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Japan Invites Comments for Genome-Edited Foods Handling Procedure

Report Categories:
Biotechnology and Other New Production Technologies
Agricultural Situation
Grain and Feed

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Report Highlights:
On June 27, 2019, the Ministry of Health, Labour and Welfare (MHLW) published a draft of the Handling Procedure of Foods and Food Additives Derived from Genome Editing Technology under Food Sanitation Act. Comments must be submitted in Japanese via an online system, mail, or fax by Friday, July 26, 2019. A WTO-SPS notification is unlikely since there are no legal changes.

General Information:
MHLW released a genome-edited food policy on March 27, 2019 (JA9050), however, internal discussion to establish the specific guideline for the handling of genome edited foods has continued.

On June 27, 2019, MHLW published a draft of the Handling Procedure of Foods and Food Additives Derived from Genome Editing Technology under Food Sanitation Act. Comments must be submitted in Japanese via an online system, mail, or fax by Friday, July 26, 2019. A WTO-SPS notification is unlikely since there are no legal changes.

How to Submit Comments

1. Comments on regulatory proposals by the Japanese Government can be sent electronically via the "e-Gov" system. The site can be found at: https://search.e-gov.go.jp/servlet/Public?CLASSNAME=PCMMSTDETAIL&id=495190105&Mode=0

1. Comments can be mailed to the address below:

Office of Health Policy on Newly Developed Food Food
Safety Standards and Evaluation Division
Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare
1-2-2, Kasumigaseki, Chiyoda-ku
Tokyo 100-8916
Japan

The envelope containing comments should include the note
"ゲノム編集技術応用食品等の食品衛生上の取扱要領（案）等について"（meaning "the draft of Handling Procedure of Foods and Food Additives Derived from Genome Editing Technology under Food Sanitation Act). Mailed submissions must arrive to MHLW by July 26, 2019.

1. Comments can be sent via fax to the number indicated below:

Facsimile number: 03-3501-4868 (from outside Japan, +81-3-3501-4868)
Office of Health Policy on Newly Developed Food
Food Safety Standards and Evaluation Division
Pharmaceutical Safety and Environmental Health Bureau

The comment should have the title
"ゲノム編集技術応用食品等の食品衛生上の取扱要領（案）等について"（meaning "the draft of Handling Procedure of Foods and Food Additives Derived from Genome Editing Technology under Food Sanitation Act).

Comments must be submitted in Japanese and should contain the name (private individual or

corporate body), address, and contact information (either phone number or email address) of the submitter. The filed comments may be released to the public without name, address and contact information.

(Provisional Translation)

Food Sanitation Guidelines on the Handling of Genome-edited Foods and Food Additives (Draft)

1. Definition

(1) Genome-editing Technology

Genome-editing technology is defined as technology that modifies a specific site of a base sequence using an enzyme recognizing specific base sequences on a chromosome in order to add a specific function. In addition, in case foreign genes or fragments of such genes are contained in the end, it shall fall under recombinant DNA techniques.

(2) Genome-edited Foods

Genome-edited Foods shall fall under any of the following.

1) Whole or part of a living organism obtained by genome-editing technology
2) Those containing the whole or part of the concerned organism
3) Those produced using microorganisms obtained by genome-editing technology or those containing the concerned microorganism

(3) Genome-edited Food Additive

A Genome-edited food additives are defined as additives produced using living organism obtained by genome-editing technology or containing the concerned materials.

In addition, among the genome-edited food additives, in case the end product is a highly purified non-protein additive, such as an amino acid, and meets requirements [1] and [2] described below, it shall be handled as a "highly purified additive" like food additives produced using recombinant DNA technology.

1) The purity of the product is equal to or greater than that of, for example, amino acids, nucleotides, vitamins, and monosaccharides, which are announced as a designated additives in a public notice.
2) Compared to conventional additives, the content of existing non-active ingredients have not increased significantly in said additive to a level that could cause a safety issue, and no new non-active ingredients suggested to be harmful are included.

2. Genome-edited Foods Subject to Notification

Among Genome-edited Foods, in case a food is;

- the whole or part of a living organism obtained by genome-editing technology,
- produced using microorganisms obtained by genome-editing technology,

wherein no foreign genes or fragments of such genes remain, and those of which results in deletion of base(s), substitution and insertion of a few bases caused by cleavage by an enzyme recognizing specific base sequences, and the consequent insertion of mutations of one to several bases due to failure of repair at the cleavage site of an artificial restriction enzyme, shall be subject to notification.

Therefore, food products manufactured and processed by using the notified genome-edited foods do not require notification.

In addition, those excluded from the above, that contain foreign genes or fragments of foreign genes, shall follow the Procedures of Application for Safety Assessment of Foods and Food Additives Produced by Recombinant DNA Techniques (Ministry of Health, Labour and Welfare Notification No. 233, 2000, hereinafter referred to as "Safety assessment notification") and undergo the safety assessment.

Necessity of notification or safety assessment for those of which are not described above shall be judged individually and specifically by the Ministry of Health, Labour and Welfare.

3. Genome-edited Food Additives Subject to Notification

(1) In case genome-edited food additives are derived from microorganisms

As for additives, it is basically assumed that they conform to the component standards defined in the standards for food, additives, etc. (notice No. 370 of the Ministry of Health and Welfare, 1959, hereinafter referred to as "standards notification").

Regarding microorganisms used to produce genome-edited food additives;

- those of which no foreign genes or fragments of such genes introduced by using genome-editing technology remain,
- those of which results in deletion of base(s), substitution and insertion of a few bases caused by cleavage by an enzyme recognizing specific base sequences, and the consequent insertion of mutations of one to several bases due to failure of -repair at the cleavage site of an artificial restriction enzyme,

shall be subject to notification.

However, those meeting 1) or 2) described below do not require notification.

1) The said additive is produced using the microorganism obtained by genome-editing technology and it is clear that the gene composition is equivalent to that of the microorganisms that belong to the same taxonomy species or exist in nature.
2) The said additive is produced using the microorganism obtained by genome-editing technology and is a highly purified additive.

In addition, those excluded from the above, that contain foreign genes or fragments of the genes, shall follow Safety assessment notification and undergo the safety assessment.

Necessity of notification or safety assessment for those that are not described above shall be judged individually and specifically by the Ministry of Health, Labour and Welfare.

(2) In case genome-edited food additives are derived from others than microorganisms

Equivalent to handling described in Section 2.

4. Procedure for notification, etc. (See Annex)

(1) For foods and food additives derived from genome-editing technology that are subject to notification described in the above Section 2 and 3, the developer, agent or those who can submit appropriate documents (hereinafter referred to as "developers, etc.".) have to file certain information in principle before launching, and Ministry of Health, Labour and Welfare shall announce some of the filed contents.

(2) As for genome-edited foods, etc., to confirm whether the concerned foods, etc., fall under the subject of notification or safety assessment, developers, etc., have to apply for prior consultation to the

Office of Health Policy on Newly Developed Food, Food Safety Standards and Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare via the Attached form 1-1 for foods and via the Attached form 1-2 for food additives.

In addition, foods, etc. that become the subject of prior consultation shall basically be limited to those that have already been developed for commercialization.

At the consultation, information in (1) and (2) of Section 5 shall be attached as far as possible.

(3) The Ministry of Health, Labour and Welfare shall confirm with the Pharmaceutical Affairs and Food Sanitation Council / Food Sanitation Section Meeting / Newly Developed Foods Advisory Committee / Genetically Modified Food Subcommittee (hereinafter referred to as "Subcommittee".) if needed, and answer developers, etc., whether foods, etc., subjected to prior consultation fall under the subject of notification or safety assessment via the Attached form 2.

In addition, in case it is judged that it is required to ask for the opinions of the Food Safety Commission of Japan (hereinafter referred to as "Food Safety Commission".) during the confirmation process in the Subcommittee, the Minister of Health, Labour and Welfare shall consult with the Food Safety Commission, and determine its handling based on the answer from Food Safety Commission and provide the result to the developers, etc.

(4) As for genome-edited foods, etc., confirmed to fall under notification in the prior consultation, developers, etc. shall notify the Ministry of Health, Labour and Welfare of information described in (1) or (2) of Section 5 via the Attached form 3 (Notification and announcement form) with the required attached documents before launching.

However, the month/year of launching shall be announced via the Attached form 4 later when the concerned food, etc., is launched.

(5) The Ministry of Health, Labour and Welfare shall post and announce the information described in (3) or (4) of Section 5 on the website of the Ministry of Health, Labour and Welfare without delay.

However, the month/year of launching shall be announced after receiving a report of the Attached form 4 from the developers, etc.

(6) The same procedure shall be taken for imported products. If it is possible, an importer is allowed to perform the procedure on behalf of the developers, etc.

(7) For genome-edited food additives that developers, etc. judge to fall under the following [1] or [2] among the genome-edited food additives that are subject to notification, they shall apply for prior consultant with the reason and references if required.

The procedures described in the above (4) and (5) are not required for those judged to fall under 1) or 2) as a result of the prior consultation since the notification is considered to be done through the said prior consultation.

1) The said additive is produced using the microorganism obtained by genome-editing technology and it is clear that the gene composition is equivalent to that of microorganisms that belong to the same species or exist in nature.
2) The said additive is produced using the microorganism obtained by genome-editing technology and is a highly purified additive.

5. Notification and Information to Be Announced

(1) Regarding genome-edited food that becomes subject to notification, the developers, etc., are required to provide the following information as a notification to the Ministry of Health, Labour and Welfare
1) Crop and variety name, summary (usage and purpose of use) of the developed food
2) Method of the genome-editing technology applied and the details of the modification
3) Information regarding confirmation of absence of introduced foreign genes or residual fragments thereof
4) Information regarding confirmation that the identified changes in the DNA do not produce allergens or enhance known inherent toxic substances, and do not result in adverse effects on human health
5) In case modifications have been made to change a metabolic pathway to enhance or reduce specific components, information regarding changes in the main components (nutrient components only) involved in the targeted metabolic pathway
6) The month/year of launch (*Submit to Ministry of Health, Labour and Welfare after launching)

(2) Regarding genome-edited food additives, the developers, etc., are required to provide the following information as a notification to the Ministry of Health, Labour and Welfare.
1) Name and summary (usage and purpose of use) of the developed food additive
2) Method of the genome-editing technology applied and the details of the modification
3) Information regarding confirmation of absence of introduced genes or residual fragments thereof
4) Indication of meeting compositional standards defined in the standards notification
5) The month/year of launch (*Submit to the Ministry of Health, Labour and Welfare after launching)

(3) Regarding genome-edited food, the Ministry of Health, Labour and Welfare shall announce the following information.
1) Name of notifier and developer, date of notification
2) Crop and variety name, summary (usage, and purpose of use)
3) Method of the genome-editing technology applied and the summary of the modification of the gene
4) Summary regarding confirmation that the identified changes in the DNA do not result in adverse effects on human health
5) Summary regarding changes in the main components (nutrient components only) involved in the targeted metabolic pathway
6) The month/year of launch (*Announced after receiving notification of Section 5, (1), 6))

(4) Regarding genome-edited food additives, the Ministry of Health, Labour and Welfare shall announce the following information.
1) Name of notifier and developer, date of notification
2) Item name
3) Methods of genome-editing technology applied and the summary of the modification of the gene
4) Indication of meeting the compositional standards defined in the standards notification
5) The month/year of launch (*Announced after receiving the notification of Section 5, (2), 5))

6. Handling of Crossbred Progeny

(1) Regarding genome-edited food, notification is not required for the following.
1) Progenies crossbred between varieties of which notification to the Ministry of Health, Labour

and Welfare was announced or crossbred with a conventional breed variety.

2) Crossbred progenies between a variety of which notifications to the Ministry of Health, Labour and Welfare were announced, and a living organism obtained using recombinant DNA technology of which safety assessment was completed.

(2) Among genome-edited foods, prior consultation with the Ministry of Health, Labour and Welfare is required for progenies crossbred between those of which are judged that safety assessment is required or crossbred with a living organism of which the metabolic pathway is modified by recombinant DNA technology

7. Others

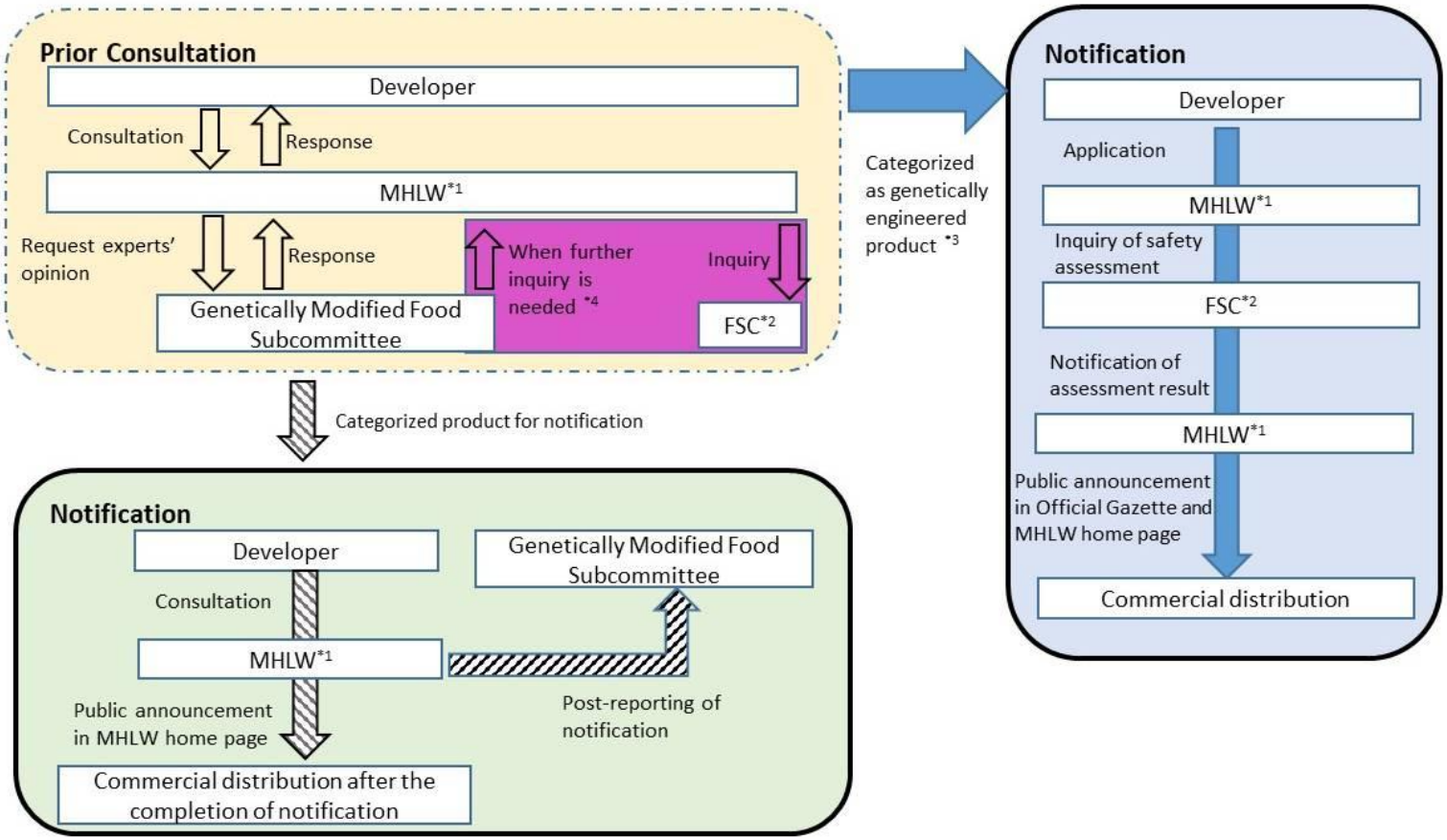
Items in this guidelines shall be revised based on records of use of genome-edited foods, etc., future advances in scientific knowledge and international movements as necessary.

It should be noted that in case the fact that this guideline is not followed is identified, such violation may be announced with the information of the said developers, etc. after confirming the background.

Annex: Flow of genome-edited foods, etc. to distribution
Attached sheet 1-1 (Prior consultation form: food)(abbreviated)
Attached sheet 1-2 (Prior consultation form: food additive)(abbreviated)
Attached sheet 2 (Answer form)(abbreviated)
Attached sheet 3-1 (Notification and announcement form: food)(abbreviated)
Attached sheet 3-2 (Notification and announcement form: food additive)(abbreviated)
Attached sheet 4 Commercialization notification (abbreviated)

Annex: Flow of genome-edited foods, etc. to distribution

Attachment - Handling of Genome-edited Foods



*1: The Ministry of Health, Labour and Welfare
*2: Food Safety Commission
*3: If the product is required to have safety assessment as the product from recombinant DNA tequnieus, the Procedures of Application for Safety Assessment of Foods and Food Additives Produced by Recombinant DNA Techniques (Ministry of Health and Welfare Announcement No. 233 of 2000) will be applied
*4: Newly developed food and/or new technology shall be inquired to FSC, and its management will be decided in Newly Developed Foods Advisory Committee

(Provisional Translation)

Points of concern regarding the notifications (draft)

I Points of concern regarding the description method etc. of the notification form

Points of concern regarding the description method etc. of the "Notification form" in the Attached sheets 3-1 and 3-2 of the handling guideline notice are as follows:

1 Add the name of person in charge who will respond to inquiries concerning the notification form and his or her contact information (address, phone number, e-mail address, etc.) in the remarks column.

2 The name of the item to be notified should clearly represent the characteristics of the food and food additives.
(e.g.) XX-enhanced line_YY (food name); XX resistant to YY (food name)
(e.g.) XX produced using *Escherichia coli* YY strain (food additive name)

3 The notification form should be submitted with the necessary information materials attached. Also note that the particulars described in the notification form will be published on the website of the Ministry of Health, Labour and Welfare.

4 Note the following regarding genome-edited foods.

(1) Crop and variety name, and summary (usage and purpose of use) of the developed food

- Regarding names of crop and variety, the information and lineage name by which the item can be specified must be presented. In addition, presentation of only the lineage name is acceptable.
- Regarding the usage and purpose of use, describe the summary as well if there are any differences from conventional foods.

(2) Method of the genome-editing technology applied and the details of the modification

- Describe the type of genome-editing technology applied and the actually performed operation.
- Specify the name of the target gene and its function.
- Describe the breeding processes to establish the variety such as passages and selections.
- Confirm the modifications to the target gene and trait changes caused by the modifications at the appropriate stage of the breeding selection process, and describe them. The modifications to the target gene should be confirmed using a sequencer or other methods. The trait changes should be confirmed individually and specifically based on the method selected by the developers.
- When analytical instruments are used, record the names of the analytical methods used, the instruments used, the test conditions, and the detection limits, etc.

(3) Information regarding confirmation of absence of introduced foreign genes or residual fragments thereof

- If foreign genes are introduced at the time of gene editing and then removed, confirm absence of the foreign genes and fragments of them by appropriate methods such as Southern blotting, next-generation sequencing, and PCR analysis.

- When analytical instruments are used, clarify the names of the analytical methods used, the instruments used, the test conditions, and the detection limits, etc.

- In case foreign genes are present or appropriate data have not been submitted to judge that the foreign genes have been removed, the product is subject to recombinant DNA techniques. In such a case, it is necessary to perform safety assessment procedures based on the Procedures of Application for Safety Assessment of Foods and Food Additives Produced by Recombinant DNA Techniques (Ministry of Health and Welfare Announcement No. 233 of 2000 (hereinafter referred to as "Safety assessment notification").

(4) Information regarding confirmation that the identified changes in the DNA do not produce allergens or enhance known inherent toxic substances, and do not result in adverse effects on human health.

- Sequences presumed to be highly probable to generate off-target effects should be identified by appropriate search tools such as CRISPRdirect or their combinations if necessary, as well as should be checked about the homology with allergens and known toxic substances using sequence homology searches for submission. In addition, clarify the names and versions of the search tools used for analyses.

- As the result of homology search, if no applicable substances was hit then mention so.

(5) In case modifications have been made to change a metabolic pathway to enhance or reduce specific components, information regarding changes in the main components (nutrient components only) involved in the targeted metabolic pathway.

- Information on an increase or decrease in other substances associated with the metabolic modifications, such as the list of substances related to the targeted metabolic system must be submitted. (e.g., a table of fatty acid compositions, a map of metabolic pathways, etc.)

- If the metabolic modifications cause the accumulation of a specific substance, estimate its toxicity and accumulation based on existing information to submit the assessment describing that the substance does not affect human health (e.g., information on the risk of excessive intake, etc. collected by the developers based on the literature). If the toxicity of the substance cannot be

confirmed, no further information is required.

- When analyzing food, perform analysis of multiple samples and clarify the names of the analytical methods used, the instruments used, the test conditions, and the detection limits, etc.

(6) The month/year of launch (*Submit to Ministry of Health, Labour and Welfare after launching)

- Among the genome-edited foods or foods obtained using such concerning foods notified, report the month/year of launch for the food that was commercialized the earliest.

5 Note the following regarding genome-edited food additives.

(1) Name and summary (usage and purpose of use) of the developed food additive

- Regarding the name, the information that will identify the item must be presented.

- Regarding the usage and purpose of use, describe the summary as well if there are any differences from conventional additives.

(2) Method of the genome-editing technology applied and the details of the modification

- Describe the type of genome-editing technology applied and the actually performed operation.

- Specify the name of the target gene and its function.

- Use the microorganisms used for production to confirm the modifications to the target gene and trait changes caused by the modification, and describe them. The modifications to the target gene should be confirmed using a sequencer or other methods. The trait changes should be confirmed individually and specifically based on the method selected by the developers.

- When analytical instruments are used, record the names of the analytical methods used, the instruments used, the test conditions, and the detection limits, etc.

- Clarify the safety of the microorganisms used for production and the outline of the production processes.

- In the summary to be published, describe the main genome-editing technology applied and clearly state the effects that have been exerted on the metabolic system associated with the modification of the target genes as well.

(3) Information regarding confirmation of absence of introduced foreign genes or residual fragments

thereof

- If foreign genes are introduced at the time of gene editing, confirm absence of the foreign genes and fragments of them by appropriate methods such as Southern blotting, next-generation sequencing, and PCR analysis.

- When analytical instruments are used, clarify the names of the analytical methods used, the instruments used, the test conditions, and the detection limits, etc.

- In case foreign genes are present or appropriate data have not been submitted to judge that the foreign genes have been removed, the product is subject to recombinant DNA techniques. In such a case, it is necessary to perform safety assessment procedures based on the "Safety assessment notification."

(4) Indication of meeting compositional standards defined in the Notification of Specification and Standards

- Confirm that the obtained additive conforms to the "Specifications and Standards for Food, Food Additives, etc." (Ministry of Health and Welfare Announcement No. 370 of 1959, hereinafter referred to as the "standards notification") However, it is not required to submit the confirmed information.

- When analytical instruments are used, record the names of the analytical methods used, the instruments used, the test conditions, and the detection limits, etc.

- Also note that, should it be found that the obtained additive does not conform to the ingredient standards stipulated in the standards notification, it may be subject to punishment under the Food Sanitation Act.

(5) The month/year of launch (*Submit to Ministry of Health, Labour and Welfare after launching)

- Among the genome-edited additives notified, report the month/year of marketing of launch for the additive that was commercialized the earliest.

II Other

- Before notification, apply for prior consultation with the Office of Health Policy on Newly Developed Food, Food Inspection and Safety Division of the Pharmaceutical Safety and Environmental Health Bureau, the Ministry of Health, Labour and Welfare.