Application form for safety assessment of Food enzyme that have not been prescribed under the Notification of Ministry of Public Health Re: Enzyme for Food Processing

Company/Partnership/Shop.....

Address.....

.....

Tel.....Fax.....

E-mail.....

Date.....Month.....B.E.....

Re: Request to evaluate the safety of food enzymes that have not been prescribed under the Notification of Ministry of Public Health Re: Enzyme for Food Processing

To: Secretary General of Food and Drug Administration

Attachment: Numbers of evidenced documents for consideration .....items

Since I am..... on behalf of (Company/Partnership/Shop)..... intend to..... (produce/import) a product of enzymes for food production which such product contains enzyme ..... (common name and code in IUBMB system (EC number) (if any))..... from source of enzyme.....that not yet been prescribed qualities or standards under the Notification of Ministry of Public Health Re : Enzyme for Food Processing.

So that evidenced documents and all data required according to a safety assessment application form of enzyme that qualities or standards have not been prescribed under Notification of Ministry of Public Health Re: Enzyme for Food Processing are enclosed for further consideration of its specification.

Sign..... Business operator

(.....)

Name-last name (an applicant).....tel.....

Checklist for safety assessment of food enzyme that have not been prescribed under the Notification of Ministry of Public Health Re: Enzyme for Food Processing

Details of an applicant Name –last name of the applicant/authorized person.....tel..... E-mail .....name of producing/import premise..... License No.of production/import/producing premise..... **address for document delivery (if any)** No..... Trok/soi.....street.....Moo..... tambol/subdistrict..... ampoe/district.....Province..... Tel.....	Please bring this document together with an application form attached with correction of incompleteness for the next time (if any).
Details of applied enzyme **Name of the enzyme:**..... (in Thai) **Name of the enzyme:**..... (in English) **Technological function:**..... **To be used in food:**.....	

Explanation: Request an applicant to arrange documents in sequence as indicated in the following list and also check with mark ✓ by yourself.

Part 1 : Administrative documents				
No.	**Item of document**	**Checked by the applicant**	**Verified by an official**	**Incompleteness record**
1.	Two copies of application forms for safety assessment of enzyme that qualities or standards (Specification) have not been prescribed under the Notification of Ministry of Public Health Re: Enzyme for Food Processing	☐ yes ☐ none	☐ complete ☐ incomplete	
2.	One copy of identification card or passport of the applicant	☐ yes ☐ none	☐ complete ☐ incomplete	
3.	One copy of Commercial Registration Certificate or Objective of Legal Entity Registration document and Authorized officer on behalf of legal entity (in case of assigning authority)	☐ yes ☐ none	☐ complete ☐ incomplete	
4.	One copy of power of attorney from a business operator (in case of assigning authority)	☐ yes ☐ none	☐ complete ☐ incomplete	
5.	Two copies of formal letter and checklist with signature to confirm completeness of documents	☐ yes ☐ none	☐ complete ☐ incomplete	
6.	One set of documents for considering enzymes assessment as specified in the checklist together with the following details:	☐ yes ☐ none	☐ complete ☐ incomplete	
	Summary of overall data of enzyme being assessed for safety (in Thai) that cover items as follows: ● Specification data (from part 2 of document item 1.1 – 1.5) ● Safety assessment data (from part 2 of document item 2.1-2.5)	☐ yes ☐ none	☐ complete ☐ incomplete	
	I have intention for confidential keeping of data/evidence number of pages ..... (if any)	☐ yes ☐ none	☐ complete ☐ incomplete	
7.	One set of CD-ROM contained with evidence and document data.	☐ yes ☐ none	☐ complete ☐ incomplete	

Note: If an applicant has intention for confidential keeping of data/evidences in some parts or whole of the application, the applicant shall arrange a list of the confidential data of safety assessment that intend to be kept secret together with reason to request for such confidential.

Part 2: Technical data					
No.	**Item of document**	**Explanations**	Checked by the applicant	Verified by an official	Incompleteness recorded
1	Identity of the enzyme				
1.1	Enzyme Name(s) and Classification(s)	Enzyme classification, Common Name(s), Trade Name(s), Synonyms and Abbreviations	☐ yes ☐ none	☐ complete ☐ incomplete	
1.2	Reference Number of the Enzyme	EC Number, IUBMB number, INS number or CAS number (if any)	☐ yes ☐ none	☐ complete ☐ incomplete	
1.3	Chemical Composition	In case of enzyme produced from plant, animal or by microorganisms which has not had history of use in food or It is a genetically modified organisms, the following information is required: (1) Molecular Mass (2) Subunit Structure (3) Amino acid sequence (if any)	☐ yes ☐ none	☐ complete ☐ incomplete	
1.4	Impurities	Chemical impurities of food enzyme as tested including the impurities oroginateing from the source and/or the production process eg. heavy metal , mycotoxin or residues of extraction solvents.	☐ yes ☐ none	☐ complete ☐ incomplete	
1.5	Propoties of enzyme	The following required: (1) Information on principal enzymatic activity, specificying substrates, co-factors (if any) and products. (2) the condition of the intended use e.g. optimum temperature and pH, inhibitors and co-factors etc. (3) Any subsidiary, side activities or toxic metabolites which occur from enzyme activity and method of analysis.	☐ yes ☐ none	☐ complete ☐ incomplete	
1.6	Reactions and Fate of Enzyme in Food	Information should be provided on the fate of the enzyme during food processing or food preparation and it behavior in the food products. If any relevant data on the reaction between enzyme and othor nutrients or subtraces in food.	☐ yes ☐ none	☐ complete ☐ incomplete	
1.7	Measurement of enzyme activity	Measurement of the activity should be based on a reference method, the Combined Compendium of Food Additive Specification or Food Chemical Codex. In case the assay method or enzyme activity units differ from the refrence, the detail of method, standard substrace and enzyme activity unit should be provided.	☐ yes ☐ none	☐ complete ☐ incomplete	
1.8	Enzyme specification	Proposed specifications should be provided in a format of the General Specifications and Considerations for Enzyme Preparations used in Food Processing as follows: (1) Enzyme Nomenclature and source (2) Active Component (3) Physical propoties (4) Activity and Unit (5) Optimum condition and method recommend (6) Limit of chemical contaminant (7) Packaging and storage condition	☐ yes ☐ none	☐ complete ☐ incomplete	

Part 2: Technical data					
No.	**Item of document**	**Explanations**	Checked by the applicant	Verified by an official	Incompleteness recorded
2	Source of Enzyme and Manufacturing Process (**Note:** The description should be sufficient to aid in understanding for safety assessment)				
2.1	Source Materials				
	(1) Production from animal sources	Information should be provided on scitific name of animal and which tissue is used for production as well as the history of use as food.	☐ yes ☐ none	☐ complete ☐ incomplete	
	(2) Production from Plant sources	Information should be provided on scitific name and which part(s) is used for the production of enzyme as well as the history of safe use as food with absence of human health adverse effects.	☐ yes ☐ none	☐ complete ☐ incomplete	
	(3) Production from Microbial sources	Provide the information on scientific name, taxonomic identity of strain as well as toxigenic potential, pathogenic potential, history of use in food and antimicrobial production. This include detail on storage condition of the microbail strain, pre-culture and culture condition and procedures to control or monitoring that the strain in use is the same as that described.	☐ yes ☐ none	☐ complete ☐ incomplete	
	(4) Production from genetically modified micro-organisms (GMM)	Following information required;			
		1. Detail of the genetically modified micro-organisms (the recombinant-DNA microorganism) should be provided including, 1.1 Group of microoganism eg. bacteria, yeast or mold, 1.2 Strain, 1.3 Modified gene, 1.4 the objective of gene modification 1.5 safety the recombinant-DNA microorganism.	☐ yes ☐ none	☐ complete ☐ incomplete	
		2. Information on recipient or host identity should be provide:			
		2.1 Scientific name of recipient or host cell;	☐ yes ☐ none	☐ complete ☐ incomplete	
		2.2 Common name (if any) or other name(s);	☐ yes ☐ none	☐ complete ☐ incomplete	
		2.3 Taxonomy classification or strain designation or information about the strain and its source;	☐ yes ☐ none	☐ complete ☐ incomplete	
		2.4 accession numbers or other information from a recognized culture repository from which the organism or its antecedents may be obtained;	☐ yes ☐ none	☐ complete ☐ incomplete	
		2.5 history of use and cultivation, known information about strain development, identifying traits that may adversely impact human health; history of safe use in food production or safe consumption in food; and	☐ yes ☐ none	☐ complete ☐ incomplete	
		2.6 information on genotype and phenotype relevant to its safety, including any known toxins, antibiotics, antibiotic resistance factors or other factors related to pathogenicity, or immunological impact, and information about the genetic stability of the microorganism;	☐ yes ☐ none	☐ complete ☐ incomplete	

Part 2: Technical data					
No.	**Item of document**	**Explanations**	Checked by the applicant	Verified by an official	Incompleteness recorded
	(4) Production from GMM source(s) - con't	3. In formation on donor organism(s) including:			
		3.1 The description of the donor or intermediate organism(s) should include: 3.1.1 scientific name, 3.1.2 common name or other name(s) used to reference the organism, 3.1.3 strain designation, 3.1.4 information about the strain and its source, or accession numbers or other information from a recognized culture repository from which the organism or its antecedents may be obtained, if applicable, information supporting its taxonomic assignment; 3.1.5 information about the organism or related organisms that concerns food safety; 3.1.6 information on the organism's genotype and phenotype relevant to its safety including any known toxins, antibiotics, antibiotic resistance factors or other factors related to pathogenicity, or immunological impact; and information on the past and present use, if any, in the food supply and exposure route(s) other than intended food use (e.g., possible presence as contaminants).	☐ yes ☐ none	☐ complete ☐ incomplete	
		3.2 In cases of the synthetic DNA and it is not a copy of the natural nucleotide sequence of a gene following information require: 3.2.1 Functional and role of synthetic DNA, 3.2.2 given the sequence of amino acids.	☐ yes ☐ none	☐ complete ☐ incomplete	
		4. information on the genetic modification including vector and construct should be provided: 4.1 information on the specific method(s) used for genetic modification, 4.2 information on the DNA added, inserted, deleted, or modified, including: - the characterization of all genetic components including marker genes, vector genes, regulatory and other elements affecting the function of the DNA; - the size and identity; C) the location and orientation of the sequence in the final vector/ construct; and - the function.	☐ yes ☐ none	☐ complete ☐ incomplete	
		5. Information should be provided on the DNA modifications in the recombinant DNA microorganism; this should include:			
		5.1 Information of genetic modification in GMM 5.1.1 the characterization and description of the added, inserted, deleted, or otherwise modified genetic materials, including plasmids or other carrier DNA used to transfer desired genetic sequences. This should include an analysis of the potential for mobilization of any plasmids or other genetic elements used, the locations of the added, inserted,	☐ yes ☐ none	☐ complete ☐ incomplete	

Part 2: Technical data					
No.	**Item of document**	**Explanations**	Checked by the applicant	Verified by an official	Incompleteness recorded
	(4) Production from GMM source(s) - con't	deleted, or otherwise modified genetic materials (site on a chromosomal or extra-chromosomal location); if located on a multi-copy plasmid, the copy number of the plasmid; 5.1.2 The number of insertion sites 5.1.3 the organisation of the modified genetic material at each insertion site including the copy number and sequence data of the inserted, modified, or deleted material, plasmids or carrier DNA used to transfer the desired genetic sequences, and the surrounding sequences. This will enable the identification of any substances expressed as a consequence of the inserted, modified or deleted material.			
		5.1.4 Identification of any open reading frames within the inserted DNA or created by insertion with contiguous animal chromosome or plasmids including those that could result in fusion proteins; 5.1.5 particular reference to any sequences known to encode, or to influence the expression of, potentially harmful functions.			
		5.2 Information should be provided on any expressed substances in the recombinant-DNA microorganism; this should include: 5.2.1 The gene product(s) (e.g. a protein or an untranslated RNA) or other information such as analysis of transcripts or expression products to identify any new substances that may be present in the food; 5.2.2 The gene product(s)' function; 5.2.3 The phenotypic description of the new trait(s); 5.2.4 The level and site of expressed gene product(s), and the levels of its metabolites - Gram netgative bacteria, please specify gene product(s) found in cell or periplasm - Eukaryotes, please specify gene product(s) found in organelle or secretion and, when applicable, the levels of its metabolites in the organism; 5.2.5 The amount of the insert gene product(s) if the function of the expressed sequence(s)/gene(s) is to alter the level of a specific endogenous mRNA or protein; and 5.2.6 the absence of a gene product, or alterations in metabolites related to gene products, if applicable to the intended function(s) of the genetic modification(s).	☐ yes ☐ none	☐ complete ☐ incomplete	

Part 2: Technical data					
No.	**Item of document**	**Explanations**	Checked by the applicant	Verified by an official	Incompleteness recorded
	(4) Production from GMM source(s) - con't	5.3 In addition, information should be provided to: 5.3.1 demonstrate whether the arrangement of the genetic material used for insertion has been conserved or whether significant rearrangement have occurred upon integration 5.3.2 demonstrate whether deliberate modifications made to the amino acid sequence of the expressed protein result in changes in its post-translational modification or affected sites critical for its structure or function 5.3.3 demonstrate whether the intended effect of the modification has been achieved and that all expressed traits are stable and are expressed as expected	☐ yes ☐ none	☐ complete ☐ incomplete	
		5.3.4 demonstrate whether the newly expressed trait(s) are expressed as expected in the appropriate tissues in a manner and at levels that are consistent with the associated regulatory sequences driving the expression of the corresponding gene 5.3.5 indicate whether there is any evidence to suggest that one or several genes in recombinant DNA microorganisms has been affected by the transformation process 5.3.6 The identity and expression pattern of any new fusion proteins			
		6. Demonstration of the absence of the GMM in the product 6.1 The technique used to remove microbial cells and DNA in the course of the product preparation process should be detailed 6.2 The procedure has to ensure the detection of production strain 6.3 The procedure has to ensure the detection of stressed cells	☐ yes ☐ none	☐ complete ☐ incomplete	
3.1	Manufacturing process	Detail of enzyme production process or fermentation and control factors e.g. temperature, amount of nutrient or gas, chemical that use in fermentation process and purification should be described as completely as possible. A flow chart diagram showing the most important steps in the process should accompany the description.	☐ yes ☐ none	☐ complete ☐ incomplete	
3.2	Immobilization procedure (if any)	In the case of immobilised enzymes, information on the immobilization procedure is required: enzyme support materials, immobilisation agents include its propoties and characteristic.	☐ yes ☐ none	☐ complete ☐ incomplete	

Part 2: Technical data					
No.	**Item of document**	**Explanations**	Checked by the applicant	Verified by an official	Incompleteness recorded
4	Safety data of enzyme				
4.1	In case source of enzyme does not has history of use in food/food production process or enzyme produced by using genetic modification microorganisms, safety information should be provided as follow:				
4.1.1	Toxicological study that specify the following indicators	Experimental design as specified by Organization for Economic Co-operation and Development (OECD) as the following case: - Repeated Dose 90-Day Oral Toxicity Study in Rodents or - Repeated Dose 90-Day Oral Toxicity Study in Non-Rodents	☐ yes ☐ none	☐ complete ☐ incomplete	
4.1.2	Assessment of genotoxicity	Gene mutation in bacteria (Ames test, OECD Guideline 471) and chromosomal aberration (OECD Guideline 473) or micronucleus assay (OECD Guideline 487) or mouse lymphoma TK assay (OECD Guideline 476)	☐ yes ☐ none	☐ complete ☐ incomplete	
4.1.3	Allergenicity	The allergenicity of the food enzyme should be considered and a search for amino acid sequence and/or structural similarities between the expressed protein at least 2 database and the database must not old than 3 years from the day after submission.	☐ yes ☐ none	☐ complete ☐ incomplete	
4.1.4	Dietary exposure and risk assessment of the enzyme	1. Health risk assessment has to describe information as follow: - Food consumption in Thailand for 7 age groups for average and hight percentile of whole population (per capita). - Conversion factors refer from standard component formulas of general recipes or refer to the Food and Agriculture Organization of the United Nations. - The maximum concentration of enzyme recommended for using in each food which calculated as mg (TOS) / kg food. 2. Safety assessment by calculating the margin of exposure (MOE) that obtained from compared the amount of exposure with point of departure (POD), which is the NOEL or NOAEL, or the benchmark dose level that obtained from the study of subchronic oral toxicity studies	☐ yes ☐ none	☐ complete ☐ incomplete	
4.1.5	Acceptable Daily Intake: ADI	Acceptable Daily Intake (ADI) spacify by: (1) No-Observed-Effect Level (NOEL) and/or the No-Observed-Adverse-Effect Level (NOAEL) (2) Safety factor for calculation (3) Toxicological versus physiological responses (4) MOE	☐ yes ☐ none	☐ complete ☐ incomplete	
4.2	In case source of enzyme has history of use in food/food production process that has to describe safety information as follow:				
4.2.1	Plant or animal	Information or evudences on history of use of that plant or animal as human food.	☐ yes ☐ none	☐ complete ☐ incomplete	
4.2.2	Microorganism	Information or evidences on history of use as human food or the safety assessment to allowe for using in	☐ yes ☐ none	☐ complete ☐ incomplete	

Part 2: Technical data					
No.	**Item of document**	**Explanations**	Checked by the applicant	Verified by an official	Incompleteness recorded
		food production process, the reference e.g. Qualified Presumption of Safety (QPS) or Bulletin of the *International Dairy Federation* (IDF).			
5	Safety assessment report or legal document associated (if any)				
5.1	Safety evaluation report or opinion from risk assessment body of other countries	Safety assessment report or opinion on existing authorisations or bordies of other country e.g. USA, Canada, EU, Australia-New Zealand, Japan or South-Korea.	☐ yes ☐ none	☐ complete ☐ incomplete	
5.2	Other document	Response letter or Permit from agency or Patent document that describe technical or the method of enzyme production	☐ yes ☐ none	☐ complete ☐ incomplete	

I do hereby certify that supporting evidence documents for consideration of safety assessment attached herewith are true and trustworthy and if an official have any query in these documents, I agree to give more additional data for official when requesting.

Sign ..... an applicant/authorized person

(.....)

Checking result of completeness of supporting documents

For an applicant only	For official only
1st submission ***Part 1 Submission for checking an application and evidenced documents*** ☐ Sign to accept checking result of the completeness of evidenced documents Sign .....an applicant/authorized person (.....) Date.....time..... ☐ Request to return supporting documents for assessmentof specification in case of incomplete documents Sign .....an applicant/authorized person (.....) Date.....time..... ☐ Agree with defects and will further finish for correction **within 15 working days** from the day after the date of checking the completeness of evidenced documents of the application. (from date.....to date.....) If it is overdue, cancellation and return of the application and evidenced documents can be undertaken. Sign .....an applicant/authorized person (.....) Date.....time.....	1st submission ***Part 1 Checking for the completeness of evidenced documents*** ☐ Complete documents, the applicant request has safety assessment report from the Food and Drug Administration. ☐ Complete documents, the applicant request has safety assessment report from International safety assessment unit at least 2 contries. ☐ Incomplete documents and the applicant request to return the documents. ☐ Incomplete documents and consider to accept the application with a condition due to incomplete or incorrect documents as specify in checklist (defects found as above specified). The applicant shall correct or submit additional documents for the first round **within 15 working days** from the day after the date of receiving the application (from date.....to date .....). If it is overdue, the application will be terminated and further returned (the applicant shall be informed by signing and receive a copy) notify to proceed..... .... Sign by an official..... (.....) Date.....Time.....
Part 2 Submission the application and evidenced documents for evaluation of technical documents (case of complete documents) ☐ I have submitted the application and evidenced documents that are checked for its completeness in the number of.....set together with receipt of payment for technical document evaluation. Sign .....applicant/authorizedperson (.....) Date .....time.....	***Part 2 Acceptance of the application for technical document evaluation*** ☐ Document is complete, accept the request for prescribing standard ☐ Document is complete, receipt of payment for technical document evaluation is presented and to accept the application is considered. Signed by checking officer..... (.....) Date .....time.....

Checking results of completeness of supporting evidenced documents (continued)

The applicant only	Officer only
2nd time (1st round of submission to correct the defects) ***Part 1 Submission the application and evidenced documents*** ☐ I have submitted correcting or additional documents in the number of……items as specified in the incomppleteness recorded form. Sign …… applicant/authorized person (……) Date ……time…… ☐ Sign to accept checking result of the completeness of evidenced documents Sign …… applicant/authorized person (……) Date ……time…… ☐ Request to return supporting documents for assessment of specification and safety in case of incomplete documents Sign …… applicant/authorized person (……) Date ……time…… ☐ Agree with incompleteness and will further finish for correction **within 15 working days** from the day after the date of checking the completeness of evidenced documents of the application (from date……to date……). If it is overdue, agree for cancellation and return of the application and evidenced documents. Sign …… applicant/authorized person (……) Date ……time……	2nd time (1st round of submission to correct the defects) ***Part 1 Checking for the completeness of evidenced documents*** ☐ Complete documents, the applicant request has safety assessment report from the Food and Drug Administration. ☐ Complete documents, the applicant request has safety assessment report from International safety assessment unit at least 2 contries. ☐ Incorrect or incomplete documents and the applicant request to return the documents of safety assessment. ☐ Incomplete documents and consider to accept the application with a condition due to incomplete or incorrect documents as specify in checklist (defects found as above specified). The applicant shall correct or submit additional documents for the second round **within 15 working days** from the day after the date of receiving the application (from date……to date ……). If it is overdue, the application will be terminated and further returned (the applicant shall be informed by signing and receive a copy) notify to proceed…… …… ☐ Return the application together with supporting documents for assessment of specification since the correction is not undertaken or additional documents are not submitted on due date. You have right to renew the submission by providing with accurate and complete documents or may appeal for document return at this time by submit a letter of appeal to the Secretary General of the Food and Drug Administration within 15 working days from the day of receiving the returned application. Signed by checking official…… (……) Date ……time……
Part 2 Submission the application and evidenced documents for evaluation of technical documents (case of complete documents) ☐ I have submitted the application and evidenced documents that are checked for its completeness in the number of……set together with receipt of payment for technical evaluation. Sign …… applicant/authorized person (……) Date ……time……	***Part 2 Acceptance of the application for technical document evaluation*** ☐ Document is complete, accept the request for prescribing standard ☐ Document is complete, receipt of payment for technical evaluation is presented and to accept the application is considered. Signed by checking official…… (……) Date ……time……

3rd time (2nd round of submission to correct the defects) ***Part 1 Submission the application and evidenced documents*** ☐ I have submitted correcting or additional documents in the number of.....items as specified in the incompleteness recorded form. Sign ..... applicant/authorized person (.....) Date .....time..... ☐ Sign to accept checking result of the completeness of evidenced documents. Sign ..... applicant/authorized person (.....) Date .....time..... ☐ Request to return supporting documents for assessment of specification. Sign ..... applicant/authorized person (.....) Date .....time.....	3rd time (2nd of submission to correct the defects) ***Part 1 Checking for the completeness of evidenced documents*** ☐ Complete documents, the applicant request has safety assessment report from the Food and Drug Administration. ☐ Complete documents, the applicant request has safety assessment report from International safety assessment unit at least 2 contries. ☐ Incorrect or incomplete documents and the applicant request to return the documents of safety assessment. ☐ Return the application together with supporting documents for assessment of specification since the correction is not undertaken or additional documents are not submitted on due date. You have right to renew the submission by providing with accurate and complete documents or may appeal for document return at this time by submit a letter of appeal to the Secretary General of the Food and Drug Administration within 15 working days from the day of receiving the returned application. Signed by checking official..... (.....) Date .....time.....
Part 2 Submission the application and evidenced documents for evaluation of technical documents (case of complete documents) ☐ I have submitted the application and evidenced documents that are checked for its completeness in the number of.....set together with receipt of payment for technical document evaluation. Sign ..... applicant/authorized person (.....) Date .....time.....	***Part 2 Acceptance of the application for technical document evaluation*** ☐ Document is complete, receipt of payment for technical document evaluation is presented and to accept the application is considered. Signed by checking official..... (.....) Date .....time.....