Ministry of Health and Welfare Announcement No.234

According to amended Specifications and Standards for Foods, Food additives and Other Related Products (the Ministry of Health and Welfare Announcement No. 370-Dec.1954), Standard for manufacturing foods and food additives produced by use of recombinant microorganisms obtained through recombinant DNA techniques is hereby determined as follows:

1st May, 2000

The Minister for Health and Welfare

Standard for Manufacturing Foods and Food Additives Produced by use of recombinant microorganisms obtained through Recombinant DNA Techniques

APPLICATION

Article 1. Regarding foods and food additives produced by use of recombinant microorganism obtained through recombinant DNA techniques, this Announcement determines Standard for manufacturing such foods and food additives in accordance with the provisions stated in paragraph 5 of Part 1 Section B and in paragraph 3 of Part 2 Section E of the Specifications and Standards for Foods, Food Additives, and Other Related Products (the Ministry of Health and Welfare Announcement No. 370-Dec. 1954).

DEFINITION

Article 2. In this Announcement, the term “recombinant DNA techniques” means the techniques as defined in Article 2 paragraph 1 of the Ministry of Health and Welfare Announcement (Announcement No.233-May 2000) enacting Procedures of Application for Safety Assessment of Foods and Food additives Produced by Recombinant DNA Techniques (hereinafter referred to as “Announcement for Procedure of Application”).

2. In this Announcement, the term “host” means a living cell or individual organism to which DNA is to be inserted in applying recombinant DNA techniques.

3. In this Announcement, the term “vector” means a DNA as defined in paragraph 3 of Article 2 of the Announcement for Procedure of Application.

4. In this Announcement, the term “inserted gene” means a gene as defined in paragraph 4 of Article of the Announcement for Procedure of Application.

5. In this Announcement, the term “inserted DNA” means a DNA as defined at paragraph 5 of Article 2 of the Announcement for Procedure of Application.

6. In this Announcement, the term “recombinant” means a host as defined at paragraph 7 of Article 2 of the Announcement for Procedure of Application.

7. In this Announcement, the term “manufacturing area” means a location where the recombinants are directly handled for manufacturing operation.
8. In this Announcement, the term “GILSP recombinant” means the recombinant when the host, vector, inserted DNA, and recombinant satisfy the GLISP criteria shown in Appendix 1.
9. In this Announcement, the term “Category 1 recombinant” means non-pathogenic recombinant other than GILSP recombinant

PRODUCTION STANDARDS

Article 3. When foods and foods additives are produced by use of recombinant microorganisms obtained through Recombinant DNA Techniques, the production shall be performed by the meeting standards stated in Appendix 2 for facility, equipment and apparatus, in Appendix 3 for operational control and in Appendix for personnel and organization.

CONFIRMATION OF COMPLIANCE WITH STANDARDS IN MANUFACTURING FACILITY

Article 4. The Minister for Health and Welfare shall confirm, after hearing opinion of the Food Safety Investigation Council, that each manufacturing facility properly complies with standards stated in the preceding articles when an application is received from an individual who intends to manufacture foods or food additives produced by use of microorganism obtained through recombinant DNA techniques.
2. The individual who intends to undergo the confirmations defined in the proceeding paragraphs shall submit an application form using Exhibit Form 1 with information indicating that the manufacturing facility complies with standards stated in Appendix 2, Appendix 3 and Appendix 4.
3. Where standards for manufacturing facility in foreign country are equal or above level of standards stated in preceding article, the facility can be regarded as complying with the standard.

REPORT

Article 5. Manufacturer shall report the Minister for Health and Welfare, with using Exhibit Form 2, condition of manufacturing operations of recombinants in each manufacturing facility at each starting and ending stage of the production as well as at the end of fiscal year.

NOTICE OF CHANGE

Article 6. Manufacturer who obtained a confirmation in accordance with Article 4, paragraph 1 shall submit a notice of change to the Minister for Health and Welfare when any minor changes are made to the facility, equipment, or apparatus.

INVALIDATION OF CONFIRMATION

Article 7. A confirmation that was made in accordance with Article 4, paragraph1 becomes invalid upon the following conditions:

1. Upon death of the individual who obtained the confirmation (Upon a corporate dissolution if it is a corporation.)
2. Upon change in manufacturing process and others (except for the case stated in the proceeding articles)

Exhibit Form -

(Date)

The Minister for Health and Welfare:

Address (Principal office address for corporate entity)
Name (Corporate name and corporate representative name for corporate entity)

In accordance with “Standards for manufacturing of Foods and Food Additives produced by Recombinant DNA Techniques” (The Ministry of Health and Welfare Announcement No. 234 - May 2000), we hereby request for your confirmation on compliance of manufacturing facility for the attached items:

Foods produced by recombinant DNA techniques
Food Additives produced by recombinant DNA techniques

Note:
1. Use Japan Industrial Standard A4 size paper
2. Write in block letter with India ink, black ink, etc.

Exhibit Form 2 -

MANUFACTURING STATUS REPORT OF FOODS AND FOOD ADDITIVES PRODUCED BY RECOMBINANT DNA TECHNIQUES

Date: _____

Manufacturer:		
	Address (including zip code)	
	Name (including telephone number)	
	Name & title of representative	
Manufacturing facility:		
	Address (including zip code)	
	Name (including telephone number)	
Product name (general name)		
Name & title of general manufacturing director		
Name & title of manufacturing sanitation manager		
Name & title of chairperson of manufacturing safety committee		
Production summary		
Commencement of production(date)		(year) (month) (day)
Present status of manufacturing safety committee(date of a meeting etc.)		
Concerned problems and countermeasures taken in case of necessity		
Others		

Notes:
1. Use Japan Industrial Standard A4 size paper.
2. Write in block letter with India ink, black ink, etc.
3. If there is not enough space to answer the questions above, please write “See Attached ____” and attach a separate sheet to answer.
4. If there are any changes from the previous report, please indicate the mark “*” to the changed items.

Appendix 1

CRITERIA OF PROPERTIES OF RECOMBINANTS REQUIRED FOR SAFETY BY GILSP

Classification	Criteria of Properties
Host	• Non-pathogenic, • No contamination with exogenous pathogenic factors (virus etc.) • Existing long history for industrial safety use • Having characteristics that properly grow in industrial conditions with limited survival and without adverse consequences in external environment.
Vector and inserted genes	• Well characterized and free from known harmful genes sequences, • Limited in size as much as possible to the DNA required to perform the intended function, • Not increase the stability of the recombinants in an environment unless that is requirement of the intended function, • Poorly mobilisable, • Not transfer any resistance markers to microorganisms not known to acquire them naturally
Recombinants	• Non-pathogenic, • As safe in industrial condition as host organism, with limited survival and without adverse consequences in the external environment.

Appendix 2 STANDARDS FOR FACILITIES, EQUIPMENT AND APPARATUS

I. Foods or food additives obtained through GILSP recombinants should be manufactured in the facilities, equipment and apparatus which are appropriate for such production of foods or food additives, and which satisfy the following conditions:

1. There should be manufacturing area.
2. The manufacturing area should be separated from other areas, and provided with the culture and fermentation apparatus for manufacturing foods or food additives by using recombinants.
3. There should be facilities for testing of biological properties of recombinants and for testing specifications of product
4. The following facilities should be provided:
   (1) Storage facilities for recombinants (freezer, refrigerator, etc. to store recombinants separately from others)
   (2) Facilities for preparing culture media, etc. in sanitary conditions.
   (3) Facilities for washing and sterilizing equipment, apparatus, containers, etc. which are used in the manufacturing operation or in analysis and testing.
5. There should be facilities for manufacturing the products without contamination of recombinants.
6. There should be facilities which can prevent formation of harmful impurities on manufacturing process or which can prevent their contamination into the products.
7. There should be other necessary facilities and equipment.

II. Foods or food additives obtained through Category 1 recombinants should be manufactured in the facilities, equipment and apparatus which satisfy the following requirements in addition to the conditions described in the proceeding paragraphs:

1. Recombinants should be handled in a closed system that physically separates the process from the environment.
2. Contamination of substances such as recombinants to gases exhausted from the closed system should be diminished as low as possibly achievable.
3. Leakage of substances such as recombinants should be minimized on sample collection, addition of materials to the closed system, and transfer of recombinants to another closed system.
4. Culture mediums should not be transferred or removed from the closed system unless the recombinants in the mediums have been removed or inactivated by validated means
5. Seals should be designed so as to minimize leakage of substances such recombinants.
6. Biohazard signs should be posted at a manufacturing area in the closed systems if it is necessary.

7. Entry to a manufacturing area in the closed systems should be restricted to registered manufacturing personnel as limited as possible.
8. Manufacturing personnel in a manufacturing area in the closed systems should wear protective clothing for exclusive use.
9. In a manufacturing area in the closed systems, facilities for decontamination and washing should be provided for manufacturing personnel.
10. In a manufacturing area in the closed systems, ventilation facilities should be provided to minimize air contamination.
11. Effluent and waste should be treated by validated means for inactivation before final discharges.

Appendix 3 CONTROL ITEMS

I. Control of Facilities and Equipment

1. After completion of manufacturing operations, the facilities and equipment used should be thoroughly washed and sterilized.
2. Culture equipment, sterilizing equipment and the likes should be inspected for air-tightness and other functions immediately after their installation and periodically thereafter
3. Whenever parts that are involved in the functions of the facilities or equipment are modified and replaced, the air-tightness and other function of such facilities or equipment should be inspected.
4. Sterilizing equipment should be sterilized by the validated method at the time of replacement, periodic inspections and any change in the contents of the product to be manufactured.
5. In the control of the manufacturing facilities and equipment using Category 1 recombinants, the conditions listed under Appendix 2, paragraph 2 must be satisfied.

II. Prevention of Contamination

1. In carrying out the operation in manufacturing area, attention should be paid to avoid contamination by recombinants.
2. Countermeasures for massive leakage of culture mediums containing recombinants and specific emergency procedures should be established.
3. In manufacturing area in which Category 1 recombinants is safely handled, particular attention should be paid to the following:
   (1) To minimize the leakage of aerosol from the facilities and equipment
   (2) To minimize the contamination of the external wall, etc. of the equipment in transferring the recombinant into or taking a sample from the culture equipment.
   (3) To minimize contamination by leakage of recombinants in transferring a recombinant from one culture to another culture equipment or to other facilities or equipment.
   (4) To dispose waster substance and fluid after inactivated them by the validated method.

III. Handling of Recombinants

1. Storage
   (1) Materials that contain recombinants should be clearly labeled as “Recombinants”.

(2) In storage facilities for recombinants, a sign corresponding to the level of manufacturing operations (i.e., “GILSP recombinants in storage”, “Category 1 recombinants in storage”) should be posted in a conspicuous place.

2. Transport
   (1) In case of transporting materials containing recombinants outside the manufacturing area, such material should be placed in a container with sufficient strength and then should be hermetically sealed to prevent leakage of the contents.
   (2) The transport container for the material containing recombinants should be clearly labeled on a conspicuous part of the surface with a warning in red “Handle with care”.

3 Test of biological properties
   (1) At the time of preparation and storage of the master cell bank (It, hereafter, refers the original seed lot of a recombinant from which all manufacturing seed lots are made. It generally consists recombinants, which have been prepared and cloned in the experimental stage and stored in a manner which gives reasonable assurance of genetic stability, after the genetic properties of the recombinants are confirmed to be sufficiently stable within a certain range of serial subcultures.), the stability of recombinants should be verified by conducting tests on the following items:
      • Maintenance of the intended functions. (The properties of recombinants which were provided through recombinant DNA techniques should be maintained.)
      • Maintenance of the basic structure of the vector and the inserted DNA in the recombinant.
      • Any other necessary items on identification and homogeneity of the recombinant. (Master cell bank should be kept away from other organisms for contamination.)
   (2) If the tests performed during storage of the master cell bank indicate occurrence of a mutation affecting the quality or safety of the product, the manufacture should be suspended immediately, and appropriate countermeasures should be taken.
   (3) Safety assurance should be confirmed by testing of biological properties in each production.
   (4) Other items deemed to be necessary.

4. Handling of products
   (1) To establish control standards for products, based upon the safety assessment of the products.
   (2) To inspect each production to verify compliance of the product with the control standards.
   (3) To immediately suspend the manufacturing and take necessary countermeasures, if the product does not comply with the control standards.

Appendix 4 STANDARDS OF PERSONNEL AND ORGANIZATION

I. Organizer or Head of Manufacturing Plant

An organizer or a head of manufacturing plant should perform the following responsibilities:

1. To designate a general manufacturing director and a manufacturing sanitation manager at each manufacturing plant.
2. To establish a manufacturing safety committee, and to designate the members thereof in order to assure manufacturing safety. To request the manufacturing safety committee to investigate and discuss assurance of sanitation in the manufacturing business.
3. To arrange for periodic health examination of manufacturing personnel, and according to the results, to prohibit engaging of the inappropriate personnel in manufacturing operations for foods or food additives.
4. To collect information on recombinant DNA techniques, and, upon obtaining any information which might influence the assessment of the recombinant or safety assessment of the product, to immediately submit a report on that finding to the Minister for Health and Welfare by the organizer of the manufacturing plant.
5. To prepare a procedure manual to countermeasure emergencies, based on advice from the manufacturing safety committee, to handle any emergency situations including accidents.
6. To ensure that the general manufacturing director fulfills his/her duties without impediments.

II. General Manufacturing Director

The general manufacturing director should have a full understanding of the manufacturing standards and perform the following duties:

1. To prepare production operation manual concerning the handling of recombinants, etc. in planning and executing the production plan, comply with the manufacturing standards, etc. and to maintain appropriate control and supervision of all manufacturing operations in close communication with the manufacturing sanitation manager.
2. To have the manufacturing personnel thoroughly understand the manufacturing standards and the production operation manual before commencing the production operation, and to give education and training on the following items:
   (1) Information on safety of recombinants (The origin, production methods, properties, etc. of recombinants).
   (2) Techniques relating to the safe handling of recombinants for manufacture.
   (3) Information and techniques concerning the facilities and equipment.
   (4) Information on sanitary administration, contamination prevention, and others during the manufacturing process.
   (5) Information concerning countermeasures to be taken in the event of an accident (Thoroughly understanding of emergency procedure manual).

3. Records of the following items should be retained for five years from the completion day of manufacture for the foods or food additives:
   (1) Name of the recombinant and the number attached to the container for the recombinant.
   (2) Status of storage and passage of the recombinant (Storage location, storage condition, number of passage, a person in charge of storage, starting date of storage, status of storage and subculture of recombinants, etc.).
   (3) Biological properties of the recombinant and the date tests were performed.
   (4) Name and address of the parties from which the recombinant was obtained, the receiving date, and the recipient name.
   (5) Results of health examinations
   (6) Records of discussion by the manufacturing safety committee (including materials used as a basis of confirming that the production operation manual is in compliance with the manufacturing standards).
   (7) Records of periodical inspections of facilities and equipment, and manufacturing records.
   (8) Records of tests conducted on the products
4. To prepare and maintain a detailed list of the stored items including recombinants.
5. To post a list of necessary information concerning the handling of the recombinants in conspicuous places in the manufacturing area and the recombinant storage facility.
6. To limit the entry of persons other than manufacturing personnel into the manufacturing area, and to direct such persons to follow the instructions of the manufacturing personnel when they enter the area
7. To maintain good communications with the manufacturing safety committee, and to report any necessary information to the committee.
8. To take, in addition to the above, measures necessary for the sanitation assurance of the products.

III. Manufacturing Sanitation Manager

1. The manufacturing sanitation manager should assist the manufacturing director in the operation concerning recombinant DNA technology, and possess required knowledge and advanced skill to assure safety in manufacturing operations.
2. The manufacturing sanitation manager should have a full understanding of the manufacturing standards and perform the following duties.
   (1) To confirm that the manufacturing operations are carried out in compliance with the manufacturing standards, etc.
   (2) To give advice and submit reports to the general manufacturing director.
   (3) To handle, in addition to the above, any necessary items with regard to sanitary assurance of the products.

IV. Manufacturing Personnel

1. The manufacturing personnel should be those who have received education and training from the general manufacturing director.
2. The manufacturing personnel should observe the following items:
   (1) To be fully aware of the necessity of sanitary assurance for the products in the manufacturing operations, and carry out the work in compliance with the production operation manual.
   (2) To wear in the protective clothes for exclusive use in manufacturing area according to the manufacturing level.
   (3) To display a sign in the respective manufacturing area describing the operation being performed during the manufacturing operation which is in accordance with the GILSP or Category 1.

V. Manufacturing Safety Committee

1. The manufacturing safety committee, which is in a position to make judgments on the basis of highly specialized knowledge, technology, and the broad perspective, should be composed of members from appropriate field.
2. The manufacturing safety committee should assess the following matters at the request of the manufacturer, and report the results to the manufacturer:
   (1) Compliance of manufacturing manuals to the manufacturing standards.
   (2) Status of sanitary education and training, and health care of manufacturing personnel.
   (3) Countermeasure and methods of improvement in the event of an accident, including preparation of emergency procedure manuals.
   (4) In addition to the above, any necessary matters related to the sanitary assurance of the products.
3. The manufacturing safety committee may, as occasion demands, request reports from the general manufacturing directors or the manufacturing sanitation manager.

Note: This English version of the Notice is translated to meet the need of the non-Japanese speaking people. In the case of any discrepancy between the Japanese original and the English translation, the former will take priority.