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Report Name: Final MAFF Guidelines for the Handling of Genome Edited Feed and Feed Additives

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Report Highlights:

On February 7, 2020, Japan's Ministry of Agriculture, Forestry, and Fisheries released the final handling procedure guidelines for genome edited feed and feed additives. This report contains a provisional translation of the guidelines.

General Description:

On February 7, 2020, Japan's Ministry of Agriculture, Forestry and Fisheries (MAFF) released the final "Feed Safety Guidelines on the Handling of Genome Edited Feed and Feed Additives" (see [JA2020-0034](#)). These procedures describe how developers of genome edited feed and feed additives should inform the Government of Japan of their product prior to commercialization in Japan. The guidelines also provide definitions for genome edited feed and feed additive products.

MAFF requests that developers apply for a "prior consultation" with the Animal Products Safety Division of the Food Safety and Consumer Affairs Bureau. Based on the consultation, MAFF will inform the developer if the product is subject to the notification requirement described in the guidelines or the Procedures for Safety Assessment on Feeds and Feed Additives Derived from Recombinant DNA Techniques (see [JA8086](#)). If MAFF determines the product is subject to notification, then the developer is requested to submit the information package described in the guidelines. MAFF will then publicly release information about the product, such as the name of the developer, item name, a summary of the genome editing technology used to create the product, and the genetic modification.

The official guidelines and related documents are available in Japanese only and can be found on MAFF's Food and Agricultural Materials Inspection Center website, links below. The attachments listed on the final page of the provisional translation of the Guidelines (Appendix 1) have not been provided in this translation. Appendix 2 of this report is a provisional translation of additional information provided by MAFF about the notification process.

Feed Safety Handling Procedures for Genome-edited Feed and Feed Additives (English provisional translation in Appendix 1)

http://www.famic.go.jp/ffis/feed/obj/r1_4605.pdf (Japanese Only)

Points of Attention Regarding Notifications (English provisional translation in Appendix 2)

http://www.famic.go.jp/ffis/feed/obj/r1_4606.pdf (Japanese Only)

For specific inquiries, such as, product specific questions, official English translation, or consultation forms in English, please reach to MAFF's contact point as below.

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Appendix 1

(Provisional Translation)

Feed Safety Handling Procedures for Genome-edited Feed and Feed Additives

1. Definition

(1) Genome-editing Technology

Genome-editing technology is defined as a technology that modifies a specific site in a base sequence through the use of an enzyme that recognizes specific base sequences on a chromosome, for the purpose of conferring or inactivating a specific function. In the case where foreign genes or fragments of such genes ended up remaining, the said technology shall fall under recombinant DNA techniques [techniques specified in the Ministerial Ordinance on the Specifications and Standards of Feeds and Feed Additives (Ordinance No. 35, 1976 of the Ministry of Agriculture and Forestry, hereinafter referred to as “Ministerial Ordinance on the Specifications and Standards”); the same shall apply hereinafter].

(2) Genome-edited Feeds

Genome-edited feeds shall include those feeds falling under any of the following.

- 1) All or part of a living organism obtained by genome-editing technology
- 2) Those containing all or part of a living organism obtained by genome-editing technology
- 3) Those produced through the use of microorganisms obtained by genome-editing technology, or those containing the said microorganisms

(3) Genome-edited Feed Additives

Genome-edited feed additives are feed additives defined as those produced using a living organism obtained by genome-editing technology, or additives containing the said organism.

Among genome-edited feed additives, if the said additive is an amino acid, vitamin, or etc. and is meeting all of the following requirements 1) to 5), it shall be handled as a “highly purified feed additive,” in the same manner as feed additives produced using recombinant DNA techniques (feed additives derived from recombinant DNA techniques).

- 1) An outline of the manufacturing method [production method for organisms obtained by genome-editing technology used for the manufacture of a feed additive (hereinafter referred to as “genome-edited organisms”), as well as extraction and purification methods for the feed additive], usage, chemical structure, chemical composition, physical/chemical properties, and

quality must be clarified.

- 2) The purity of the product is equal to or greater than existing feed additives.
- 3) The product does not contain non-active ingredients that are contained in existing feed additives, to such an extent as to pose a safety problem.
- 4) The product does not contain non-active ingredients that have been suggested to be harmful and are not contained in existing feed additives.
- 5) Genome-edited organisms are not present in the product.

2. Genome-edited Feeds Subject to Notification

Among genome-edited feeds, in case a feed is;

- 1) All or part of a living organism obtained by genome-editing technology, or
- 2) Those produced using microorganisms obtained by genome-editing technology, wherein no foreign genes or fragments of such genes ended up remaining in the genome of the organism or microorganism, and those which result in the deletion of base(s), substitution or insertion of several bases or the consequent insertion of one to several base mutations due to cleavage by an enzyme that recognizes specific base sequences, etc., it shall be subject to notification.

In addition, those in which foreign genes or fragments of such genes are contained shall undergo a safety assessment, in accordance with the Procedures for Safety Assessment on Feeds and Feed Additives Derived from Recombinant DNA Techniques (Ministry of Agriculture, Forestry and Fisheries Notification No. 1780, 2002, hereinafter referred to as a “Safety Assessment Notification,”) as those falling under recombinant DNA techniques. Necessity of notification or safety assessment for those of which are not described above shall be judged on a specific case-by-case basis by the Ministry of Agriculture, Forestry and Fisheries.

Note that feed products that were manufactured and processed using the notified genome-edited feeds do not require notification.

3. Genome-edited Feed Additives Subject to Notification

(1) Genome-edited feed additives derived from microorganisms

As for feed additives, it is basically assumed that they conform to the specifications and standards stipulated in the Ministerial Ordinance on the Specifications and Standards.

Among genome-edited feed additives, if a feed additive is produced using microorganisms obtained, wherein no foreign genes or fragments of such genes remain, and those which result in deletion of base(s), substitution and insertion of several bases or the consequent insertion of mutations of one to several base mutations due to cleavage by an enzyme that recognizes specific base sequences, etc., it shall be subject to the notification of Section 4.

However, those meeting the following 1) or 2) do not require notification.

- 1) The said additive is produced using a microorganism obtained by genome-editing technology, and it is clear that the genetic composition of the said microorganism is equivalent to that of microorganisms belonging to the same taxonomic species or existing in nature.
- 2) The said additive is produced using a microorganism obtained by genome-editing technology and is a highly purified feed additive.

In addition, those that finally contain foreign genes or fragments of such genes shall undergo a safety assessment, in accordance with the Safety Assessment Notification, as those falling under recombinant DNA techniques.

Moreover, if the situation of the gene does not fall under any of the above, the Ministry of Agriculture, Forestry and Fisheries shall make a judgement on a specific case-by-case basis regarding the necessity of notification or safety assessment.

(2) Genome-edited feed additives derived from sources other than microorganisms
It conforms to the handling method described in Section 2.

4. Procedure for Notification, etc. (See Attachment)

(1) For feeds and feed additives derived from genome-editing technology that are subject to the notification described in the above Section 2 and 3 (hereinafter referred to as “genome-edited feeds, etc.”), the developer, agent, or those capable of submitting appropriate documents (hereinafter referred to as “developers, etc.”) shall apply for prior consultation with the Animal Products Safety Division of the Food Safety and Consumer Affairs Bureau of the Ministry of Agriculture, Forestry and Fisheries using the Attachment 1 -1 in the case of feeds, and Attachment 1 -2 in the case of feed additives before submitting the notification, in order to confirm whether the said genome-edited feeds, etc. are subject to notification or safety assessment.

Genome-edited feeds, etc. to be the subject of prior consultation shall be limited to those that have already been developed for commercialization, in principle. Moreover, for such prior consultation, the information described in (1) or (2) of Section 5 shall be provided as much as possible.

- (2) The Ministry of Agriculture, Forestry and Fisheries shall confirm with the Genetically Modified Feed Subcommittee of Feed Committee, Agricultural Materials Council (hereinafter referred to as the "Subcommittee") as necessary, and provide the result to the developers, etc. using Attachment 2, regarding whether the feeds, etc. that have undergone prior consultation fall under the subject of notification or safety assessment.

In addition, in cases where it is judged to be necessary to request the opinions of the Food Safety Commission of Cabinet Office (hereinafter referred to as "Food Safety Commission") during the confirmation process in the Subcommittee, the Minister of Agriculture, Forestry and Fisheries shall consult with the Food Safety Commission, determine its handling based on the advice from the Food Safety Commission, and provide the result to the developers, etc.

- (3) As for genome-edited feeds, etc. that have been confirmed to fall under notification in prior consultation, the developers, etc. shall notify the Ministry of Agriculture, Forestry and Fisheries of the information described in (1) or (2) of Section 5 using Attachment 3, with the necessary attachments before launch of the product. However, the month/year of the launch shall be reported using Attachment 4 at a later date, when the said feeds, etc. are launched.
- (4) The Ministry of Agriculture, Forestry and Fisheries shall post and announce the information described in (3) or (4) of Section 5 on the website of the Ministry of Agriculture, Forestry and Fisheries without delay, after receiving the notification described in (3) above. However, the month/year of the launch shall be announced after receiving a report from the developers, etc. using Attachment 4.
- (5) The same procedure shall be taken for imported products. Importers, etc. are allowed to perform the procedure on behalf of the developers, etc., when feasible.
- (6) For genome-edited feed additives that the developers, etc. judge to fall under either 1) or 2) of (1) in Section 3, among the genome-edited feed additives that are subject to notification, prior

consultation shall be applied for, along with a description of the reason, and with the relevant documents attached, if required. The procedures described in (3) and (4) above are not required for those judged to fall under 1) or 2) of (1) in Section 3, as a result of prior consultation.

5. Information to Be Notified and Announced

- (1) Regarding genome-edited feeds that become subject to notification, the developers, etc., are required to notify the following information to the Ministry of Agriculture, Forestry and Fisheries
 - 1) Names of item and variety, and a summary (usage and purpose of use) of the developed genome-edited feed
 - 2) Method of the genome-editing technology applied and the details of the genetic 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 result in an increase of known toxic substances
 - 5) Information regarding changes in the main components (nutrient components only) involved in the targeted metabolic pathway in cases modifications have been made to change a metabolic pathway in order to increase or reduce specific components
 - 6) The month/year of the product launch (*submitted to the Ministry of Agriculture, Forestry and Fisheries after the launch)

- (2) Regarding genome-edited feed additives, the developers, etc., are required to notify the following information to the Ministry of Agriculture, Forestry and Fisheries.
 - 1) Names of item and strain, and a summary (usage and purpose of use) of the developed genome-edited feed additive
 - 2) Method of the genome-editing technology applied and the details of the genetic modification
 - 3) Information regarding confirmation of absence of introduced foreign genes or residual fragments thereof
 - 4) A statement on conformance with the specifications and standards stipulated in the Ministerial Ordinance on the Specifications and Standards
 - 5) The month/year of the product launch (*submitted to the Ministry of Agriculture, Forestry and Fisheries after the launch)

- (3) Regarding genome-edited feeds, the Ministry of Agriculture, Forestry and Fisheries shall announce the following information.
 - 1) Names of notifier and developer, and date of notification

- 2) Names of item and variety, and a summary (usage and purpose of use)
- 3) Summary of the genome-editing technology applied and the genetic modification
- 4) A statement on confirmation that the identified changes in the DNA do not result in adverse effects on the health of livestock or human health through livestock products
- 5) Summary of changes in the main components (nutrient components only) involved in the targeted metabolic pathway
- 6) The month/year of the product launch (*announced after receiving the notification in 6) of (1) in Section 5)

(4) Regarding genome-edited feed additives, the Ministry of Agriculture, Forestry and Fisheries shall announce the following information.

- 1) Names of the notifier and developer, and date of notification
- 2) Item name
- 3) Summary of genome-editing technology applied and the genetic modification
- 4) A statement on conformance with the specifications and standards stipulated in the Ministerial Ordinance on the Specifications and Standards
- 5) The month/year of the product launch (*announced after receiving the notification 5) of (2) in Section 5)

6. Handling of Crossbred Progeny

For crossbred progeny that are obtained by crossbreeding a variety notified as a genome-edited feed with a conventional variety* using traditional breeding techniques, and falls under any of the following 1) to 3), the notification shall be requested.

- 1) Properties newly acquired through genome-editing technology have changed in the crossbred progeny.
- 2) A cross between subspecies has been performed.
- 3) There is a change in the amount of feed for livestock animals, the parts used as feed, or the processing methods, due to changes in traits.

For organisms other than those with a history of safe use as food or feed, or with a record of safety assessment (fish and seafood, etc.), inquiries regarding the crossbred progeny shall be made to the Animal Products Safety Division in advance, and notification shall be requested if the Council determines that it is necessary to notify the said progeny as genome-edited feeds, etc.

- ※ In addition to conventional varieties, varieties notified as genome-edited feeds, etc., and varieties which have undergone a safety assessment as feeds derived from recombinant DNA techniques are included

7. Others

The matters specified in these Guidelines are for the purpose of contributing to the accumulation of scientific knowledge on genome-edited feeds, etc. and to understand their development status, and those matters shall be reviewed as necessary, based on the experience of utilization as feeds, or international trends, etc. at the stage when such scientific knowledge has been accumulated.

Furthermore, in cases where non-compliance with this notice has been confirmed, the person who has failed to comply with this notice shall be requested to undertake the said procedures. It should be noted that in cases of violation of the Act on Safety Assurance and Quality Improvement of Feeds, information regarding the said developers, etc. may be announced.

Attachment 1 -1 (Prior Consultation Form: Feed)

Attachment 1 -2 (Prior Consultation Form: Feed Additive)

Attachment 2 (Response Form)

Attachment 3 -1 (Notification and Publication Form: Feed)

Attachment 3 -2 (Notification and Publication Form: Feed Additive)

Attachment 4 (Notification Form for Commercialization)

Appendix 2

(Provisional translation)

Points of Attention Regarding Notifications

Section 1 Points of Attention Regarding Notifications

Notifiers shall prepare materials showing that the following point of attention 4 or 5 has been satisfied, together with the necessary attachments in the form of Attachment 3 -1 or 3 -2 of the Handling Procedures, and submit the said materials to the Ministry of Agriculture, Forestry and Fisheries.

- 1 The name of the person in charge of making inquiries regarding the notification form, along with contact information (address, phone number, e-mail address, etc.) shall be written in the remarks column of the form.
- 2 The name of the notified product shall briefly indicate the characteristics of the feed and feed additive to be notified.
(Example) oo line with enhanced xx (feed name), oo with an anti-xx property (feed name)
(Example) oo produced using the *Escherichia coli* xx strain (feed additive name)
- 3 Please be aware that the items written in the publication form will be published on the website of the Ministry of Agriculture, Forestry and Fisheries.
- 4 With regard to genome-edited feeds, attention shall be given to the following points.
 - 1) Names of item and variety, and a summary (usage and purpose of use) of the developed feed
 - With regard to the item and variety name, information and the line name that can allow the identification of the item shall be presented. The line name alone is also acceptable.
 - With respect to the purpose and method of use, a summary shall also be provided in cases where there are differences from conventional feeds.
 - 2) Method of the genome-editing technology applied and the details of the modification
 - Both the type of the applied genome-editing technology and the operations that are actually performed shall be described.
 - The name of the target gene and its function shall be specified.
 - The breeding process, such as selection for producing the developed feed variety, shall be described from generation to generation, so that the breeding operations, such as self-

breeding or cross-breeding, are clarified.

- Occurrence of the changes to the target gene of interest and the resulting changes in traits shall be confirmed at appropriate stages of the breeding selection process and described. Changes to the target gene of interest shall be confirmed using a sequencer, etc. Changes in traits shall be confirmed on a specific case-by-case basis using methods selected by the developers, etc.
- When analytical instruments, etc. are used, details such as the name of the analytical method employed, equipment used, test conditions, and detection limits shall be recorded.

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

- If a foreign gene is introduced during the use of genome-editing technology and then removed, the absence of the introduced foreign gene and residual fragments thereof shall be confirmed using appropriate techniques, such as Southern blotting, next-generation sequencing, and PCR.
- When analytical instruments, etc. are used, details such as the name of the analytical method employed, equipment used, test conditions, and detection limits shall be specified.
- In cases where a foreign gene is present, or no appropriate data are submitted to determine that a foreign gene has been removed, the method shall be deemed to fall under recombinant DNA techniques, and the procedure for safety assessment shall be followed, in accordance with the Procedures for Safety Assessment on Feeds and Feed Additives Derived from Recombinant DNA Techniques (Ministry of Agriculture, Forestry and Fisheries Notification No. 1780, 2002, hereinafter referred to as "Safety Assessment Notification"), based on the Ministerial Ordinance on the Specifications and Standards of Feeds and Feed Additives (Ordinance No. 35, 1976 of the Ministry of Agriculture and Forestry, hereinafter referred to as the "Ministerial Ordinance on the Specifications and Standards").

4) Information regarding a confirmation that the identified changes in the DNA do not result in an increase of known toxic substances that may impose adverse effects on human health through livestock products or on the health of livestock

- Sequences for which there is a high probability of off-target occurrence shall be checked by combining multiple appropriate search tools such as CRISPRdirect as necessary, and cross-checked via homology searches with known toxic substances, and the results shall be submitted. The names and versions of the search tools employed shall be specified.
- If there are no applicable substances, as a result of confirmation, that fact shall be described.

- 5) Information regarding changes in the main components (nutrient components only) involved in the targeted metabolic pathway in cases modifications have been made to change a metabolic pathway in order to increase or reduce specific components.
- Information regarding the increase or decrease of other substances due to modification of the metabolic system [list of substances relevant to the targeted metabolic system (e.g., fatty acid composition tables, metabolic pathway maps, etc.)] shall be submitted.
 - If a certain substance accumulates due to modification of the metabolic system, information that can be used to explain no adverse effects on human health through livestock products or the health of livestock shall be submitted by estimating the toxicity and the amount of accumulation of the said substance based on existing information (e.g., information on the risk of overfeeding livestock, collected by the developers, etc. based on the literature). It shall be noted that if the toxicity of the substance cannot be confirmed, no further information shall be requested.
 - When a feed is analyzed, it shall be analyzed using multiple samples, and details such as the name of the analytical method employed, equipment used, test conditions, and detection limits shall be specified.

- 6) The planned product launch date (*submitted, after the launch, to the Ministry of Agriculture, Forestry and Fisheries in the form of Attachment 4 of the Handling Procedure)
- The month/year of the launch of the feed that was commercialized the earliest, among the notified genome-edited feeds or the feeds produced by the use of the said genome-edited feeds, shall be reported.

5 With regard to genome-edited feed additives, attention shall be given to the following points.

- 1) Name of item and a summary (usage and purpose of use) of the developed feed additive
 - As for the item name, information that can allow the identification of the item shall be presented.
 - With respect to the purpose and method of use, a summary shall also be provided in cases where there are differences from conventional feed additives.
- 2) Method of the genome-editing technology applied and the details of the modification
 - Both the type of the applied genome-editing technology and the operations that are actually performed shall be described.
 - The name of the target gene and its function shall be specified.
 - Occurrence of the changes to the target gene of interest and the resulting changes in traits shall be confirmed using the microorganisms used for production and described. Changes to the target gene of interest shall be confirmed using a sequencer, etc. Changes in traits shall be confirmed on a specific case-by-case basis using methods selected by the developers, etc.

- When analytical instruments, etc. are used, details such as the name of the analytical method employed, equipment used, test conditions, and detection limits shall be recorded.
 - The safety of the microorganisms used in production, as well as a summary of the production process shall be clearly indicated.
 - In the summary for publication, the genome-editing technology mainly employed shall be described, while the effects of the target gene modification on the metabolic system shall also be briefly described.
- 3) Information regarding confirmation of absence of introduced foreign genes or residual fragments thereof
- If a foreign gene is introduced through the use of a genome-editing technology, the absence of the introduced foreign gene and residual fragments thereof shall be confirmed using appropriate techniques, such as Southern blotting, next-generation sequencing, and PCR.
 - When analytical instruments, etc. are used, details such as the name of the analytical method employed, equipment used, test conditions, and detection limits shall be specified.
 - In cases where a foreign gene is present, or no appropriate data are submitted to determine that a foreign gene has been removed, the method shall be deemed to fall under recombinant DNA techniques, and the procedure for safety assessment shall be followed, in accordance with the Safety Assessment Notification.
- 4) A statement on conformance with the specifications and standards stipulated in the Ministerial Ordinance on the Specifications and Standards
- It shall be confirmed that the obtained feed additives conform to the specifications and standards stipulated in the Ministerial Ordinance on the Specifications and Standards. It shall be noted that submission of the confirmed information is not requested.
 - When analytical instruments, etc. are used, details such as the name of the analytical method employed, equipment used, test conditions, and detection limits shall be recorded.
 - It shall be kept in mind that if non-compliance with the specifications and standards stipulated in the Ministerial Ordinance on the Specifications and Standards is found, it will be subject to the penalty based on the Act on Safety Assurance and Quality Improvement of Feeds (Act No. 35 of 1953).
- 5) The planned product launch date (*submitted, after the launch, to the Ministry of Agriculture, Forestry and Fisheries in the form of Attachment 4 of the Handling Procedure)
- The month/year of the launch of the feed additive that was commercialized the earliest, among the notified genome-edited feed additives, shall be reported.

Section 2 Others

- As for notification, notifiers shall apply for prior consultation with the Animal Products Safety Division of the Food Safety and Consumer Affairs Bureau of the Ministry of Agriculture, Forestry and Fisheries, using Attachment 1 -1 or 1 -2 of the Handling Procedures.

Attachments:

No Attachments.