Feed Safety Guidelines for Genome Edited Feeds and Feed Additives

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1. Definition

(1) Genome editing technology

Genome editing technology is defined as a technology to modify a specific site of a specific base sequence on a chromosome using an enzyme recognizing the base sequence in order to provide or inactivate specific functions. The technology eventually refers to technology that falls into the recombinant DNA technology when a foreign gene and its parts remain (It refers to the technology specified in the Ministerial Ordinance on the Specifications and Standards of Feeds and Feed Additives (Ministry of Agriculture, Forestry and Fisheries (MAFF) Notification No. 35 of 1976, which is hereinafter referred to as "Ministerial Ordinance on the Specifications and Standards.") The same applies hereafter.).

(2) Genome edited feeds

Genome edited feed is feed that falls under any of the following:

1) An entire organism or its parts obtained by genome editing technology
2) A feed including an entire organism or its parts obtained by genome editing technology
3) A feed manufactured using microorganisms obtained by genome editing technology or feed containing such feed

(3) Genome edited feed additives

Genome edited feed additives are defined as feed additives manufactured using organisms obtained by genome editing technology or additives containing such additives.

Among genome edited feed additives, when amino acids, vitamins, or etc. that satisfy all of the following requirements of 1) to 5), the additives are handled as "highly purified feed additives" as with the feed additives using a microorganism obtained by recombinant DNA technology (feed additives derived from recombinant DNA technology).

1) The summary of the manufacturing method (the method of producing an organism used for manufacturing and obtained by genome editing technology (hereinafter referred to as "genome edited organism"), the method of extracting and purifying a feed additive), usage, chemical structure, chemical composition, and physical/chemical characteristics and quality are clear.
2) Compared with the existing feed additives, the degree of the refinement is equivalent or higher.
3) Inactive components contained in the existing feed additives are not contained to

a degree that cause safety problems.

4) Inactive components that are suggested to be harmful and not contained in the existing feed additives are not contained.

5) A genome edited organisms must not be mixed in the product.

2. Genome edited feeds for which notification is required

A genome edited feed that falls under one of the following:

1) An entire organism or its parts obtained by genome editing technology

2) A feed manufactured using microorganisms obtained by genome editing technology

Notification is required when the feed falls under one of the above and when the organisms or microorganisms meet the following conditions:

- the gene status indicates no remaining foreign gene or its parts; and
- deletion of bases, substitution and insertion of several bases, resulting insertion of one to several mutations by cleavage, etc. with an enzyme recognizing the specific base sequence occur.

When the gene status finally shows that a foreign gene and its parts remain, the technology used for the item falls under recombinant DNA technology and such item is subject to a safety assessment according to the Procedures for Safety Assessment of Feeds and Feed Additives Derived from Recombinant DNA technology (MAFF Notification No. 1780 of 2002, hereinafter referred to as "Procedures for Safety Assessment"). Besides the above, the necessity of notification or safety assessment is determined on a specific case-by-case basis by the MAFF.

Feeds manufactured and processed using the notified genome edited feed do not require notification.

3. Genome edited feed additives for which notification is required

(1) Genome edited feed additives using microorganisms

Basically, it is assumed that feed additives comply with the compositional standards specified in the Ministerial Ordinance on the Specifications and Standards.

Notification described in section 4 is required for genome edited feed additives when the microorganisms used in manufacturing of such feed additives meet the following conditions:

- the gene status indicates no remaining foreign gene or its parts; and
- deletion of bases, substitution and insertion of several bases, resulting insertion of one to several mutations by cleavage, etc. with an enzyme recognizing the specific base sequence occur.

However, notification is not required for items that fall under the following 1) or 2).

1) Such additive is manufactured using a microorganism obtained by genome editing technology and it is clear that the gene constitution of the microorganism is equal to that of microorganisms belonging to the taxonomically identical species or naturally occurring microorganisms.

2) Such additive is manufactured using a microorganism obtained by genome

editing technology and is a highly purified nonprotein feed additive.

When the gene status finally shows that a foreign gene and its parts remain, the technology used for the item falls under recombinant DNA technology and such item is subject to safety assessment according to the Procedures for Safety Assessment.

When the gene status of feeds does not fall under the above conditions, the necessity of notification or safety assessment is determined on a specific case-by-case basis by the MAFF.

(2) Genome edited feed additives not using microorganisms

Follow the handling in section 2.

4. Procedure for notification, etc.

(1) Regarding genome edited feeds and feed additives subject to notification shown in the above sections 2 and 3 (hereinafter referred to as "genome edited feed, etc."), a developer, a substitute, or other persons who can submit appropriate supporting data (hereinafter referred to as "developer, etc.") apply for prior consultation according to Attachment 1-1 for feeds and Attachment 1-2 for feed additives to Animal Products Safety Division, Food Safety and Consumer Affairs Bureau, MAFF before the notification to check whether the genome edited feed, etc. subject to notification or a safety assessment.

Genome edited feed, etc. to be subject to prior consultation are limited to those which have been developed for commercialization. For consultation, the information mentioned in section 5 (1) or (2) is provided as much as possible.

(2) Regarding whether the feed, etc. subject to notification or a safety assessment, the MAFF returns the result to developer, etc. with Attachment 2 after checking it with the Genetically Modified Feed Committee of the Feed Subcommittee of the Agricultural Material Council (hereinafter referred to as "Genetically Modified Feed Committee") if necessary.

During the confirmation with the Genetically Modified Feed Committee, when the Subcommittee determines to request advice from the Food Safety Commission, Cabinet Office (hereinafter referred to as "the Food Safety Commission"), the Minister of Agriculture, Forestry and Fisheries consults with the Food Safety Commission, and then based on the advice, determines how to proceed, and gives the results to the developer, etc.

(3) For genome edited feed, etc., which has been confirmed to be subject to notification in a prior consultation, the developer, etc. notify the MAFF of the information mentioned in section 5 (1) or (2) about the feed, etc. using Attachment 3 with necessary supporting data prior to marketing. The year and month of marketing are reported using Attachment 4 at a future date when such feed, etc. is marketed.

(4) After receiving the notification of above (3), the MAFF posts and publishes the information mentioned in section 5 (3) or (4) on the MAFF website promptly. The year and month of marketing are published after receiving a report of Attachment 4 by the developer, etc.

(5) The same procedures are followed for imported products. Importers, etc. may perform

the procedures instead of the developer, etc. when feasible.

(6) Out of genome edited feeds subject to notification, those which are determined to fall under section 3 (1) 1) or 2) by the developer, etc. are subject to prior consultation with the reasons of determination and supporting data as necessary. Items that fall under section 3 (1) 1) or 2) based on the results of prior consultation do not require the procedures in the above sections (3) and (4).

5. Information to be notified and published

(1) For genome edited feeds subject to notification, the developer, etc. notify the MAFF of the following information.
1) Name of item/breed and summary (usage and intended use) of the developed genome edited feed
2) Information on method of genome editing technology and genetic modification used
3) Information on confirmation that there are no remaining foreign genes or their parts
4) Information on confirmation that confirmed changes in DNA do not cause increase of known toxic substances
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
6) Year and month of marketing (*Notify the MAFF of it after marketing)

(2) For genome edited feed additives, developer, etc. notify the MAFF of the following information.
1) Name of the developed genome edited feed additive
2) Information on method of genome editing technology and genetic modification used
3) Information on confirmation that there are no remaining foreign genes or their parts
4) The fact that the additive complies with the compositional standards specified in the Ministerial Ordinance on the Specifications and Standards.
5) Year and month of marketing (*Notify the MAFF of it after marketing)

(3) For genome edited feeds, the MAFF publishes the following information.
1) Names of notifier and developer, and date (year/month/day) of notification
2) Names of item and breed and summary (usage and intended use)
3) Summary of genome editing technology and genetic modification used
4) The fact that it is confirmed that confirmed changes in DNA do not cause adverse effects on livestock health and human health through livestock products
5) Summary of changes in major components (nutrient components only) related to the target metabolic system
6) Year and month of marketing (*Published after receipt of notification mentioned in section 5 (1) 6)

(4) For genome edited feed additives, the MAFF publishes the following information.

1) Names of notifier and developer, and date (year/month/day) of notification
2) Name of item
3) Summary of genome editing technology and genetic modification used
4) The fact that the additive complies with the compositional standards specified in the Ministerial Ordinance on the Specifications and Standards
5) Year and month of marketing (*Published after receipt of notification mentioned in section 5 (2) 5)

6. Handling of crossbred progeny

Notification is not required for crossbred progeny that is obtained by crossbreeding conventional products etc.* by a traditional breeding method with respect to the item notified as a genome edited feed.

*In addition to the conventional breeds, breeds already notified as genome edited feed, etc., and breeds which have been subjected to safety assessment as feeds obtained using recombinant DNA technology.

7. Others

The items specified in this procedures are used to contribute to accumulate scientific knowledge on genome edited feed, etc. and to understand the developmental status. They are reviewed, if necessary, based on usage record, global trends, etc. as feeds when scientific knowledge is accumulated.

When it turns out that this notice is not followed, the person who failed to follow the notice will be required to follow the procedure. It should be noted that when the Act Concerning the Safety Assurance and Quality Improvement of Feeds is violated, information such as developers may be published.

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 Marketing

Attachment 1-1: Prior Consultation Form: Feed

Date:

To Animal Products Safety Division,
Food Safety and Consumer Affairs Bureau,
Ministry of Agriculture, Forestry and Fisheries

Consulter address (location of the principal office for corporations)

Name (corporate name and representative name for corporations)

I would like to apply for the prior consultation regarding the genome edited feed below based on “Feed Safety Guidelines for Genome Edited Feeds and Feed Additives” (notification No. 4605 issued by the Director-General of Food Safety and Consumer Affairs Bureau, Ministry of Agriculture, Forestry and Fisheries on February 7, 2020).

Details

Name

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

2) Information on method of genome editing technology and genetic modification used

3) Information on confirmation of remaining foreign genes or their parts

4) Confirmation that confirmed changes in DNA do not cause adverse effects on livestock health and human health through livestock products or increase of known toxic substances
□ Confirmed □ Unconfirmed

5) Presence of modification affecting the metabolic system for increasing or decreasing specific components
□Modification affecting the metabolic system was performed
□ No effect on the metabolic system

6) Scheduled year and month of marketing (if it is determined)

Note 1: 1) to 3) must be answered.
Note 2: For 3) to 5), attach supporting data used for confirmation.

Attachment 1-2: Prior Consultation Form: Feed Additive

Date:

To Animal Products Safety Division,
Food Safety and Consumer Affairs Bureau,
Ministry of Agriculture, Forestry and Fisheries

Consulter address (location of the principal office for corporations)

Name (corporate name and representative name for corporations)

I would like to apply for the prior consultation regarding the genome edited feed additive below based on “Feed Safety Guidelines for Genome Edited Feeds and Feed Additives” (notification No. 4605 issued by the Director-General of Food Safety and Consumer Affairs Bureau, Ministry of Agriculture, Forestry and Fisheries on February 7, 2020).

Details

Name

1) Name of the developed feed additive

2) Details on method of genome editing and modification used

3) Information on confirmation of remaining foreign genes or their parts

4) Confirmation that the additive complies with the compositional standards specified in the Ministerial ordinance on the compositional standards of feeds and feed additives
□ Confirmed □ Unconfirmed

5) Scheduled year and month of marketing (if it is determined)

6) For consultation regarding the following, information on the reason for the judgment must be attached.

□ When the additive is manufactured using a microorganism obtained by genome editing technology and it is clear that the gene constitution of the microorganism obtained by genome editing technology is equal to that of microorganisms belonging to the taxonomically identical species or naturally occurring microorganisms

□ When the additive is manufactured using a microorganism obtained by genome editing technology and is a highly purified nonprotein feed additive

Note 1: 1) to 4) must be answered.
Note 2: For 3), attach supporting data used for confirmation.

Attachment 2: Response Form

Notice
Date:

To:

From Animal Products Safety Division,
Food Safety and Consumer Affairs Bureau,
Ministry of Agriculture, Forestry and Fisheries

The answer to the consultation on XX by ○○ is as follows.

The genome edited feed, etc. under consultation

(1) are subject to notification. Submit a notification based on "Feed Safety Guideline for Genome Edited Feeds and Feed Additives" (notification No. 4605 issued by the Director-General of Food Safety and Consumer Affairs Bureau, Ministry of Agriculture, Forestry and Fisheries on February 7, 2020).

(2) are feed, etc. derived from the recombinant DNA technology and subject to a safety assessment. Consult with the Ministry of Agriculture, Forestry and Fisheries about the necessary safety assessment procedure.

(3) fall under 3 (1) $\begin{pmatrix} 1) \\ 2) \end{pmatrix}$ of "Feed Safety Guidelines for Genome Edited Feeds and Feed Additives" (notification No. 4605 issued by the Director-General of Food Safety and Consumer Affairs Bureau, Ministry of Agriculture, Forestry and Fisheries on February 7, 2020).

Attachment 3-1: Notification Form: Feed

Date:

To Animal Products Safety Division,
Food Safety and Consumer Affairs Bureau,
Ministry of Agriculture, Forestry and Fisheries

Notifier address (location of the principal office for corporations)

Name (corporate name and representative name for corporations)

Prior to commercial use, I would like to submit notification regarding the genome editing technology below based on “Feed Safety Guidelines for Genome Edited Feeds and Feed Additives” (notification No. 4605 issued by the Director-General of Food Safety and Consumer Affairs Bureau, Ministry of Agriculture, Forestry and Fisheries on February 7, 2020).

Details

Name

Developer, etc. (corporate name and representative name for corporations)

Remarks

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

2) Details on method of genome editing and modification used

3) Confirmation that there are no remaining foreign genes or their parts
□ Confirmed □ Unconfirmed

4) Confirmation that DNA changes due to the genome editing technology do not cause adverse effects on livestock, livestock products, etc. or increase of known toxic substances
□ Confirmed □ Unconfirmed

5) Presence of modification affecting the metabolic system for increasing or decreasing specific components
□Modification affecting the metabolic system was performed
□ No effect on the metabolic system
*Summary of changes in major components (nutrient components only) related to the target metabolic system in the case where modification affecting the metabolic system was performed

Attachment 3-1: Publication Form: Feed

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

2) Summary of genome editing technology and gene modification used

3) Confirmation that DNA changes due to the genome editing technology do not cause adverse effects on livestock health and human health through livestock products or increase of known toxic substances
□ Confirmed □ Unconfirmed

4) Presence of modification affecting the metabolic system for increasing or decreasing specific components
□ Modification affecting the metabolic system was performed
□ No effect on the metabolic system
*Summary of changes in major components (nutrient components only) related to the target metabolic system in the case where modification affecting the metabolic system was performed

Note: This information may be published on the website of the Ministry of Agriculture, Forestry and Fisheries.

Attachment 3-2: Notification Form: Feed Additive

Date:

To Animal Products Safety Division,
Food Safety and Consumer Affairs Bureau,
Ministry of Agriculture, Forestry and Fisheries

Notifier address (location of the principal office for corporations)

Name (corporate name and representative name for corporations)

Prior to commercial use, I would like to submit notification regarding the genome edited feed additive below based on “Feed Safety Guidelines for Genome Edited Feeds and Feed Additives” (notification No. 4605 issued by the Director-General of Food Safety and Consumer Affairs Bureau, Ministry of Agriculture, Forestry and Fisheries on February 7, 2020).

Details

Name

Developer, etc. (corporate name and representative name for corporations)

Remarks

1) Name of the developed feed additive

2) Details on method of genome editing and modification used

3) Confirmation that there are no remaining foreign genes or their parts
□ Confirmed □ Unconfirmed

4) Confirmation that the additive complies with the compositional standards specified in the Ministerial Ordinance on the Specifications and Standards of Feeds and Feed additives
□ Confirmed □ Unconfirmed

Attachment 3-2: Publication Form: Feed Additive

1) Name of the developed feed additive

2) Summary of genome editing technology and gene modification used

3) Confirmation that the additive complies with the compositional standards specified in the Ministerial Ordinance on the Specifications and Standards of Feeds and Feed additives

□ Confirmed □ Unconfirmed

Note: This information may be published on the website of the Ministry of Agriculture, Forestry and Fisheries.

Attachment 4: Notification Form for Marketing

Date:

To Animal Products Safety Division,
Food Safety and Consumer Affairs Bureau,
Ministry of Agriculture, Forestry and Fisheries

Notifier address (location of the principal office for corporations)

Name (corporate name and representative name for corporations)

I would like to submit notification regarding the sales start of the genome edited feed, etc. below based on “Feed Safety Guidelines for Genome Edited Feeds and Feed Additives” (notification No. 4605 issued by the Director-General of Food Safety and Consumer Affairs Bureau, Ministry of Agriculture, Forestry and Fisheries on February 7, 2020).

Details

Name

Developer, etc. (corporate name and representative name for corporations)

Year and date of marketing

Handling Flow of Genome-Edited Feeds and Feed Additives

Prior consultation (with Animal Products Safety Division)
(Attachment 1-1/1-2) or
(Materials that can determine self cloning/natural occurrence/high purification)

Developer, etc.

MAFF

Notification/determination on safety check[*1] (opinions obtained from the Agricultural Materials Council if necessary) (additional opinions obtained from the Food Safety Commission when the Agricultural Materials Council determines them to be necessary)

Submission of additional information (if necessary)

Response (Attachment 2)

Subject to notification

Official notification
Import, distribution, etc., become possible
(Attachment 3-1/3-2)

Publication

Report on year and month of marketing (Attachment 4)

Publication of year and month of marketing

Subject to safety check

Application for safety check[*1]/high purification[*2]

Confirmation procedure for safety check[*1]/high purification[*2]

[Only for microorganisms]
Subject to self cloning/natural occurrence/high purification[*2]

Notification unnecessary

*1: Ministry of Agriculture, Forestry and Fisheries Notification No. 1780 of 2002
*2: Ministry of Agriculture, Forestry and Fisheries Notification No. 2565 of 2015