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**NEW DIETARY INGREDIENT (NDI)  
SAFETY INFORMATION**

**CANTECH PHARMA, INC.**



## Instructions

In this template, which supplements the data entry screens in the NDI notification electronic submission portal, you will describe the scientific information on which you base your conclusion that the dietary supplement containing the NDI will reasonably be expected to be safe. Safety information includes, among other things, (1) information showing that the NDI is identical or related to substances documented as having a history of use as food; (2) information showing that the NDI is identical or related to test articles used in safety studies; (3) information showing that a substance or product has a history of use as food; and (4) safety data, including the results of genetic toxicology studies, pharmacokinetic studies, animal toxicology studies and human clinical studies. This template asks for details about the identity of the NDI, verification of that identity, information about history of use as food, and any other evidence relevant to the safety of the NDI under its proposed conditions of use in the dietary supplement. After filling in the template, you will upload the completed template as an attachment to your online NDI notification and attach files containing the scientific publications cited in your notification.

For a notification that concerns the use of an NDI in a dietary supplement that contains no other ingredients, the safety of the NDI and the dietary supplement would be synonymous.

In other situations, however, that may not be the case. For example, when an NDI is used in a dietary supplement with one or more other NDIs, the safety of the dietary supplement may not be the sum of the safety of the individual NDIs. In such circumstances, you should document your basis for concluding that the dietary supplement will reasonably be expected to be safe and explain why that conclusion is reasonable. For example, if two botanical extracts have separate histories of use in traditional medicine, but no history of being used together, the safety of the combination may not be clear from the safety information pertaining to the individual NDIs. On the other hand, if an extract of a medicinal herb is combined with an extract of a material that has a long history of safe use as food, then it may be reasonable to conclude that the combination is safe based on information about the safety of the individual NDIs. If you wish to submit a notification for the use of an NDI in a dietary supplement with other NDIs, the FDA recommends that you confer with a member of the New Dietary Ingredient Review Team in FDA’s Division of Dietary Supplement Programs about how to proceed. If you have any questions concerning this matter please contact the New Dietary Ingredients Review Team, which can be reached on (240) 402-1756 or by email at [fred.hines@fda.hhs.gov](mailto:fred.hines@fda.hhs.gov).

If a section or subsection is not applicable to your notification, mark “N/A” in your response.

Sections marked as “Required” in the template’s section headings must have complete responses in all subsections for which you have data. If you leave a “Required” section blank or respond “N/A,” FDA will consider your notification incomplete for failure to comply with 21 CFR 190.6(b). An incomplete notification does not satisfy the requirement



## FDA New Dietary Ingredient Notification Safety Information

to submit an NDI notification. You may not introduce your NDI, or a dietary supplement containing the NDI into interstate commerce or deliver the NDI or dietary supplement for introduction into interstate commerce, until at least 75 days after you have submitted a complete notification to FDA.

- Please include full citations for all published and unpublished sources cited or relied on in your notification in the Reference List (Section 5). You will be prompted to attach e-copies of these sources when you return to the electronic submission portal after filling in this template.
  
- The template includes some sections identified as “Recommended.” These sections solicit information that FDA considers helpful in evaluating NDI notifications. You are encouraged but not required to respond to template sections that are identified as “Recommended.” However, if you leave a “Recommended” section blank or respond “N/A” and FDA determines that the information is needed to establish safety, your notification may be considered inadequate to conclude that the NDI will reasonably be expected to be safe under its proposed conditions of use in the dietary supplement.



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**1. New Dietary Ingredient Identity Information (Recommended)**

Cantech Pharma, Inc. ImmuneBooster

**1.1 Description of the identity of the NDI**

A combined suspension of Inactivated Pepsin Fragment (IPF) that comes from the purified extract of Pepsin from Porcine gastric mucosa powder under the NDI number of 1083 and ascorbic acid (vitamin C). The combined products contain a chain of amino acids from the IPF and vitamin C from the ascorbic acid in a liquid form to be ingested orally via a dropper applicator. The IPF compound contains Pepsin from Porcine and Sodium Chloride, as dietary ingredients and other ingredients such as Sodium Citrate, Ammonium Sulfate and Sodium Acetate (USP grade) that serve as buffering agents. Ascorbic acid (USP grade) is added for vitamin C.

**1.2 Description of the evidence verifying the identity of the NDI**

We verify the identity of this NDI in several documents of which we have enclosed copies:

The first relates to the actual extraction from porcine. These procedures are established in the document called: *Pepsin extraction process from swine* published in August 2012 at the 20th International Congress of Chemical and Process Engineering CHISA by authors E. Jurado a\*, J. M. Vicaria, M. Lechuga, I. Moya-Ramírez of the Department of Chemical Engineering, Faculty of Sciences, University of Granada, Spain.

The second illustrates the profound scientific research and development of pepsin as a commonly used for human on a diversity of ways with consistency and safety. This document is: *Inactivated pepsin inhibits neutrophil activation by Fcγ-receptor-dependent and independent stimuli*, presented by Iwan Kustiawan, Ninotska Derksen, Theo Rispen from the Sanquin Research, Department of Immunopathology, and the Landsteiner Laboratory, Academic Medical Centre, University of Amsterdam, The Netherlands

The third comes from Sigma Aldrich for the Pepsin from Porcine Gastric mucosa powder product P-7000 specification sheet as provided by this company.

The fourth document referring to the extract or amino acid chain Inactivated Pepsin Fragment that is listed under US Patent Number: US 7479538 Document Kind: B2 Patent Title: Irreversibly-inactivated pepsinogen fragment Named Inventors: ZHABILOV HARRY H Applicants (Assignees): ZHABILOV TRUST Agents: Cislo & Thomas, LLP Filing Date: 7/11/2005 Issue/Pub Date: 1/20/2009 Patent Termination: Expires: 7/11/2025.



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The fifth document refers to the ascorbic acid specification chart outlining product, nutrition, and toxicological facts of the product provided by the ascorbic acid supplier.

**1.3 NDI manufacture**

Cantech Pharma ImmuneBooster is commercialized and distributed by Cantech Pharma, Inc. and manufactured by:

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(b) (4) specializes in contract manufacturing, analytical services, product development, formulation, fill/finish/lyophilization, and supporting laboratory services compliant with cGMP guidelines for all Phases of drug product development and supply from preclinical toxicology batches to commercial launch and supply. These services include formulation, processing, and filling capabilities for both vial and syringe applications. The company has FDA approved installations and a very comprehensive in-house QA/QC program that adheres to the applicable regulatory requirements with attention to the specifics as outlined in the Good Laboratory Practice (GLP) and current Good Manufacturing Practice (cGMP) guidelines, as well as European standards.

We have enclosed for this point two documents: a presentation of the manufactures and a copy of its drug manufacturing license.

**1.3.1 Raw materials**

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### 1.3.2 Formulation ingredients

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**1.3.3 Manufacturing process**

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### 1.3.4 NDI specifications

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### 1.3.5 Methods of analysis

Reversed phase chromatography, a bonded phase chromatographic technique uses water as the base solvent. Separation based on solvent strength and selectivity may also be affected by column temperature and pH. In general, the more polar components elute faster than the less polar components.

Reversed-phase high-performance liquid chromatography of peptides of porcine pepsin prepared by the use of various forms of immobilized  $\alpha$ -chymotrypsin.

Reversed-phase high-performance liquid chromatography (RP-HPLC) separation was used for the comparison of peptide maps of pepsin after its digestions by different forms of immobilized  $\alpha$ -chymotrypsin. Porcine pepsin was hydrolyzed with soluble  $\alpha$ -chymotrypsin, with  $\alpha$ -chymotrypsin glycosylated with lactose or galactose coupled to hydrazide derivative of cellulose, with  $\alpha$ -chymotrypsin attached to poly(acrylamide-allyl glycoside) copolymer or to glycosylated hydroxyalkyl methacrylate copolymer Separon or to agarose gel Sepharose 4B. Efficiency of enzymatic protein cleavage with regard to peptide mapping of porcine pepsin has been examined by the use of  $\alpha$ -chymotrypsin immobilized by different methods. Best results were achieved after hydrolysis with  $\alpha$ -chymotrypsin immobilized on poly (acrylamide-allyl glycoside) copolymers.  $\alpha$ -Chymotrypsin immobilized by this way has further three times higher relative specific activity in comparison with the soluble one. Modified  $\alpha$ -chymotrypsin was not suitable for efficient pepsin cleavage.

Journal of Chromatography B: Biomedical Sciences and Applications

Volume 753, Issue 1, 25 March 2001, Pages 37-43 H. Vaňkováa Z. Kučerováa and J. Turková1b

Enclosed the Reviewer Guide Validation of Chromatographic Methods for CDER at FDA.

Reversed-phase high-performance liquid chromatography (RP-HPLC) involves the separation of molecules on the basis of hydrophobicity. The separation depends on the hydrophobic binding of the solute molecule from the mobile phase to the immobilized hydrophobic ligands attached to the stationary phase, i.e., the sorbent.



Suitability:

- Solutions at pH 4.4 are stable at -20°C for about 2-3 months.<sup>1</sup>
- Since pepsin is not active when not at an acidic pH, solution stability should be good at pH 6-7. Bringing the pH up to 8, however, will irreversibly inactivate pepsin.
- Pepsin is irreversibly denatured at pH 8.5 - 11 at room temperature.<sup>2</sup>
- In a 0.1 N sodium acetate buffer, pH 4.6 - the enzyme remains fully active and inactivation of the enzyme begins at temperatures above 60 Deg. C.<sup>3</sup>

Specificity:

Demonstrated by analyzing diluent, buffer and pepsin, found that no interference was observed.

Linearity:

The report of coefficient of determination ( $r^2$ ) from linear regression is NLT 0.995

### **1.3.6 Analysis of potentially toxic processes**

Skin Contact:

Causes skin irritation. May cause allergic skin reaction. May cause allergic contact dermatitis.

Eye Contact:

Causes eye irritation.

Inhalation:

Irritating to respiratory system. May cause allergic respiratory reaction due to allergic sensitization of the respiratory tract.

Enclosed you will find the analysis and complete figures performed by Pyramid Laboratories Inc. following GMP and approved by FDA. It is pertinent to add that some values of the study pertain to analysis performed considering to uses that can be different to a dietary supplement, nevertheless the values of identification as well as all applicable for this supplement are valid since it is the same substance.

Chronic Toxicity:

Prolonged or repeated exposure may cause allergic respiratory and skin reactions.

**Sensitization:**

May cause sensitization by inhalation and skin contact.

Pepsin from Porcine 1:10,000 is classified under U.S. regulations: FDA - Food Additives Generally Recognized as Safe (GRAS): 21 CFR 184.159 FDA - 21 CFR - Total Food Additives 137.305 184.1595

Ascorbic Acid is classified under U.S. regulations: FDA – Food Additives Generally Recognized as Safe (GRAS): 21 CFR 182.8031

**1.3.7 Disintegration and dissolution profile**

The application is in a liquid form therefore a Profile of Disintegration and Dissolution does not apply for either compound, but Irreversible Pepsin Fraction is soluble in deionized water at 1% (10 mg/ml) and at 0.4% (4 mg/ml) in cold 10 mM hydrochloric acid. Solutions at pH 6 - 7 are stable at 2 - 8 °C for one year.

**1.3.8 Shelf-life and conditions of storage**

The solution at pH 6 - 7 is stable at 2 - 8 °C for one year. Storage should be at the mentioned temperature. Stability was performed on three separate batches of IPF to determine shelf-life and conditions of storage by measuring the pH of the final product and using the Lowry method for measuring the concentration of the protein. The product itself doesn't have a hard expiration date. According to our supplier they have it set up on a retest schedule every two years. Most of the time they will sell out of a lot prior to the 2-year retest date. When this happens, they do not re-test. According to the manufacturer of the ascorbic acid, shelf-life is estimated to be at 3 years maximum. We are reasonably estimating a very conservative one-year expiration date for the combination of IPF and ascorbic acid.

The solution stability information that we have is below.

We have not tested the solution but have accumulated several references from which this information is gleaned.

- Solutions at pH 4.4 are stable at -20°C for about 2-3 months.<sup>1</sup>
- Since pepsin is not active when not at an acidic pH, solution stability should be good at pH 6-7. Bringing the pH up to 8, however, will irreversibly inactivate pepsin.
- Pepsin is irreversibly denatured at pH 8.5 - 11 at room temperature.<sup>2</sup>
- In a 0.1 N sodium acetate buffer, pH 4.6 - the enzyme remains fully active and inactivation of the enzyme begins at temperatures above 60 Deg. C.<sup>3</sup>

1. Rajagopalan, T. G., et al., Pepsin from Pepsinogen. Preparation and Properties, J. Biol. Chem.,



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241(21), 4940-4950, (1966).

2. Ryle, A. P., The Porcine Pepsins and Pepsinogens, *Methods in Enzymol.*, **XIX**, 316-336, (1970).

3. Perlman, G. in *PNAS* 45, 915-922, 1959.



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**2. Dietary Supplement Manufacture (Recommended)**

- 2.1. **Raw materials.** *NOT APPLICABLE*
- 2.2. **Formulation ingredients other than the NDI** *NOT APPLICABLE*
- 2.3. **Manufacturing process** *NOT APPLICABLE*
- 2.4. **Product specifications** *NOT APPLICABLE*
- 2.5. **Methods of analysis** *NOT APPLICABLE*
- 2.6. **Analysis of potentially toxic processes** *NOT APPLICABLE*
- 2.7. **Disintegration and dissolution profile** *NOT APPLICABLE*
- 2.8. **Shelf-life and conditions of storage** *NOT APPLICABLE*



### 3. History of Use or Other Evidence of Safety (Required)

#### 3.1 History of use

Studies on gastric digestion during 1820–1840 led to the discovery of pepsin as the agent which, in the presence of stomach acid, causes the dissolution of nutrients such as meat or coagulated egg white. Soon afterward it was shown that these protein nutrients were cleaved by pepsin to diffusible products named peptones. Efforts to isolate and purify pepsin were spurred by its widespread adoption for the application to digestive disorders, and highly active preparations were available by the end of the nineteenth century. There was uncertainty, however, as to the chemical nature of pepsin, for some preparations exhibited the properties of proteins while other preparations failed to do so. The question was not settled until after 1930, when Northrop crystallized swine pepsin and provided convincing evidence for its identity as a protein. The availability of this purified pepsin during the 1930s also led to the discovery of the first synthetic peptide substrates for pepsin, thus providing needed evidence for the peptide structure of native proteins, a matter of debate at that time. After 1945, with the introduction of new separation methods, notably chromatography and electrophoresis, and the availability of specific proteinases, the amino acid sequences of many proteins, including pepsin and its precursor pepsinogen, were determined. Moreover, handling of pepsin with chemical reagents indicated the participation in the catalytic mechanism of two aspartyl units widely separated in the linear sequence. Studies on the kinetics of pepsin action on long chain synthetic peptides suggested that the catalytic site was an extended structure. Similar properties were found for other “aspartyl proteinases,” such as chymosin (used in cheese making), some intracellular proteinases (cathepsins), and plant proteinases. After 1975, the three-dimensional structures of pepsin and many of its relatives were determined by means of x-ray diffraction techniques, greatly extending our insight into the mechanism of the catalytic action of these enzymes.

Abstract from journal article “A History of Pepsin and Related Enzymes” Joseph S. Fruton *The Quarterly Review of Biology* Vol. 77, No. 2 (June 2002), pp. 127-147 Published by: The University of Chicago Press.

Pepsin from Porcine and ascorbic acid have been commonly used in nutritional supplements in many commercial brands and are determined as safe for human consumption. Pepsin from Porcine 1:10,000 is classified under U.S. regulations: FDA - Food Additives Generally Recognized as Safe (GRAS): 21 CFR 184.159 FDA - 21 CFR - Total Food Additives 137.305 184.1595

Ascorbic acid (vitamin C) has been recognized as a consumable dietary supplement by the FDA and is also considered to be an antioxidant given its ability to react with free radicals in the human body. As stated in “The Antioxidant Role of Vitamin C”, “Vitamin C (ascorbic acid), a water soluble vitamin, has diverse functions in the body including an essential role in hydroxylation reactions necessary for collagen formation and carnitine synthesis as well as the facilitation of iron absorption”. The NIH Office of Dietary Supplements has also stated its importance in protein metabolism which would be an essential for the processing of pepsin. Although vitamin C is found



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in a variety of fruits and vegetables, most individuals who do not consume the recommended amount of these essential foods should supplement their diets with the adequate values of vitamins and minerals.

NIH Office of Dietary Supplements, Vitamin C Fact Sheet for Health Professionals.

Commissioner, Office of the. "Fortify Your Knowledge About Vitamins." *U.S. Food and Drug Administration*, FDA, 2 Feb. 2009.

**3.1.1 Description of the relationship between the historically consumed material and the NDI or dietary supplement containing the NDI**



**3.1.2 Describe identity information verifying the relationship between the historically consumed material and the NDI or dietary supplement containing the NDI**





### **3.1.3 Historical conditions of use and cumulative exposure estimate for the historically consumed material**

Pepsin is a compound whose zymogen (pepsinogen) is released by the chief cells in the stomach and that degrades food proteins into peptides. It was the first enzyme to be discovered, and, in 1929, it became one of the first enzymes to be crystallized, by John H. Northrop. Pepsin is a digestive protease, a member of the aspartate protease family.



Pepsin is one of three principal protein-degrading, or proteolytic, enzymes in the digestive system, the other two being chymotrypsin and trypsin. The three enzymes were among the first to be isolated in crystalline form. During the process of digestion, these enzymes, each of which is specialized in severing links between particular types of amino acids, collaborate to break down dietary proteins into their components, i.e., peptides and amino acids, which can be readily absorbed by the intestinal lining. Pepsin is most efficient in cleaving peptide bonds between hydrophobic and preferably aromatic amino acids such as phenylalanine, tryptophan, and tyrosine. Joseph S. Fruton Yale University New Haven, Connecticut USA.

Vitamin C is an essential part of the everyday diet and is required to maintain a healthy immune system. Historically, individuals that did not consume enough vitamin C developed scurvy and other disease associated with a deficiency in vitamin C. Vitamin C's role in the metabolism of protein is also a vital role in maintaining a healthy lifestyle. It is commonly found in a variety of foods and is sold as a dietary supplement. Although intake of this vitamin is recommended through foods, most individuals now consume extra vitamin C through dietary supplements widely found on the market today.

**3.1.4 Adverse events associated with historically consumed material**

- May cause a mild allergic skin reaction.
- May cause mild eye irritation if directly applied to them.
- May cause mild allergy or asthma symptoms

**3.1.5 Alternative rationale for reasonable expectation of safety based on history of use**

The adverse events stated in the last point are of very exceptional occurrence. The amounts applied and contained in our presentation are not sufficient to be constantly adverse but more of an exceptional event. No serious adverse effects have been recorded. The cautions stated are intended for precaution of these exceptions, even so the consequences of their adverse effect are not transcendent or serious enough to cause any physical damage what so ever to tissue, organs or biological systems. As an example, cleaning compounds for hair including shampoo or soap may cause more irritability to skin and eyes than our compound because their components are chemically more complex and less natural.

**3.2 Other evidence of safety**

Code of Federal Regulations  
 Title 21, Volume 3



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Revised as of November 5, 2019

CITE: 21 CFR184.1595

TITLE 21--FOOD AND DRUGS  
CHAPTER I--FOOD AND DRUG ADMINISTRATION  
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
SUBCHAPTER B--FOOD FOR HUMAN CONSUMPTION (CONTINUED)  
PART 184 -- DIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY  
RECOGNIZED AS SAFE

Code of Federal Regulations

Title 21, Volume 3

Revised as of November 5, 2019

CITE: 21 CFR 182.3013

TITLE 21--FOOD AND DRUGS  
CHAPTER I--FOOD AND DRUG ADMINISTRATION  
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
SUBCHAPTER B--FOOD FOR HUMAN CONSUMPTION (CONTINUED)  
PART 182 – SUBSTANCES GENERALLY RECOGNIZED AS SAFE



Subpart B--Listing of Specific Substances Affirmed as GRAS  
Sec. 184.1595 Pepsin.

(a) Pepsin (CAS Reg. No. 9001-75-6) is an enzyme preparation obtained from the glandular layer of hog stomach. It is a white to light tan powder, amber paste, or clear amber to brown liquid. Its characterizing enzyme activity is that of a peptide hydrolase (EC 3.4.23.1).

(b) The ingredient meets the general requirements and additional requirements for enzyme preparations in the Food Chemicals Codex, 3d ed. (1981), p. 110, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from the National Academy Press, 2101 Constitution Ave. NW., Washington, DC 20418, or may be examined at the Office of Food Additive Safety (HFS-200), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740, 240-402-1200, and at the National Archives and Records Administration (NARA).

(c) In accordance with §184.1(b)(1), the ingredient is used in food with no limitation other than current good manufacturing practice. The affirmation of this ingredient as GRAS as a direct food ingredient is based upon the following current good manufacturing practice conditions of use:

(1) The ingredient is used as an enzyme as defined in §170.3(o)(9) of this chapter to hydrolyze proteins or polypeptides.

(2) The ingredient is used in food at levels not to exceed current good manufacturing practice.

[60 FR 32911, June 26, 1995, as amended at 78 FR 14667, Mar. 7, 2013]

Subpart B--Listing of Specific Substances Affirmed as GRAS  
Sec. 184.1595 Pepsin.

(a) According the FDA, “vitamin products are regulated by FDA as ‘Dietary Supplements.’ The law defines dietary supplements, in part, as products taken by mouth that contain a ‘dietary ingredient’ intended to supplement the diet”.

### **3.2.1 Safety study type**

Pepsin from porcine and ascorbic acid are ingredients approved by the FDA as a GRAS (generally recognized as safe) substance under CFR Sec. 184.1595 and 182.3031, respectively.

A substance may be GRAS only if its general recognition of safety is based on the views of experts qualified to evaluate the safety of the substance. GRAS status may be based either





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on a history of safe use in food prior to 1958 or on scientific procedures, which require the same quantity and quality of evidence as would be required to obtain a food additive regulation. Because GRAS status may be either affirmed by FDA or determined independently by qualified experts, FDA's regulations do not include all GRAS ingredients and the specific uses described in the GRAS regulations may not be comprehensive for the listed ingredients.

**3.2.2 Safety study title, if any**

*NOT APLICABLE*



**3.2.3 Citation for the safety study (either public or non-public), if any**

Pepsin (CAS Reg. No. 9001-75-6) CITE: 21 CFR184.1595  
Ascorbic Acid CITE: 21 CFR182.3031

**3.2.4 Identity information verifying the relationship between the test article and the NDI or the dietary supplement**

Food Chemicals Codex, 3d ed. (1981), p. 110, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51.

**3.2.5 Route of administration, serving size, frequency of use, interval between servings, and duration of use of the test article**

*NOT APPLICABLE*

**3.2.6 Study design and safety metrics**

*NOT APPLICABLE*

**3.2.7 Discussion of toxicity and conclusion**

Since the discovery of pepsin from porcine and it has been deemed as a safe ingredient for human consumption as affirmed in CFR 184.1595 cite 21, this new ingredient is just a purified version that creates a particular chain of amino acids that are included with in the ones integrating pepsin form porcine and are known to be beneficial and safe for human consumption and can possibly be taken as a supplement in daily ingestion as it may support of the immune system. Ascorbic acid, not synthesized in the human body, is necessary to health for the maintenance of several biosynthetic pathways. It has been deemed safe by the FDA for human consumption in CFR 182.3031 cite 21.

**3.2.8 Alternative rationale for reasonable expectation of safety based on other evidence of safety**

Besides the safety regulations stated, we conclude that the amounts of this substance and the liquid format it is presented in can give a reasonable expectation of safety due to the amounts a person can ingest at once, even if deliberately overstating the recommended daily dosage and because it contains ingredients that have been extensively and for some time considered to be safe.

**4. Basis for Concluding That the New Dietary Ingredient Will Reasonably Be Expected to Be Safe for Use in the Dietary Supplement (Required)**



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The scientific data and information about the use of this substance is widely known and there is a consensus among qualified experts that those data and information establish that the substance is



safe under the conditions of its intended use. Pepsin from porcine and ascorbic acid are affirmed to have GRAS determinations which are made in this manner and said to be made through scientific procedures.

**41 Determination of the No-Observed-Adverse-Effect-Level (NOAEL) or Lowest-Observed Adverse Effect Level (LOAEL)**

We have no information on NOAEL or LOAEL.

**42 Determination of safety factor**

General recognition of safety through experience based on common use and a substantial history of consumption for food use by a significant number of consumers.

**43 Determination of the Acceptable Daily Intake (ADI)**

No acceptable daily intake has been determined.

**44 Determination of Estimated Daily Intake (EDI) and the EDI/ADI Ratio**

We determined our estimated daily intake based on common use and user convenience. Consumer should ingest 3 ml per day for two consecutive days per week (each serving contains roughly 450 mg ascorbic acid), totaling 6 ml per week for 8 consecutive weeks summarizing 48 ml in 8 weeks. Suspend for one week and repeat two 8-week series, including in-between suspension week for a total 48 ml in 3 8-week series with one-week suspended use between them. We observed that the ingestion of pepsin from porcine and ascorbic acid should be in a moderate and balanced fashion, as with any nutritional or dietary intake in human consumption. We have no EDI/ADI ratio since no ADI has been determined. The target population for this product is any adult looking to boost their immune system. Individuals with porcine allergies should not take this product. If pregnant or nursing, consult your healthcare practitioner before use.

These are the basis to establish our criteria for serving size, frequency and duration of our supplement. Our diet should take in account that protein quality is dependent on having all the essential amino acids in the proper proportions. If one or more amino acids is not present in enough amounts, the protein in your diet is considered incomplete.

In a typical American diet, the consumption of proteins is recommended by FDA is 50 g a day for adults, despite that recent statistics from various sources which indicate that in the USA this consumption overpasses the daily recommended value. It is the quality of the protein in the intake that is not quite adequate. This depends on the source of the proteins, which our biggest intake derives from vegetables at 57% and only 18% from meat or beef products. Also, the PDCAAS value of protein (Protein digestibility corrected amino acid score) provides a 92% for beef. If we consider the recommendations of the FDA to complement our diet with supplements in order to complete our intake of proteins, our compound based on amino acids does give some supplemental nutrition by providing some of the amino acids that might create



high quality proteins.



We base our consumption recommendation on the basis of approximately double the protein of the consumption of pork per capita in the USA, considering an average of 43.1 pounds with an approximate value of 134 to 140 protein grams per pound, depending on the mix. Ascorbic acid consumption is based on the Recommended Dietary Allowances as provided by the NIH and commonly sold dietary supplements containing vitamin C.

**4.5 Determination of margin of safety**

Pepsin from porcine and ascorbic acid safety margins are generally accepted from a consensus of expert opinion regarding the safety of the use of the substance.

**4.6 Safety narrative and conclusion**

We consider the FDA definition of ‘safe’ as ‘a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use’.

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	Weeks	Weekly Milliliters	Total Milliliters
	8	6	48
	1	0	0
	8	6	48
	1	0	0
	8	6	48
	1	0	0
Per bottle	27		144

Supplementing with twice the amount and spread of amino acids approximately to the consumption of pork annually. Average American consumes 43.1 pounds of pork with an average between 134 and 140 grams of protein per pound.

**4.7 Alternative basis for reasonable expectation of safety**

There is no alternative basis for expectation of safety, but the ones established by FDA regulations particular to pepsin from porcine and ascorbic acid.