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Research Article

Clarifying Discussion Topics in Regulatory Reviews of Foods with Health Claims in Japan for Food Business Operators and Regulators Around the World

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Abstract

Background: The Food for Specified Health Uses (FOSHU) system was introduced in Japan in 1991 to regulate health claims for the third function of foods, namely the regulation of physiological condition. Concerns raised by regulators can delay approval and product release times. Identifying frequent and important discussion topics in FOSHU review meetings will therefore facilitate communication and promote effective discussion between regulators and food business operators, enhancing the Foods with Heath Claims (FHC) process.

Aim: To identify discussion topics raised in meetings for approval review of FOSHU in Japan to improve the FHC process.

Methodology: We investigated the minutes of final approval reviews for new FOSHU applications conducted by the Consumer Commission's new food development subcommittee between April 1, 2012 and March 31, 2017. Four major discussion categories and their sub-categories were predefined and analyzed.

Results and Discussion: The 31 meeting minutes raised 253 discussion topics under four major categories: food labeling (50.6%), efficacy and safety (25.7%), other (15.4%) and product (8.3%). To ensure consumers make appropriate and informed choices, food labeling should be based on scientific evidence and provide important efficacy and safety information on functional substance(s) in an easy-to-understand format. However, labelling gaps between ideal and actual conditions may affect consumer understanding, particularly regarding label descriptions.

Conclusion: Food labeling of FOSHU was identified as an important discussion point. Correct labelling can help ensure that consumers understand and select the most suitable products for their health needs.

Keywords: Food labeling; Foods with health claims; Approval review; Regulatory science; Japan

Abbreviations

FOSHU: Food For Specified Health Uses; FHC: Foods With Heath Claims; FFC: Functional Foods With Claims; MHLW: Ministry of Health, Labor and Welfare

Introduction

The third of the three defined functions of foods is to regulate physiological conditions. To evaluate health claims for foods possessing this third function, Japan introduced the Foods for Specified Health Uses (FOSHU) approval system in 1991 under the administration of the Ministry of Health, Labor and Welfare (MHLW). Administration was subsequently transferred to a new government agency, the Consumer Agency, at the time it was established in 2009. However, the responsibility for reviewing food labeling of nominated FOSHU products remains with the HLWM, which manages and approves drug and medical device applications, and checks for conflicts with pharmaceutical drug labels. The involvement of multiple government agencies in the review process, including the Consumer Agency, MHLW, Cabinet Office, and the National Institutes of Biomedical Innovation, Health and Nutrition, has lengthened the approval process for FOSHU applications (Figure 1). Thus, the change in administration has in fact caused longer approval times, thereby reducing the commercial value of products, interfering with sales strategies, and unnecessarily burdening food business operators.

A new regulatory system, called Foods with Functional Claims (FFC), was implemented in April 1, 2015. Food business operators consider the FFC system to be more reasonable than FOSHU because it removes the need for approval by the Consumer Agency and other government agencies. Briefly, the Cabinet Office recognized that the lengthy FOSHU approval process could cause major losses to companies, and in June 2015 undertook regulatory reform of the FOSHU system [1]. This regulatory overhaul converted the

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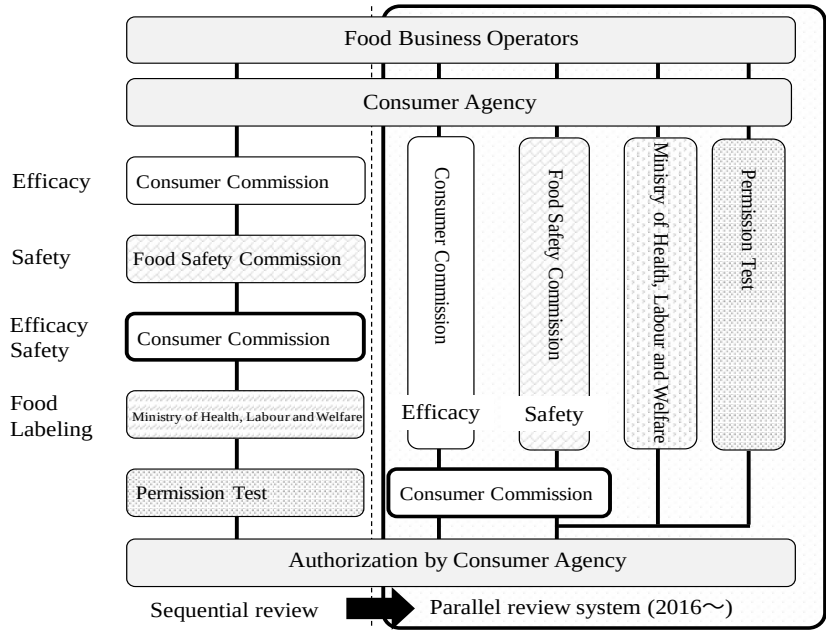

Figure 1: Flow of the review process for foods for specified health uses.

sequential review system to a parallel review system (Figure 1), which allows for concurrent review of the efficacy (namely function in another expression) and safety of FOSHU. This system change allots regulators a 5-month review time [2]. However, a lag in response by food business operators is not taken into consideration in this review process time but can cause a significant delay in approval.

The success of the new system is therefore highly dependent on the quality of the content of a submitted application. Regulator concern over poor scientific evidence in an application will delay the approval decision [3]. A full understanding of up-to-date FOSHU requirements by both food business operators and regulators will facilitate the review process and discussion, and decrease the total review time. Such knowledge will also benefit global food business operators intending to export value-added Foods with Health Claims (FHC) to Japan and inform empirical business decision-making while maintaining scientific quality in efficacy and safety in its applications.

The aim of this study was to identify and categorize discussion topics raised at meetings for approval review on FOSHU in Japan.

Materials and Methods

This study investigated the minutes of the final regulatory approval review meetings for nominated FOSHU held by the Consumer Commission's new food development investigation subcommittee between April 1, 2012 and March 31, 2017 [4-21]. Final review meetings are held following pre-regulatory meetings that separately review the safety and efficacy of FOSHU.

We calculated the number of topics raised per minute by the type of FOSHU, including new or existing functional substance(s). These latter substances had already undergone review and approval by the authorities.

The discussion topics of the minutes were classified according to the four major predefined categories with some sub-categories: 1) efficacy and safety, 2) product, 3) food labeling, and 4) other (Table 1). We also calculated the proportion of discussion topics which required reconsideration after receiving findings from the committee. Finally, we examined discussion topics which required the most reconsideration by food business operators in more detail. Data analysis was done using JMP® 13 (SAS Institute Inc., Cary, NC, USA).

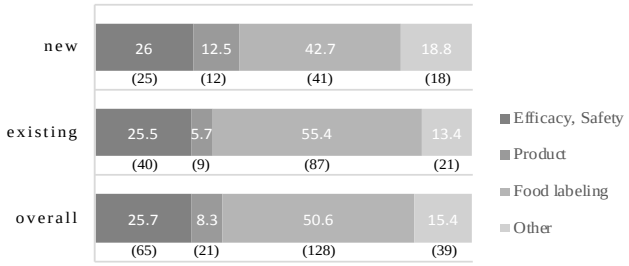

Figure 2: Number of discussion topics under the four categories raised at the FOSHU review meetings. The proportion of sub-categories was calculated for overall, and new or existing functional substances(s). The numbers in parentheses represent the number of discussion topics, predefined in Table 1, within each category.

Results and Discussion

A total of 64 minutes were prepared for 24 meetings held during the study period, from which we abstracted 253 discussion topics (4.0 topics per minute). The number of topics raised per minute was slightly higher for new functional substances (5.3 topics per minute, 96 topics and 18 minutes) than for existing substances (3.4 topics per minute, 157 topics and 46 minutes).

Trends of topics on FOSHU

Figure 2 summarizes the discussion points covered under each

Table 1: Classification criteria of discussion topics; category and sub-category.

Category	Sub-category
Efficacy and safety	Scientific evidence, functional mechanism, study design, set of study population, study method, study period, statistical analysis, analysis set, outcome, usage and administration, safety, over-usage safety test, consumption history
Product	Possibility of misusage, handling of food classification, expiration date, food form, product standard, bioequivalence study, quality control
Food labeling	Product name, authorization representation, catch phrase, ingredients label, warning label, other label, easily comprehensible description on the label
Other	Advertisement, enlightenment, consumer behavior, actual survey, review standard, application document, compliance with other recommendations

Table 2: Discussion topics needed reconsideration classified every category.

Category	Sub-category	No. times discussed n		Reconsideration	
				n	%
Efficacy and safety	Scientific evidence	14		5	35.7
	Functional mechanism	3		2	66.7
	Study design	3		-	
	Set of study population	3		-	
	Study method	4		1	25.0
	Study period	3		-	
	Statistical analysis	2		2	100.0
	Analysis set	3		3	100.0
	Outcome	4		2	50.0
	Usage and administration	13		3	23.1
	Safety	4		1	25.0
	Consumption safety test	6		1	16.7
	Consumption history survey	3		1	33.3
Product	Possibility of misusage	2		-	
	Handling of food classification	3		-	
	Expiration date	2		1	50.0
	Food form	6		4	66.7
	Product standard	4		-	
	Bioequivalence study	3		-	
	Quality control	1		1	100.0
Food labeling	Product name	5		3	60.0
	Authorization representation	29		16	55.2
	Catch phrase	20		7	35.0
	Ingredients label	3		-	
	Warning label	29		19	65.5
	Other label	1		-	
	Easily comprehensible description on the label	41		23	56.1
Other	Advertisement	3		-	
	Enlightenment	4		-	
	Consumer behavior	1		-	
	Actual survey	8		-	
	Review standard	6		2	33.3
	Application document	10		7	70.0
	Compliance with other recommendations	7		5	71.4

of the 4 categories abstracted from the review meeting minutes. The number and proportion of discussion points was highest for the category of food labeling (n = 128, 50.6%), followed by efficacy and safety (n = 65, 25.7%), other (n = 39, 15.4%) and product (n = 21,

Table 3: The most likely reconsideration discussion topics during the review process for the category of food labeling.

Sub-categories	The content of reconsideration topics
Easily comprehensible description on the label	1) easy-to-follow expression for consumers, 2) text size, 3) text position, 4) appropriateness of expression on usage and administration on the basis of foods' characteristics, 5) letter color, 6) mismatch in the description for functional substance(s) with that of another, 7) number of characters on labeling, 8) explanation with illustration.

8.3%). The overall trend was similar to another stratification by new and existing functional substance(s) (Figure 2), and differed to that for new drug applications in the pharmaceuticals field [22].

These final meetings for approval review on FOSHU were held following separate pre-regulatory meetings for safety and efficacy. Despite that fact that these pre-regulatory meetings preceded the final meeting, the number of topics concerning efficacy and safety in the final review meetings surprisingly accounted for 25.7% of all subjects raised. Therefore, careful attention to the topics of food labeling and efficacy and safety may facilitate the approval of FOSHU applications.

Discussion topics to consider for FOSHU applications by both food business operators and regulators

Food labeling: The discussion topics under the 4 categories which both food business operators and regulators should pay attention to in both new and existing FOSHU are shown in Table 2. Under the category of food labeling, 4 sub-categories required greater consideration than the average of 4.0 points/minute, including an easily comprehensible description on the label, 56.1% (23/41); warning label, 65.5% (19/29); authorization representation, 55.2% (16/29); and catch phrase, 35% (7/20). Table 3 summarizes the most frequently detected discussion topics, under the predetermined display sub-category, in more detail.

A previous survey by the Consumer Agency also revealed the importance of increasing text size on labels to enhance readability. In that survey, 36.2% (3858/10648) of responses indicated that the highest consumer need was a decrease in the amount of label information of limited importance, and a larger text size [21]. Optimizing the balance between understandability and the increasing amount of food label information is a key point for food business operators to address, considering the consumer's right to select FHCs for their health promotion effects. The same issue was pointed out regarding the format of front-of-pack food labels, which are important for comprehension and enhancing informed food choices by consumers [23,24].

Appropriate user testing from the viewpoint of the consumer should consider the problem of "easily comprehensible description on the label" in the food labeling system. A previous study found that consumers noticed catch phrases displayed in large characters on labels but tended to ignore other important information such as warnings in small text [25]. Discrepancies in the meaning of authorization representations and catch phrases on FOSHU product labels have also been reported. The Codex Alimentarius, or "Food Code", also highlights the importance of information presented on labels and instructs that labels should not be misleading or give erroneous impressions [26]. These reports are consistent with the points argued by the food development investigation subcommittee, as shown in this study.

Food labeling is also very important for judging the value of the food. FHC with functional substance(s) must display specified requirements as standard label items, as well as information on safety and efficacy, usage and administration, and so on. This study also detected a lack of scientific evidence in the expression of authorization representations and catch phrases.

All items on the label must be squeezed into the limited space available on packaging.

Therefore, labels on food packaging must provide sufficient information to ensure that consumers can select the most appropriate FHC for their health needs by determining the most effective way of selecting products with valid scientific evidence from consumer science research.

Efficacy and Safety

The second most frequently discussed category at the final review meetings for FOSHU applications was efficacy and safety. In particular, the discussion topic of scientific evidence (35.7%; 5/14) was most frequently argued about, and several problems that can affect the functional evidence of health claims on FOSHU were identified.

The first discussion topic was the validity of statistically significant results obtained in clinical trials with multiple, undefined outcomes. Clinical trial guidelines for new drug development recommend the use of a single pre-defined primary endpoint in later development phases. This recommendation is also particularly applicable to the evaluation of function of FFC [27,28]. Moreover, they recommend that sample size for trials should be estimated prior to starting the trial based on the primary outcome and expected differences [27,28]. Statistical significance is therefore more likely to be convincing and statistically valid when these study design parameters have been set a priori. While there are limited guidelines for FOSHU trials [29], clinical trial guidelines can be simply applied to benefit food business operators who are applying for FOSHU claims.

The second problem was the absence of reproducibility in the trials. Reproducibility is important to ensure that a study result is not obtained by chance. This is of particular importance where random errors in the evaluations of efficacy or safety can directly affect consumers. The Good Clinical Practice guideline for clinical trials also values trial reproducibility in judging the validity of the presented evidence [29]. It is therefore important that a scientifically valid and appropriate study plan is used from the start to the end of a trial such that the final results can be duplicated.

Finally, the committee pointed out that the applications did not clearly show the benefit of additional consumption of functional substance(s) above daily use. This may be due to a lack of consideration of the daily consumption of the proposed food, which may contain the same functional substance(s) as other approved FOSHU or normal foods. It is important to prepare a valid clinical trial protocol to provide scientific evidence for a functional substance(s). However, protocol design for FOSHU trials is more difficult than that for drug development due to the presence of ambiguity in evaluation methods. This is because the study population must be healthy people in this

type of trials, which hampers good study results on the efficacy of functional substance(s). It is therefore important to develop the most appropriate evaluation methods for the intended end-use of functional substance(s) in reference of the updated FHC regulation on study evaluation methods. The above points gave significant rights to food business operators and regulators in Japan who aim to streamline the FOSHU approval process.

Limitations

Some limitations of this research warrant mention. First, details of the pre-regulatory review meeting on the function of newly submitted FOSHU conducted by the Cabinet Office's first/second investigation subcommittee between April 1, 2012 and March 31, 2017 were out of the scope of this study.

Second, we did not consider the type or characteristics of the reviewed FOSHU because this information was not disclosed in the minutes of the review meetings on new FOSHU applications conducted between April 1, 2012 and March 31, 2017.

Conclusion

The food labeling of FOSHU should be considered carefully with scientific evidence under the process of development, which is an important process in ensuring that consumers understand and select the most suitable products for their health needs.

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