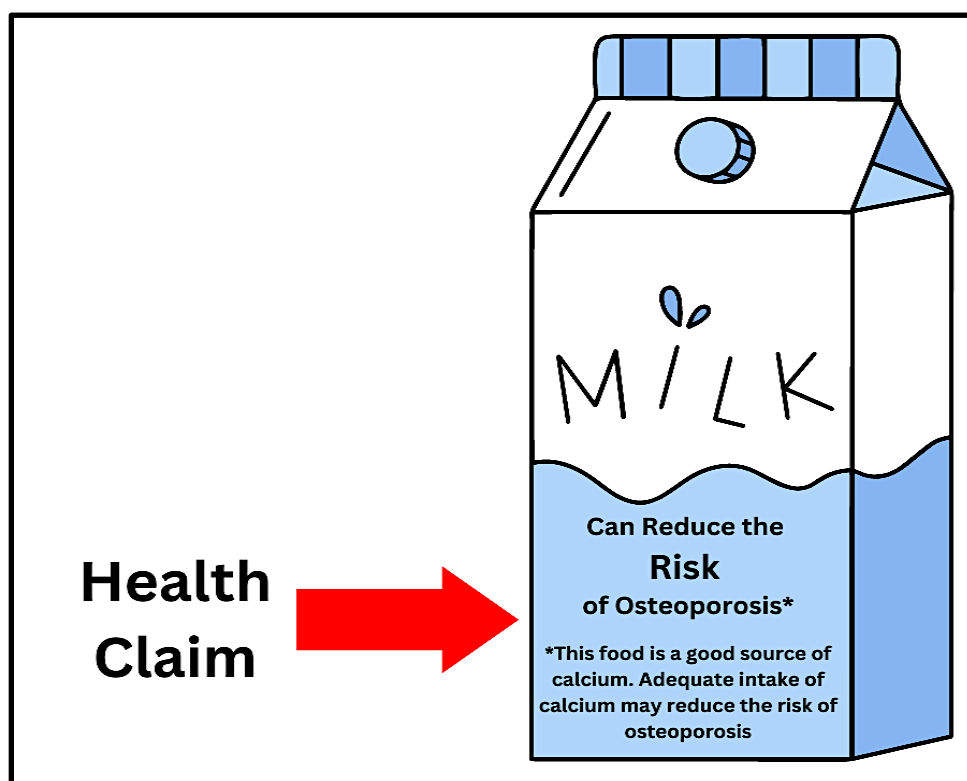


Image 3: Example of an appropriately labeled health claim.

Submission Format: The submission format for an FDA health claim follows a specific structure. It typically includes an introduction section, background information, scientific evidence supporting the claim, a discussion on the significance of the claim, and a conclusion. The submission should be well-organized, with clear headings and subheadings. In-text citations should be provided with numbered references [9,15], and so on, to acknowledge the sources of scientific evidence and studies. At the end of the document, a reference page should be included, listing the full citations of the sources referenced in the submission. The reference page should follow the appropriate citation style, such as APA or MLA, providing all necessary information for each source cited. Adhering to this submission format helps ensure the transparency and credibility of the health claim presented to the FDA [12].

The submission should be accompanied by a cover letter summarizing the petition's contents and indicating

the petitioner's intent to seek approval for the health claim. Electronic submission is the preferred method, using the FDA's Electronic Submissions Gateway (ESG) or other designated electronic submission systems. The use of in-text citations with numbered references is crucial to acknowledge the scientific evidence and studies included in the petition. A reference page should be provided at the end of the document, listing the full citations of all the sources referenced in the petition. Adhering to these guidelines ensures a proper and transparent submission process to the FDA [16].

Pertinent Information: In the process of submitting a health claim petition to the FDA, the petitioner can reference previously submitted information from FDA's files [9,17]. This means that if there is relevant information already available in FDA's records, it can be cited and referenced in the petition. Additionally, the petitioner can include findings from relevant outside

panels that have conducted studies or research related to the health claim [9]. These panel findings can provide additional support and credibility to the petition.

When it comes to published information, the petitioner should provide reprints or readable copies of the relevant articles or studies [9]. This ensures that the FDA can review the information accurately and effectively. It is important to include the full publication details to facilitate proper referencing.

The data and information included in the health claim petition are generally publicly available, with some necessary deletions made to protect the identity of individuals or confidential information [15]. This is done to ensure privacy and comply with relevant regulations regarding the protection of personal data. The FDA emphasizes the need for robust scientific evidence, including human studies, intervention trials, and observational studies, to establish the validity of the claimed relationship. The quality and methodological rigor of the studies are also evaluated, and the strength of the body of evidence is considered in determining the validity of the health claim [17]. By submitting pertinent information, petitioners enable the FDA to make informed decisions based on scientific substantiation.

Functional Food Center and FDA Comparison: While both institutions play a role in ensuring the safety and efficacy of food products, their processes and guidelines differ significantly. By comparing the FDA's process for health claim submission and the FFC's guidelines for regulating functional foods, we can gain a deeper understanding of the distinct approaches these organizations take in evaluating the scientific evidence, establishing criteria for labeling and marketing, and interacting with governmental agencies. Such a comparison sheds light on the unique perspectives and objectives driving the regulatory landscape for health claims and functional foods [43].

The Functional Food Center (FFC) proposes a 17-step process for the classification and regulation of functional foods, see Table 1. This involves identifying bioactive compounds, evaluating scientific evidence for health benefits, assessing risks and benefits, and establishing appropriate regulations and labeling requirements [18, 19]. At the core of their framework is the identification of bioactive compounds within these foods, which contribute to their health benefits. The FFC places great emphasis on evaluating scientific evidence to establish the efficacy and safety of these bioactive compounds in improving health outcomes. This involves conducting preclinical studies to assess safety and efficacy before moving on to rigorous human clinical trials. By understanding the specific pathways and mechanisms through which these compounds act, the FFC can better evaluate the health benefits and potential risks associated with functional foods [22]. The FFC's framework aims to ensure the safe and effective use of functional foods in improving health outcomes [18, 19]. The FDA holds regulatory authority over health claims in the United States, ensuring that food labeling and claims meet specific criteria to protect public health [9]. The FDA provides specific criteria for health claims, including the need for substantial scientific evidence supporting the claim's relationship between a food or its components and a disease or health-related condition [19]. In contrast, the FFC's guidelines focus on defining functional foods as natural or processed foods containing biologically active compounds that provide clinically proven health benefits utilizing specific biomarkers for chronic disease prevention, management, or treatment [5,20].

FDA regulations require significant scientific evidence, including well-controlled clinical trials, epidemiological studies, or other scientific data, to substantiate health claims [21]. The FFC emphasizes the use of biomarkers and clinically proven evidence to

demonstrate the health benefits of functional foods, as human trials [20]. promoting the use of in vitro and in vivo studies, as well

Table 1: FFC’s 17-step process for the classification and regulation of functional foods

Step Number	Description of Step
1	Establishes a goal of the functional food product
2	Determines relevant bioactive compound(s)
3	Establishes the appropriate dosage of bioactive compound(s)
4	Establishes the appropriate time of consumption of bioactive compound(s)
5	Determines the specific pathway and mechanism of action
6	Establishes relevant biomarker(s)
7	Chooses an appropriate food vehicle for bioactive compound(s)
8	Provides preclinical studies on efficacy and safety
9	Provides clinical trials for dosage, efficacy, and safety
10	Creates a special label that informs the consumers of the most effective way to consume the product
11	Publications are submitted to peer-reviewed journals, preferably in open access
12	Educates the general public
13	Sends information to credible governmental agencies, such as the FDA, for approval
14	Official establishment of the accredited functional food product,
15	Release the functional food product to the market. (Receive the basic category (level C))
16	Provides epidemiological studies. (Reapply for approval for a new category (level B))
17	Provides after-market research. (Reapply for approval for a new category (level A))

FDA regulations outline specific requirements for health claim labeling, including accurate presentation, absence of false or misleading information, and adherence to specific wording [21]. The FFC emphasizes the importance of proper labeling for functional foods, including information on daily usage amounts, duration of usage, and the effectiveness of bioactive compounds [20]. The FFC's guidelines also encourage educating the

public about functional foods' health benefits [5,20]

The FDA acts as the governing body responsible for evaluating and approving health claims, ensuring compliance with established regulations [6,21] In contrast, the FFC takes a proactive approach by directly contacting governmental agencies such as the FDA and NIH, urging them to accept their functional food definition and work towards establishing standardized

regulations [20].

Future considerations: The growing popularity and consumption of functional foods underscore the need for a regulatory framework to ensure safety, efficacy, and accurate health claims [24]. Without proper regulation, misleading claims and unverified health benefits may mislead consumers, leading to potential health risks and erosion of trust in the industry [25, 26]. A robust regulatory framework would not only safeguard public health but also foster innovation in the development of new functional food products [18, 27]. The FDA has established regulatory frameworks for conventional foods, dietary supplements, and medical foods that are involved in health claims. However, functional foods do not currently have a specific regulatory category [1, 28]. The establishment of effective regulation for functional foods holds paramount importance in ensuring manufacturers' transparency and consumer safety [29]. However, without proper regulation, manufacturers may be tempted to make exaggerated or unsubstantiated health claims, leading to misleading marketing and potential health risks for consumers [30, 36, 37]. A comprehensive regulatory framework would oblige manufacturers to provide clear, evidence-based information about the health benefits of their products, fostering transparency and accountability [31]. The FFC has demonstrated expertise in addressing the challenges associated with regulating functional foods. Their established framework encompasses a comprehensive approach that considers the biological mechanisms, safety, efficacy, and substantiation of health claims associated with functional foods [32, 33]. Through collaboration with scientific experts, the FFC has defined criteria for classifying functional foods, ensuring that these products meet specific health-related criteria and possess scientifically supported claims [20, 39]. This structured approach has facilitated the development of a

diverse array of functional foods that can cater to various health conditions and preferences while adhering to stringent safety and quality standards. The partnership between the Functional Food Center (FFC) and the FDA offers substantial advantages in overseeing, defining, and evaluating functional foods. The FFC is widely recognized for its comprehensive approach to evaluating functional foods through a well-structured 17-step process [5, 18], positioning it as a key player in the field. Leveraging its extensive network of professionals in the functional food industry [20], the FFC enhances the FDA's regulatory endeavors. This collaborative environment promotes cutting-edge research across various fields, driving advancements in functional food science [34]. By adopting a multidisciplinary approach, the FFC ensures a thorough evaluation of functional foods, considering their nutritional, health, and safety aspects, thereby assisting the FDA in making well-informed regulatory decisions that ultimately safeguard public health. Furthermore, the FFC's practical business expertise significantly contributes to the progress and commercialization of functional food products [35]. Serving as a link between academia and industry, the FFC facilitates the introduction of innovative functional food products to both domestic and international markets [5]. Through this collaborative initiative, the regulatory framework for functional foods can be fortified, instilling consumer confidence and promoting the responsible growth of the industry.

A further future consideration regards the quantum and tempus theories of functional food science. The quantum theory posits that functional foods' bioactive compounds may operate at the subatomic level, influencing cellular processes through quantum effects, such as quantum coherence and entanglement [19, 44]. On the other hand, the tempus theory suggests that the timing of functional food consumption may play a crucial role in optimizing its health benefits, as certain bioactive

components might interact differently with the body at different times of the day or during specific physiological states [44]. Although both theories hold immense potential in advancing the understanding and application of functional foods, their complex and cutting-edge nature poses challenges for traditional regulatory frameworks. Recognizing the significance of integrating these theories into the regulatory landscape, the Functional Food Center has taken a pioneering role in spearheading research to facilitate a potential collaboration between the scientific community and the FDA for functional food product regulation.

CONCLUSION

Health claims play a crucial role in informing consumers about the relationship between nutrients and health outcomes. The FDA ensures the accuracy of health claims through a rigorous evaluation process that relies on robust scientific evidence [1,2]. Health claims on food labels provide valuable information to consumers, helping them make informed choices and promoting transparency in the food industry. Compliance with FDA regulations ensures that health claims are accurate, truthful, and not misleading, enhancing consumer trust [7,12]. Additionally, the FFC's focus on defining and regulating functional foods contributes to the development of evidence-based claims and the safe and effective use of these products [5,18]. Understanding the FDA's evaluation process and the FFC's guidelines enables researchers, food manufacturers, and policymakers to navigate the regulatory landscape and promote informed consumer choices.

Scientific evidence is the foundation of health claims, supported by well-designed clinical trials, epidemiological studies, and mechanistic research [11,12]. The FDA places significant emphasis on the quality and reliability of the evidence presented in health claim submissions. Compliance with scientific standards

and rigorous methodologies strengthens the credibility of health claims and increases their chances of being authorized by the FDA. Clear and accurate communication of health claims through labeling is essential for consumers to understand the potential health benefits associated with specific products [7,12]. Adhering to FDA labeling requirements ensures that health claims are presented clearly and understandably, empowering consumers to make informed dietary choices. The popularity of functional foods necessitates a regulatory framework for safety and accurate health claims [24]. Misleading claims can lead to health risks and erode trust [25, 26]. Effective regulation ensures transparency, and consumer safety, and fosters innovation [18, 27]. Currently, functional foods lack a specific regulatory category [1, 28]. Collaborating with the FFC, the FDA can address regulatory challenges [32, 33], promoting public health and responsible industry growth [5, 20]. By promoting collaboration and adherence to regulatory guidelines, the FDA and the FFC contribute to the development of evidence-based health claims, fostering transparency and trust in the food industry while empowering consumers to make informed choices for their well-being.

Abbreviations: The FDA Modernization Act of 1997 (FDAMA); U.S Food and Drug Administration (FDA); Significant scientific agreement (SSA); National Institutes of Health (NIH); Centers for Disease Control and Prevention (CDC); Functional Food Center (FFC); Electronic Submissions Gateway (ESG).

Conflicts of Interest: No conflicts of interest are associated with this study.

Authors' contribution: The original idea (A Comprehensive Guide to Submitting Health Claim Petitions to the FDA) was conceived by DM and was discussed with SS. SS collected data and wrote the

manuscript. DM advised and participated in writing and editing the manuscript. All authors read and approved the final version of the manuscript.

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