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Report Name: China Expands Application of Genetically Modified Microorganisms Derived Products in Food Processing

Country: China - People's Republic of

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Report Highlights:

On September 13, 2024, China's National Center for Food Safety Risk Assessment (CFSA) released Requirements for Application Materials for Safety Evaluation of Genetically Modified Microorganisms Used in Food Processing (Trial), which allows genetically modified microorganisms (GMMs) derived products without residual of exogenous genes and GMMs to be used as new food raw materials and new varieties of food-related products in addition to food additives.

Executive Summary

On September 13, 2024, CFSA, under the National Health Commission (NHC), released Requirements for Application Materials for Safety Evaluation of Genetically Modified Microorganisms Used in Food Processing (Trial) (link in Chinese) to clarify the safety evaluation requirements for new food raw materials, new varieties of food-related products, and new varieties of food additives produced from GMMs. The release of this document signifies that, in addition to food additives, GMMs derived products without residual of exogenous genes and GMMs can also be used as new food raw materials and new varieties of food-related products. According to industry interpretation, NHC is responsible for evaluation and approval when the final products contain no residual exogenous genes and residual live cells of GMMs, which means these products do not need to undergo GMO safety approval from MARA. This report provides an unofficial translation of the document.

BEGIN TRANSLATION

Requirements for Submitting Application Materials for Safety Evaluation of Genetically Modified Microorganisms Used in Food Processing (Trial)

Applicants applying for the use of genetically modified microorganisms (GMMs) to produce new food ingredients, new varieties of food additives, and new varieties of food-related products (hereinafter referred to as "three new foods") should follow this document to submit relevant information when the products do not contain newly introduced gene fragments or GMMs.

1. Product Information

1.1 Detection Data for Composition of the Product, Target Product Content, etc.

1.2 Detection Data for Exogenous Gene Residues in the Product

A detailed description of the process steps and parameters for removing exogenous genes during production should be provided, along with a test report confirming the absence of exogenous gene residues in the product. Polymerase Chain Reaction (PCR) should be used to detect specific deoxyribonucleic acid (DNA) fragments (including target genes, reporter genes, marker genes, etc.) of the production strain. See Annex I for requirements related to sample collection, DNA extraction, PCR amplification, and quality control in the PCR method.

1.3 Detection Data for Genetically Modified Microorganism Residues in the Product

A detailed description of the process steps and parameters for inactivating and removing GMMs during production should be provided, along with a test report confirming the absence of residues of viable GMM cells in the product. Microbiological culture methods should be used to detect viable GMM cells in the product. See Annex II for specific requirements related to sample collection, sample pre-treatment, culture and observation, colony counting, quality control, and identification confirmation.

1.4 Environmental Risk Control Measures and Their Effectiveness

A commitment letter stating no risk of environmental release and its supporting materials should be provided, including but not limited to preventive and control measures to ensure that GMMs and their exogenous genes do not enter the environment or undergo gene transfer during production, along with evaluation data and reports on their effectiveness (e.g., at least 3 batches of test data showing no reproducible or transferable genetically modified microorganism residues in waste gas, wastewater, and waste residues generated during production).

1.5 Product Classification

Based on the above data and reports, classify the product. Category I represents purified products, and Category II represents composite products**2. Information Related to GMMs**

2.1 Basic Information

Name (including Chinese name, Latin name, alias, etc.), strain number, source, and intended use.

2.2 Taxonomic and Identification Information

Provide identification reports based on phenotype, genotype, and the latest sequencing technology to the species or subspecies level.

2.3 Biological Characteristics

Including but not limited to the phenotypic and microscopic characteristics, physicochemical properties, etc., of GMMs.

2.4 Information on Growth Environmental Conditions

Provide information on the suitable culture medium and growth conditions for GMMs (including but not limited to culture time, temperature and humidity, aerobic conditions, light, etc.), as well as preservation and rejuvenation methods.

2.5 Regulatory Information of Other Countries

Provide relevant regulatory information of other countries where the genetically modified microorganism-produced products have been approved or recognized.

2.6 Safety Evaluation of GMMs for Food Processing

2.6.1 Survival ability of GMMs in nature, ability to transfer genetic material to other organisms, and possible consequences;

2.6.2 Safety of GMMs

(1) Analysis of virulence genes, drug resistance genes, toxin-producing genes, etc., based on whole-genome sequencing;

(2) Test reports on the pathogenicity, drug resistance, and toxin-producing ability of GMMs;

(3) Bioinformatic comparison data of newly introduced gene expression products from GMMs with known toxic proteins or toxins, as well as with known allergens;

(4) For non-protein products derived from newly introduced gene expression products in GMMs, provide protein residue data from at least 3 batches of samples;

(5) Analyze potential off-target sites and off-target situation based on whole-genome sequencing data. If off-target situation occurs, analyze the possible unintended effects;

(6) Other safety information.

2.6.3 Determine the safety level of GMMs.

3. Safety Evaluation of Recipient Microorganisms

3.1 Background Information

3.1.1 Name (including Chinese name, Latin name, alias, etc.), strain number, source;

3.1.2 Taxonomic information;

3.1.3 Clarify whether it is a naturally occurring wild strain or an artificially cultured strain. If it is an artificially cultured strain, provide information on the original strain;

3.1.4 Safety background information: including but not limited to its application status at home and abroad, long-term safety records, whether there have been any adverse effects on human health or the ecological environment, and whether there is possibility of evolving into a harmful organism.

3.2 Biological Characteristics

3.2.1 Growth cycle and generation time;

3.2.2 Reproduction mode and ability;

3.2.3 Nutritional requirements for optimal growth;

3.2.4 Modes, abilities, and influencing factors of colonization, survival and spread in the environment;

3.2.5 Potential risks to human health and animals (including toxicity, pathogenicity, drug resistance, etc.);

3.2.6 Other biological characteristics.

3.3 Adaptive ecological environment

3.3.1 Geographic distribution and natural growth environment in China, and whether its natural distribution will change due to certain conditions;

3.3.2 Ecological conditions required for growth, including temperature, humidity, pH, light, air, etc.;

3.3.3 Whether it has ecological specificity, such as adaptability in the environment;

3.3.4 Ecological relationships with other microorganisms in the ecosystem, and whether it is susceptible to infection by human and animal pathogens (e.g., viruses). Include the impact of ecological environment changes on these relationships and whether they may result in or increase adverse effects on human health and the ecological environment;

3.3.5 Impact on the ecological environment and potential risks.

3.4 Genetic Variation

3.4.1 Genetic stability;

3.4.2 Plasmid status, plasmid stability, and potential risks;

3.4.3 Transposon status and potential risks;

3.4.4 Whether there is any possibility of genetic variation leading to adverse effects on human health or the ecological environment;

3.4.5 Whether there is any possibility of genetic material exchange with other microorganisms (especially pathogens) under natural conditions.

3.5 Other Information

3.6 Safety Level

4. Safety Evaluation of Genetic Manipulation

4.1 Description of Traits and Characteristics Introduced or Modified in GMMs for Food Processing

4.2 Information on Actually Inserted or Deleted Sequences

4.2.1 Size and structure of the inserted sequence, along with analytical methods to determine its characteristics;

4.2.2 Size and function of the deleted region;

4.2.3 Safety of the target gene;

Detailed description of the donor source, nucleotide sequence, and derived amino acid sequence, function, and safety of the target gene.

(1) Structure: complete DNA or complementary DNA (cDNA) sequence and derived amino acid sequence;

(2) Source of donor microorganism;

(3) Biological characteristics and functions of the donor microorganism;

(4) Safety: comprehensive description of the safety of the target gene based on the donor microorganism's characteristics, safe use history, gene structure, toxicity, pathogenicity, drug resistance, function, etc.

4.2.4 Copy number of the inserted sequence.

4.3 Vector Information

Name and source of the vector, vector characteristics and safety, and whether it can transfer to microorganisms in nature that do not naturally contain such genes. Construct a vector map, detailing the names, locations, and restriction sites of all vector elements.

4.4 Information on Fragments Inserted into the Vector

4.4.1 Names, sizes, DNA sequences, functions, and safe application records of promoter and terminator donor organisms;

4.4.2 Names, sizes, DNA sequences, functions, and safe application records of marker and reporter gene donor organisms;

4.4.3 Names and sources (e.g., synthetic or donor organism) of other expression regulatory sequences, along with their sizes, DNA sequences, functions, and safe application records.

4.5 Gene Manipulation Methods

4.6 Genetic Stability

4.6.1 Stability of target gene integration: use PCR or other methods to amplify exogenous gene fragments, sequence the amplification products, analyze the insertion of exogenous gene fragments or microbial gene deletions, and provide test data from at least 5 generations of subculture;

4.6.2 Stability of target gene expression: use Western Blot, mass spectrometry, chromatography, etc., to analyze the stability of exogenous gene expression in the expression product and provide test data from at least 5 generations of subculture.

4.7 Detection and Identification Techniques for the Target Gene

4.8 Determination of the Safety Type of Genetic Manipulation

Annex I

DNA Detection of Production Strains in Genetically Modified Microbial Products Used in Food Processing

The specific DNA fragments (such as target genes, reporter genes, marker genes, etc.) of the production strain are detected using PCR methods. The requirements for sample collection, DNA extraction, PCR amplification, and quality control involved in the PCR method are as follows:

1. Sample Collection

Each genetically modified microbial product should include at least 3 batches, and each batch should have at least 3 samples for testing. Samples should be collected from the industrial production line, and the specific production steps at the sampling point should be recorded. If there is no industrialized product, pilot-scale products can be used, but it should be clear that the pilot-scale production process (fermentation and post-treatment process) is representative of the industrialized production process.

2. DNA Extraction

Extract DNA from at least 1 g (mL) of sample. If the concentration of the upstream fermentation intermediate product is higher than that of the final product, DNA can be extracted using the upstream fermentation intermediate product.
DNA extraction methods suitable for various cell forms (such as bacterial cells and spores) of the production strain should be used to ensure that potentially residual DNA can be extracted from the product.

3. PCR Amplification

Specific primers are designed for specific DNA fragments of the production strain, and the amplification product should not exceed 1 Kb. The specific DNA fragments, specific primers, polymerase, and amplification conditions of the production strain should be described in detail.

If the production strain contains a drug resistance gene as a reporter/marker gene, multiple pairs of primers can be designed to ensure that the amplification product covers the entire DNA fragment of the drug resistance gene.

4. Quality Control

The following control and sensitivity tests should be included in the PCR test:

(1) The total DNA extracted directly from the production strain is used as a positive control for PCR amplification;
(2) Microbial DNA without the target gene is used as a negative control;
(3) During the experiment, to exclude the presence of PCR inhibitors, nucleases, etc., add total DNA directly extracted from the production strain to the DNA extracted from the sample as a quality control for PCR amplification;

(4) After gradient dilution of the total DNA directly extracted from the production strain, add it to the sample respectively, extract the DNA, perform PCR amplification, and calculate the detection limit;
(5) The detection threshold should not be higher than 10 ng DNA/g(mL) sample.

Appendix II

Evaluation of Absence of Living Production Strains in Genetic Modified Microbial Products Used in Food Processing

The microbial culture method is used to detect the presence of viable genetically modified microorganism cells in the product. The specific requirements for sample collection, sample pre-treatment, culture and observation, colony counting, quality control, and identification & confirmation are as follows:

1. Sample Collection

Each genetically modified microbial product should include at least 3 batches, and each batch should have at least 3 samples for testing. Samples should be collected from the industrial production line, and the specific production process at the sampling point should be recorded. If there is no industrialized product, pilot-scale products can be used, but it should be clear that the pilot-scale production process (fermentation and post-treatment process) is representative of the industrialized production process.

2. Sample Pre-Treatment

Take at least 25 g (mL) of each sample for pre-treatment and then prepare the test solution. Solid sample: Take 25 g, add 225 mL of sterile saline, shake and mix thoroughly to disperse and suspend, and after standing, take the supernatant as a 1:10 diluted test solution. Water-soluble liquid sample: take 25 mL (g), add 225 mL of sterile saline, and mix well to make a 1:10 diluted test solution. Take 1 mL of the above-mentioned test solution and culture the viable production strain cells in a suitable medium for detection. 10 parallel samples are required to calculate the content of the microorganisms to be tested in 1 g (mL) of the sample.

3. Culture and Observation

After placing the above-mentioned plates under suitable conditions for a certain period of time, observe the survival and growth of the producing strain.

4. Colony Counting

Calculate the total number of colonies of the microorganisms to be tested in 10 parallel sample plates and express it as the content of the microorganisms to be tested in 1g(mL) of sample.

5. Quality Control

During the cultivation and testing phase, a positive control should be included for each batch of samples. This involves inoculating a small number of living production strains (e.g., 30-300 colonies per plate) into one sample from each batch to confirm that the culture medium and conditions are suitable for the growth of living production strains in the product.

The specificity of the detection method should be considered to avoid contamination and interference from other microorganisms in the sample.

6. Identification and Confirmation

The result report should provide pictures of colony culture. After the sample is cultured, if colonies similar to the positive control grow on the plate, it should be identified to confirm whether it is a production strain.

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Attachments:

No Attachments.