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Monther Elnajjar
VP of Business Development
Avicenna Nutraceutical, LLC
290 Prospect Place,
Alpharetta, GA
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Dear Mr. Elnajjar

Re: Regulatory Status of "AVC-H2" for Use as an Ingredient in Food and Supplement Products Marketed in the United States

Avicenna Nutraceutical (AVC Nutraceutical), is a manufacturer of a hydrolyzed collagen preparation obtained from chicken full-frame sternum cartilage. The ingredient is marketed under the trade name AVC-H2 and is intended for use in food and supplement products sold in the United States and global marketplaces. AVC Nutraceutical has requested that Intertek Scientific & Regulatory Consultancy (Intertek) provide an opinion on the regulatory status of the ingredient for the aforementioned food uses. It is Intertek's view that AVC-H2 can be legally marketed in the United States as a nutrient food ingredient, and can be added to food products quantum status, and as an ingredient in dietary supplement products regulated under the Dietary Supplement Health and Education Act (DSHEA). Further discussion of the basis for this opinion is presented below.

Identity

AVC-H2 is produced from chicken full-frame sternum cartilage that is subjected to acid hydrolysis by heating in the presence of an aqueous acid (*e.g.*, HCl) at a temperature range of 55°C - 75°C for 12 to 17 hours. Solid waste is then filtered and discarded. The acidic solution is then neutralized using a basic solution (*e.g.*, NaOH, Calcium Carbonate, Calcium Hydroxide), and the neutralized solution is then spray dried. The final ingredient is a high purity protein ingredient and contains a collagen content of ≥70%. The ingredient contains an ash content of ≤7%, which is largely accounted for by sodium chloride and calcium chloride salts originating from the acid/base treatments. Appropriate specification limits for potential heavy metal and microbial contaminants have been established. The manufacturing conditions are common processes utilized by the food industry and all processing-aids are permitted for their respective uses in accordance with an appropriate federal regulation. AVC provided results of batch analyses from 5 non-consecutive lots of the ingredient demonstrating that the manufacturing process is adequately controlled to produce a consistent product that is compliant with the ingredient specifications. Intertek has concluded that the manufacturing process is suitable for production of food ingredients and that the ingredient is well characterized. Appropriate specifications have been established for the ingredient and it can be concluded that the ingredient is food grade quality.

Intended Use and Dietary Exposure

Intertek notes that oral consumption of type II collagen has been associated with various nutritional health outcomes including maintenance of bone, joint and skin health, and Intertek has seen increased interest in

companies developing collagen-based ingredients for the U.S. marketplace. AVC-H2 will be marketed in food and supplement products targeted to consumers seeking dietary sources of type II collagen for sports performance and general wellness. AVC-H2 is intended for use in conventional food types (*e.g.*, enhanced fortified water beverages, sports nutrition gels, fortified flavored milk beverages, enhanced or fortified fruit-flavored beverages) and dietary supplement products (*e.g.*, powder sachets, pills, capsules) at levels of 1 to 3 grams per serving. No self-limiting use levels have been identified. Intertek does note however, that type II collagen is not a balanced source of protein and should not be marketed as a source of dietary protein to support growth[1]. Notwithstanding this specific limitation in use, it is Intertek's view that AVC-H2 could be used *quantum satis* in food and supplements; pre-market clearance under the GRAS procedure for food uses or submission of a 75-day New Dietary Ingredient Notification (NDIN) for supplement uses would not be required. Further discussion of the regulatory status of the ingredient is described below.

Regulatory Status

Based on the identity and conditions of manufacture of AVC-H2, it is Intertek's view that the ingredient meets the definition of hydrolyzed protein under 21 CFR §184.1553 and can be sold in the United States as a general-purpose food ingredient on the basis of its FDA affirmed GRAS status under the regulation. Under 21 CFR §184.1553 hydrolyzed protein, referred to as peptones under the regulation, is defined as follows

§184.1553 Peptones.

*(a) Peptones are a variable mixture of polypeptides, oligopeptides, and amino acids that are produced by **partial hydrolysis** of casein, **animal tissue**, soy protein isolate, gelatin, defatted fatty tissue, egg albumin, or lactalbumin (whey protein). Peptones are produced from these proteins using proteolytic enzymes that either are considered to be generally recognized as safe (GRAS) or are regulated as food additives. Peptones are also produced by denaturing any of the proteins listed in this paragraph with safe and suitable **acids or heat**.*

*(b) The ingredients must be of a **purity suitable for their intended use**.*

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

*(1) These ingredients are used as **nutrient supplements** as defined in §170.3(o)(20) of this chapter; as processing aids as defined in §170.3(o)(24) of this chapter; and as surface-active agents as defined in §170.3(o)(29) of this chapter.*

*(2) These ingredients are **used in food at levels not to exceed current good manufacturing practice**.*

AVC-H2 a mixture of hydrolyzed protein (*i.e.*, polypeptides, oligopeptides, and amino acids) produced from chicken full-frame sternum cartilage by acid and heat processing, and therefore the conditions under (a) of the regulation are met. AVC has established suitable food grade specifications for AVC-H2,

[1] For example, the use of AVC-H2 as a sole source of protein in a meal replacement product would not be appropriate.

which in-line with the definition of hydrolysed protein described in the Food Chemicals Codex (see below), and therefore conditions under (b) also are met.

> ***FCC, 2010 – Partially Hydrolyzed Proteins***
>
> *Partially hydrolyzed proteins occur as liquid, paste, powder, or granules. They are composed of peptides and polypeptides resulting from the partial or incomplete hydrolysis of peptide bonds present in edible proteinaceous materials catalysed by **heat**, food-grade proteolytic enzymes, **and/or suitable food-grade acids**. Their degree of hydrolysis typically ranges from 3% to 85% on the basis of peptide bond cleavage. During processing the proteinaceous raw material may be treated with **safe and suitable alkaline materials**. The edible proteinaceous materials used as raw materials are derived from casein and other milk products such as whey protein; from **animal tissue**, including gelatine, defatted animal tissue, and egg albumen; from yeast; and from soy protein products, wheat protein products, and other suitable and safe plant sources.*

As a matter of due-diligence, AVC Nutraceutical has evaluated the GRAS status of AVC-H2 in accordance with 21 CFR 170.30(a)(b). AVC prepared documentation supporting the identity, manufacture, intended uses and safety of the ingredient in accordance with 21 CFR 170 Subpart E – Generally Recognized as Safe Notice. Based on information characterizing the identity and manufacture of AVC-H2, AVC has demonstrated analytically that the ingredient can be defined as a type II collagen product which is consistent with the definition of hydrolyzed protein in the Food Chemical Codex. Based on published information relevant to the safety of collagen, AVC did not identify any new information relevant to the safety of collagen as a food ingredient to call into question the current GRAS status of hydrolyzed protein under 21 CFR §184.1553. Although AVC intended to notify the FDA of the company's conclusion on the GRAS status of the AVC-H2 under the agency's voluntary GRAS notification program, it is Intertek's view that the FDA will refuse to file a GRAS notice for the ingredient. This conclusion is based on a recent discussion that Intertek has had with the agency where the FDA stated that collagen from animal tissue is GRAS for general purpose food use under 21 CFR §184.1553, and therefore there is no regulatory need to file a GRAS notification; based on limited resources available to the agency, re-evaluation of the GRAS status of collagen, which the FDA has previously affirmed as GRAS would not be supported by the agency.

With respect to use in dietary supplements, Intertek notes that as defined in the *Federal Food, Drug, and Cosmetic Act* (FD&C Act) and the *Dietary Supplement Health and Education Act of 1994*, a dietary supplement:

- is a product (other than tobacco) that is intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract, or combinations of these ingredients;
- is intended for ingestion in pill, capsule, tablet, or liquid form;
- is not represented for use as a conventional food or as the sole item of a meal or diet;
- is labeled as a "dietary supplement";

- includes products such as an approved new drug, certified antibiotic, or licensed biologic that were marketed as a dietary supplement or food before approval, certification, or license (unless the Secretary of Health and Human Services waives this provision)."

As AVC-H2 is permitted for food use under 21 CFR §184.1553, the ingredient can be defined as a "*dietary substance for use by man to supplement the diet by increasing total dietary intake*". AVC-H2 therefore qualifies for addition to dietary supplements.

Once it has been established that a dietary ingredient qualifies for use in dietary supplement products under DSHEA, it must then be determined whether the dietary ingredient constitutes as a "new dietary ingredient" (NDI), and if so, whether pre-market notification is required prior to its marketing in dietary supplements. Under DSHEA, a new dietary ingredient (NDI) is defined as "*a dietary ingredient that was not marketed in the United States before October 15, 1994 and does not include any dietary ingredient which was marketed in the United States before October 15, 1994*". A dietary supplement which contains a NDI must meet at least one of the following requirements (21 USC §350b) (U.S. FDA, 2014):

1. *contain only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered;*

2. *have a history of use or other evidence of safety establishing that the dietary ingredient when used under the conditions recommended or suggested in the labeling of the dietary supplement will reasonably be expected to be safe and, at least 75 days before being introduced or delivered for introduction into interstate commerce, the manufacturer or distributor of the dietary ingredient or dietary supplement shall provide the Secretary with information, including any citation to published articles, which is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe.*

With respect qualification of AVC-H2 as a "new dietary ingredient" or an 'old' dietary ingredient, it is likely that type II collagen has a long-history of use as a dietary supplement ingredient prior to 1994. Strictly speaking a determination that an ingredient is an 'old' dietary ingredient would require some form of published evidence (*e.g.*, clinical trial publication, magazine article); however, it seems unlikely that anyone would question that collagen was used in supplements prior to 1994. Notwithstanding this conclusion, even if AVC-H2 was considered a NDI, it can be demonstrated on the basis of its regulatory status as a food under 21 CFR §184.1553 that AVC-H2 has been used for food in a form in which the food has not been chemically altered, therefore supplements containing this ingredient would meet condition (1) above and could be marketed as a dietary supplement without the need to file a New Dietary Ingredient Notification with the Agency prior to marketing.

Conclusions

Intertek has concluded that AVC-H2 meets the definition of hydrolyzed protein under 21 CFR §184.1553. AVC Nutraceutical has established suitable food grade specifications for the ingredient that are in-line with the FCC definition of hydrolyzed protein and can be used in food on the basis of its FDA affirmed GRAS status with no limitation in use other than cGMP.

On the basis of the regulatory status of AVC-H2 as a food ingredient under 21 CFR §184.1553, Intertek also has concluded that the addition of AVC-H2 to dietary supplement products would be permitted without the need to file a New Dietary Ingredient Notification to the offices of the FDA on the basis that the ingredient is

present in the food supply as an article used for food in a form in which the food has not been chemically altered.

We hope this letter accurately describes the regulatory status of AVC-H2 as a safe and suitable source of dietary collagen for use in food and supplements in the United States marketplace. Should you have any additional questions about the regulatory status of the ingredient please do not hesitate to reach out to us.

Yours sincerely,

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Food & Nutrition Group
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DISCLAIMER