Points to be noted regarding the notification

I. Points to be noted regarding entry methods for notification forms, etc.

The points to be noted regarding entry methods for Notification Forms, Attachments 3-1 and 3-2 in the notice of handling are as follows:

1. **The submission of the Forms and the Notifications should be in Japanese.**

The name and contact (address, telephone number, e-mail address, etc.) of the person in charge of inquiry concerning notification forms are added in the remarks column.

2. The name of notified item is written to clearly describe characteristics of the notified food and additive.
(ex.) ***-enhanced *** strain (name of food), anti-*** *** (name of food)
(ex.) *** produced using *Escherichia coli* *** strain (name of additive)

3. Notification forms are submitted with necessary materials attached. It should be noted that the entries in the Publication Form are published on the website of the Ministry of Health, Labour and Welfare (MHLW).

4. For foods derived from genome editing technology, the following should be noted.

(1) Names of item and breed and summary (usage and intended use) of the developed food

○ The names of item and breed indicate the information and strain name which can identify the item. Also, the strain name alone is acceptable.
○ When the intended use and usage are different from those of the existing food, their summaries are described.

(2) Method of genome editing technology used and details of modification

○ The type of genome editing technology used and the operation which was actually performed are described.
○ The name of target gene and its function is specified.
○ The fact that the breeding process, including passage and selection, was underwent to establish a breed shall be described.
○ It is confirmed and described that intended changes in the target gene and the resulting transformation have been achieved in an appropriate stage of the breed selection process. The intended changes in the target gene are confirmed using a sequencer, etc. The transformation is confirmed by the method selected by

developer, etc. on a specific case-by-case basis.

○ When analytical instruments, etc. are used, the name of analysis method used, instruments used, testing conditions, detection limits, etc. are recorded.

(3) Information on confirmation that there are no remaining foreign genes or their parts

○ When a foreign gene is transferred in the use of genome editing technology and subsequently removed, it is confirmed that no foreign gene or its parts remain using appropriate methods, including Southern blot, next-generation sequencer, and PCR.

○ When analytical instruments, etc. are used, the name of analysis method used, instruments used, testing conditions, detection limits, etc. are recorded.

○ When a foreign gene is present or valid data to determine that the foreign gene has been removed are not submitted, the technology is regarded as recombinant DNA technology and the process of safety assessment has to be gone through based on the Procedures for safety assessment of foods and additives derived from recombinant DNA technology. (Ministry of Health and Welfare Notification No. 233 of 2000, hereinafter referred to as “Procedures for safety assessment”)

(4) Information on confirmation that confirmed changes in DNA do not cause production of new allergens having adverse effects on human health or increase of known toxic substances contained.

○ Sequences which are presumed to have a high probability of off-target effect occurring are confirmed, as appropriate, by a combination of several appropriate search tools, such as CRISPRdirect, and then checked by searching homology with allergens and existing toxic substances and the results are submitted. The names and versions of search tools used, etc. are specified.

○ The fact of confirmation results showing no corresponding substances is mentioned.

(5) Information on changes in major components (nutrient components only) related to the target metabolic system for items which modification affecting the metabolic system was performed in order to increase or decrease specific components.

○ Information on increase or decrease of other substances associated with modification of the metabolic system (list of substances related to the target metabolic system (ex. Table of fatty acid composition, metabolic pathway map, etc.)) is submitted.

○ When specific substances accumulate due to modification of the metabolic system, the toxicity and the accumulation of such substances are estimated and then the

information indicating that they do not affect human health (ex. Data on risk of excessive intake a developer, etc. collected based on the literature) is submitted. When the toxicity of the substances cannot be confirmed, further information is not required.

○ In a food analysis, multiple samples are analyzed and the name of analysis method used, instruments used, testing conditions, detection limits, etc. are specified.

(6) Year and month of marketing (*Notify the MHLW of it after marketing)

○ The year and month when the food which was first commercialized out of the notified foods derived from genome editing technology or foods obtained using such foods was marketed are reported.

5. For additives derived from genome editing technology, the following should be noted.

(1) Name of item and summary (usage and intended use) of the developed additive

○ The name of item indicates the information which can identify the item.

○ When the intended use and usage are different from those of the existing food, the details are described.

(2) Details of method of genome editing technology and modification used

○ The type of genome editing technology used and the operation which was actually performed are described.

○ The name of target gene and its function are specified.

○ It is confirmed and described that intended changes in the target gene and the transformation have been achieved by microorganisms used in manufacturing. The intended changes in the target gene are confirmed using a sequencer, etc. The transformation is confirmed by the method selected by a developer, etc. on a specific case-by-case basis.

○ When analytical instruments, etc. are used, the name of analysis method used, instruments used, testing conditions, detection limits, etc. are recorded.

○ The safety of microorganisms used in manufacturing and the summary of manufacturing process are specified.

○ The summary to be published includes major genome editing technology used and clear description of effects of modification of the target gene on the metabolic system.

(3) Information on confirmation that there are no remaining foreign genes or their parts

○ When a foreign gene is transferred in the use of genome editing technology, it is confirmed that the foreign gene and its parts does not remain using appropriate methods, including Southern blot, next-generation sequencer analysis, and PCR.

○ When analytical instruments, etc. are used, the name of analysis method used, instruments used, testing conditions, detection limits, etc. are be recorded.

○ When a foreign gene is present or valid data to determine that the foreign gene has been removed are not submitted, the technology is regarded as recombinant DNA technology and the process of safety assessment has to be gone through based on the Procedures for safety assessment.

(4) The fact that the additive complies with the compositional standards specified in the Specifications and standards.

○ It is confirmed that additives obtained comply with the compositional standards specified in the specifications and standards for food and food additives, etc. (Ministry of Health and Welfare Notification No. 370 of 1959, hereinafter referred to as “Notification for specifications and standards”). Submission of the information confirmed is not required.

○ When analytical instruments, etc. are used, the name of analysis method used, instruments used, testing conditions, detection limits, etc. are recorded.

○ It should be noted that non-compliance with the compositional standards specified in the Notification for specifications and standards is subject to the penalty based on the Food Sanitation Act.

(5) Scheduled year and month of marketing (*Notify the MHLW of it after marketing)

○ The year and month when the additive which was first commercialized out of the notified additives derived from genome editing technology was marketed, are reported.

II Others

○ For notification, a prior consultation with the Office of Health Policy on Newly Developed Food, Food Safety Standards and Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, the MHLW is performed.