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Basic Approach of the Safety Assessment of Food for Specified Health Uses (FOSHU)

1. Background

The safety and effectiveness of food products submitted for the approval of Food for Specified Health Uses (FOSHU) had been evaluated by the Ministry of Health, Labor and Welfare (MHLW) until June 2003.

After the Food Safety Basic Law was enforced in July 2003, the Food Safety Commission of Japan (hereinafter referred to as the “FSCJ”) has become responsible for conducting the safety assessment of FOSHU in response to a request from the Minister of the MHLW¹. Expert Committee on Novel Foods (hereinafter referred to as “Expert Committee”) established under the FSCJ now conducts science-based safety assessments. The Expert Committee has completed several assessments to date upon request from the MHLW¹. This basic approach was compiled to ensure greater transparency of the safety assessment of FOSHU in the future.

2. Basic Approach

The safety assessment of FOSHU is conducted on a case-by-case basis for individual food products, while, in principle, safety shall be evaluated for the functional components relevant to its specified health use, thoroughly considering the composition of the food, history of safe food use of the products and/or its functional component, and food form types.

In the case where the FOSHU is in a form different from that of conventional food, such as tablets, capsules, extracts and powders, they are likely to be consumed excessively. Therefore, the safety of such FOSHU shall be evaluated thoroughly considering the dosage form, possible intake amount, and other factors.

As for such types of foods, cooking/processing methods and the highest possible intake

¹Jurisdiction of the approval for FOSHU was transferred to the Consumer Affairs Agency in September 2009.

(amount and concentration) are different from those of traditional foods. Therefore, the safety of such FOSHU should be carefully evaluated.

Consequently, the safety assessment of FOSHU shall be conducted based on (1) to (4) listed below.

(1) History of safe food use

Generally, foods that have been consumed in traditional ways by people over a certain period of time can be regarded as safe on the basis of long-term experience. Therefore, it is important to assess the history of safe use of the product and/or its functional component by reviewing the history of consumption using actual consumption data and information.

If the food is produced without changing the ingredients and/or production process compared to traditional food, and is recognized as substantially equivalent to existing food (its functional component) with a long history of safe use, then a safety assessment may not be required.

On the other hand, the following cases require an appropriate safety assessment.

- Insignificant or insufficient history of safe food use. For example, in the case where the consumed amount of the products and/or its functional component is excessive compared to the usual intake of traditional foods.
- Component contained in the food other than the functional component is not generally used as food component.
- Production process, type of food (e.g. tablet, capsule, extract) are significantly different from those of traditional foods.

(2) *In vitro* and animal (*In vivo*) studies

Human health effects can be reasonably estimated by using information, including dose-response relationship, for safety and toxicological findings obtained from *in vitro* and animal studies. Therefore, these tests are important for evaluating the safety of the product and/or its functional component. Information on toxicological test samples (for example, whether or not the functional component used for the manufacturing of the food is tested) is also necessary.

For cases in which there is insignificant or insufficient history of safe food use, appropriate safety assessment based on these tests is required.

(3) Human studies

In human studies, it is necessary to thoroughly evaluate the safety of the intake of the product and/or its functional component, including chronic intake for a relatively long-term

period and high/excessive intake. Generally, foods can be consumed by anyone. Therefore, the safety assessment of FOSHU should be conducted considering that they may be consumed by all population groups, including infants, children, the elderly, pregnant women, women of childbearing potential, and lactating women. In many cases, FOSHU targets healthy people and people in a preliminary stage of a disease or a borderline condition of at-risk groups. Thus, in some cases, it is reasonable to discuss a warning label.

In case that the FOSHU is consumed by persons under medical treatment, excessive effects may occur or the effectiveness of medicine may be attenuated. Thus, sufficient discussion and consideration should be given to the presumed effects for patients (e.g. diabetes and hypertension etc.) and the effects of concomitant administration with therapeutic medication to assess safety.

In addition, clinical investigations require to be conducted in conformance with the Declaration of Helsinki. Moreover, the test data should be processed with appropriate statistical methods.

(4) Other

- a. In the safety assessment of FOSHU, the production process of the product and/or its functional component should be evaluated. It is also important to determine or estimate the relevant substance for the safety assessment, and to examine changes in composition of components in the product and/or its functional component after extraction and/or concentration, as well as to investigate the possibility of contamination by hazardous substances during the production process.
- b. When evaluating the safety of the functional component, in some cases, the upper limit of acceptable dose (such as the threshold dose) of the component may be determined. If the upper limit of acceptable dose (level) is established as a result of the safety assessment, a safety assessment will generally not be required for the subsequent FOSHU containing the same functional component within that acceptable quantity. However, in some cases, it may be necessary to consider the total intake of the functional component from various sources.
- c. This approach shall be reviewed as necessary in accordance with accumulation of scientific evidence and development of the assessment method.

<Appendix>

The following data and information may be required for the safety assessment of FOSHU. These are provided as a general reference, listed by taking the requirements in the previous safety assessment of FOSHU into account.

The safety assessment of FOSHU is conducted on a case-by-case basis for individual product, therefore the data and information provided in this appendix are neither essential nor restrictive.

Basic information on FOSHU product and/or its functional component

- Description of production process and quality control system.
- Compositional data and specification (methods used for qualitative/quantitative analytical determination), mechanisms of action (beneficial physiological action) and kinetics (absorption, distribution, metabolism, excretion and bio-accumulation) of the functional component.
- Information on the identities and the quantities of chemical contaminants (e.g. heavy metals, pesticide residues) and allergenicity, when necessary.
- In the case where the functional component of an applying product is the same or similar to that of already approved FOSHU, an explanation of the difference between them.

Data and information on history of safe food use

- Data on daily intake of the functional component or foods containing the component based on dietary habits (estimates of intake from national food consumption surveys etc.).
- Data on content of that functional component in other foods already existing on the market.
- Data on history of safe food use and intake of the food in other countries.
- Information on cooking methods (e.g. boiling, baking, steaming, microwaving, extracting, etc.).
- For cases in which a functional component is used in already-approved FOSHU or other foods already existing on the market, data of content in those foods, date of the approval or the launch, and the actual sales amount.

*Data should be provided as concrete numeric value as possible.

Data and information on *in vitro* and animal studies

- Data should be provided on:
 - Genotoxicity study
 - Single-dose oral toxicity (acute toxicity)

- Repeated-dose 28-day or 90-day oral toxicity (subchronic toxicity)
 - When needed, data on 1-year chronic toxicity, carcinogenicity, reproductive and developmental toxicity, antigenicity, allergenicity and teratogenicity.
 - For cases in which the upper limits of acceptable dose are to be specified, supplementary information such as acceptable daily intake (ADI) of food additives when the functional components are food additives.
 - For cases in which the functional component is microorganisms, information on the plasmid characteristics of antimicrobial resistance genes and their potential horizontal transfer.
- * Interpretation of data obtained from animal studies requires sufficient consideration about abnormalities in clinical values and in autopsy findings while taking account of cases that data is extrapolated to humans.

Data and information on human studies

- Data and literature on human studies carried out with appropriate study subjects should be sufficient for statistical analysis. Such data should be analyzed using appropriate statistical techniques on a case-by-case basis. The following are examples of study designs:
 - In randomized, double-blind, placebo-controlled studies, differences in outcomes between subjects given either test food or its control (placebo) are statistically analyzed.
 - In uncontrolled studies, difference of individuals' health condition before, during, and after the test food intake is statistically analyzed.
- Generally, safety data obtained from target population including healthy people and people in a preliminary stage of a disease or a border-line condition of at-risk groups, for example those who wish to control specific health condition related to the intended health-claim of FOSHU (e.g. clinical-parameter and -biomarker values etc.).
- Human study data sufficient to evaluate the effect of successive intake, especially long-term chronic intake and/or multiple-exposures and high/excessive intake.
 - * If abnormal changes and findings are observed in animal studies, careful considerations of their relevance to humans based on the result of human studies are required.
 - * If continuous changes of safety-related parameters are observed during the intake period, sufficient considerations for the safety of long-term chronic intake are required.
 - * Base on the human studies of high/excessive intake, effect of single oral exposure to a high-dosage should also be evaluated.
- When necessary, the below additional information is required:
 - Human health hazard data in populations with specific diseases (e.g. diabetes,

hypertension and hyperlipidemia, etc.).

- Data and consideration on the safety of concomitant administration of the product and/or its functional component and medicines.
- Health effects according the age groups of the target population, particularly in the cases of specific uses in at-risk populations such as infants, children, and the elderly.

Other information

- Provided data should be derived from studies of sufficient credibility/reliability and adequacy.