BUREAU VERITAS
Certification

Certification

Awarded to

AMANO ENZYME INC.
NAGOYA PLANT

27, HANNO, KUNOTSUBO, KITANAGOYA-SHI, AICHI, 481-8533, JAPAN

Bureau Veritas Certification Holding SAS – UK Branch certify that the Management System of the above organisation has been audited and found to be in accordance with the requirements of the management system standards detailed below.

STANDARD

FSSC 22000
Certification scheme for food safety systems including ISO 22000:2005, ISO/TS 22002-1:2009 and additional FSSC 22000 requirements

SCOPE OF SUPPLY

MANUFACTURE OF ENZYMES FOR FOOD INDUSTRY.
Product category : L1 Bio Chemical Manufacturing.

This certificate is provided on the base of the FSSC 22000 certification scheme, version 3, published 10 April, 2013. The certification system consists of an annual audit of the food safety management systems and an annual verification of the PRP elements and additional requirements as included in the scheme and the ISO/TS 22002-1:2009.

Original approval date: 04 DECEMBER 2014

Date of certification decision: 04 DECEMBER 2014

Subject to the continued satisfactory operation of the organisation´s Management System, this certificate is valid until: 03 DECEMBER 2017

To check the validity of this certificate, please call: +81 45 651 4784.

Further clarification regarding the scope of this certificate and the applicability of the system requirements may be obtained by consulting the organisation

Certificate Number: DNKFRC98770FH *Date:* 04 DECEMBER 2014

UKAS MANAGEMENT SYSTEMS
008

[redacted]

Signed on behalf of BVCH SAS UK Branch

Certification body address: 66 Prescot Street, London E1 8HG, United Kingdom
Managing office: Bureauveritas Japan Co., Ltd. Silk Building 2F, 1, Yamashita-cho, Naka-ku, Yokohama, 231-0023 Japan

Food Safety System Certification 22000

CERTIFICATE

This is to certify that the firm's quality system conforms to the Self-Imposed Standard of Good Manufacturing Practice for Food Additives (JAFA GMP) in the applicable scope as a result of audit based on the JAFA Quality Assessment and Registration Scheme for JAFA GMP.

Registered number : JAFAGMP – 011 – (4)
Registered date : February 10 , 2003
Registered firm : Amano Enzyme Inc.
Applicable scope :

* Applicable plant & its address

Nagoya Plant

27 Hanno, Kunotsubo, Kitanagoya-shi, Aichi-pref. 4818533 Japan

*Applicable production unit(s) in the plant

Solid fermentation team（Fermentation・Purification）

Products team（Preparation・Processing・Shipping）

*Applicable product(s) in the production unit(s)

All of the food additives to be manufactured at the applicable production units in the applicable plant.

Renewal date : February 2 , 2015
Expiry date : February 9 , 2018
The date of issue : February 2 , 2015

Japan Food Additives Association (JAFA)

[redacted]

[redacted], President

Japan Food Additives Association

[redacted] Tokyo 1030001, Japan

SAFETY AND REGULATORY ASPECTS OF ENZYMES

The safety evaluation of fermentation enzymes should take three levels into account:

- the potential health hazard for the staff involved in the manufacturing and handling of the enzyme (occupational safety)
- the potential risk to the environment in which the micro-organism and/or its products may be released (environmental safety)
- the safety of use by the consumer (consumer safety)

For this last aspect, please refer to the food, feed and industrial uses.

1. Occupational safety

In an occupational setting, two issues have to be addressed:

- possible risks to employees associated with the production organism used
- possible risks to employees associated with the enzyme produced

1.1. Organisms

In the fermentation enzyme industry organisms are commonly used which have a long history of safe use or which have recently been established as being non-pathogenic (i.e. they have never been reported to be able to cause disease in healthy human beings) and non-toxicogenic (i.e. they have been proven not to produce toxic metabolites). In other words, the organisms used in the enzyme industry are not hazardous.

This is further underpinned by the fact that the so-called Biological Agent Directive (Directive 2000/54/EC, see References) does not require any additional measure for handling these organisms. This Directive essentially divides micro-organisms into four hazard categories, ranging from non-dangerous to very dangerous and it lays down occupational measures when using these micro-organisms in a manufacturing process. The dangerous micro-organisms (Group 2 to 4) are listed in Annex III of the Directive. None of the organisms used in the fermentation enzyme industry are listed.

Although the Directive defines the term "biological agent" as micro-organisms including those which have been genetically modified, no consideration has been given to genetically modified micro-organisms when drawing up the list. However, genetically modified micro-organisms are covered by another EU law (see below under Environmental Safety).

1.2. Enzymes

In the early days of the application of enzymes in the detergent industry it became apparent that enzymes could pose an occupational health risk. In hindsight this is not surprising since enzymes are essentially proteins and, like many proteins, inhalation of dust or aerosols may lead to respiratory allergy in susceptible individuals. The symptoms can be compared with those of allergy to pollen (hay-fever) and, like hay-fever, they will disappear when exposure is eliminated.

The risks can be minimised by minimising the exposure, either by engineering controls (ventilation), good handling practices and personal protection measures or by using enzyme preparations which are specifically designed to minimise inhalatory exposure (e.g. liquids, encapsulated or immobilised preparations). In this way the risks can be brought to acceptable levels (i.e. the enzyme preparation can be handled safely) as is proven by the safety record of the present detergent factories. More details on the safe handling of enzymes can be found in the **AMFEP Guide to the Safe Handling of Enzymes**.

Some enzymes, particularly proteases, may cause irritation when they come into contact with skin, eyes or mucous membranes. There is no evidence that enzymes may cause allergy by skin contact, a detailed summary of the relevant literature can be found in the **AISE/AMFEP document Enzymes: Lack of Skin Sensitisation Potential.**

Within the European Union this area is covered by quite a number of regulatory instruments. The most relevant for enzymes are the so-called Dangerous Substances Directive (Council Directive 67/548/EEC and its amendments, see References) and Dangerous Preparations Directive (Directive 1999/45/EC, see References). Both aim to protect man and the environment and one of the instruments to achieve this, is an obligatory provision of information on the hazards of products put on the market in the European Union. It should be noted that the classification, labelling and safety data sheet provisions apply to all enzyme preparations marketed by Amfep.

The system to be followed is:

- hazard identification of the product (also called classification) according to criteria laid down in the Directives
- if the product is classified as dangerous, it has to be labelled. This warning label consists of an indication of danger (symbol), risk phrases (R-phrases) describing the hazard in some detail and Safety phrases (S-phrases) giving a short advice on handling and/or first aid. All of these elements are standardised
- the label information has to be supplemented by a Safety Data Sheet, the contents of which have to comply with yet another Directive (Commission Directive 91/155/EEC and its amendments, see References).

The regulations require that manufacturers classify their products on the basis of the available data and label them accordingly. This label applies until the authorities have agreed on a classification/label and the product has been included onto a list, which is Annex 1 of an amendment to the Dangerous Substances Directive (Commission Directive 96/54/EC, see References).

16 enzymes are presently included in Annex I. All 16 enzymes are classified as R42 (May cause sensitisation by inhalation) and associated with a warning label symbol Xn (Harmful), risk phrase R 42 and the safety phrases S (2-)-22-24-36/37 .

Proteases other than subtilisin are additionally classified as Xi (irritant), R 36/37/38 (Irritating to eyes, respiratory system and skin) and are labelled Xn, R 36/37/38-42, S (2-)-22-24-26-36/37. Subtilisin is additionally classified as Xi (irritant), R 37/38-41 (Irritating to respiratory system and skin, risk of serious damage to eyes) and labelled Xn, R 37/38-41-42, S (2-)-22-24-26-36/37/39.

In case of classification of both Xn and Xi, only Xn is required on the label.

Amfep considers that the risk and safety phrases set by the EU Commission reflects a precautionary and reasonable approach to the risks and good handling practices associated with enzymes.

The above classification and labelling applies to the (pure) enzyme substances. No specific concentration limits have been entered in Annex 1 and in order to decide on the proper labelling of enzyme preparations according to the Dangerous Preparations Directive, the preparation can be tested for the exact amount of enzyme present. Normally, however, a default concentration limit for Xn, R 42 of 1% is used in the case of enzyme preparations.

As a result of the Dangerous Preparations Directive, enzyme containing products not classified Xn, R 42 but containing at least one allergenic component above 0.1%, must bear the inscription 'Contains (name of sensitising substance): May cause an allergic reaction' on the product label. The Dangerous Preparations Directive also introduces environmental classification of preparations but this will not in general affect enzyme preparations.

As enzymes derived from genetically modified organisms are proteins like all other enzymes, the above applies irrespective of the fact if genetic modification of the production organism has been involved.

2. Environmental safety

Also in the area of environmental safety the risks of the enzyme and of the production organism when released into the environment have to be assessed. Since enzymes are just proteins - albeit with a specific catalytic activity - and consequently readily biodegradable, their release into the environment does not raise concerns. Numerous studies have demonstrated that enzymes from all major classes (subtilisins, amylases, cellulase, lipase, etc) are biodegradable. This is expected considering their globular protein structure. Ready biodegradability tests with enzymes from genetically modified organisms, including protein-engineered variants, have not shown any different characteristics compared to naturally occurring or wild type enzymes. This would also be expected, since these techniques do not change the general globular protein structure.

The release of the production organism itself - whether it is genetically modified or not - is controlled by two categories of safety measures. The first one is called physical containment and consists of a fermenter system and recovery (downstreaming) equipment meeting high standards of hygiene, i.e. minimisation of micro-organisms entering or escaping from the equipment. The second, complimentary one, is called biological containment. Essentially, this is the inbred incapability of the organism to survive efficiently in the environment.

The production organisms used in the fermentation enzyme industry are specially bred - again either by traditional methods or by modern genetic techniques - to produce large amounts of one specific substance, the enzyme. Therefore, the production organisms are adapted to grow optimally only under the very specific fermenter conditions. The experience of our industry indicates that the growth in nature of these organisms, should they break the physical containment, is severely handicapped and they cannot compete with other micro-organisms which are present in the environment.

The EU Regulations which cover specifically genetically modified organisms are the so-called Contained Use Directive (Council Directive 90/219/EEC and its amendments, see References) and the Deliberate Release Directive (Directive 2001/18/EC, see References)). They deal exclusively with genetically modified organisms. The second directive is hardly relevant for the fermentation enzyme industry, since typically the enzyme products do not contain the production organism and consequently no genetically modified organisms are put on the market (i.e., they are not "deliberately released"). The Contained Use Directive lays down requirements to ensure a safe and controlled use of genetically

modified organisms, which are in summary:

- Assessment of the potential hazards of the organism
- Requirements for containment (physical and biological) of the organism, which become more stringent as the potential hazard of the organism increases
- A risk assessment of the use of the organism
- Notification of a competent authority before activities (R&D, manufacturing) start
- Depending on the risk category and the scale of the activities, authorisation from the competent authority is needed.

The organisms used in the production of enzymes invariably are classified in the least hazardous category for which no other containment measures are needed than Good Industrial Large Scale Practice (GILSP). These guidelines were formulated by the Organisation of Economic co-operation and Development (OECD) in 1986 and incorporated into the Contained Use Directive.